SECOND EDITION

Electrophysiological Disorders of the Heart

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Dedication

To Diane, Joy, and our parents and families, whose unfailing support and understanding made this work feasible.

This book is dedicated to the pioneers in our field, who made such progress possible; our mentors, who imbued us with the desire to help advance this science; and our younger colleagues all across the world, who continue to inspire us with their energy and innovation and bring with them great hope for the future.

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Foreword

The field of cardiac electrophysiology has undergone dramatic increases in new basic and clinical knowledge, ranging from the pathophysiology of heart rhythm disturbances, to cellular and molecular research, to expanding clinical diagnostics and therapeutics. These have been accompanied by huge advances in technology. All of this has emerged over a relatively short period of approximately 50 years, with particularly dramatic acceleration during the past 10 years. From its beginnings in deductive reasoning applied to clinical electrocardiography—leading ultimately to insights into ion channel physiology, the translation of genetics and genomics to clinical concepts, the development of highly specialized procedures, and the related evolution of technologically advanced device therapy—the field has constantly pushed on its borders of knowledge in the directions of the basic sciences, bedside clinical skills, and advanced therapeutics.

In an attempt to bring together the multiple aspects of the field of cardiac electrophysiology into a single source of information for the convenience of both researchers and clinicians, the first edition of the multi-authored text *Electrophysiological Disorders of the Heart* was developed and edited by Sanjeev Saksena and John Camm. Published in 2005, the book provided broad coverage of the relevant knowledge base in this field at the time and was well received. However, with the continued growth of the knowledge base since then, and evolution of new horizons in the field of electrophysiology—such as the rapidly evolving field of genetics and genomics, interventional procedures for common arrhythmias such as atrial fibrillation, and better insight into both rare clinical arrhythmia syndromes and the evolution and testing of noninvasive testing techniques—an update of the content was necessary.

In the second edition of *Electrophysiological Disorders of the Heart*, Saksena and Camm have expanded existing topics, added new topics of current interest, and broadened the scope of the book in areas that were touched upon less comprehensively in the previous edition. The added topics include the fields of noninvasive electrophysiological imaging and its current and future applications for clinical evaluation and risk profiling, a broader development of topics in pediatric electrophysiology, and comprehensive coverage of the topics of ablation techniques and devices for cardiac arrhythmias.

Updating the original content and adding new content could stand alone in identifying the value of the text, but, in addition to that, the editors have taken care to provide insights into where each of the subfields within the general topic may be heading in the future, providing the investigator and the clinician with orientation in anticipation of future progress. It is axiomatic in science that narrow fields of study tend to expand beyond their original boundaries; the second edition of *Electrophysiological Disorders of the Heart* passes the previous boundaries, taking the readers to the current boundaries, and giving glimpses into future directions. As such, the primary editors, Drs. Saksena and Camm, as well as the section editors, Drs. Penelope Boyden, Paul Dorian, Nora Goldschlager, Victoria Vetter, and Wojciech Zareba, are to be commended for their efforts and congratulated on the final product.

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Foreword

This is a new edition of a book whose previous edition was well appreciated by the cardiac arrhythmia community. Obviously, the many advances in recent years in basic and clinical arrhythmology require a timely review of what has been accomplished, more so because the increasing use of the Internet as a (the only?) source of information favors the development of tunnel vision. The person performing catheter ablation of atrial fibrillation becomes inclined to focus on Internet information for what is new in his or her area of daily activities and not follow new developments in genetic arrhythmology or advances in the electrocardiography of arrhythmias. Therefore, the challenge for the editors was to ask key leaders from the different clinical areas to present new information in an easily readable format.

I recommend this book. All the editors and authors lived up to the expectations created by the first edition. For me, it reflects the incredible progress we are making in our understanding of basic mechanisms, including the genetic background, and our growing ability to diagnose, risk stratify, and treat cardiac arrhythmias.

Still, we are not at the end of the line. To name a few areas: sudden cardiac death continues to elude us. Better selection of candidates for device therapy for primary prevention of sudden cardiac death and cardiac resynchronization therapy for heart failure, leading to better guidelines, is needed. Will cell transplantation be able to restore cardiac function? Will pharmacogenetics make drug therapy more effective and safe? And so on.

So, digest this new edition well. Five years from now you will need a new one!

Hein Wellens

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Preface

In the theatre, the second act inevitably builds on the first act. In medicine, swift progress in medical knowledge often requires a second edition of a textbook to revisit, and even rebuild, part of the original foundation. In the first edition of this book, we sought to "analyze and distill new information and meld it with classical concepts of arrhythmology." We have continued this effort in this edition, but with the realization that the foundations of knowledge in our discipline have broadened, often with completely new and novel constructs. Our original goal of approaching the subject matter from the viewpoint of the practicing clinician involved in the care of the arrhythmia patient or the scientist in search of understanding of disease states or current therapies remains unaltered, but the addition of new sections and the expansion of existing ones have become necessary. Since the publication of the first edition, advances in the basic and translational sciences and therapeutic technology have had continuing impact on clinical practice in cardiac arrhythmias. A strong focus on evidence-based outcomes, including understanding their methodology, is now a cornerstone of modern clinical practice and a major theme in this new edition. Thus, comprehensive analysis of clinical trials is presented by experts.

Keeping pace with changes in information delivery methods has resulted in a dynamic Expert Consult companion web site to this text. This site will be periodically updated with important new developments. Multimedia presentations are a new aspect of this book to enhance content delivery. Video presentations are linked to the online version of this text that appears on Expert Consult and have been incorporated in technical and procedural chapters. An exhaustive bibliography is available in this online version of the text to allow more content in the physical book and provide a handy reference for searches on a topic.

We have continued in our belief in moving away from specialized segmentation of information in this field. In addition, the section editors of this text have preferred a presentation oriented more toward disease states and clinical syndromes. This book remains a detailed clinical reference yet is still sufficiently detailed to serve as a comprehensive reference in all of its sections. Four new sections have been added to broaden the scope of the book. These include clinical electrophysiological techniques, cardiac pacing, and noninvasive electrophysiology as separate sections still linked to the diagnostic and treatment sections on cardiac arrhythmia and clinical syndromes. These sections now provide a comprehensive review of each area. Clinical electrophysiological techniques from basic methods to individual procedures for each dysrhythmia are fully detailed for practicing clinical electrophysiologists or cardiologists wanting to familiarize themselves with laboratory techniques. The cardiac pacing section provides treatment of pacemaker technology, engineering, physiology, and clinical implementation of device therapy and serves as a reference for all practitioners and researchers involved in the delivery of pacemaker therapy. Noninvasive electrophysiology has expanded into a stand-alone section with individual chapters examining all methods in current clinical practice that are now widely used by cardiologists and electrophysiologists alike in the assessment of the arrhythmia patient. A new section on pediatric electrophysiology reflects the burgeoning knowledge base and patient care needs in this segment of the arrhythmia patient population. Pediatric and adult cardiologists as well as arrhythmia specialists are now actively and directly engaged in care of these patients. The need for continuity of arrhythmia care for pediatric patients into their adult years and the importance of excellent arrhythmia care in the early years are now also important public health challenges.

The original book sections have also been seriously reengineered. The underlying basic science in this field has been comprehensively expanded and rearranged in two subsections, the first focusing on concepts of normal and abnormal physiology and the second on clinical investigation methods and therapies in current use. This new structure provides the reader with a full view of the enormous advances in our fundamental understanding of normal and disease states as well as the scientific bases of diagnostic and treatment methods. The section on cardiac rhythms and arrhythmias, despite extensive revisions, has maintained its distinct multi-authored chapter format that was widely appreciated in the first edition. Clinical syndromes have been updated, but the disease state model for the clinician involved in longitudinal care is continued. Finally, the section on therapeutics and interventional therapies provides state-of-the-art information on current treatment methods and strategies, with particular focus on evidence-based analysis and current practice guidelines. Each subsection provides a complete treatment of the individual therapeutic approach (drug, device, or procedural). Device therapy from implantation to surveillance methods and the full array of interventional mapping and ablation procedures (both in the catheterization laboratory and operating room) with their target population provide the clinician with a complete understanding of all potential options for patient care. Each subsection is designed to provide the arrhythmia specialist, cardiologist, or interventional electrophysiologist with an understanding of the fundamentals as well as current applications of arrhythmia therapies.

Each of these nine sections can stand alone as a focused monograph for different educational needs, yet each section complements other discussions elsewhere in the book. Overlap between sections and chapters has been limited as far as is feasible without disruption of presentation. The use of multi-authored chapters in Section V reflects our continuing bias that the information base needed for such synthesis is vast, requiring experts in each area of study to provide the core knowledge needed for that topic. This results, in our view, in a particularly compelling and authoritative treatment of the subject. We believe this will serve as a reference text for students of this field in any country and is particularly suitable for those seeking advanced certification in clinical cardiac electrophysiology.

To achieve such an ambitious revision would have been inconceivable without the energy, support, and commitment of a truly

international team of of co-editors and authors and the editorial team at our individual institutions and Elsevier. These individual contributions reflect the global interest in this field, and this unique worldwide effort has produced a truly international textbook. We have been extraordinarily fortunate to assemble a team of editors who have the knowledge and experience to provide a bridge between classic concepts and the most recent developments in the field. These distinguished educators brought their individual ideas and editorial skills to produce the core sections of this text. The individual authors and coauthors, now numbering 227 authors from 14 countries, provided the momentum for this project. Their wealth of knowledge, experience, and insight have made the content of this text unique in its spectrum and utility to the reader. To our contributors, we can only express our deepest gratitude and hope that the final product is, for them, in small measure a worthwhile outcome of their efforts.

In shepherding this project, we could not have arrived at our destination without the continuous support of our staff, colleagues, and the editorial and production staff at Elsevier. In particular, we would like to thank and acknowledge the contributions of Ms. Celeste Simmons, Dr. Irina Savieleva, Ms. Joan Ryan, Ms. Natasha Andjelkovic, Ms. Carrie Stetz, and Ms. Dolores Meloni.

As senior editors, we have had the opportunity to shape this book, and this has in turn helped us redefine and revisit our own ideas on the educational needs and best information delivery techniques in cardiac arrhythmology. It is our sincere hope that this textbook will continue to fulfill the expectations of our readers and compel and expand their interest in this great discipline. Should it do so, this second act will have found its *raison d'ĕtre.*

Sanjeev Saksena
A. John Camm

Worship the spirit of criticism. If reduced to itself, it is not an awakener of ideas or a stimulant to great things; but without it everything is fallible; it always has the last word.

—Louis Pasteur
November 14, 1888

CHAPTER 1

Basic Electrophysiological Procedures for the Clinician

David S. Park and Glenn I. Fishman

Over the past 50 years electrophysiologists have unraveled many of the molecular and cellular underpinnings of normal and pathologic cardiac rhythms. Innovations in the fields of molecular biology and biophysics have dramatically enhanced current understanding of action potentials, conduction properties, and ion channel physiology. This chapter discusses the experimental tools that have proved indispensible for the study of cardiac electrophysiology.

Electrophysiology Basic Concepts

All cells maintain electrochemical gradients across their membranes through the action of a panel of pumps, channels, transporters, and exchangers. The resulting voltage difference across the cell membrane is known as *membrane potential* (E). Although all cells maintain a resting membrane potential, excitable cells such as neurons and myocytes have the ability to generate transient, reversible, electrochemical wavefronts referred to as *action potentials.* Action potentials allow rapid signal propagation across the cell membrane. In the heart, each type of cardiac cell (e.g., nodal, atrial, ventricular, Purkinje) has a characteristic action potential that is determined by the panel of ion channels expressed (Figure 1-1, *A* and *B*).[1,2] The action potential of the cardiac ventricular myocyte is composed of five phases (Figure 1-1, *C*).[1] Phase 4 of the action potential is the resting membrane potential, which corresponds to cellular diastole. Phase 0 is the rapid depolarization phase driven by the influx of sodium (Na) ions. Phases 1 to 3 correspond to repolarization of the cell membrane. Phase 2, or the plateau phase, is maintained by the sustained influx of calcium ions and the efflux of potassium ions. This influx of calcium (Ca^{2+}) activates Ca^{2+}-induced Ca^{2+} release from the sarcoplasmic reticulum (SR), thereby activating myocyte contraction. Action potentials travel rapidly from cell to cell through low-resistance intercellular communication points called *gap junctions*. This behavior synchronizes electrical activation and facilitates coordinated muscular contraction.

The ability to study action potentials and ionic currents in biologic tissues was made possible by modeling the cell as an electrical circuit.[3] The ionic current (I, measured in *amperes*) is the net flow of ions down their electrochemical gradients via their respective channels and transporters. The cell membrane, a lipid bilayer, serves as a capacitor (F, measured in *farads*), storing charge in the form of electrochemical gradients. The resistance (R, measured in *ohms*) to ionic current depends on many factors, such as the gating characteristics of ion channels, number of available channels, and posttranslational modification of channel proteins. The gating properties of ion channels vary, depending on specific channel type, but may be regulated by factors such as transmembrane voltage, ligands such as drugs, hormones or intracellular second messengers, mechanical forces, as well as the coexpression of regulatory subunits.[4] Conductance (g), or the measure of ease of ionic current flow, is the inverse of resistance ($g = 1/R$). According to Ohm's law, the membrane potential (E) equals the product of ionic currents (I) and channel resistances (R), $E = IR$. If conductance remained constant, the relationship between the current and the potential would be linear. However, because the conductance of ion channels is not constant, the resistor is non-Ohmic; therefore, the current-voltage relation is nonlinear. A simplified example of a cellular circuit is given in Figure 1-2.[3,5]

Electrophysiologic Tools

Willem Einthoven's contribution of surface electrocardiography (ECG) was the first of many innovations that would begin to detail the heart's electrical behavior. The ECG represents the summation of the global electrical activity occurring in the heart. Despite the great success of the ECG as a clinical and laboratory tool, it lacks the temporal and spatial resolution needed to identify the local electrical events that underlie the surface ECG. Significant advancements in cellular biology and molecular biology, coupled with ever-smaller electrode designs, have made it possible to record membrane currents with much higher resolution, including at the single-channel level. The fundamentals of the electrophysiological test are (1) biologic tissue as the source of electrical activity and (2) a means of recording electrical activity (i.e., electrodes or fluorescent dyes). The remainder of this chapter is divided into four sections: (1) experimental preparations, (2) electrode-based studies, (3) optical mapping, and (4) molecular and genetic tools.

Experimental Preparations

Experimental preparations range from intact animals to artificial membrane systems. Each preparation has its own strengths and weaknesses as a model system. Therefore the suitability of the preparation for a particular question must always be considered before experimentation.

Intact Animal

Study of cardiac electrical activity in a live animal is the most physiologically representative model system. All the available tools used in human electrophysiologic testing are readily

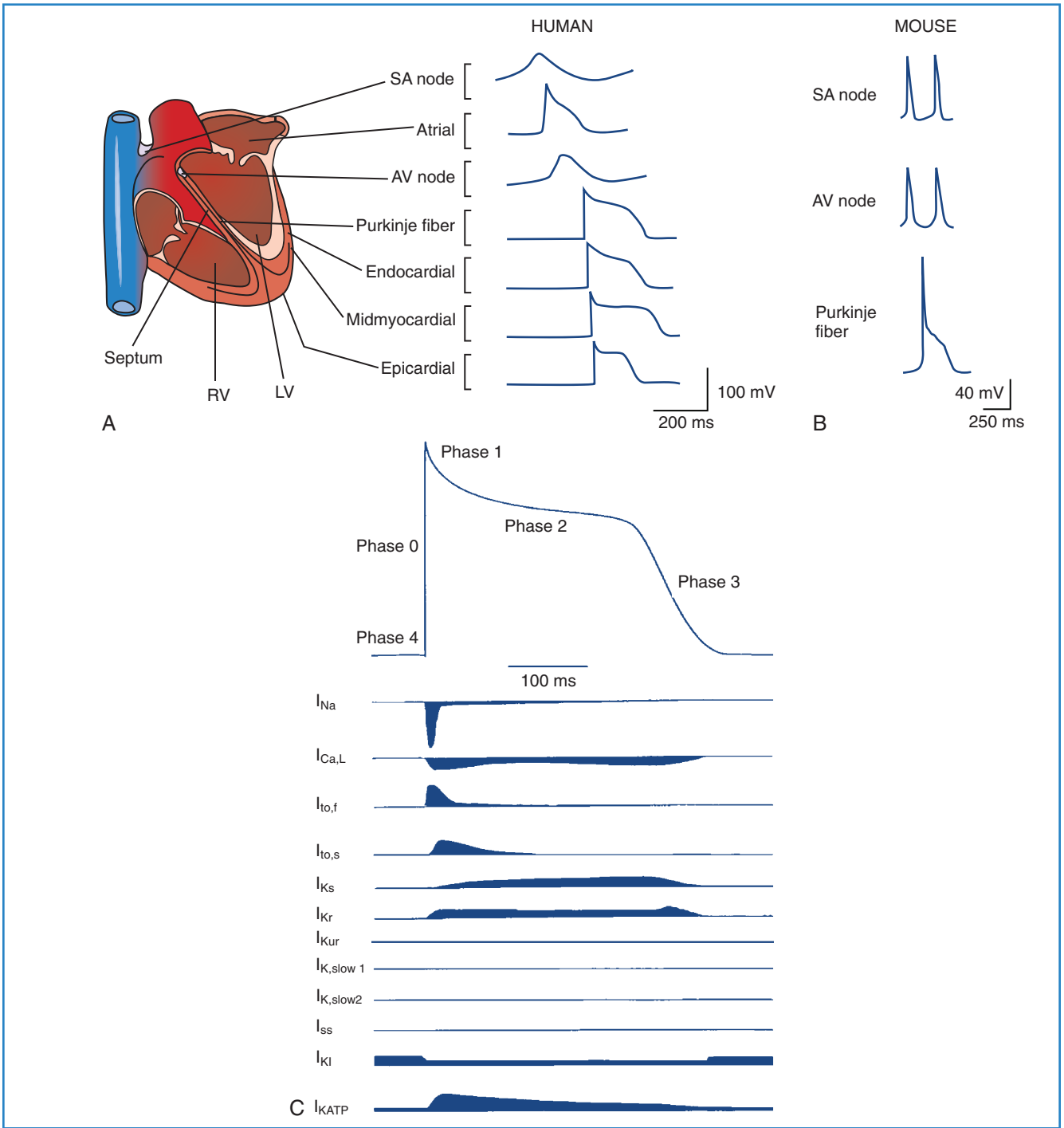

FIGURE 1-1 **A,** Schematic of action potential waveforms and propagation in the human heart. **B,** Murine action potential waveforms. **C,** Human ventricular action potential waveform with corresponding ionic currents. *AV,* Atrioventricular node; *LV,* left ventricle; *RV,* right ventricle; *SA,* sinoatrial node. *(From Nerbonne JM, Kass RS: Molecular physiology of cardiac repolarization,* Physiol Rev *85[4]:1205–1253, 2005; and Mangoni ME, Nargeot J: Genesis and regulation of the heart automaticity,* Physiol Rev *88[3]:919–982, 2008.)*

available for animal studies as well. Intracardiac[6] and epicardial electrograms,[7] monophasic action potentials,[8] and multiple-electrode mapping[9] techniques have all been used in a variety of species. However, if the ultimate goal is to understand human physiology and pathophysiology, then the choice of species for experimentation becomes a significant issue because there are considerable interspecies differences. In the case of infarct models, dogs and guinea pigs both manifest extensive coronary collateralization that limits the transmural extent of infarction. The porcine coronary system, however, more closely resembles the human anatomy and therefore serves as a better infarct model.

The murine system deserves special attention, given its increasing use in biologic research. Ease of handling, breeding,

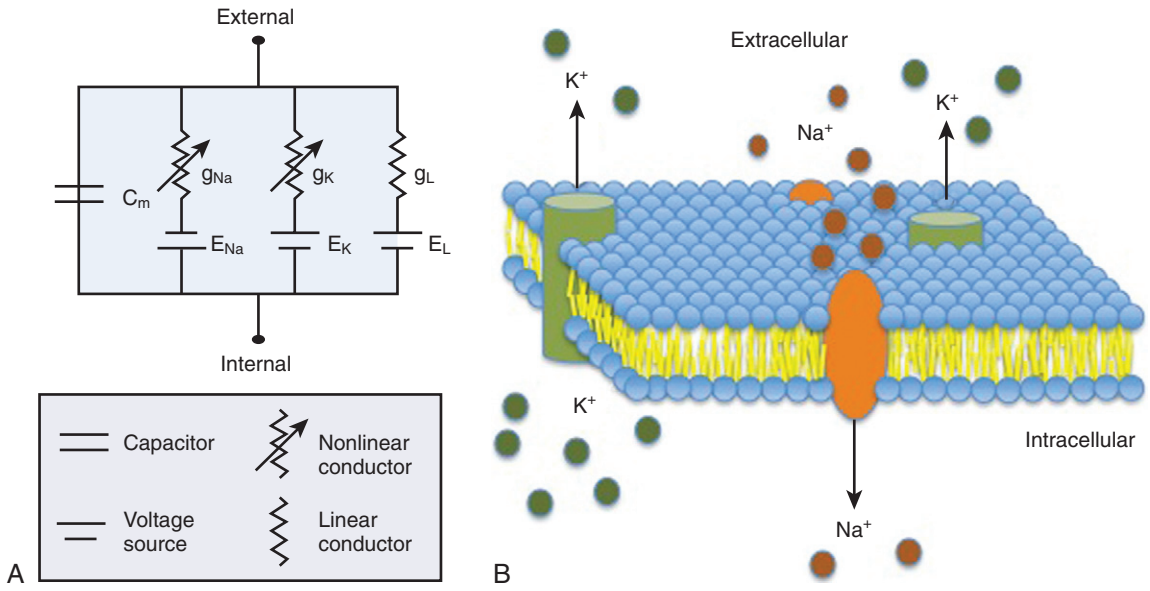

FIGURE 1-2 The Hodgkin and Huxley electrical circuit model. **A,** Current flowing across the membrane can be carried via a membrane capacitor or through ion channels situated in parallel. Voltage-gated channels are voltage dependent and time dependent and display nonlinear conductance (g_{Na} and g_K). Small leakage channels represent membrane permeability to ions and exhibit linear conductance (g_L). The electrochemical gradient of each ion at steady state is designated as E_{Na}. **B,** Corresponding cellular membrane with ion channels and electrochemical gradients. *(From Carmeliet E, Vereecke J:* Cardiac cellular electrophysiology, *Norwell, MA, 2001, Kluwer Academic Publishers.)*

and amenability to genetic manipulation has allowed the mouse to supplant many larger animals that were used in classic studies of cardiac electrophysiology. Despite these advantages, the human and the murine cardiovascular systems have clear differences. The average lifespan of inbred mouse strains is approximately 2.7 years, making chronic diseases such as atherosclerosis nonexistent in unmanipulated animals. The significant differences in the coronary anatomy between mice and humans result in different infarct distributions after coronary ligation.[10] The average heart rate of a mouse is between 400 and 600 beats/min at rest compared with humans, which is between 60 and 100 beats/min. Murine cardiomyocytes have relatively short action potential durations, making comparisons of the mechanisms of arrythmogenesis and effects of antiarrhythmic drugs with those of their human counterparts difficult (see Figure 1-1, *A* and *B*).[1,2] These factors must be considered when designing experiments and drawing conclusions from murine studies.

In addition to species-specific limitations, live animal models are confounded by extracardiac variables, for example, neurohormonal effectors that cannot be completely controlled. Live animals are incompatible with the study of unstable ventricular tachyarrhythmias and fibrillation. The type of anesthetic used can significantly alter cardiac electrophysiology. For example, sodium pentobarbital has been shown to alter action potential durations and transmural repolarization gradients by affecting late sodium currents in vivo.[11]

The Langendorff Heart System

The isolated, perfused heart preparation first described by Oscar Langendorff in 1895 allows physiologic evaluation of the beating heart removed from the neurohormonal and hemodynamic environment of the intact animal.[12] The Langendorff heart system consists of an excised heart that is perfused in a retrograde manner by cannulation of the aorta. When optimally perfused, the isolated heart can continue to beat for several hours, allowing detailed analysis of physiologic and pathophysiologic states (Figure 1-3). The advantage of the Langendorff system is the ability to manipulate many aspects of cardiac physiology in a controlled setting. A variety of drugs, toxins, and neurohormonal agents can be infused at specified levels. The isolated heart also provides an opportunity to study arrhythmias that would be hemodynamically unstable in a live animal model. Inducible arrhythmias can be mapped by using standard electrode techniques or optical mapping systems.[13] In addition, such modifications as whole-heart preparation allow hemodynamic measurements such as preload and afterload.[12]

The quality of preparation of the isolated heart is highly dependent on the experience of the investigator. The method of sacrifice before organ procurement and the ischemic time (time interval between heart extraction and initiation of artificial perfusion) can have a significant impact on the quality and internal consistency of the data acquired. Another limitation is that the intact heart makes further delineation of regional myocardial depolarization and repolarization characteristics challenging.[6]

Wedge Preparations

The ventricular myocardium is a heterogeneous structure consisting of three layers: (1) the epicardium, (2) the mid-myocardium, and (3) the endocardium. The arterially perfused wedge preparation was developed by Yan and Antzelevitch in 1996 to study the electrophysiologic heterogeneity of these myocardial layers in dogs.[14] The myocardial wedge is prepared by dissecting along the vascular supply such that the tissue can be perfused during experimentation. By isolating a three-dimensional wedge of ventricular

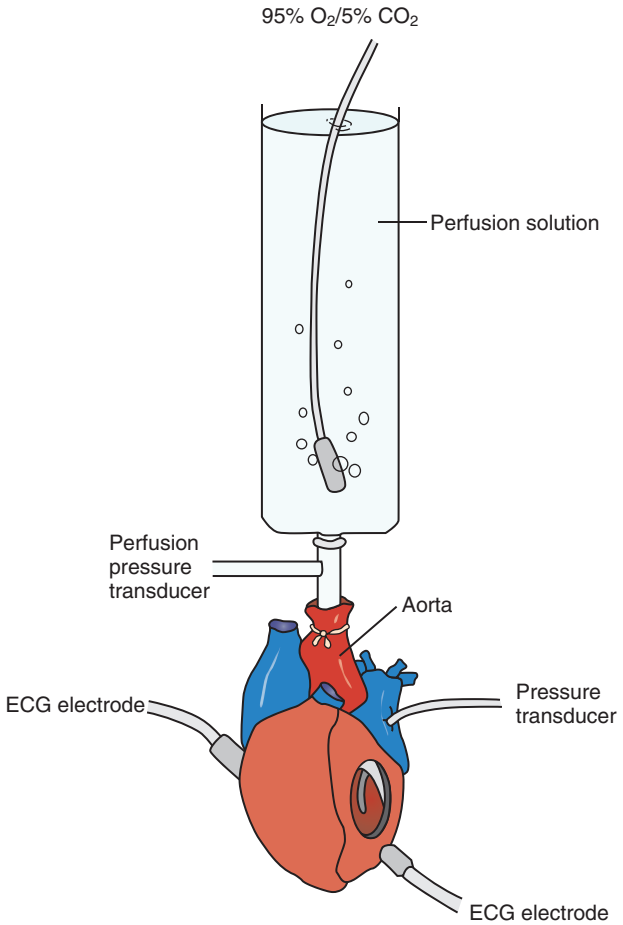

FIGURE 1-3 The Langendorff heart preparation. The aorta is cannulated and the coronary arteries are perfused in a retrograde manner with oxygenated, nutrient-rich solution. Depending on the height of the fluid column, a constant pressure of perfusate closes the aortic valve and allows the solution to enter the coronary ostia. This allows the heart to beat for several hours. Newer models use mechanical pumps to deliver constant pressure or flow to the coronary circulation. A pressure transducer catheter may be inserted into the left ventricle to transduce systolic and diastolic pressures. *(From Hearse DJ, Sutherland FJ: Experimental models for the study of cardiovascular function and disease,* Pharmacol Res *41:597–603, 2000.)*

myocardium, the transmural preparation can be studied in electrical and hemodynamic isolation (Figure 1-4).[15,16] As with Langendorff hearts, the quality of the wedge preparation depends on the ischemic time. In addition, extensive dissection is necessary to isolate a perfused wedge, leaving significant injury at exposed edges. Wedges that are not adequately perfused must be discarded. Wedge preparations have a limited lifespan, typically 4 to 5 hours, so experiments should be completed within this timeframe.[15]

Tissue Strips and Slices

Tissue slices are thin preparations of the myocardium that allow diffusion of nutrients and gas exchange. These thin sections can be isolated from various cardiac regions or transmural depths.[17] Newer techniques use microtomes to section short-axis slices of whole ventricles measuring 150 μm in thickness.[18] Once isolated, activation mapping and action potential characteristics can be evaluated (Figure 1-5).[9] Limitations are similar to those of wedge preparations and include the need for long equilibration times (up to 6 hours for epicardial strips) to resolve injury currents before data acquisition.[17]

Dissociated Myocytes

Dissociated myocytes allow detailed electrophysiologic study of a single cell. Myocyte isolates can be prepared from any species at any developmental stage and from any cardiac region. Isolated myocytes are usually prepared by enzymatic dissociation by using trypsin, collagenase, or a combination of proteases. The ability to study the action potential characteristics of a single cell by using microelectrode techniques has yielded unparalleled insights into how different cell populations functionally contribute to the beating heart. Detailed study of the ion channels that dictate the shape and duration of the action potential could not have been possible without the isolated myocyte. Dissociated myocytes that are virally transformed or harvested from genetically modified mice expressing mutated ion channels have significantly increased the understanding of human channelopathies.[19,20] A significant disadvantage of using isolated cells is the loss of the syncytium. Significant changes or exaggeration of action potential features make extrapolations to the intact heart challenging. Furthermore, with prolonged time in culture, the electrophysiologic properties of the myocyte tend to drift and become less representative of the in vivo state.[21,22]

Artificial Bilayers

Bilayers, unlike an intact cell or native cell membrane, allow the study of ion channels in a more controlled environment. Conditions such as ionic concentration and lipid composition can be precisely manipulated. The artificial bilayer also allows ion channels located on intracellular membranes, such as the ryanodine receptor, to be studied electrophysiologically.[23] Single-channel recordings have been performed on numerous channel proteins by using planar bilayer techniques. The two major limitations of this technique are (1) difficulty incorporating ion channels into artificial membranes and (2) the inherent fragility of artificial bilayers.[24]

Electrode-Based Tools

Electrodes transduce biologic, electrochemical activity into electrical signals that can be recorded. Cardiac recordings of a single channel to a whole heart can be made, so electrodes range in size from micrometer-scale glass pipettes to macroscopic metallic needles and discs. Recordings can be obtained extracellularly or intracellularly, depending on the type and resolution of the data needed.

Extracellular Recordings

Extracellular recordings can be acquired by using either unipolar or bipolar lead systems. The surface ECG uses both bipolar and unipolar recordings. Leads I, II, and III are bipolar leads, and the remaining leads are unipolar. Unipolar leads have a single positive pole and an "indifferent" pole acting as the ground, whereas bipolar leads consist of a positive pole and a negative pole.

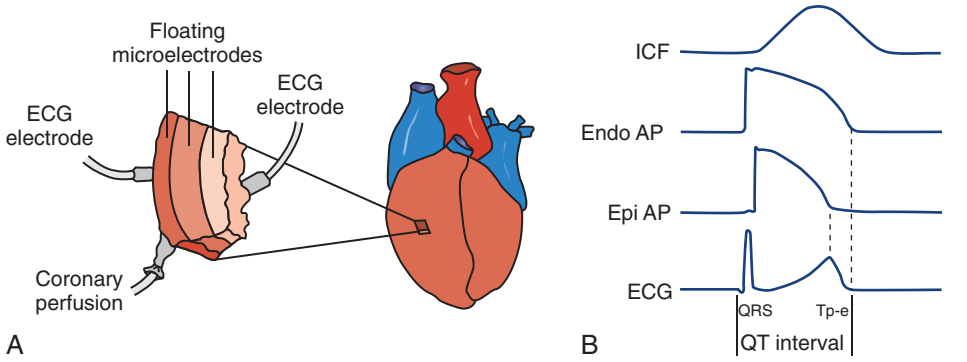

FIGURE 1-4 The myocardial wedge preparation. **A,** The perfused myocardial wedge is dissected along the vascular supply. A transmural electrocardiogram *(ECG)* can be recorded with extracellular ECG electrodes. Epicardial, mid-myocardial, and endocardial action potentials can be recorded by using floating microelectrodes. **B,** Simultaneous recordings of ECG, action potentials, and isometric contractile force from a rabbit wedge preparation. $T_{p\text{-}e}$, the interval between peak to end of the T wave, is a measure of heterogeneity of transmural repolarization. *AP,* Action potential; *ICF,* isometric contractile force. *(From Wang D, Patel C, Cui C, et al: Preclinical assessment of drug-induced proarrhythmias: Role of the arterially perfused rabbit left ventricular wedge preparation,* Pharmacol Ther *119[2]:141–151, 2008.)*

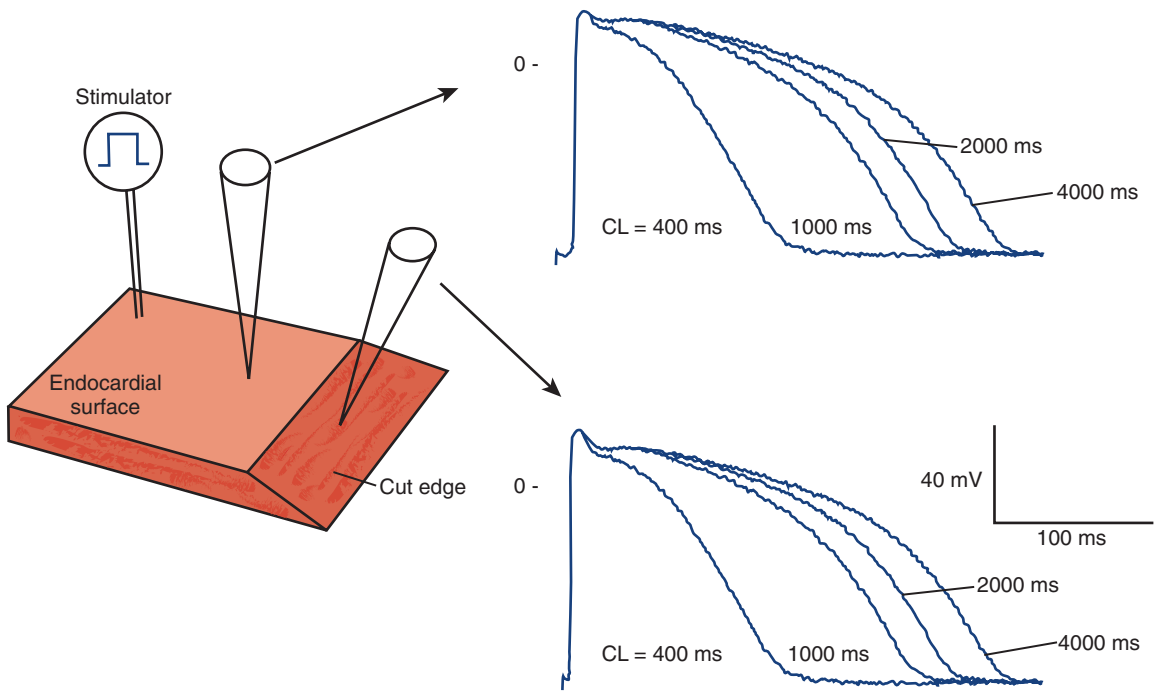

FIGURE 1-5 Tissue strips can be prepared from any layer of the myocardium. In this example, an endocardial strip with an obliquely cut edge is demonstrated. Once the injured myocardium has recovered, the oblique surface allows direct access to subendocardial cells for microelectrode impalement. Simultaneous recordings of transmembrane action potentials from endocardial and subendocardial cells at varying cycle lengths (*CL*) is shown. *(From Anyukhovsky EP, Sosunov EA, Rosen MR: Regional differences in electrophysiologic properties of epicardium, mid-myocardium, and endocardium. In vitro and in vivo correlations,* Circulation *94[8]:1981–1988, 1996.)*

Unipolar electrograms reflect local and distal depolarization and repolarization events in the heart because they transduce any biopotential above or below the indifferent pole. Bipolar electrograms record local electrical activity by summing the biopotentials recorded by the two poles. The advantages of unipolar recordings are that they provide a more sensitive assessment of local activation; however, inclusion of far-field signals results in a low signal/noise ratio, thus limiting spatial resolution.[25] Therefore bipolar recordings are used for detecting discrete electrical events, such as His bundle recordings.[26]

The electrophysiology study (EPS) uses a combination of unipolar and bipolar electrodes to evaluate the conduction properties of normal and diseased tissue and to perform activation mapping of arrhythmias. In 1996, Charles Berul reported the first in vivo murine cardiac EPS using a combined endocardial and epicardial approach.[7] His seminal work described normal sinus node

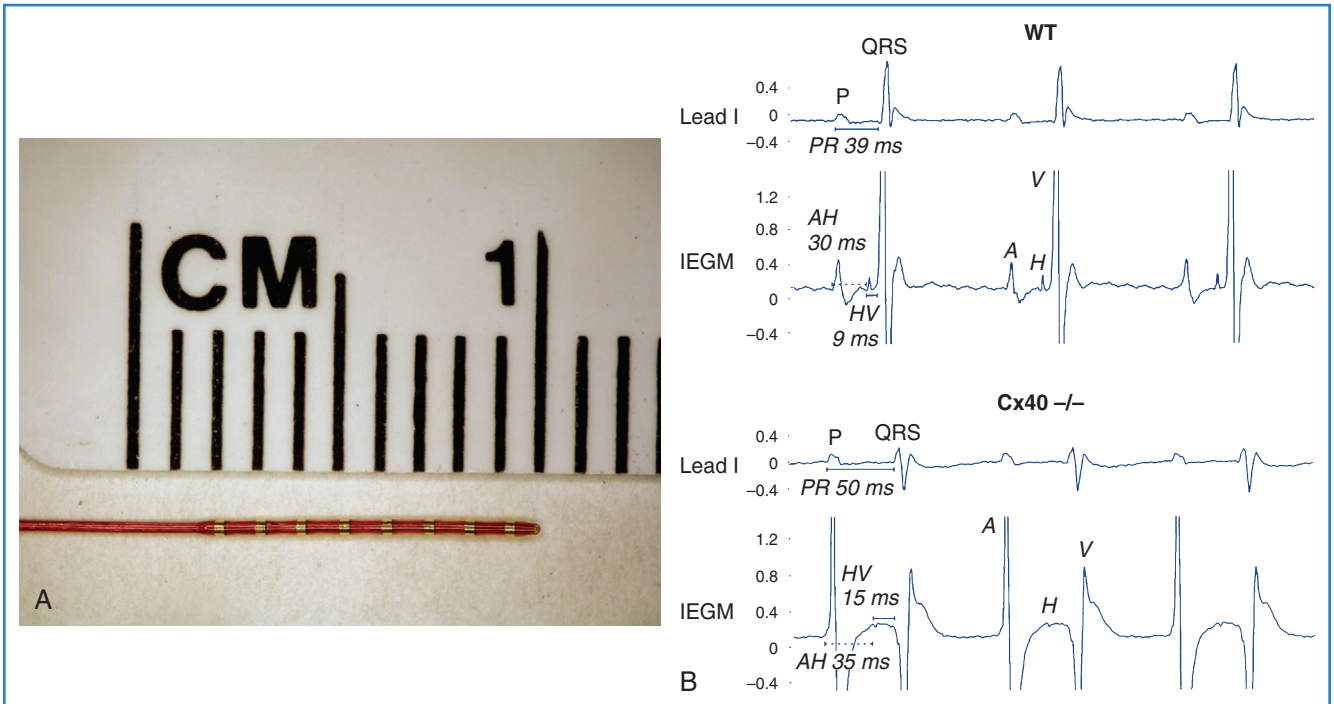

FIGURE 1-6 Intracardiac electrograms in wild-type (*WT*) and connexin40 knockout mice *(Cx40 –/–)*. **A,** 1.1 Fr octapolar murine electrophysiology catheter. **B,** An octapolar electrode catheter was introduced via a right internal jugular vein approach. The catheter was positioned to situate the center electrodes at the tricuspid valve annulus to record atrial, His bundle, and ventricular local electrograms by bipolar configuration. Wild-type mice display normal surface electrocardiogram intervals and normal intracardiac atrial-His (*AH*) and His-ventricular (*HV*) intervals. In contrast, connexin40 null mice display PR prolongation on the surface electrocardiogram and prolonged AH and HV intervals. *(From Bevilacqua LM, Simon AM, Maguire CT, et al: A targeted disruption in connexin40 leads to distinct atrioventricular conduction defects,* J Intervent Card Electrophysiol *4(3):459–567, 2000.)*

recovery times; atrioventricular (AV) conduction properties; and atrial, AV, and ventricular effective refractory periods in mice. Subsequently, an intracardiac, octapolar electrode catheter was developed to study the murine AV nodal and infra-Hisian conduction system.[27] Intracardiac electrograms have been a powerful tool in evaluating transgenic and knockout murine models for conduction disturbances. For example, loss of connexin40 (Cx40), predominantly expressed in the atria and His-Purkinje system, results in significant PR prolongation on surface ECG. Further analysis with intracardiac EPS demonstrated prolonged atrial-His (AH) and His-ventricular (HV) conduction times (Figure 1-6).[6,9]

An extension of electrode-based tools is the multi-electrode array (MEA). MEAs configure multiple electrodes onto array assemblies that allow temporal and spatial resolution of impulse propagation, creating an activation map. MEAs can be affixed to different media, allowing direct contact of the electrodes to cells or tissue. MEAs can be used on tissue culture plates, on patches, and in "socks" for epicardial activation mapping, as well as on catheters for intracardiac recordings.[28] van Rijan et al. used MEA technology to characterize Cx40 knockout mice using a 247-point multi-terminal electrode arranged in a 19 × 13 grid.[29] As shown in Figure 1-7, activation maps created from the right and left surfaces of the interventricular septa demonstrate right bundle branch activation blockade and significantly delayed conduction velocity in the left bundle branch in Cx40 null mice.[29]

Electrode techniques restricted to the epicardial or endocardial surface limit the EPS to those regions of the myocardium. However, as previously mentioned, the ventricular myocardium consists of three layers—epicardial, endocardial, and mid-myocardial—with different electrophysiologic properties. Acquiring local electrograms from the mid-myocardial layer requires the use of plunge or stab electrodes. By simultaneously recording from all three sites, transmural heterogeneity can be studied. The major limitation of plunge electrograms is the degree of injury that results directly at the recording site. Injury patterns can significantly alter electrogram morphology, requiring varying degrees of time to resolve.[17]

One electrode-based method that takes advantage of the injury pattern is the monophasic action potential (MAP). MAPs are extracellularly recorded depolarization/repolarization wavefronts that can reproduce the time course of action potentials recorded intracellularly. This is achieved through the contact electrode technique developed by Franz.[8] Although some controversy regarding MAP generation exists, it is clear that a source of injury must be applied to the myocardium to form a MAP.[30] They have been used to measure action potential duration and dispersion characteristics (i.e., the differences in action potential duration at different regions of the heart). One limitation of MAPs is that, compared with transmembrane recordings, MAPs significantly underestimate amplitude and maximum upstroke velocity.[8]

Intracellular Recordings

Intracellular recordings became possible with the development of the microelectrode. The microelectrode consists of a glass pipette pulled to a submicrometer tip filled with ionic solution. Microelectrodes are mounted onto mechanical micromanipulators that allow single cells to be attached or pierced and electrochemical activity to be recorded. On a single-cell level, current (current

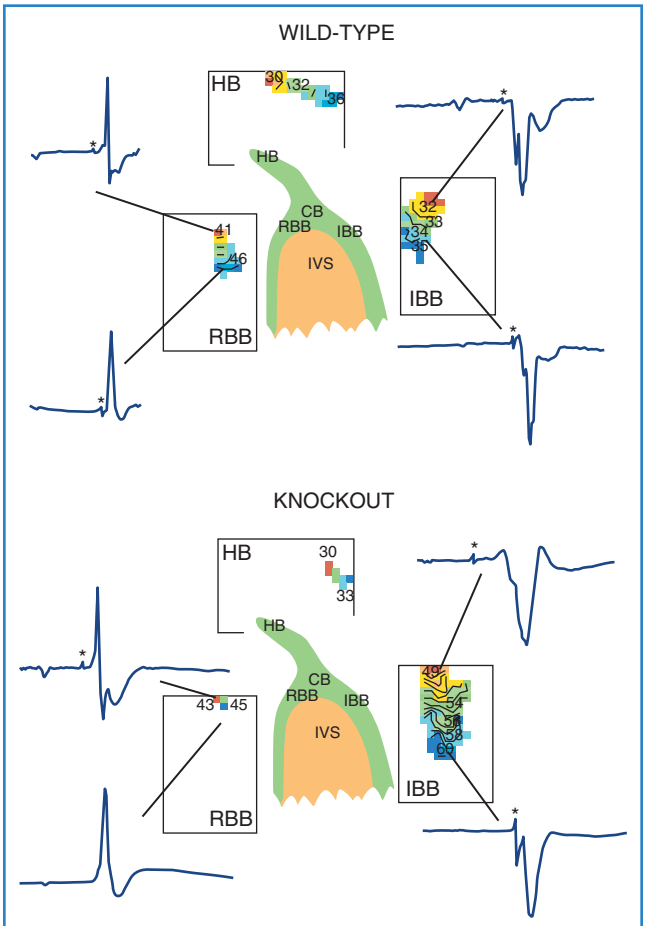

FIGURE 1-7 Activation mapping using multiple-electrode arrays in wild-type and connexin40 (Cx40) null mice. A 247-electrode grid was placed on the endocardial surface of the right and left interventricular septa to generate activation maps and calculate conduction velocities. Onset of far-field P waves was designated as t = 0, and time to activation of the bundle branches (*asterisk*) was recorded and displayed in color-coded format. Large deflections represent depolarization of the interventricular septum. Note the right bundle branch block and slowed conduction through the left bundle branch in Cx40 knockout mice. *(Reproduced from van Rijen HVM, van Veen TA, van Kempen MJ, et al: Impaired conduction in the bundle branches of mouse hearts lacking the gap junction protein connexin40,* Circulation *103:1591–1598, 2001.)*

clamp) or voltage (voltage clamp) can be controlled, and the resultant effect on the current-voltage relationship can be studied. Current clamp recordings are used to measure membrane potentials while current injection is held constant. The system uses a sharp glass microelectrode to impale cells to record resting membrane potentials and action potentials (see Figure 1-1).[1,2]

A voltage clamp recording sets the membrane voltage as a fixed variable and then measures the effect on the net ionic current. The voltage clamp fixes the membrane voltage via a differential amplifier that adjusts for differences between the recorded membrane potential and the desired potential by injecting current to maintain the holding potential. Techniques have been developed to parse out the contributions of individual ion channels. To isolate particular ion currents, the composition of the electrode filling solution can be manipulated by controlling the intracellular concentration of ions or by introducing nonpermeable ions, specific chelators, intracellular drugs, or second messenger analogs.[31]

The patch clamp, a variation of the voltage clamp, was developed by Neher and Sakmann in 1976. The advantage of the patch clamp is its ability to resolve single-channel recordings. Instead of a sharp microelectrode impalement, the patch clamp uses a blunt electrode that measures only a few microns. This fire-polished tip allows a tight seal to be applied to the surface of the cell membrane through light suction, thus effectively isolating a small "patch" of membrane within the mouth of the electrode. An effective seal produces a seal resistance greater than 10 giga-ohms (thus the term *gigaseal).* The importance of a proper seal is twofold: (1) the electrical isolation of the patched membrane and (2) the significant reduction of background noise. These are highly critical in single-channel recordings, for which current amplitudes are extremely low. The variations of the gigaseal patch, demonstrated in Figure 1-8, include the whole-cell patch, perforated patch, and excised patch. *Cell-attached recordings* provide the most physiologic responses because the intracellular compartment is left intact. This was the method first used by Neher and Sackmann to resolve ionic currents at a single-channel level. The fine tip of the pipette electrode allows isolation of a single channel or a few channels. An *inside-out patch* simply pulls away the gigasealed patch from the cell such that the inside of the cell membrane is exposed to the bath solution. These systems allow manipulation of the intracellular environment, such as changes in calcium concentration or introduction of secondary messengers. An *outside-out patch* creates a gigaseal with the cell membrane such that the exterior membrane is exposed to the bath solution. The benefit of this system is that dose-response curves to drugs or biochemical agents can be achieved by changing extracellular bath conditions with a single patch. The main disadvantage of excised patches is that the intracellular and extracellular environments are artificial. *Whole-cell recordings* are produced by suctioning off the gigasealed patch such that the interior of the pipette is continuous with the cell's interior. This technique is most akin to the classic, single-electrode voltage clamp, in which the voltage electrode impales the cell's interior. The advantage over a voltage clamp is that the pipette is larger and, therefore, has lower resistance over the microelectrode, thus offering better signal fidelity. However, the larger pipette leads to eventual dilution of intracellular components, which is known as *the dialysis effect. Perforated patches* overcome the dialysis effect by introducing perforations in the patch membrane with antibiotic agents. This maintains the intracellular compartment for a longer period; however, the added resistance of the perforated membrane diminishes the fidelity of the voltage and current recordings.[32] An example of single-channel and whole-cell patch clamp techniques is given in Figure 1-9.[33]

Optical Techniques

Optical techniques use fluorescent dyes that allow visualization of biologic processes, for example, electrical or metabolic activity, at a subcellular or whole-organ level.[34] Over the past decade, optical mapping has proved to be an invaluable tool in cardiac electrophysiology. Electrode-based techniques have some limitations, including technical difficulties of acquiring data from a nonuniform structure, the inability to record during and after defibrillation, and a limited ability to record repolarization characteristics. These limitations have been overcome by optical mapping systems. Advancements in the understanding of impulse

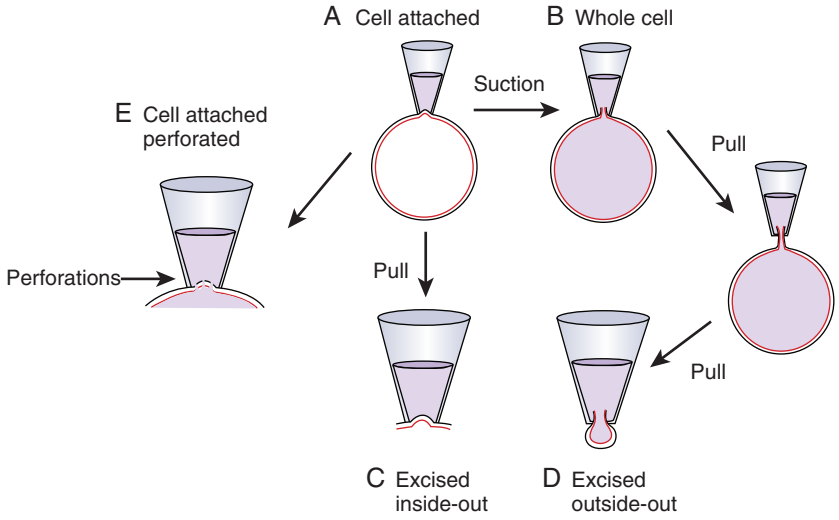

FIGURE 1-8 Variations of patch clamp technique. *A,* Cell-attached patch, *B,* whole-cell patch, *C,* inside-out excised patch, *D,* outside-out excised patch, *E,* perforated cell-attached patch. *(From Ogden D, Stanfield P: Patch clamp techniques for single channel and whole-cell recording.* Microelectrode techniques: The Plymouth workshop handbook*, ed 2, Cambridge, 1987, The Company of Biologists.)*

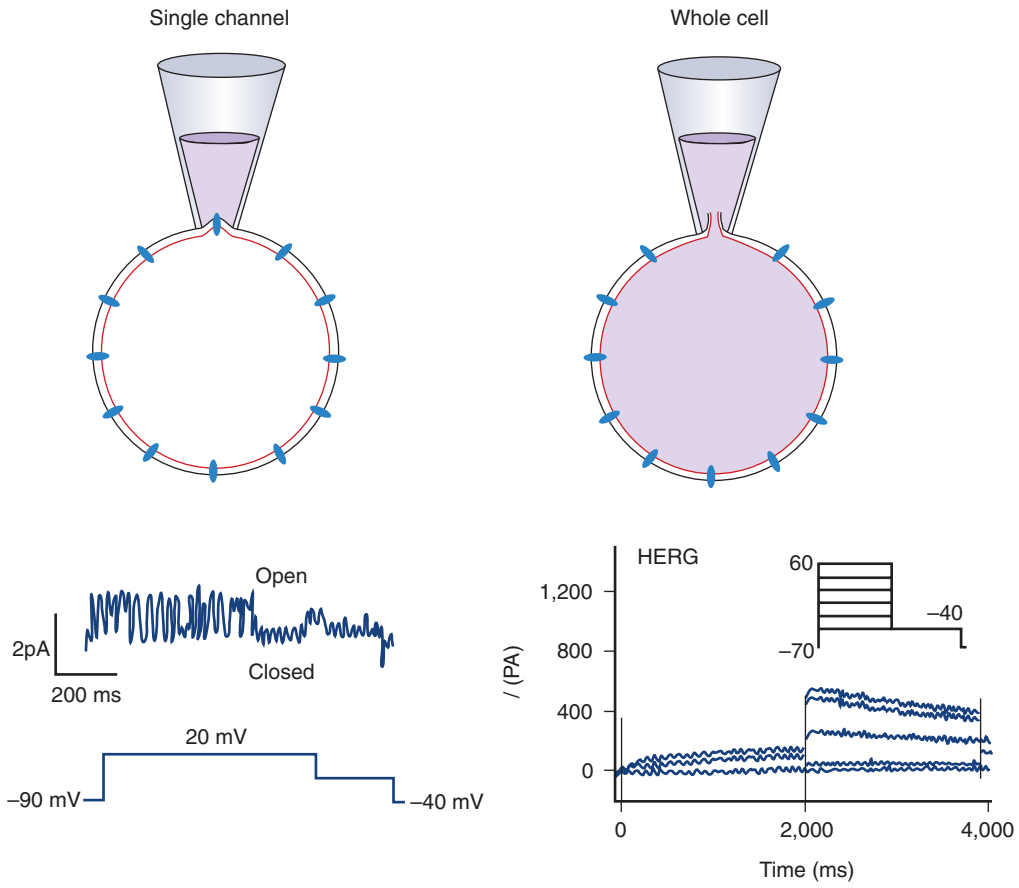

FIGURE 1-9 Patch clamp recordings from single channels and whole cells. Stable clones of CHO cells heterologously expressing the potassium channel, *HERG*, were studied with cell-attached (*left*) and whole-cell (*right*) patch clamp techniques. HERG is a voltage-gated K^+ channel that is more likely in an open-state at positive potentials. Single K^+ channel currents (*left*) or whole-cell K^+ current (*right*) can be measured by various voltage protocols. *(From McDonald TV, Yu Z, Ming Z, et al: A minK-HERG complex regulates the cardiac potassium current I(Kr),* Nature *388[6639]:289–292, 1997.)*

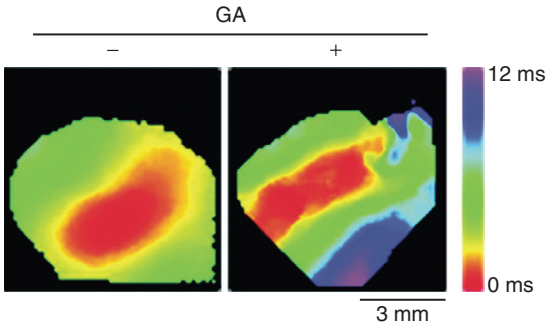

FIGURE 1-10 Optical mapping to study impulse propagation. Epicardial conduction velocity measurements were obtained from the left ventricular surface of murine hearts. Representative optical maps demonstrate slowing of conductance velocity when hearts were treated with a relatively selective gap junction uncoupler, 18-glycyrrhetinic acid (*GA*). *(From Qu J, Volpicelli FM, Garcia LI, et al: Gap junction remodeling and spironolactone-dependent reverse remodeling in the hypertrophied heart,* Circ Res *104[3]:365–371, 2009.)*

generation and propagation in the mechanisms of supraventricular and ventricular arrhythmias and advancements in recording electrical activity during stimulation or defibrillation have all been made possible through optical mapping techniques. The effect of channel mutations, pathologic states, or drugs on cardiac conduction velocity can be readily studied, as shown in Figure 1-10.[35,36]

Although the repertoire of available dyes has grown, voltage-sensitive dyes remain the cornerstone of cardiac optical mapping. Voltage-sensitive dyes interact with the cell membrane and emit fluorescent signals in proportion to the membrane potential. Ideally, potentiometric dyes should react to voltage changes on a microsecond time scale, maintain a linear response curve, have relatively low toxicity, and exert minimal biologic activity. Optical recordings of cardiac action potentials have been very consistent with transmembrane recordings and surface ECGs. Modifications to the technique include the concomitant use of voltage-sensitive and calcium-sensitive dyes that fluoresce at different emission spectra, allowing simultaneous recording. This allows the study of the relationship between calcium handling and action potential characteristics.[34]

Movement artifact can significantly degrade optical action potential images, so mechanical or pharmacologic stabilization is often needed to achieve optimal recordings. The emission spectra of voltage dyes do not give absolute measurements of the membrane potential. Instead, they accurately reflect relative changes in the membrane potential as a function of time. Despite these limitations, the next generation of optical imaging techniques promises a broader array of biosensitive dyes and detectors with improved tissue penetration that offer three-dimensional optical mapping.[34]

Genetic Approaches to Electrophysiology

Molecular cloning technology has revolutionized modern cardiac electrophysiology. Genes can be cloned into expression constructs that are driven by various viral or mammalian promoters. Ion channels can be genetically manipulated using polymerase chain reaction (PCR)–based technology to express missense, nonsense, and frame shift mutations that mimic human disease or create novel mutations at putative functional or regulatory sites. These gene products can then be expressed in virtually any cell type or introduced into transgenic mice by traditional transfection techniques or viral transduction strategies.

Heterologous Expression Systems

The expression of ion channels in heterologous cells allows channel properties to be studied free of the native cellular environment. This offers the investigator an increased level of control by limiting exposure to accessory proteins (subunits, second messengers, scaffolding proteins, dimerization partners) and post-translational modifications (phosphorylation, glycosylation) that may alter channel function in the endogenous cell. The best-characterized cellular systems for cardiac electrophysiology include the *Xenopus laevis* frog oocyte and immortalized mammalian cell lines. Each offers unique advantages to the study of cardiac cellular electrophysiology.[37,38]

X. laevis oocytes have long been used in cellular electrophysiology because of their large size and ability to express heterologous proteins effectively.[38] Their size (approximately 1 mm) makes them well suited for nucleic acid injection and microelectrode recording. After direct injection of complementary ribonucleic acid (cRNA) or complementary deoxyribonucleic acid (cDNA) encoding the channel of interest, current recordings can be made the next day for the former or after several days for the latter. Another benefit of the large size of *X. laevis* oocytes is that they make it possible to perform standard two-electrode voltage clamp recordings, which obviate the need for more expensive equipment for smaller cells. In addition, the endogenous currents of *Xenopus* oocytes are small relative to the large-amplitude heterologous current, making detection with low-noise equipment unnecessary. The next generation of *Xenopus* oocyte technology takes advantage of these benefits in high-throughput methods that allow multiple cells to be studied in parallel with automated systems. This will greatly enhance screening protocols for expression libraries, mutational analysis, and drug testing.[39]

Established mammalian cell lines offer a more physiologically similar cellular environment for analysis of murine and human channels. Commonly used cell lines include mouse fibroblasts (L cells), human embryonic kidney cells (HEK293), SV40-immortalized, African green monkey (Cos) cells, and Chinese hamster ovary (CHO) cells. These cell lines are easily grown in culture, are readily transfectable, are capable of high-level, exogenous protein expression, and have relatively few endogenous currents. Stable transfection of wild-type or mutant channels can be achieved by introducing antibiotic selection. Known mutations from human channelopathies can be propagated in stable cell lines, allowing detailed electrophysiologic analysis. Because clones of stable transfectants have more uniform expression levels, the effects of changing conditions on channel function can be studied.

Methods of Gene Delivery

Transfection protocols use various nonviral means of introducing nucleic acid into cells. The standard techniques use calcium phosphate, cationic polymers, liposomal, nanoparticles, and electroporation. Calcium phosphate transfection is an inexpensive method that allows calcium phosphate–bound DNA to be taken up by dividing cells. Cationic particles, such as DEAE-dextran, bind negatively charged DNA that is taken up by cells through

Table 1-1 Comparison of Major Viral Vector Systems for Cardiovascular Gene Transfer

VECTORS	ADENOVIRUS	ADENO-ASSOCIATED VIRUS	LENTIVIRUS
Functional titer (per mL)	Up to 10^{12}	Up to 10^{10}	Up to 10^{9}
Genome	dsDNA	ssDNA	ssRNA
Insert capacity	7–30 kb	4.8 kb	7–10 kb
Integration	No	Yes: chromosome 19 for wild-type No: for recombinant vectors	Pseudorandom
Pattern of transgene expression	Transient	Long term	Long term
Cell cycle–dependent transduction	No	No	No
Host/vector interactions	Cytotoxic and immunogenic	Minimally immunogenic	Minimally immunogenic
Clinical trial approved	Yes	Yes	No

ds, *Double-stranded;* ss, *single-stranded.*
From Ly H, Kawase Y, Yoneyama R, et al: Gene therapy in the treatment of heart failure, Physiology *22:81–96, 2007.*

endocytosis. Liposomal-based transfection packages DNA into liposomes that gain entry into the cell by fusing with cell membranes. Nanoparticles can be made of gold or magnetic particles that are bound to DNA and subsequently delivered into cells by mechanical or magnetic force, respectively.

Viral vectors as a means of gene delivery have become mainstream because of their high transduction efficiencies of postmitotic cells. Ideally, viral vectors should be replication defective to minimize risk to handlers, have low cytotoxicity, have minimal biologic activity, and be able to infect postmitotic cardiomyocytes. The viruses most commonly used in cardiac electrophysiology that satisfy these criteria are adenovirus, adeno-associated virus (AAV), and lentivirus (Table 1-1).[40]

Adenovirus, a double-stranded DNA virus, is the most commonly used viral delivery system in cardiovascular research. The advantages of adenovirus include its broad tropism for cardiovascular cells, nearly 100% transduction efficiency, high levels of protein expression, ability to transduce nondividing cells, and third-generation vectors that can accommodate inserts up to 30 kb. Adenovirus has been used to express channel proteins both in in vitro and in vivo systems. In addition, the viral DNA remains episomal, minimizing the risk of insertional mutagenesis, although this feature also means that expression is transient. Another limiting feature of adenovirus is the profound inflammatory response that can be seen in animals and humans.[40,41]

AAV overcomes many of the shortcomings of adenovirus and will likely supplant adenovirus in cardiovascular therapeutic applications. Recombinant AAV is a single-stranded DNA virus that has no known pathogenicity in humans, has minimal immunogenicity, and transduces nondividing cells. On conversion to double-stranded DNA, the recombinant AAV vector remains stable for years as an episomal concatamer in postmitotic host nuclei. One significant drawback of the AAV system is the limited insert capacity of approximately 4.8 kb.[40]

Lentivirus is a single-stranded RNA retrovirus derived from the human immunodeficiency virus 1 (HIV-1) that transduces a wide array of cell types through genomic insertion. Genomic integration is the major advantage of lentiviral vectors over adenovirus and AAV systems because integrated genes can be passed on to daughter cells. Unlike other retroviruses, lentivirus is able to transduce dividing and postmitotic cells, making them widely used in cardiovascular research. One of their major emerging uses is the gene-silencing technique using RNA interference technology.[42,43] The major issue with the lentivirus system concerns biosafety. Elimination of accessory genes, separation of packaging genes into different plasmids, and modifications of the long terminal repeats have minimized these risks.[40]

RNA Interference Technology

RNA interference (RNAi) plays a major role in the regulation of gene expression. One pathway of the RNAi system uses short interference RNA (siRNA) that forms a complex with the RNA-induced silencing complex (RISC). RISC, in turn, degrades messenger RNA (mRNA) that is complementary to the siRNA. The two methods of introducing siRNA into a cell are (1) transient transfection of synthetic siRNA and (2) transfection or transduction of expression vectors encoding short hairpin RNA (shRNA) under the control of RNA polymerase III promoters. shRNA is then processed into functional siRNA through ribonuclease activity.[43]

shRNA constructs can be designed for any gene through published protocols and packaged into lentiviral vectors for the creation of stable cell lines or transgenic knockdown animals.[43] RNAi-knockdown animals can be produced significantly faster in this manner than by using traditional knockout methods. Conditional expression of the RNAi system is also available to regulate the temporal and spatial knockdown of genes. RNAi-based technology typically achieves 85% to 95% gene downregulation, so the technique is ineffective if a protein can function at 5% expression levels.[44]

Genetically Modified Mice

Genetically engineered murine models have contributed enormously to the understanding of ion channel function in vivo. Mice can be engineered to underexpress or overexpress wild-type or mutant proteins in a time-specific and tissue-specific manner. Channel proteins subjected to site-directed mutagenesis can be expressed in mice to model human channelopathies or be used for mutational analysis.

The generation of transgenic mice uses the same strategy for creating stable transfected cell lines. Typically, fertilized murine eggs are injected with an expression vector that codes a gene of

interest driven by a ubiquitous or tissue-specific promoter. Cardiac-specific expression in postnatal stages is usually achieved with the α-myosin heavy chain (α-MHC) promoter. The strategy of cardiac-specific expression of dominant negative ion channel mutants was widely used in the study of long QT syndrome (LQTS).[19] Several transgenic lines need to be evaluated to confirm that phenotypes observed in transgenic mice are not attributable to insertional mutagenesis.

Gene targeting strategies alter the host genome through homologous recombination, thereby mutating the endogenous gene. This approach minimizes the risk of insertional mutagenesis at unintended sites. In addition, expression of the modified gene remains under the control of the endogenous promoter, allowing physiologic levels of expression. Advancements in genetic engineering have now made knockout, knockin, and conditional expression systems standard technology in the basic electrophysiology research laboratory.

Knockout mice introduce inactivating mutations into the gene of interest, typically by inserting an antibiotic resistance gene into the coding region and disrupting normal transcription. In some cases, a reporter gene, such as green fluorescent protein or LacZ, is introduced as part of the knockout cassette replacing the endogenous gene product with reporter gene expression. This technique delivers a knockout and reporter system in one murine model. A reporter mouse provides temporal/spatial expression patterns of a gene of interest in vivo (Figure 1-11).[9]

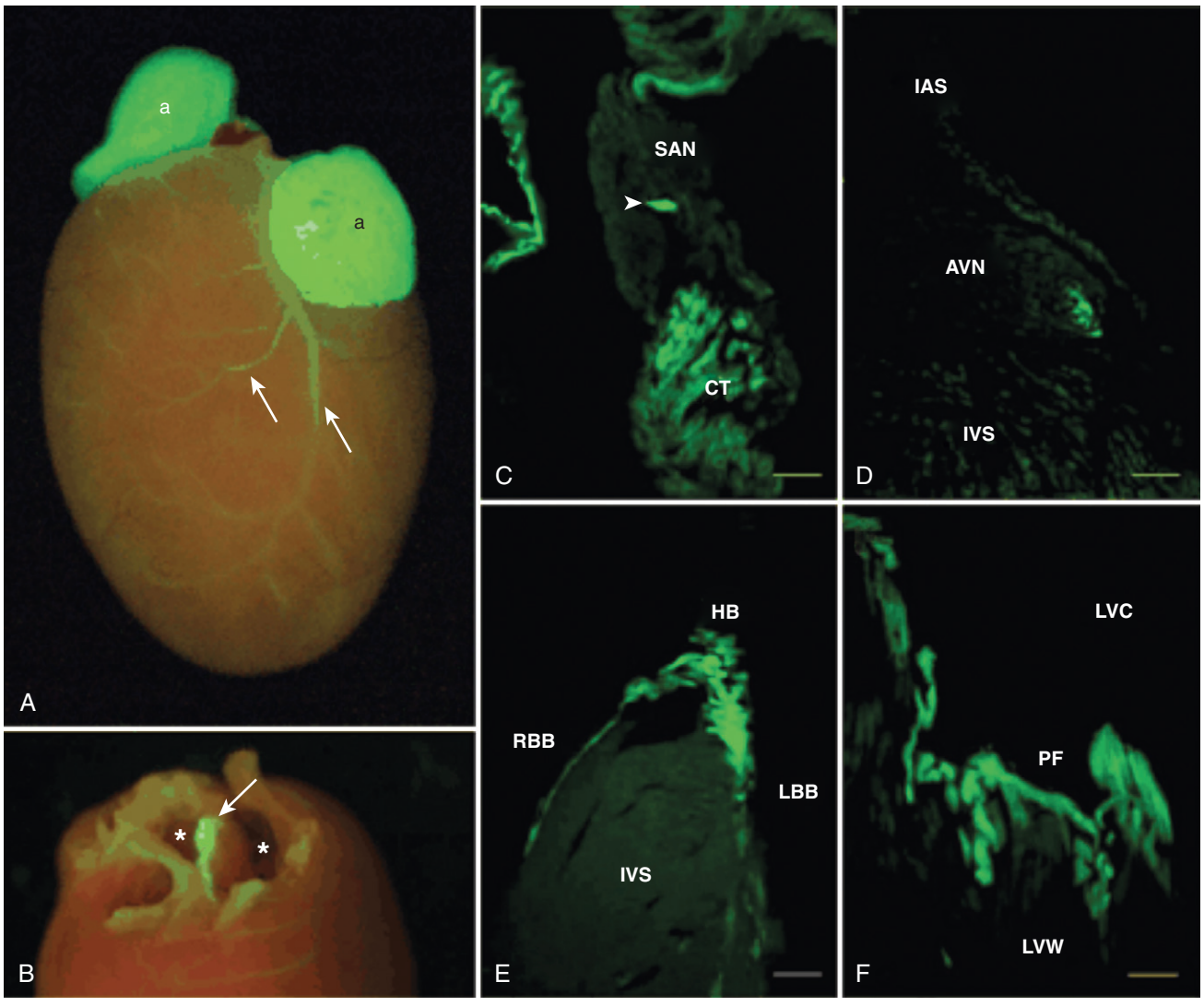

FIGURE 1-11 Connexin40-enhanced green fluorescent protein reporter mice. Green fluorescent protein was placed under the control of the Cx40 promoter. Cx40 expression is restricted to the atria, coronary arteries, and parts of the cardiac conduction system. **A,** Atria (*a*) and coronary arteries (*arrows*). **B,** Atria removed with cranial view of interventricular septum (*arrow*), with *asterisks* marking left and right ventricles. The Cx40 signal is absent in nodal cells. **C** to **F,** Cx40 expression can be appreciated in the crista terminalis (*CT*), nodal artery (*arrowhead*), interatrial septum (*IAS*), His bundle (*HB*), left bundle (*LBB*) and right bundle (*RBB*) branches, and Purkinje fibers (*PF*). *AVN,* Atrioventricular node; *LVC,* left ventricular chamber; *LVW,* left ventricular free wall; *SAN,* sinoatrial node. Scale bars: 100 μm in **C, D,** and **F**; 200 μm in **E**). *(From Miquerol L, Meysen S, Mangoni M, et al: Architectural and functional asymmetry of the His-Purkinje system of the murine heart,* Cardiovasc Res *63[1]:77–86, 2004.)*

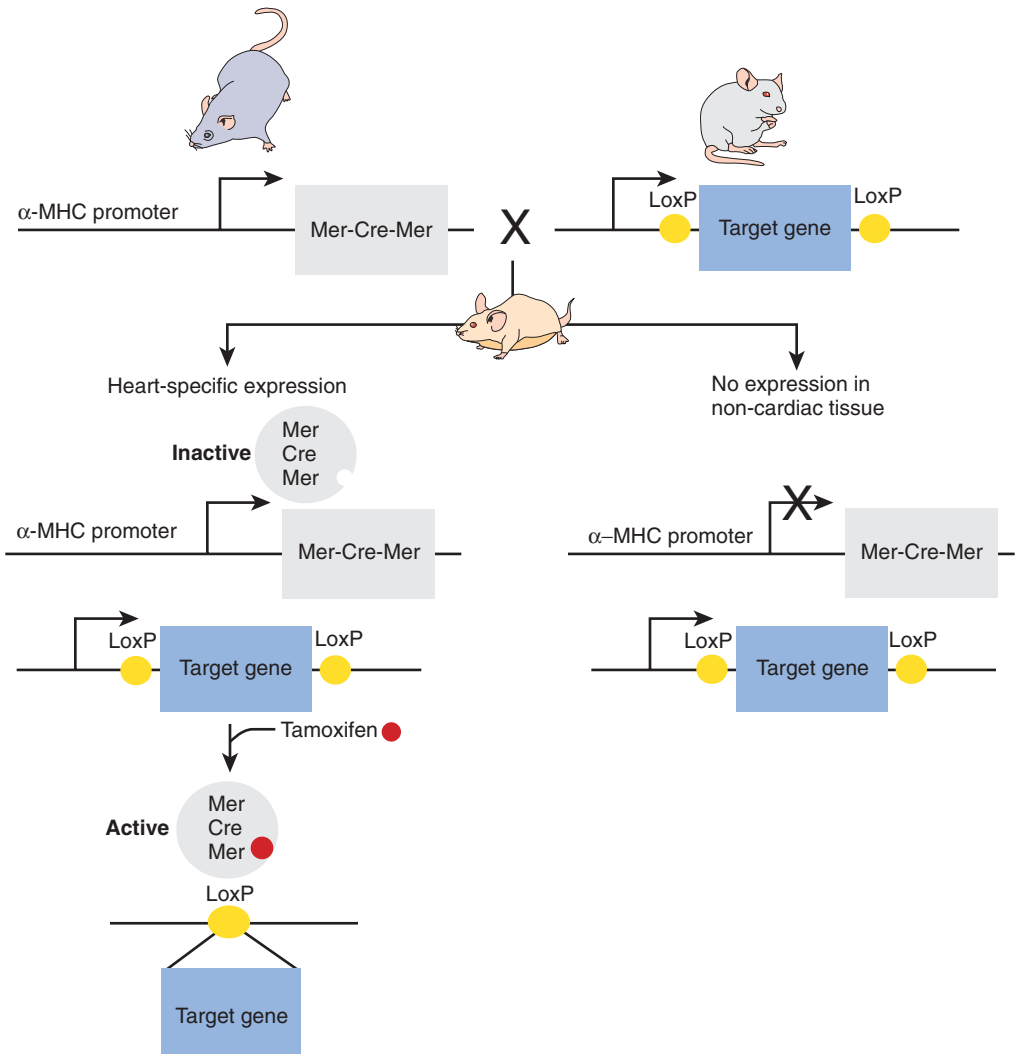

FIGURE 1-12 Schematic flow diagram of the Mer-Cre-Mer system. The white mouse expressing the floxed target gene is mated with a black transgenic mouse expressing Mer-Cre-Mer under the control of a cardiac-specific promoter. The heart-restricted Mer-Cre-Mer cannot access LoxP sites in the nucleus until activated by tamoxifen. Once the tan mouse is injected or fed tamoxifen, Mer-Cre-Mer enters the nucleus, allowing Cre to access LoxP sites and inactivating the target gene. This method allows spatial and temporal control of gene expression in vivo.

The creation of knockin mice uses the same principles of knockout technology; instead of eliminating functional exons, however, specific missense, nonsense, or frameshift mutations are substituted through homologous recombination. The effects of these mutations on channel activity can then be studied.[45] The benefit of this system is that most human channelopathies are not null mutations but, rather, missense or frameshift mutations; knockin mice therefore provide a more representative model of human disease.

The conditional knockout system was developed to overcome the embryonic lethality of some null mutations and to parse out the effect of gene loss in a specific tissue. The Cre-Lox recombination system has been widely used to create cardiac-specific knockout mice. The system takes advantage of the ability of Cre recombinase to effectively cut out DNA fragments that are flanked by LoxP sites. In conditional knockout mice, LoxP sites are engineered into the flanking ends of crucial exons, termed a *floxed gene*. These floxed mice can then be mated with Cre transgenic mice that are under the control of any number of tissue-specific promoters, such as α-MHC—a protein expressed only in cardiomyocytes. In this example, Cre expression will be limited to cardiomyocytes, resulting in heart-restricted knockout of the floxed gene.

An additional level of temporal control is available through the Mer-Cre-Mer conditional murine system (Figure 1-12). The Mer-Cre-Mer system takes advantage of a mutated estrogen receptor (Mer) that is only responsive to tamoxifen and not 17β-estradiol for nuclear localization. When Mer is fused with Cre recombinase, Cre nuclear localization is regulated by tamoxifen. An α-MHC promoter–Mer-Cre-Mer construct would therefore have two levels of control: spatial and temporal. The cardiac-specific promoter would determine where Mer-Cre-Mer recombinase is expressed, and the Mer fusion protein would dictate when Cre is activated. This model system is particularly useful when loss of the gene of interest in a specific organ leads to embryonic lethality. The Mer-Cre-Mer system would allow the floxed gene to be

knocked out in a tissue-specific manner at any developmental stage.[46]

SUMMARY

The past 50 years have seen significant advances in the field of cardiac electrophysiology. The reductionist approach has produced powerful molecular genetic and physiologic tools that have yielded tremendous insights into the structure and function of ion channels. The holistic approach has applied electrode- and optical-based mapping techniques to decipher how local electrical events translate into a beating heart. Continued advances from both approaches will be necessary to expand current knowledge of cardiac function. As such, the next generation of electrophysiologic tools promises to be as exciting as those in the past 50 years. Real-time cardiac imaging as well as mapping studies, new fluorescent dyes that allow three-dimensional activation mapping, and high-throughput automated systems streamlining cellular electrophysiology are all in progress. It is worth noting that even as the level of technological sophistication increases, the thoughtful experimental design of the investigator will remain the true strength of any electrophysiologic experiment.

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CHAPTER 2

Principles of Cellular Architecture and Physiology with Applications in Electrophysiology

Thomas J. Hund, Shane R. Cunha, and Peter J. Mohler

Specialized Excitable Cells Tightly Regulate Cardiac Depolarization

The highly coordinated and efficient propagation of electrical activity through the heart is maintained by the combined activities of a diverse set of specialized excitable cardiac cells, each with its own structural, electrical, and molecular signature. The cardiac sinoatrial (SA) node, a small group of spontaneously active cells in the right atria, is the primary initiation site of cardiac electrical activity because of its relatively positive threshold potential.[1] Once generated by the sinus node, the cardiac action potential propagates through the atria to the atrioventricular (AV) node (the maximum diastolic potential of the AV node is only slightly more negative than that of the SA node), a second small but critical group of specialized cells that display slow conduction properties preventing inappropriate depolarization of the ventricles. In fact, the slow conduction of the AV node is a critical safeguard against the development of ventricular arrhythmias from pathologic atrial pacing defects (i.e., atrial flutter/fibrillation). After the AV node, the cardiac action potential propagates through the cardiac conduction system comprising the AV bundle (bundle of His), the left and right bundle branches, and the cardiac Purkinje system. Interestingly, this conduction system, particularly the cardiac Purkinje fibers, has evolved to rapidly propagate cardiac electrical activity at up to 2 to 4 m/s for the nearly instantaneous spread of depolarization through the sub-endocardium of the left and right ventricles.[2] In comparison with the rapid conduction pathways of the Purkinje system, left ventricular tissue conduction velocity is significantly slower (0.3 to 1 m/s).[2] Importantly, Purkinje fibers communicate with the ventricular mass at well-defined discrete loci (Purkinje-muscle junctions).

Form Fits Function: The Ventricular Cardiomyocyte and Excitation-Contraction Coupling

As is discussed in detail in Chapter 3, the electrical activity of cardiac cells (the action potential) is primarily modulated by the coordinated movement of sodium (Na^+), calcium (Ca^{2+}), and potassium (K^+) across the external plasma membrane (sarcolemma) and the internal sarcoplasmic reticulum (SR) membrane. The specialized function of each cardiac cell type is the result of the evolution of specific molecular and structural components that regulate ion flux across the membrane and dictate specific cell properties.[3] In this section, the primary structural and molecular components of different cardiac cells is discussed in relation to cell type–specific action potentials. Because of its central role in cardiac excitability, the ventricular cardiomyocyte will be used as the central point of comparison for other excitable cardiac cell types.

The ventricular action potential is notable for its hyperpolarized resting membrane potential, rapid upstroke, and prolonged plateau (Figure 2-1). The resting membrane potential of the ventricular cardiomyocyte (held at ~−90 mV, roughly 30 mV more negative than the human sinus node) is the most negative of all excitable cell types (hence the final cell type to depolarize), primarily because of a large inwardly rectifying K^+ current, I_{K1}, prominently expressed in these cells.[4] The rapid upstroke, because of the presence of rapidly activating voltage-gated Na^+ channels, allows for rapid propagation of the electrical signal through the ventricles, which is required for synchronized muscle contraction. Finally, the extended plateau allows sufficient time for Ca to enter the cell and signal contraction.[3]

Once the excitation reaches the ventricles through the cardiac conduction system (see above), the electrical signal passes from cell to cell as a flux of ions through specialized intercellular ion channels called *gap junctions* (discussed in detail below). This flow of ions into the cell from neighboring activated cells depolarizes the membrane potential. If the membrane reaches a threshold potential (~−60 mV), a large population of voltage-gated Na^+ channels (primarily $Na_v1.5$, encoded by *SCN5A*) is activated, which results in a large inward influx of Na^+ across the membrane into the myocyte. Na^+ channels are functionally well suited to this task as they undergo rapid activation (activation time constant <0.5 ms) in response to membrane depolarization. Importantly, these channels also experience rapid voltage-dependent inactivation, which prevents reactivation until the membrane has returned to rest. The inward flux of Na^+ ions carried by voltage-gated Na^+ channels produces the initial rapid spike of the ventricular action potential (phase 0; see Figure 2-1).[3] Depolarization of the cardiac membrane by rapidly activating voltage-gated Na^+ channels activates higher threshold, more slowly activating voltage-gated Ca^{2+} channels (primarily *CACNA1C*-encoded $Ca_v1.2$ in the ventricle; see Figure 2-1).[2] Ca^{2+} influx through voltage-gated Ca^{2+} channels serves two major purposes: (1) maintaining the action potential

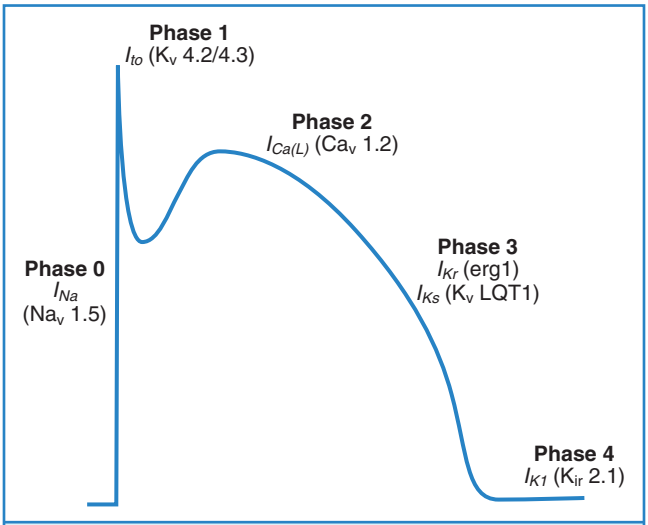

FIGURE 2-1 Key ion currents responsible for the phases of the cardiac ventricular action potential. A mathematical model of the ventricular cardiac myocyte was used to generate representative ventricular action potential with rapid phase 0 (upstroke), characteristic phase 1 repolarization ("spike"), prominent phase 2 plateau ("dome"), delayed phase 3 repolarization, and stable rest potential (phase 4, ~–90 mV). *(From Hund TJ, Rudy Y: Rate dependence and regulation of action potential and calcium transient in a canine cardiac ventricular cell model,* Circulation *110[20]:3168–3174, 2004; Hund TJ, Decker KF, Kanter E, et al: Role of activated CaMKII in abnormal calcium homeostasis and I(Na) remodeling after myocardial infarction: insights from mathematical modeling,* J Mol Cell Cardiol *45[3]:420–428, 2008.)*

plateau (important for controlling heart rhythm), and (2) triggering Ca^{2+} release from internal stores for the purpose of triggering the mechanical contraction of the heart (*excitation-contraction coupling*).[2] During excitation-contraction (EC) coupling, a small inward Ca^{2+} current across the plasma membrane is sensed by functional SR ryanodine receptor (RyR2 in the ventricle, encoded by *RYR2*) clusters, which subsequently release large quantities of Ca^{2+} from the internal SR stores into the cytosol, giving rise to a dramatic increase (order of magnitude) in intracellular Ca^{2+} (the *Ca^{2+} transient*).[2] In this process, termed *Ca^{2+}-induced Ca^{2+} release*, a small increase in local Ca^{2+} via $Ca_v1.2$ produces a relatively large release of SR Ca^{2+} (high *gain function*).

While voltage-gated Na^+ and Ca^{2+} channels are responsible for myocyte depolarization and contraction, a host of plasma membrane–associated K^+ channels regulate ventricular cardiomyocyte repolarization during phases 1, 2, and 3, as well as the rest potential.[4] Specifically, the characteristic repolarization "notch" of phase 1 is modulated by the outward flux of K^+ carried by the transient outward K^+ current, I_{to} (primarily $K_v4.2/K_v4.3$ channels; see Figure 2-1). The duration of the action potential plateau (phase 2) is determined by a delicate balance between the inward Ca^{2+} current and the outward delayed rectifier K^+ currents I_{Kr} and I_{Ks} (erg1/MiRP1 and KvLQT1/MinK channels encoded by *KCNH2/KCNE2* and *KCNQ1/KCNE1*, respectively; see Figure 2-1).[4] As the action potential proceeds, the Ca^{2+} current decreases because of deactivation as well as inactivation, and the K^+ currents I_{Kr} and I_{Ks} increase, ultimately tilting the balance in favor of the late repolarization phase (phase 3; see Figure 2-1).[4] The cell eventually returns to a resting potential maintained primarily by the time-independent inward rectifier current I_{K1} (see Figure 2-1). Other currents such as I_{KATP}, while not central to the healthy control action potential, may have key roles in disease. Finally, the Na^+-K^+ adenotriphosphatase (ATPase) (which uses ATP to remove 3 Na^+ from the cell and bring in 2 K^+) is a key feature for generating and maintaining the myocyte electrochemical gradient.

Proper functioning of ion channels is required for normal cardiac physiology, as channel dysfunction has been linked to both congenital and acquired forms of heart disease and arrhythmias. For example, genetic mutations in Na^+, K^+, and Ca^{2+} channels and channel subunits have been associated with lethal cardiac arrhythmia syndromes, including congenital long QT syndrome (mutations in *KCNQ1, KCNH2, SCN5A*, *KCNE1*, *KCNE2*, and *KCNJ2* genes), short QT syndrome (mutations in *KCNH2*, *KCNQ1*, and *KCNJ2* genes), Brugada syndrome (mutations in the *SCN5A* gene), and Timothy syndrome (mutations in the *CACNA1C* gene). Ion channel defects arising from electrical remodeling in the setting of acquired heart disease have also been linked to arrhythmia. Specifically, Na^+ channel changes after myocardial infarction have been linked to slowed conduction, and changes in K^+ and Ca^{2+} channels have been linked to action potential prolongation in failing hearts.

Cell Membrane Architecture Defines Myocyte Local Electrical Activity

Over the past 15 years, the use of high-resolution imaging techniques in the field of molecular cardiology has revolutionized the understanding of cardiac cell biology and electrical function. Specifically, unlike the first plant cell imaged by Hooke in the mid-1600s, it is now known that the vertebrate myocyte is not simply a large pool of cytosol surrounded by a simple membrane. Rather, the metazoan myocyte has evolved complex membrane structures to facilitate efficient electrical activity and signaling to regulate cardiac physiology. Not surprisingly, specific cell types in the heart possess a distinct set of membrane structures based on their unique function.

The ventricular cardiomyocyte plasma membrane, or *sarcolemma*, is divided into multiple and unique membrane structures (Figure 2-2). In addition to the external sarcolemma (resident proteins include the Na^+-Ca^{2+} exchanger (NCX1) and plasma membrane Ca^{2+}-ATPase [PMCA1]), the ventricular cardiomyocyte contains a large array of regularly spaced (~1.8 μm) plasma membrane invaginations, termed *transverse tubules*, or *T-tubules*. This membrane system, instrumental in myocyte EC coupling, evolved to facilitate coordinated EC coupling in the relatively large ventricular cardiomyocyte (system not present in smaller atrial and sinoatrial node cells). T-tubule–resident proteins include the L-type Ca^{2+} channel $Ca_v1.2$, the Na^+-Ca^{2+} exchanger, and Na^+-K^+-ATPase.[2] Finally, a highly specialized domain is present where the ventricular cardiomyocyte plasma membrane lies in close apposition to the plasma membrane of a neighboring cell. This complex membrane system, termed the *intercalated disc*, is required for myocyte cell-cell adhesion as well as intercellular action potential propagation and comprises three subdomains: (1) the gap junction, (2) the adherens junction, and (3) the desmosome (Figure 2-3).[2] The gap junction comprises hundreds of hemi-channels (*connexons*) that span the lipid bilayer and allow electrical and metabolic coupling when docked with hemi-channels from a neighboring cell. At least four different connexin

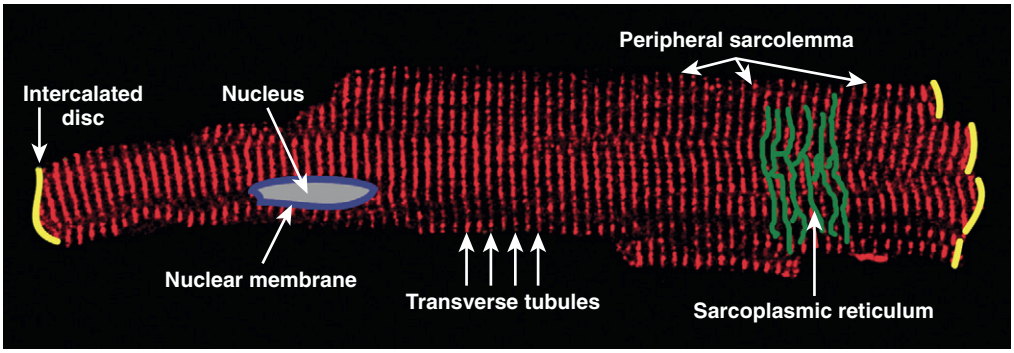

FIGURE 2-2 Local membrane architecture, which is critical for vertebrate cardiomyocyte electrical activity and physiology. Image of ventricular cardiomyocyte with denoted membrane structures, including the intercalated disc (yellow), transverse tubules overlying the cellular Z-line (red, stained with α-actinin antibody), sarcoplasmic reticulum (green), nucleus (silver), and nuclear envelope (violet).

proteins (functional units of the connexon) with distinct biophysical properties are expressed throughout the heart. Gap junctions in ventricular tissue consist primarily of connexin43, which forms large conductance channels to allow rapid conduction. In contrast, gap junctions in the sinus node contain mostly connexin45, which forms lower conductance channels ideal for slow but safe conduction. The adherens junction is maintained by the function of a cadherin-catenin complex that provides a stabilizing link from the intercalated disc to the actin cytoskeleton (see Figure 2-3). Finally, the desmosome also supports cell adhesion through a complex, including plakoglobin (γ-catenin, also found in the adherens junction), desmoplakin, and plakophilin, that interacts with intermediate filaments (see Figure 2-3). Interestingly, defects in desmosomal proteins have been linked to cardiomyopathies and arrhythmias, including arrhythmogenic right ventricular cardiomyopathy (ARVC). In fact, loss of plakoglobin immunostaining in human heart biopsies has been recently developed into a diagnostic marker for *Naxos disease*, a cardiocutaneous syndrome characterized by wooly hair, palmoplantar keratoderma, and severe cardiomyopathy.[5]

In addition to the external plasma membrane, the cardiac myocyte (as well as many other excitable cells, including neurons and skeletal muscle) contains SR, the specialized endoplasmic reticulum that has key roles in the regulation of intracellular Ca^{2+}.[2] The cardiac SR is an extensive network of tubules linking key signaling networks, including the plasma membrane, nuclear envelope, nucleus, and mitochondria, to mediate a host of diverse functions. The pre-eminent role of the cardiac SR is to regulate myocyte EC coupling. Specifically, the vertebrate SR sequesters a large pool of releasable Ca^{2+} (1 mM inside SR vs. 100 nM in cytosol[2]) that serves as the primary source of Ca^{2+} for troponin-C (TnC) activation and muscle contraction (discussed in detail below).[2] The majority of this Ca^{2+} is internally buffered by the Ca^{2+}-binding protein calsequestrin, which forms a critical RyR2 regulatory complex with triadin and junctin. However, Ca^{2+} entry into the cell during the action potential plateau through voltage-gated Ca^{2+} channels activates SR ryanodine receptor Ca^{2+} channels. These RyR2 channels then rapidly release sequestered SR Ca^{2+} into the cytosol (see below) to signal contraction. During diastole, SR Ca^{2+}-ATPase (SERCA2) and its regulatory protein phospholamban play central roles in the reuptake of released Ca^{2+} from the myocyte cytosol into the SR. Interestingly, inappropriate regulation of SR Ca^{2+} because of defects in either Ca^{2+} buffering (i.e., human calsequestrin-2 gene mutations) or Ca^{2+} release (human RyR2 gene mutations) has been linked with potentially fatal human arrhythmia (catecholaminergic polymorphic ventricular tachyarrhythmia). SR membrane–resident proteins also include inositol 1,4,5 trisphosphate ($InsP_3$) receptors that have been linked to cardiac hypertrophy and arrhythmia.[6]

During the ventricular action potential, the rise in cytosolic Ca^{2+} via the SR membrane–associated RyR2 is rapidly translated into mechanical activity between the thick myosin filaments and the thin actin filaments through the regulatory functions of the troponin-tropomyosin complex.[2] This complex consists of four subunits. Tropomyosin is a double-stranded α-helical molecule, which, under basal conditions (low Ca^{2+}), covers myosin-binding sites along a span of seven actin monomers.[2] Troponin T (TnT; tropomyosin-binding subunit) connects tropomyosin to the two remaining subunits TnC (Ca^{2+}-binding) and troponin I (TnI; inhibitory subunit). The cardiac isoform of TnC has two high-affinity binding sites for Ca^{2+} or Mg^{2+} in the C-terminal domain and a low-affinity regulatory binding site that is Ca^{2+} specific in the N-terminal domain. During diastole, the C-terminal domain of TnI interacts with actin. During systole, Ca^{2+} binds to a low-affinity binding site in the TnC N-terminal domain, causing an increased affinity between this domain and the TnI N-terminal domain. As a result, the TnI-actin interaction is destabilized, which ultimately leads to a conformational change in the troponin-tropomyosin complex.[2] Specifically, this complex is shifted and exposes myosin binding sites on actin, leading to "cross-bridge" formation between actin and myosin, force production, and cellular shortening.[2] On removal of Ca^{2+} from the cytosol (primarily by the activities of SERCA2A and the plasma membrane Na^+-Ca^{2+} exchanger), these molecular events are rapidly reversed, which results in cellular relaxation.[2] Specifically, as cytosolic Ca^{2+} levels decrease, Ca^{2+} is removed from the TnC low-affinity binding site, causing TnI to dissociate from TnC and then reassociate with actin, effectively re-establishing the steric hindrance imposed by the troponin-tropomyosin complex.

As discussed in detail below, the dynamic range of cardiac excitation-mechanical coupling is, in part, regulated by phosphoregulation of key ion channels and transporters, which modulate intracellular Ca^{2+} in addition to altering the Ca^{2+} sensitivity of contractile proteins. For example, protein kinase A (PKA) phosphorylation of phospholamban at serine 16 relieves inhibition of phospholamban on SERCA2, thereby increasing SR Ca^{2+} uptake

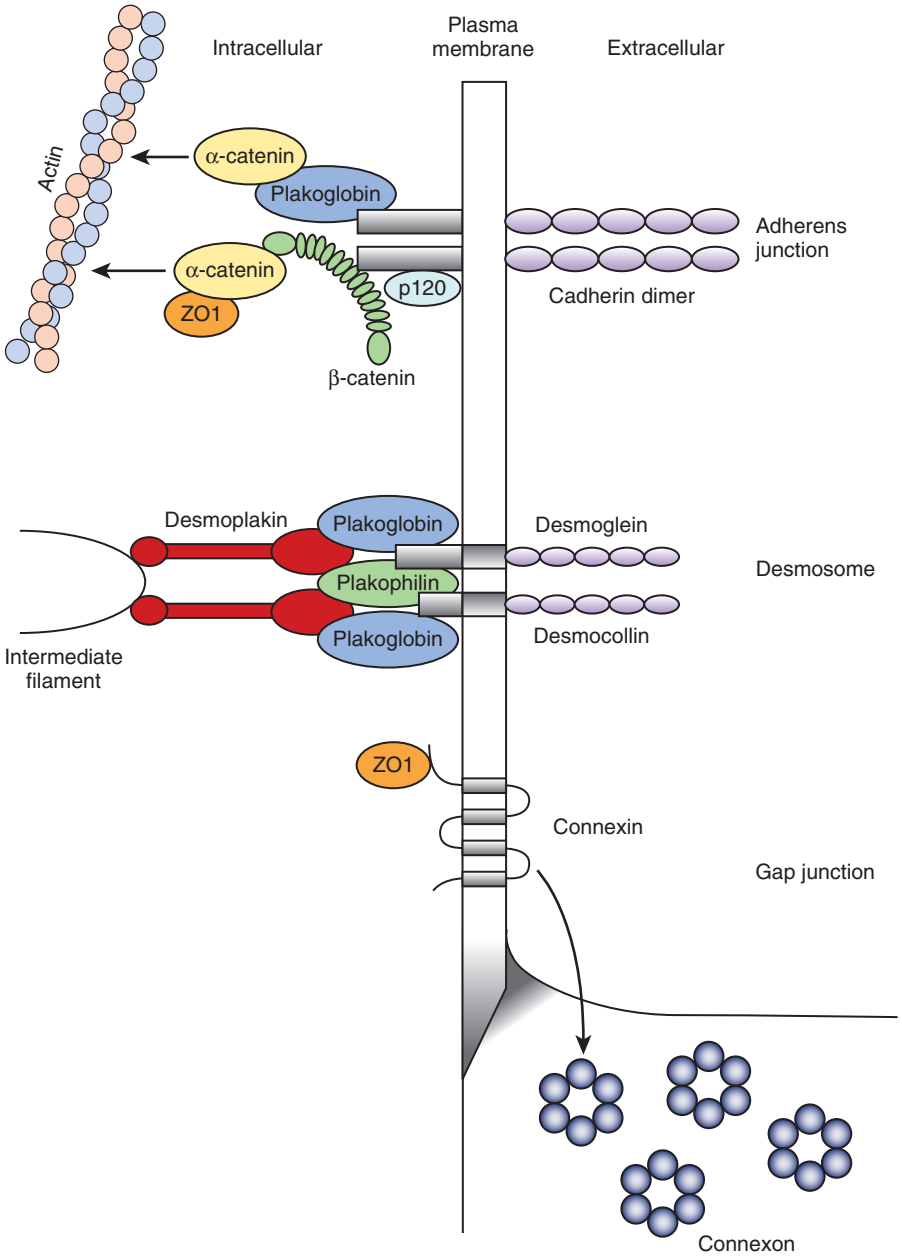

FIGURE 2-3 Structures of the intercalated disc. The adherens junction contains a catenin-cadherin complex that anchors the disc to actin. The desmosome provides a link to intermediate filaments and contains primarily desmoplakin, plakoglobin (γ-catenin), plakophilin-2, and the desmosomal cadherins (desmoglein-2 and desmocollin-2). Finally, the gap junction establishes electrical and metabolic communication between neighboring cells. Six individual connexin proteins (primarily Cx45 in the SA node, Cx40 to Cx45 in the atria, and Cx43 in the ventricle) combine to form heteromeric connexon hemi-channels that dock with apposing connexons from the adjoining cell.

and promoting muscle relaxation.[7] In addition to phosphorylating membrane proteins, PKA also phosphorylates contractile proteins to decrease their Ca^{2+} sensitivity, thereby promoting muscle relaxation. These modifications allow for increased cycle frequency elicited by exercise. For example, the N-terminal domain of cardiac TnI is phosphorylated by cyclic adenosine monophosphate (cAMP)-dependent PKA phosphorylation at serines 22 and 23. Phosphorylation of these residues desensitizes TnI to Ca^{2+}-bound TnC and reduces the Ca^{2+} affinity of the Ca^{2+}-specific regulatory site on TnC.[8] Thus, these findings clearly illustrate the highly collaborative roles of structural, electrical, mechanical, and signaling proteins in the modulation of myocyte EC coupling and cardiac function.

Recent findings demonstrate key cellular roles for nuclear and mitochondrial membranes in the regulation of myocyte transcriptional pathways and in metabolism. The nuclear envelope is a complex structure comprising outer and inner nuclear membranes. The outer nuclear membrane is continuous with the SR, and the inner membrane contains a number of critical membrane proteins involved in nuclear assembly and gene transcription,

such as *lamins*, which create a structural lattice for nuclear envelope integrity, and *emerins*, which bind directly to actin filaments. Mutations in lamin A/C and emerin have been linked to Emery-Dreifuss muscular dystrophy, a degenerative muscle disease featuring cardiac conduction defects. Human mutations in the nuclear lamina protein emerin (*EMD*), which are relevant to cardiac arrhythmia, have also been linked to familial atrial fibrillation and sinus node disease.[9] Specifically, identified probands display a complex arrhythmia phenotype, including irregular, chaotic atrial rhythm and first-degree atrioventricular block.[9] One proband displayed premature atrial complexes with rate variability (30 to 100 beats/min), and sinus arrest with junctional escape rhythm.[9] Interestingly, the identified *EMD* mutation is hypothesized to affect the interaction between the emerin LEM domain and intranuclear binding proteins.[9] Moreover, analysis of emerin localization in *EMD* mutation carriers revealed defects in nuclear emerin localization.[9] These findings clearly demonstrate the unexpected link between cardiac atypical cellular architecture, in this case the nuclear lamina, and normal cellular excitability. In addition to having clear roles in orchestrating cellular structure and intermediate filament organization, the nuclear membrane also contains an autonomous system for Ca^{2+} signaling. $InsP_3$ receptors located on both the inner and outer nuclear membranes allow Ca^{2+} release from the nuclear membrane lumen into the nucleoplasm and cytosol, respectively.[10] In fact, work by Bers and colleagues demonstrated that Ca^{2+} in the nuclear membrane is tightly regulated by SR Ca^{2+}, and this Ca^{2+} is central to cardiac *excitation-transcription* signaling via $InsP_3$ receptor-dependent signaling.[11]

Cardiac mitochondria play an important role not only in energy production but also in Ca^{2+} homeostasis and apoptosis. Mitochondria occupy a large percentage of the cell volume (about 30%) and are concentrated near myofilaments, T-tubules, and the SR.[12] Mitochondria comprise inner and outer membranes surrounding the mitochondrial matrix, where oxidative phosphorylation drives ATP production. A large potential gradient ($\Delta\Psi_m$ about −180 mV) across the inner mitochondrial membrane, together with a proton gradient (ΔpH), is necessary for the conversion of adenosine diphosphate (ADP) to ATP. Respiration is regulated by many factors, including ADP and Ca^{2+}, which activate key enzymes in the tricarboxylic acid (TCA) cycle. Highly selective Ca^{2+} uniporters expressed in the inner mitochondrial membrane use the electrical gradient across the inner mitochondrial membrane to move Ca^{2+} from the myoplasm into the mitochondria. The proximity of mitochondria to the Ca^{2+} channels at T-tubules and to the Ca^{2+} release sites on the SR create a local Ca^{2+} domain that provides mitochondria with access to an important resource for respiration and enables mitochondria to serve as an important buffer of intracellular Ca^{2+}. Interestingly, disruption of the normal mitochondrial arrangement within the cell has been linked to mitochondrial dysfunction, apoptosis, and arrhythmias in a murine model of desmin-related cardiomyopathy. The mitochondrial Na^+-Ca^{2+} exchanger helps maintain mitochondrial Ca^{2+} homeostasis, and the Na^+-H^+ exchanger and the Na^+-K^+-ATPase use the proton gradient and ATP, respectively, for maintaining mitochondrial Na^+ homeostasis. Ion homeostasis in the myoplasm and in the mitochondrial matrix are coupled such that dysregulation of homeostasis in the myoplasm may alter mitochondrial energetics. Thus, myoplasmic Na^+ accumulation in the setting of heart failure may accelerate Ca^{2+} removal from the mitochondrial matrix via the Na^+-Ca^{2+} exchanger, leading to decreased mitochondrial Ca^{2+}, decreased NADH production via the TCA cycle, and decreased ATP production.[13] Conversely, myoplasmic Ca^{2+} overload (e.g., during myocardial ischemia) may lead to the accumulation of mitochondrial Ca^{2+} and the opening of the mitochondrial permeability transition pore, a large nonspecific conductance in the inner mitochondrial membrane that discharges the mitochondrial membrane potential, which leads to cell death.[13]

The Cardiac Dyad

A striking example of the evolution of cardiac molecular and structural components converging on function is the cardiac *dyad*. Franzini-Armstrong and colleagues identified the dyad using electron microscopy and showed that it represents the preeminent cardiac signaling unit for EC coupling.[14] Specifically, the cardiac dyad is a key juxtaposition of cardiac external plasma membrane (T-tubules) to internal SR membrane (Figure 2-4).[2] Central to the dyad T-tubule membrane is a large population of membrane-associated L-type Ca^{2+} channels (comprising a central α-subunit pore and multiple regulatory β-subunits).[15] Across the tiny dyadic cleft (~15 nm) reside large clusters of ryanodine receptor Ca^{2+} release channels in the SR membrane.[15] Thus, the dyad structure has evolved to provide spatial constraints that, together with the high gain of the Ca^{2+}-induced Ca^{2+} release process, allows for the activation of internal Ca^{2+} release by a very small influx of Ca^{2+} through L-type Ca^{2+} channels. Since the divalent cation Ca^{2+} is used for a host of cellular processes, including contraction, transcription, and apoptosis, the spatially privileged environment of the dyad is critical for maintaining the fidelity of intracellular Ca^{2+} signaling.

A second key component of cardiac architecture for physiology illustrated by the dyad is the convergence of local signaling networks for function. For example, multiple key proteins in the cardiac dyad, including the L-type Ca^{2+} channel and RyR, are dynamically regulated by phosphorylation and dephosphorylation cascades. In fact, phosphorylation of both $Ca_v1.2$ and RyR2 by both protein kinase A and Ca^{2+}-calmodulin–dependent protein kinase II (CaMKII) regulates channel activity. Recent work has illustrated that phosphorylation signaling pathways are tightly regulated at the local level. For example, PKA is directly linked to its target molecule RyR2, by direct interaction of RyR2 with the PKA-anchoring protein mAKAP.[16] Moreover, PKA-dependent regulation of RyR2 is directly antagonized by local phosphatase 2A, also directly linked to RyR2 via mAKAP.[16] Similarly, PKA-dependent regulation of $Ca_v1.2$ activity at the cell membrane occurs via a protein complex that involves AKAP150. Like PKA, CaMKII regulates the activities of proteins on either side of the dyad. CaMKII directly phosphorylates the $Ca_v1.2$ channel complex to produce an alternative channel-gating mode characterized by long open times (mode 2) and current facilitation.[17] Recent studies have identified the $Ca_v1.2$–auxillary subunit β_{2a} as a critical target for CaMKII-mediated current facilitation.[18] Moreover, β_{2a} contains a CaMKII-binding site with high homology to established motifs in the NR2B subunit of the NMDA receptor and in the CaMKII association domain.[18,19] Thus, in addition to playing an important role in regulating $Ca_v1.2$ activity, β_{2a} also serves as a $Ca_v1.2$-specific anchoring protein for CaMKII.[18] CaMKII co-localizes with and phosphorylates RyR2 to regulate channel activity, although the nature of this association and the functional effects (increase or decrease in activity) remain uncertain.[20,21] However, several studies have provided compelling evidence that

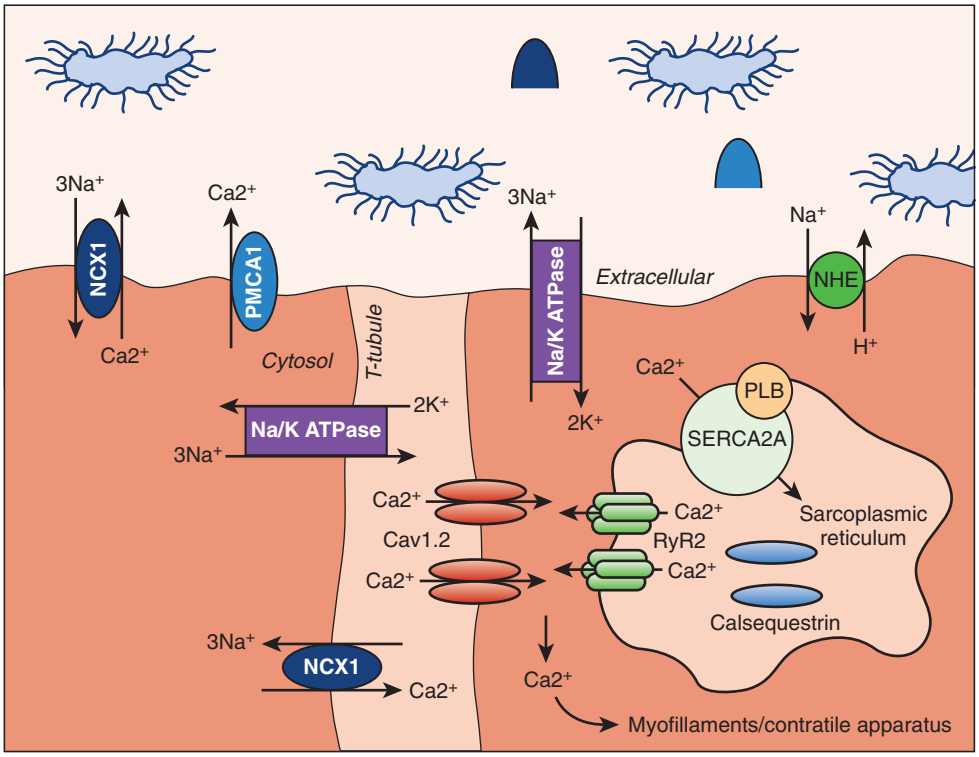

FIGURE 2-4 The cardiac "dyad." Voltage-gated Ca^{2+} channels ($Ca_v1.2$) along transverse tubules communicate across a small cleft with ryanodine receptor Ca^{2+} release channels (RyR2) in the sarcoplasmic reticulum (SR) membrane to create a local domain for Ca^{2+} signaling. A small amount of Ca^{2+} entry through Ca^{2+} channels causes a large release of SR Ca^{2+} through ryanodine receptors into the cytoplasm. This Ca^{2+} signals myofilament shortening and cell contraction through binding to troponin. Relaxation occurs as Ca^{2+} is removed from the cell via the Na^+-Ca^{2+} exchanger, Na^+-K^+-ATPase, and PMCA1 and resequestered into the SR via SERCA2A/PLB.

CaMKII hyperphosphorylation of RyR2 in the setting of heart failure leads to inappropriately active channels that promote diastolic Ca^{2+} leak from the SR, reduced SR Ca^{2+} content, and contractile dysfunction.[22] Thus, the cardiac dyad, by functionally linking key ion channel components on closely apposed excitable membrane structures and by recruiting key signaling proteins, has evolved into an all-in-one signaling unit for the regulation of cardiac excitability.

The presence of large membrane complexes for local cardiac signaling extends far beyond the dyad (Figure 2-5). As discussed above, ventricular repolarization is regulated by the activity of I_{Ks}. The I_{Ks} current is the result of a heteromeric channel complex encoded by KCNQ1 (α-subunit) and KCNE1 (β-subunit).[4] In fact, the importance of I_{Ks} for cardiac repolarization is clearly illustrated by human gene mutations in *KCNQ1* and *KCNE1* linked with both atrial and ventricular arrhythmias.[4] Similar to the cardiac L-type Ca^{2+} channel and RyR2, I_{Ks} is dynamically regulated by PKA-dependent phosphorylation, and this regulation is coordinated by a protein complex involving the AKAP, Yotiao (see Figure 2-5). Yotiao interacts with the *KCNQ1* C-terminus as well as with protein phosphatase 1 (PP1) and PKA to create a macromolecular signaling complex for regulating cardiac repolarization. Interestingly, mutations in *KCNQ1* that affect the binding of *KCNQ1* to Yotiao result in cardiac arrhythmia (long QT syndrome).[16,23] Similarly, Yotiao (AKAP9) mutants that block binding to *KCNQ1* result in defects in I_{Ks} and are associated with human long QT syndrome.[24] Thus, in addition to inherent channel biophysical properties, regulation of signaling at the level of the local membrane microdomain is essential for normal cardiac excitability and human physiology.

Biogenesis and Maintenance of Local Signaling Domains

Cardiac ion channel and transporter activity is critical for normal myocardial function. Vital to this function are intrinsic channel biophysical properties (e.g., activation, inactivation) that largely determine the time course of the ensemble current. The precise localization of ion channels and transporters at specialized membrane domains (i.e., T-tubule, intercalated disc) is equally critical for normal channel function (and therefore cardiac physiology) but is often overlooked. Over the past decade, analyses of ion channel and transporter targeting in myocytes have revealed a host of new cellular pathways required for the trafficking and retention of cardiac membrane proteins. Moreover, a growing body of literature supports the notion that dysfunction in these ion channel and transporter targeting pathways may result in cardiac electrical dysfunction and disease.

Ankyrins, a family of cytoskeletal adapter proteins, were first identified in the erythrocyte in the late 1970s as a structural link between plasma membrane proteins and the actin-spectrin–based cytoskeleton.[25] However, recent findings have clearly demonstrated key roles for ankyrin polypeptides in ion channel and

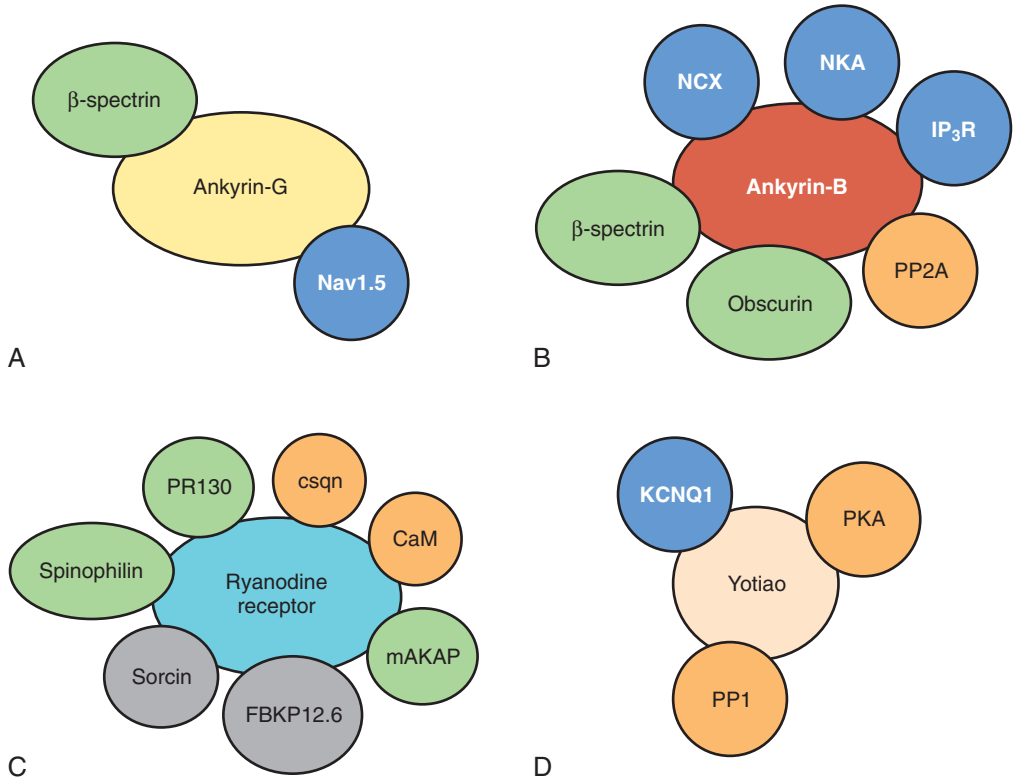

FIGURE 2-5 Macromolecular protein complexes in the cardiac cell. **A,** Ankyrin-G interacts with the voltage-gated Na^+ channel ($Na_v1.5$) and the cytoskeletal protein β-spectrin in heart. **B,** Ankyrin-B–associated proteins include ion channels, pumps, and transporters (Na^+-Ca^{2+} exchanger, Na^+-K^+-ATPase, and $InsP_3$ receptor), signaling molecules (PP2A), and cytoskeletal proteins (obscurin, β-spectrin). **C,** The ryanodine receptor macromolecular complex consists of anchoring proteins (mAKAP, PR130, spinophilin), regulatory elements (sorcin, FKBP12.6), and signaling molecules (calsequestrin, calmodulin). **D,** The AKAP Yotiao complexes the I_{Ks} complex (KCNQ1/KCNE1) with signaling molecules PP1 and PKA to regulate channel activity.

transporter expression and localization in diverse cardiac cell types.[26] As described above, the voltage-gated Na^+ channel $Na_v1.5$ is required for the rapid upstroke of the ventricular action potential (phase 0). As discussed in Chapters 3 and 7, defects in $Na_v1.5$ biophysical activity resulting in aberrant inward I_{Na} are associated with sinus node disease, conduction defects, and ventricular arrhythmias. In ventricular cardiomyocytes, $Na_v1.5$ is primarily localized to the cardiac intercalated disc, although it may also be found at T-tubules and the peripheral sarcolemma in less abundance.[27,28] In fact, ankyrin-G (encoded by human *ANK3*) is required for the expression and localization of $Na_v1.5$ at the intercalated disc (see Figure 2-5).[28,29] Myocytes lacking ankyrin-G display loss of $Na_v1.5$ expression at the cardiac intercalated disc and corresponding reductions in cellular I_{Na}.[29] Interestingly, the ankyrin-G membrane–targeting pathway appears specific for $Na_v1.5$ versus other cardiac ion channels and transporters, as the localization, expression, and functioning of $Ca_v1.2$ and the Na^+-Ca^{2+} exchanger are unaffected in myocytes lacking ankyrin-G.[29] Moreover, the loss of $Na_v1.5$ targeting is rescued by exogenous expression of wild-type ankyrin-G, but not a mutant ankyrin-G lacking key $Na_v1.5$ binding residues.[29] Therefore, ankyrin-G is critical for the localization and functioning of $Na_v1.5$ at the cardiac intercalated disc. Consistent with these findings, loss of ankyrin-G in the murine cerebellum results in defects in neuronal Na^+ channel targeting, defects in neuronal action potentials, and ataxia.[30] Defects in the ankyrin-G–based pathway for $Na_v1.5$ membrane targeting are associated with human arrhythmia. Specifically, key residues in the $Na_v1.5$ domain I-II cytoplasmic domain are required for interaction with ankyrin-G.[28] Interestingly, a human Brugada syndrome mutation is located in this $Na_v1.5$ motif and blocks the interaction of $Na_v1.5$ with ankyrin-G.[28] Moreover, consistent with the role of ankyrin-G in targeting $Na_v1.5$, the human $Na_v1.5$ Brugada syndrome mutant displays aberrant trafficking to the intercalated disc.[28] Instead, the mutant channel is trapped intracellularly in the biosynthetic process.[28] Thus, these findings illustrate the importance of membrane-targeting pathways for normal human cardiac excitability. While ankyrin-G is required for $Na_v1.5$ targeting to the intercalated disc, the pathways for Na^+ channel targeting to other excitable domains are not yet known. However, alternative pathways are almost certainly required for these domains. Likely protein suspects for peripheral sarcolemmal targeting for $Na_v1.5$ include syntrophin and dystrophin.[31]

While ankyrin-G is required for protein targeting to the intercalated disc, a second ankyrin-gene product, termed *ankyrin-B* (human *ANK2*), is responsible for targeting key cardiac ion channels and transporters to the ventricular cardiomyocyte T-tubule and the SR. Specifically, ankyrin-B directly associates with the T-tubule membrane proteins Na^+-Ca^{2+} exchanger and Na^+-K^+-ATPase (see Figure 2-5).[32,33] Moreover, ankyrin-B interacts with the SR membrane protein $InsP_3$ receptor.[33,34] Ventricular cardiomyocytes from mice lacking ankyrin-B expression display striking

loss of Na^+-K^+-ATPase, the Na^+-Ca^{2+} exchanger, and $InsP_3$ receptor expression and function.[33-36] Similar to the findings on ankyrin-G, loss of ankyrin-B is specific for Na^+-K^+-ATPase, the Na^+-Ca^{2+} exchanger, and $InsP_3$ receptor membrane targeting, as ankyrin-B loss does not affect $Na_v1.5$ or $Ca_v1.2$ membrane expression.[35,37] Consistent with loss of Na^+-K^+-ATPase and the Na^+-Ca^{2+} exchanger (and similar to the effects of digitalis, which blocks Na^+-K^+-ATPase activity), ankyrin-$B^{+/-}$ cells display increased SR Ca^{2+} load and Ca^{2+} transient amplitudes.[35] Moreover, while stable in resting conditions, ankyrin-$B^{+/-}$ ventricular cardiomyocytes display cellular after-depolarizations (oscillations in membrane excitability) in response to catecholaminergic stimulation.[35] Consistent with these findings, ankyrin-$B^{+/-}$ mice may display polymorphic arrhythmia and sudden death in response to severe catecholaminergic stimulation (exercise and/or catecholamine injection).[35] Finally, consistent with the role of ankyrin-G in human arrhythmia (Brugada syndrome, see above), defects in the ankyrin-B–based pathway for ion channel and transporter targeting in ventricular cardiomyocytes result in arrhythmia in the human heart. Specifically, human loss-of-function mutations in *ANK2* (ankyrin-B gene) result in a complex arrhythmia syndrome that includes sinus node disease, atrial fibrillation, conduction block, catecholaminergic polymorphic ventricular tachycardia, and sudden death.[35,36,38] In fact, nine *ANK2* loss of function variants have been identified in a host of kindred worldwide.[35,36,38] While the clinical phenotypes of the probands may differ, depending on the variant and the environment (i.e., sinus node disease plus ventricular arrhythmia versus simple sinus node disease), the cardiac phenotypes present in these patients clearly demonstrate the importance of proper ion channel and transporter targeting for normal human cardiovascular excitability. Interestingly, while the ventricular phenotypes are primarily due to defects in the Na^+-Ca^{2+} exchanger and Na^+-K^+-ATPase, *ANK2*-associated defects in sinus node function are due to defects in ankyrin-B–based targeting of $Ca_v1.3$, an atrial and sinus node–specific isoform of the L-type Ca^{2+} channel.[39] Specifically, loss of ankyrin in the sinus node affects $Ca_v1.3$, but not $Ca_v1.2$ expression and targeting, which results in decreased $I_{Ca,L}$ and aberrant automaticity, consistent with findings from mice lacking $Ca_v1.3$ expression.[39-41] Ankyrin-B dysfunction has also been observed in electrically unstable regions of the ventricle following myocardial infarction.[42] These data suggest that changes in ankyrin-B expression may play a role in the more common, acquired forms of cardiac arrhythmia.

Following the identification of ankyrins in ion channel and transporter targeting and human arrhythmia, identical membrane components have been linked to human arrhythmia. For example, syntrophin, the large dystrophin-associated protein, is critical for targeting $Na_v1.5$ to the peripheral sarcolemma.[31] Mice lacking the dystrophin complex display defects in $Na_v1.5$ expression and aberrant cardiac electrical activity.[31] In support of these findings, a human mutation in *SNTA1* (encodes α1-syntrophin) was recently linked to long QT syndrome.[43,44] Specifically, the novel syntrophin mutation resulted in increased persistent I_{Na}. While the mutant does not directly block $Na_v1.5$-syntrophin interactions, the mutation may disrupt association of $Na_v1.5$ with PMCA4b, resulting in defective regulation of nNOS (nitric oxide synthase), S-nitrosylation of $Na_v1.5$, and increased late I_{Na}.[44]

Finally, in addition to defects in integral membrane ion channels, targeting proteins, and structural proteins, defects in membrane coat proteins have been linked to aberrant cardiomyocyte electrical activity and pathophysiology. Caveolae are small invaginations of the cell membrane that have roles in vesicular trafficking and endocytosis. In fact, work in excitable cells strongly implicates caveolae-rich membrane domains in the clustering of ion channel and receptor signaling complexes, including both voltage-gated Na^+, K^+, and Ca^{2+} channels, as well as β-adrenergic receptor signaling complexes. One key coat protein for the formation of the cardiac caveolae membrane domain is the ~20 kD protein caveolin-3 (encoded by *CAV3*). Recent data link *CAV3* mutations to human excitable cell disease. Specifically, *CAV3* mutations have been linked to long QT syndrome, limb-girdle muscular dystrophy, and sudden infant death syndrome.[45-48] Similar to type 3 long QT mutations affecting $Na_v1.5$, cardiac phenotypes associated with human *CAV3* mutations include increased late I_{Na} and QT_c prolongation.[45] However, skeletal muscle phenotypes associated with *CAV3* mutations include decreased L-type Ca^{2+} channel current.[47,48] Thus, it appears that caveolin-3 and caveolae, in general, are likely to have pleiotropic effects on cardiac and skeletal muscle membrane ion channels, transporters, and receptors, which result in complex electrical phenotypes in response to loss of function. Nonetheless, these data clearly demonstrate the importance of unlikely cellular proteins in the pathogenesis of human cardiac arrhythmias.

Conclusion

The complex architecture of the cell plays a critical role in determining the normal electrophysiological properties of the heart. Specialized membrane domains along and within the sarcolemma serve a diverse array of key cellular functions (e.g., EC coupling, electrical communication, mechanical stabilization, transcriptional regulation, respiration). Different regions of the heart possess unique architectural features that relate to their primary functions, and the disruption of cellular organization is associated with electrical instability in both congenital and acquired forms of heart disease.

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CHAPTER 3

Molecular and Cellular Basis of Cardiac Electrophysiology

Gordon Tomaselli and Dan M. Roden

This chapter reviews what is known about the fundamental basis of the excitability of the heart, starting from individual molecules and proceeding to increasingly complex levels of integration—from nucleic acids to proteins in the form of receptors, channels, and transporters, ultimately to cells and tissues. We endeavor to illustrate cellular and molecular fundamentals using clinically relevant examples.

Basic Concepts

Cellular Structure of the Heart

The myocardium is composed of *cardiac myocytes*, which are highly differentiated and specialized cells responsible for the conduction of the electrical impulse and the heart's contractile behavior, and *nonmyocytes*, which serve a number of functions. Myocytes occupy two thirds of the structural space of the heart; however, they represent only one third of all cells. Nonmyocytes include fibroblasts responsible for the turnover of extracellular matrix that predominantly consists of fibrillar collagen types I and III. The collagen scaffolding provides for myocyte alignment and coordinated transmission of contractile force to the ventricular chamber. Other nonmyocyte cells include the endothelial and smooth muscle cells of the intramural vasculature, neuronal elements (such as ganglia) and, under some conditions, inflammatory cells. The gross anatomic features of the heart, the extracellular matrix, and the intramural vasculature create both macroanatomic and microanatomic barriers that are central to both the normal electrophysiology of the heart and clinically important arrhythmias.

Cardiac myocytes are a family of structurally distinct cells, with a design commensurate with their function. Pacemaking cells such as those in the sinoatrial (SA) and atrioventricular (AV) nodes underlie the spontaneous electrical activity of the heart and contain relatively few contractile elements. In contrast, muscle cells are packed with actin and myosin filaments, which serve the main function of the heart—propulsion of blood through the vasculature. Contractile myocytes are rod-shaped cells of approximately 100×20 µm. The myocyte is enveloped by the cell membrane, a lipid bilayer 80 Å to 100 Å in thickness. This insulating bilayer permits little to no transport of ions and maintains a separation of charge established by active transporters that reside in the cell membrane. Ion channels are transmembrane proteins that serve as a conductive pathway between the inside and outside of the cell, allowing the flow of ions and, thus, charge (i.e., current). Also, no current flow exists between myocytes. However, unlike skeletal muscle, cardiac tissue is not a true syncytium; rather, cells are connected to each other by low-resistance communications called *gap junctions* that contain intercellular ion channels.

Membrane Potential and Conduction

Ion concentration and charge gradients across the cell membrane are responsible for the membrane potential of the cardiac myocyte. Transmembrane ionic and electrical gradients are maintained by a series of energy-requiring ion pumps and exchangers that perform the following functions: (1) Concentrate K^+ inside the cell, (2) keep the intracellular sodium (Na^+) low (<10 mM), and (3) tightly regulate intracellular calcium (Ca^{2+}) concentrations (100–200 nmol/L). The pump responsible for establishing and maintaining most of the monovalent cation gradients is the Na^+-K^+ ATPase (sodium-potassium adenotriphosphatase), although other pumps and exchangers that transport Na^+, Ca^{2+}, and hydrogen (H^+) play significant roles in the genesis of ionic concentration gradients and the membrane potential. Ion channels are passive but selective conduits for the flow of ions along electrical and chemical gradients established by active ion transport systems. The physicochemical basis of the membrane potential depends (as described below) on the Nernst potential (E_x):

$$E_x = RT/zF \ln([X]_o/[X]_i) = \sim 27 \ln([X]_o/[X]_i) \quad (1)$$

where R is the gas constant, T is temperature, F is Faraday's constant, and z is the valence of the ionic species. If the resting cardiac myocyte is assumed to have an intracellular $[K^+]$ of ~150 mmol/L and an extracellular $[K^+]$ of 4 mmol/L, then the Nernst potential for K^+ (E_K) is roughly –90 mV. The Nernst potential represents the voltage at which the osmotic tendency for K^+ to flow across the membrane is exactly balanced by the electrical tendency to flow in the opposite direction, which results in a net zero ionic flux and thus no net current flow. Accordingly, the K^+ Nernst potential is sometimes referred to as the *zero current potential*, at which no K^+ current would flow through open K channels. By contrast, the Nernst potential for Na^+ in the resting cell is approximately +60 mV, indicating that if a pathway for Na^+ to enter the cell were present, Na^+ would enter the cell to move the membrane voltage (mV) toward the Nernst potential for Na^+. Indeed, this is precisely what happens when Na channels are open and initiate phase 0 of the action potential. The Nernst potential for potassium is, in fact, very close to the resting membrane potential of the ventricular myocyte, indicating that the resting heart cell membrane is highly permeable to K^+. Actual resting potentials are less negative than E_K due to small conductances of other ionic species with less negative Nernst potentials. In the course of the cardiac cycle, the cell membrane becomes permeable to different ionic species, and these changes in permeability determine time-dependent changes in the

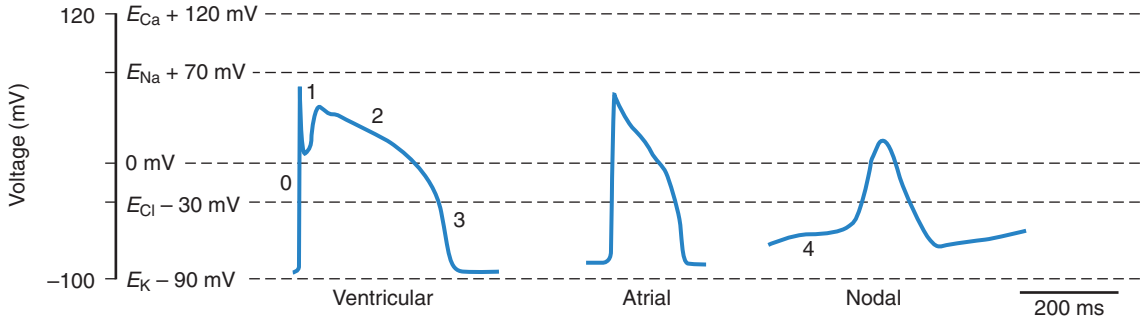

FIGURE 3-1 Schematic of action potentials in different regions of the heart. The permeability of the cell membrane determines membrane voltage. At rest, cells in all regions of the heart are more permeable to potassium (K^+) than to any other cation, hence the negative membrane potential, near the Nernst potential for K^+. The characteristic shapes of action potentials are determined by the ionic currents that are active in each cell type during the cardiac cycle.

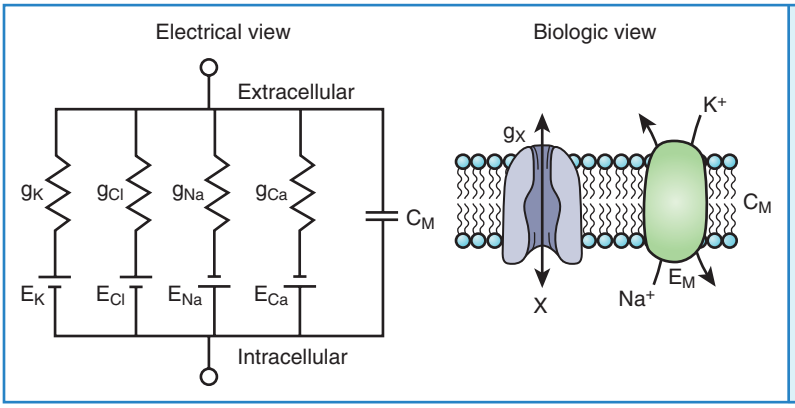

FIGURE 3-2 Electrical and biologic representations of the cardiac cell membrane. The cardiac (or any excitable) membrane can be modeled as an RC circuit with variable resistors (ion channels) in parallel with a capacitor (cell membrane). The transmembrane voltage is established by a series of energy-requiring pumps that maintain ionic gradients across the membrane.

membrane potential, with each ion striving to move the membrane voltage to its Nernst potential and inscribing regionally specific action potentials (Figure 3-1).

Passive Membrane Properties and Cable Theory

The cardiac cell membrane can be modeled as a circuit comprising variable resistors (ion channels) in parallel with a capacitor (lipid bilayer), an *RC circuit* (Figure 3-2). The flow of current across the membrane will alter the charge on the capacitor (and therefore the membrane potential) and change the membrane resistance. The flow of current occurs not only across but obviously along the inside and outside of the cell membrane from cell to cell as well, that is, current propagates.

Cable theory, originally developed to understand current flow in trans-oceanic telegraphic cables, can be used to model passive current flow and propagation in a cardiac muscle fiber. In their simplest formulation, the cable equations define the distribution of voltage along a continuous, uniform cable of infinite length stimulated by a point source. The predictions of cable theory are that (1) a change in voltage exhibits a characteristic decay along the cable defined by the space constant (distance over which voltage decays to 1/e of the value at the site of injection) (Figure 3-3, *A*); and (2) there is an inverse relationship between resistance to current flow (both transmembrane and intercellular) and the cable diameter (Figure 3-3, *B*). That is, the space constant is directly proportional to the cable diameter, and thus, greater lengths of the cable are influenced by the same current injection into a thick, rather than a thin, cable.

Substantial anatomic and biophysical limitations exist when applying the cable theory description of conduction to cardiac muscle. Anatomically, the shape of the heart is complex, and at any level of integration above a single muscle fiber, it does not resemble a cable. Conduction through the myocardium is not continuous; instead, myocardial cells are connected by gap junction channels that create a non-uniformity of intercellular resistance. Macroscopic discontinuities such as fibrous tissue and blood vessels also significantly perturb the cable view of conduction in the myocardium. Finally, the cardiac cell membrane does not just comprise RC circuits; instead, when stimulated to the threshold, it will generate action potentials (see Figure 3-3, *A*). Despite the limitations of cable theory, it serves as the foundation for several important concepts in impulse propagation and was used to demonstrate the electrical nature of conduction in the heart.[1]

Depolarization of cardiac muscle results in the generation of an action potential at the site of excitation and, in doing so, sets up a voltage gradient between the excited cells and their nearest neighbors. The current generated by the action potential serves as an excitatory current for neighboring cells (source), which at their resting membrane potential (sink) are activated by the source. Impulse propagation depends on the balance between the magnitude of the currents in the source and the sink and the resistance along the fiber. Failure of conduction may result

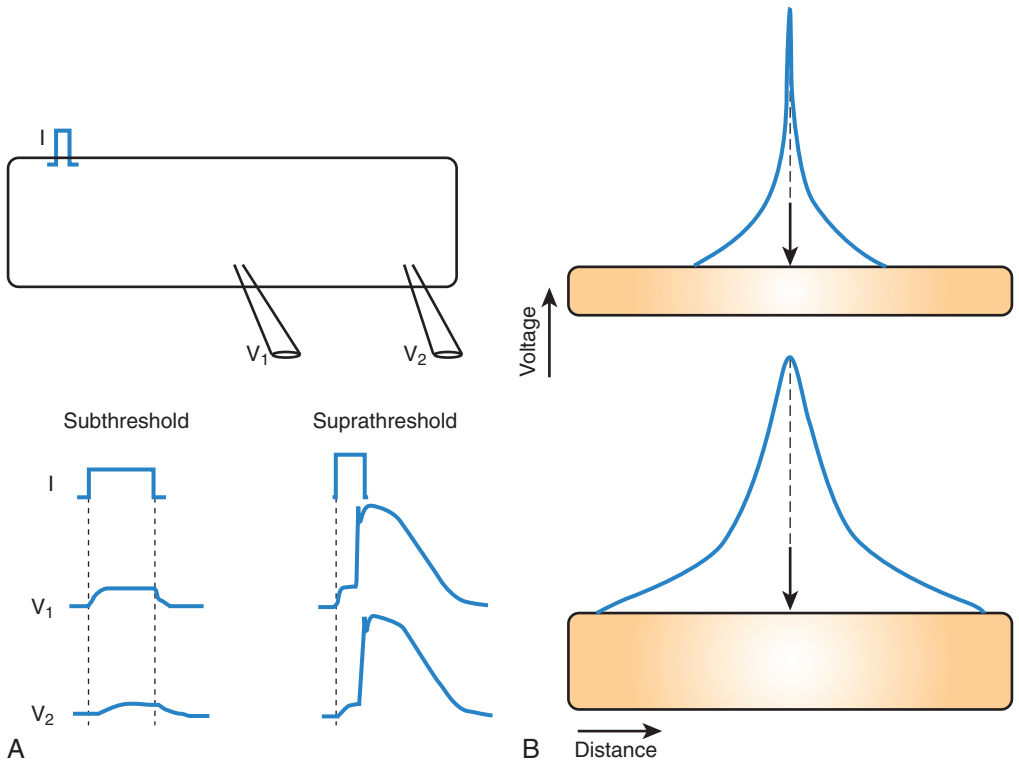

FIGURE 3-3 Spread of current in an idealized cable. **A,** Injection of current into the cable at site I produces a transmembrane voltage change of smaller amplitude, and slower kinetics are recorded at more distal sites in the cable. In an excitable tissue such as the heart, a stimulus of sufficient amplitude elicits a regenerative response (i.e., an action potential) and can propagate along the length of the preparation. Transmission of the action potential is associated with current flow across and along the membrane. **B,** The characteristics of the cable determine the distance over which the voltage difference induced by the current injection decays (space constant). In a cable of larger diameter, the voltage difference falls over a larger distance; that is, the space constant (the distance over which the voltage difference falls to 1/e of the value at the site of injection) is proportional to the radius of the cable.

from alterations in the source current; examples include reduction of the source by drug blockade of Na (atrial or ventricular muscle) or Ca^{+} channels (nodal cells) or from changes in the characteristics of the sink, such as ischemia and activation of ATP-dependent potassium channels ($I_{K\text{-}ATP}$). In the latter case, propagation fails because the tissue with greatly increased repolarizing K current, due to activated $I_{K\text{-}ATP}$, acts as an infinite sink and cannot be sufficiently depolarized to reach the threshold for the generation of an action potential. Myocardial ischemia will produce changes in the intracellular environment such as decreased pH and increased intracellular Ca^{2+} that will serve to reduce gap junctional conductance and functionally uncouple myocardial cells, altering the relationship between the source and the sink and hindering impulse propagation.

The safety factor for conduction is the magnitude of the current provided by the source that is in excess of that required to activate the sink. The main factors influencing source current are the rate of rise of the upstroke and the amplitude of the action potential, which are the metrics that reflect the magnitude of inward currents. The factors that influence the current requirements of the sink are the membrane resistance and the difference between the resting and threshold potentials. One major reason for the mismatch between the source and the sink is an abrupt anatomic change, such as that which occurs at the Purkinje fiber–ventricular muscle junction. Orthodromic conduction over the Purkinje system results in the activation of a broad band of ventricular muscle by narrow strands of Purkinje fibers. Such an abrupt transition from an anatomically narrow source to a massive sink makes propagation tenuous such that small changes in the characteristics of the source or the sink are likely to produce failure of conduction. Antidromic conduction from ventricular muscle to Purkinje fibers produces just the opposite source-sink relationship and thus a higher safety factor for conduction.

While this discussion implicitly treats the activation wave in one dimension, the behavior of propagating waves in the heart is more complex. The complexity can be appreciated if one considers propagation in two dimensions. In this circumstance, the shape of the wavefront is a major determinant of the efficiency of propagation. A convex wavefront, as might be observed after point stimulation, creates a large sink around a smaller activating source. This mismatch reduces conduction velocity and the safety factor for propagation. Conversely, a concave activation front produces a source-sink mismatch that favors the source; this results in a high safety factor and more rapid impulse transmission. Thus, not only do source-sink characteristics influence propagation, they also influence the curvature of the wave front (see Figure 3-4).

Directionally different conduction velocity is a characteristic feature of cardiac muscle known as *anisotropic conduction*. Anisotropic conduction has its basis in the structure of the myocyte and cardiac tissue; myocytes are rod shaped and are

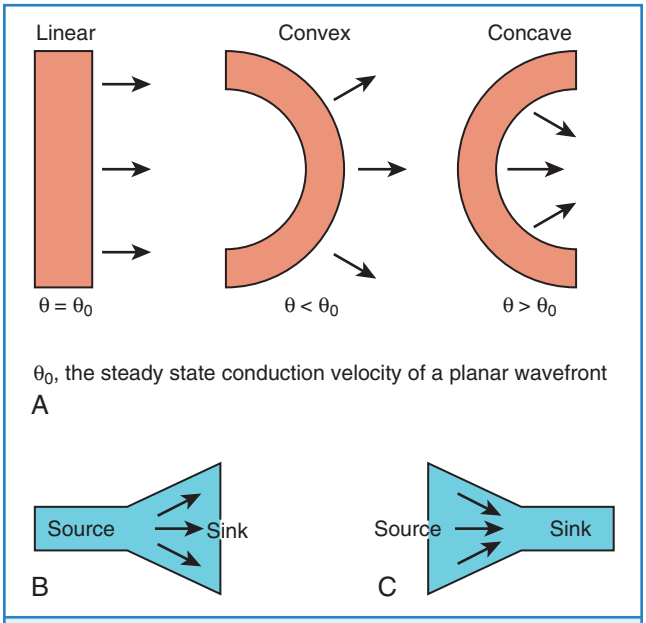

FIGURE 3-4 Relationship of current sources and sinks. **A,** Compared with the steady-state conduction velocity for the planar wavefront in a homogeneous medium (θ_0), the conduction velocity of a convex wavefront is slower, and a concave wavefront is faster with lower and higher safety margins for conduction, respectively. In situations of structural inhomogeneity, as when a Purkinje fiber activates ventricular muscle (**B**), the conduction velocity is slower, with a lower safety margin at the structural discontinuity. **C,** In the case of a larger mass of tissue activating a smaller mass, the conduction velocity is fast, with a high safety margin.

organized in bundles that are oriented along the long axis of the cell. Transmurally, the axes of these bundles undergo significant changes in orientation through the ventricular wall (~120 degrees maximal deviation).[2] Communication among myocytes occurs via gap junction channels that are non-uniformly distributed over the surface of the heart cell, with larger numbers of channel poised to propagate the impulse longitudinally, rather than transversely, to the long axis of the muscle fiber.[3] The implications of anisotropy for conduction in the longitudinal and transverse direction under pathologic conditions are controversial. In the context of uniform depression of conduction, as might exist with antiarrhythmic drug treatment, propagation in the transverse direction is preserved compared with conduction in the longitudinal direction. However, when cellular uncoupling occurs, such as in ischemia, longitudinal propagation may exhibit a higher safety factor than does transverse conduction.

Major Breakthroughs: Voltage Clamp, Molecular Cloning

A stimulus of sufficient magnitude applied to a myocyte (or any excitable cell) elicits a typical change in membrane potential known as the *action potential*. The ionic current basis of the action potential was confirmed and quantitatively studied using the voltage clamp developed in the middle of the twentieth century.[4] Voltage clamping is a technique whereby the experimenter controls the transmembrane voltage and measures the current at that defined voltage. Much of what we know about ionic currents in myocytes comes from voltage clamp experiments and a more recently developed type of voltage clamp called the *patch clamp*.[5] A variant of the patch clamp technique permits the measurement of ionic currents through *single* ion channels.

Typically, in a voltage clamp experiment, the membrane voltage (V) is held near the resting membrane potential, (approximately –80 mV for ventricular myocytes) and then stepped to more positive voltages. This voltage step induces two components of the membrane current (I_M) flow; at the instant of the voltage change, ions (I_C) flow to charge the membrane capacitance (C_M), after which the current reflects the movement of ions through the ion channels (I_i).

$$I_M = I_c + I_i = C_M * dV/dt + I_i \quad (2)$$

Capacitive current is generally small and transient and can usually be electronically compensated, so the voltage clamp provides a robust measure of current flow through ion channels, thereby permitting the study of the detailed biophysics and pharmacology of ionic currents and channels. The major limitation of such experiments in myocytes is the existence of many currents that are simultaneously active in response to the voltage step. Experimental conditions can be altered to isolate a current of interest; however, this often requires the presence of drugs, toxins, or highly nonphysiologic conditions. An alternative to the study of ionic currents in native cells was afforded with the molecular cloning and heterologous expression of ion channel genes. Expression of an ion channel gene in a non-excitable cell without other overlapping currents permits the study of the ionic current of interest under more physiologic conditions. The fundamental limitation of heterologous expression is that the ion channel is removed from its native cellular background, which may change the behavior of the channel.

The combination of highly sensitive electrophysiological methods, such as patch-clamp recording, and deoxyribonucleic acid (DNA) cloning, heralded the era of understanding of the molecular basis of cardiac excitability.

Molecular Basis of Cardiac Action Potentials

Cardiac myocytes possess a characteristically long action potential (200 to 400 ms, see Figure 3-1), compared with neurons or skeletal muscle cells (1 to 5 ms). The action potential profile is sculpted by the orchestrated activity of multiple ionic currents, each with its distinctive time- and voltage-dependent amplitudes. The currents, in turn, are carried by complex transmembrane proteins that passively conduct ions down their electrochemical gradients through selective pores (ion channels), actively transport ions against their electrochemical gradients (pumps, transporters), or electrogenically exchange ionic species (exchangers).

Action potentials in the heart are regionally distinct. The regional variability in cardiac action potentials is the result of differences in the numbers and types of ion channel proteins expressed by different cell types in the heart. Further, unique sets of ionic currents are active in pacemaking and muscle cells, and the relative contributions of these currents may vary in the same cell type in different regions of the heart.[6]

Ion Channels and Transporters: Molecular Building Blocks of the Action Potential

Currents that underlie the action potential are carried by complex, multi-subunit transmembrane glycoproteins called *ion channels*

Table 3-1 Human Ion Channel, Exchanger, and Transporter Genes

CHANNEL	GENE	CHROMOSOME	GENE ID
POTASSIUM (K) CHANNELS: α-SUBUNITS			
HERG (Kv11.1)	*KCNH2*	7q35-q36	3757
KvLQT1(Kv7.1)	*KCNQ1*	11p15.5	3784
Kv1.4	*KCNA4*	11p14	3739
Kv1.5	*KCNA5*	12p13	3741
Kv4.3	*KCND3*	1p13	3752
Kir2.1	*KCNJ2*	17q23.1-q24.2	3759
GIRK4 (Kir3.4, CIR)	*KCNJ5*	11q24	3762
GIRK1(Kir3.1)	*KCNJ3*	2q24.1	3760
Kir6.2	*KCNJ11*	11p15.1	3767
Kir6.1	*KCNJ8*	12p11.23	3764
HA-HCN2	*HCN2*	19p13.3	610
hHCN4	*HCN4*	15q24-q25	10021
Ancillary Subunits			
MinK	*KCNE1*	21q22.1-q22.2	3753
MiRP-1	*KCNE2*	21q22.12	9992
KChIP2	*KCNIP2*	10q24	30819
SUR2A	*ABCC9*	12p12.1	10060
CALCIUM (Ca) CHANNELS			
Cav1.2	*CACNA1C*	12p13.3	775
Cav3.1	*CACNA1G*	17q22	8913
Cav3.2	*CACNA1H*	16p13.3	8912
Cav3.3	*CACNA1I*	22q13.1	8911
Cavβ1	*CACNB1*	17q21-q22	782
Cavβ2	*CACNB2*	10p12	783
Cavβ3	*CACNB3*	12q13	784
Cavβ4	*CACNB4*	2q22-q23	785
Cavα2δ	*CACNA2D*	3p21.3	9254
SODIUM (Na) CHANNELS			
Nav1.5	*SCN5A*	3p21	6331
Navβ1	*SCN1B*	19q13.1	6324
Navβ2	*SCN2B*	11q23	6327
Navβ3	*SCN3B*	11q23.3	55800
Navβ4	*SCN4B*	11q23.3	6330
GAP JUNCTION CHANNELS			
Cx43	*GJA1*	6q21-q23.2	2697
Cx40	*GJA5*	1q21.1	2702
Cx45	*GJC1*	17q21.31	10052
TRANSPORTERS AND EXCHANGERS			
NCX1	*SLCBA1*	2p22-p23	6546
SODIUM-POTASSIUM (Na-K) ADENOTRIPHOSPHATASE (ATPase)			
α_1	*ATP1A1*	1p13	476
α_2	*ATP1A2*	1q21-q23	477
α_3	*ATP1A3*	19q13.2	478
β_1	*ATP1B1*	1q22-q25	481
β_2	*ATP1B2*	17p13.1	482

(Table 3-1). These channels open and close in response to a number of biologic stimuli, including a change in voltage, ligand binding (directly to the channel or to a G-protein–coupled receptor), and mechanical deformation. Other ion-motive transmembrane proteins such as exchangers and transporters make important contributions to cellular excitability in the heart. Ion pumps establish and maintain the ionic gradients across the cell membrane that permit current flow through ion channels. If pumps, transporters, or exchangers are not electrically neutral (e.g., 3 Na^+ for 1 Ca^{2+}), they are termed *electrogenic* and can further influence electrical signaling in the heart.

The most abundant superfamily of ion channels expressed in the heart consists of voltage-gated ion channels. Various structural themes are common to all voltage-dependent ion channels. First, the architecture is modular, consisting either of four homologous subunits (in K channels, see Figures 3-7 and 3-8) or of four internally homologous domains (in Na and Ca channels) (see Figures 3-5 and 3-6). Second, proteins wrap around a central pore (see Figure 3-8). The pore-lining (P segment) regions exhibit exquisite conservation within a given channel family of like selectivity (e.g., jellyfish, eel, fruit fly, and human Na channels have very similar P segments), but not among families with different selectivities. Third, the general strategy for activation gating (opening and closing in response to changes in the membrane voltage) is highly conserved: The fourth transmembrane segment (S4), typically studded with positively charged residues, lies within the membrane field and moves in response to depolarization, thus opening the channel. Fourth, most ion channel complexes include not only the pore-forming proteins (α-subunits) but also auxiliary subunits (e.g., β-subunits) that modify channel function.

Sodium Channels

Sodium (Na) channels have been highly conserved through evolution and exist in all species, from the jellyfish to humans; they are nature's solution to the conundrum of coordination and communication within large organisms, particularly when speed is of the essence. Thus, Na channels are richly concentrated in axons and muscle, where they are often the most plentiful ion channels. A mammalian heart cell, for example, typically expresses more than 100,000 Na channels but only 20,000 or so L-type (large and long-lasting) Ca channels and fewer copies of each family of voltage-dependent K channels.

Na channels were the first ion channels to be cloned and have their sequence determined.[7] In humans, more than 10 distinct Na channel genes have been cloned from excitable tissues, with striking homology to the complementary DNA (cDNA) cloned from eel electroplax. The cardiac Na channel gene (*SCN5A*) resides on the short arm of chromosome 3 (3p21) (see Table 3-1). The Na channel complex is composed of several subunits, but only the α-subunit is required for function. Figure 3-5 shows that the α-subunit consists of four internally homologous domains (labeled I to IV), each of which contains six transmembrane segments. The four domains fold together so as to create a central pore, whose structural constituents determine the selectivity and conductance properties of the Na channel.

Peptide linkers between the fifth (S5) and sixth (S6) membrane-spanning repeats in each domain, referred to as the *P segments,* come together to form the pore. The primary structure of the S5-S6 linkers of Na channels in each domain is unique. Thus, the structural basis of the permeation of Na channels differs fundamentally from that of K channels, in which four identical P segments can come together to form a K^+-selective pore (see below).

One of the seminal contributions of Hodgkin and Huxley was the notion that Na channels occupy several "states" (which are now viewed as different conformations of the protein) in the process of opening (activation); yet another set of conformations is entered when the channels close during maintained depolarization (inactivation).[4] The *m* gates that underlie activation and the *h* gate that mediates inactivation were postulated to have intrinsic

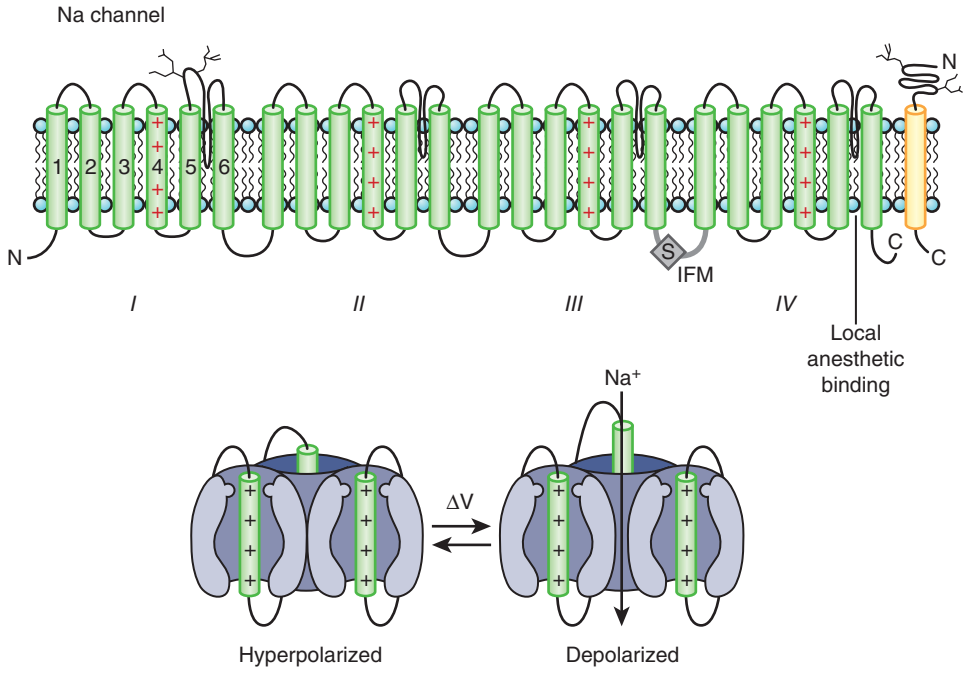

FIGURE 3-5 Models of the sodium (Na) channel. *Top*, Topographic illustration of the Na channel α-subunit with four pseudohomologous domains (*I to IV*). One or more transmembrane β-subunits coassemble with the α-subunit to form the intact channel. The fourth membrane-spanning repeat (S4) is charged and serves as the voltage sensor for channel activation. The segments or linkers between S5 and S6 in each domain, called *permeation segments*, or *P segments*, form the outer pore mouth and the selectivity filter. The linker between the third and fourth domains underlies fast inactivation and contains one of the mutations that underlies the chromosome 3–linked form of long QT syndrome. The S6 segment of the fourth domain contains residues critical for the binding of the local anesthetic to the channel. *Bottom*, Illustration of the caniliculus through which the S4 segment slides during channel activation. An outward movement of the S4 during channel activation is proposed.

voltage dependence and to function independently.[8] While some of the implicit structural predictions of that formulation have withstood the test of time, others have not. For example, the four S4 segments are now widely acknowledged to serve as activation voltage "sensors." In the process of activation, several charged residues in each S4 segment physically traverse the membrane (see Figure 3-5, *bottom panel*). The contributions of each S4 segment to activation are markedly asymmetrical; some of the charged residues play a much more prominent role than do others in "homologous" positions.[9] Other studies have revealed that activation is coupled with inactivation. Indeed, the time course of current decay during maintained depolarization predominantly reflects the voltage dependence of activation, although single-channel inactivation itself does vary with voltage (particularly in cardiac Na channels). If the S4s are the sensors, where are the activation "gates" themselves? This crucial question still remains unresolved. However, according to experimental evidence, S6 is the leading contender for the physical activation gate.

Inactivation of Na channels is as arcane a process as activation. Not only is there loose coupling to activation, but there are multiple inactivation processes. One common approach to distinguishing inactivated states is to determine the rate at which they recover the ability to activate: Repriming from the traditional "fast" inactivation occurs over tens of milliseconds, while recovery from "slow" inactivation may need tens of seconds or longer. Fast inactivation is at least partly mediated by the cytoplasmic linker between domains III and IV (the crucial residues are labeled IFM in Figure 3-5), which may function as a hinged lid, docking onto a receptor formed by amino acids in the S4-S5 linkers of domains III and IV. This notion is consistent with observations that fast inactivation can be disrupted by internal proteases. Nevertheless, it is increasingly clear that mutations scattered widely throughout the channel affect inactivation gating. The structural determinants of slow inactivation are less well localized than those of fast inactivation. Mutations in the P region of domain I affect both activation gating and slow inactivation, while various widely scattered disease mutations identified in paramyotonia congenita and other skeletal myopathies suppress slow inactivation of the Na channel.

The S6 segment of domain IV has been proposed to contain the receptor for local anesthetics that block Na channels in a voltage-dependent manner. The homologous domains on Ca and K channels are also loci for drug binding. Na current blockade is enhanced at depolarized potentials and/or with repetitive pulsing. These observations are consistent with the idea that local anesthetics act as allosteric effectors of the inactivation gating mechanism: When they bind to the channel, they facilitate inactivation. It is clear that gating interacts with local anesthetic blockade so profoundly that it is difficult to interpret the localization of a "receptor" to S6. Mutations in S6 at putative receptor sites alter gating, independent of superimposed drug effects. Further, mutations in distant parts of the molecule can also dramatically alter the phenotype of local anesthetic blockade. Despite these caveats, the S6 segments appear to play a special role in the effects of drugs in all of the voltage-gated ion channels.

Pharmacologic competition studies and mutagenesis have defined a number of neurotoxin binding sites on the Na channel. Among these, tetrodotoxin (TTX)—a guanidinium-containing

blocker—has contributed the most to our understanding of Na channel structure and function. Externally applied TTX blocks neural and skeletal muscle Na channel isoforms potently (in the nM range) but blockade of cardiac channels requires much higher concentrations (~10^{-5} M). The identity of one particular residue in the P region of domain I accounts for most of the isoform-specific TTX sensitivity: An aromatic residue at this position (373 in the human heart Na channel) confers high affinity, while its absence renders the channel TTX resistant. Many other residues in the outer mouth of the channel contribute to the binding of TTX and the related divalent guanidinium toxin saxitoxin (STX), suggesting that the toxin has a large footprint on the external surface of the channel.

Four different β-subunits ($Na_V\beta_1$ to 4, *SCN1B-SCN4B*) have been isolated, and all appear to be single membrane–spanning domain (type I topology) proteins with a large extracellular V-shaped immunoglobulin (Ig) fold often found in cell adhesion molecules and small carboxyl terminal cytoplasmic domain.[10] The effects of the particular β-subunit on the kinetics and voltage dependence of the α-subunit vary depending on the particular β-subunit and the cell expression system. Despite the expression of β_1 mRNA, using subtype-specific antisera, the functional role of β-subunits in cardiac Na currents is still being debated. Several pieces of evidence are consistent with a role for β-subunit(s) in heart cells. First, β-subunits are found in cardiac myocytes, although no $Na_V\beta1$ is found in association with the α-subunit protein from the rat heart. Second, $Na_V\beta1$ variably modulates the function of $Na_V1.5$ in heterologous expression systems, including the sensitivity of the channel to blockade by antiarrhythmic drugs and free fatty acids. Finally, mutations in β-subunits have been directly or indirectly implicated in heritable cardiac arrhythmias.

Regulation of the Na channel by serine/threonine phosphorylation is a complex process. Isoforms of the Na channel α-subunit fall into one of two groups, long (neuronal and cardiac) and short (skeletal muscle and eel). Neuronal isoforms have a substantially larger intracellular linker between domains I and II, which contains five consensus sites for cyclic adenosine monophosphate (cAMP)–dependent protein kinase (PKA) phosphorylation. In fact, PKA modulates the function of expressed neuronal and cardiac Na channels. The cardiac Na channel has eight candidate consensus PKA phosphorylation sites in the I-II linker, all of which are distinct from neuronal channels. In vitro studies of the expressed cardiac Na channel demonstrate cAMP-dependent phosphorylation on only two of these serines. Interestingly, when the cardiac channel is phosphorylated by PKA, whole-cell conductance increases, suggesting that the specific pattern of phosphorylation is responsible for the functional effect and may involve changes in the trafficking of the channel to the cell membrane.

In contrast to PKA, protein kinase C (PKC) alters the function of all of the mammalian Na channel isoforms. The PKC effect is largely attributable to phosphorylation of a highly conserved serine in the III-IV linker (see Figure 3-5). Conventional PKC isoforms reduce the maximal conductance of the channels and alter gating in an isoform-specific fashion. The macroscopic current decay of neuronal channels is uniformly slowed by PKC, which suggests destabilization of the inactivated state. Cardiac channels exhibit a hyperpolarizing shift in the steady-state availability curve consistent with an enhancement of inactivation from closed states.

Overexpression of calmodulin kinase (CaMKIIδC) in transgenic murine heart alters cardiac I_{Na} function, stabilizing inactivation and increasing persistent current; however, this finding is complicated by the presence of heart failure in this murine model. Subacute expression after adenoviral infection of adult ventricular myocytes has a similar effect on I_{Na}. In contrast, in acutely isolated guinea pig ventricular myocytes, enhanced CaMKII activity destabilizes inactivation gating and increases the persistent or late current, thus prolonging the action potential duration.

Alteration of ion channel function is an important pathophysiologic mechanism of various familial diseases of muscle and brain and of inherited arrhythmias. The Na channelopathies were among the first molecularly characterized human ion channel diseases.[11] Rare allelic variants in *SCN5A* have been linked to inherited ventricular arrhythmias,[12] conduction system disease, and sudden infant death syndrome. Complex electrophysiological phenotypes have been associated with mutations in both α- and β-subunits of Na channels. Rare variants or mutations have been associated with sudden death in women (in a population-based study) and with atrial fibrillation. More common acquired forms of long QT syndrome (LQTS), generally associated with drug ingestion, have been linked to common variants of *SCN5A*. Finally, disease-causing mutations in the Na channel have been associated with alterations in drug blockade. The highly variant phenotypes of these arrhythmic syndromes are, in part, explained by the variable effects of the mutations on channel subunit function or expression.

Calcium Channels: L-type

The pore-forming subunit (α_1) of the calcium (Ca) channel is built on the same structural framework as the Na channel.[13] As is the case with the Na channel, a number of genes encode surface membrane Ca channel α_1-subunits. The predominant sarcolemmal Ca channels in the heart are the L-type (large and long-lasting) and T-type (tiny and transient) Ca channels (Table 3-2). The cardiac L-type Ca channel ($Ca_V1.2$) is a multi-subunit transmembrane protein composed of α_{1C} (α1*1.2*) (165 kDa), β (55 kDa), and α_2 (130 kDa) to δ (32 kDa) subunits. Three genes are known to encode L-type Ca channel α_1-subunits ($Ca_V\alpha1.x$ to α1*3.x*), and the $Ca_V\alpha1.2$ is the gene expressed in the heart (see Table 3-1). Distinct splice variants of the $Ca_V\alpha1.2$ gene have been described, and these contribute to the diversity of the cardiac L-type Ca channel function. Similar to the α-subunit of the Na channel, the S5-S6 linkers (P segments) of the α_1-subunit of the Ca channel form the ion-selective pore (Figure 3-6). However, unlike Na channels, each P segment contributes a glutamic acid to a cluster that serve to bind Ca^{2+} in the channel pore. The β-subunit is completely cytoplasmic and noncovalently binds to the α_{1C} subunit, modifying its function and contributing to appropriate membrane trafficking of the channel complex. Although β_{2a} has been proposed to be the major L-type Ca channel β-subunit, splice variants of all β-subunits β_1 to β_4 are expressed in the mammalian heart in a complex spatial and temporal pattern. As many as five genes have been suggested to encode the α_2-δ subunit: These gene products undergo post-translational processing to produce the mature extracellular α_2-subunit linked by a disulfide bond to the transmembrane δ-subunit. In heterologous expression systems, α_2- to δ-subunits enhance expression of Ca channels and hasten current activation and deactivation in the presence of α_1- and β-subunits.

The α_1-subunit of the Ca channel contains a highly basic S4 transmembrane segment in each homologous domain, which, by analogy, is thought to be the voltage sensor for channel activation.

Activation of skeletal muscle and cardiac L-type Ca channels differ; skeletal muscle channels activate much more slowly than do their cardiac counterparts. Based on the properties of chimeric channels constructed from cardiac ($Ca_V\alpha_1 1.2$) and skeletal muscle ($Ca_V\alpha_1 1.1$) α_1-subunits, the difference in activation gating resides in the first homologous domain; however, it is unclear if the S4 membrane-spanning segment is the crucial structural motif.

Ca channels inactivate by both Ca^{2+}-dependent inactivation (CDI) and voltage-dependent inactivation (VDI) processes. CDI and VDI are regulated by channel phosphorylation and β-subunits, which suggests shared structural mechanisms that perhaps involve the I-II domain linker. The C-terminus contains peptide sequences that bind calmodulin (CaM) and Ca^{2+}; these are an IQ motif named for the signature amino acids (isoleucine and glutamine) in the sequence and a helix-loop-helix structural domain, referred to as an *EF hand*, that mediate CDI. CaM is permanently tethered to the channel complex and serves as a Ca^{2+} sensor for the L-type channel. The Ca^{2+}-CaM complex facilitates the interaction of CaM with the IQ motif resulting in the occlusion of the inner mouth of the Ca channel pore and terminating the inward Ca^{2+} flux despite continued depolarization. As cytoplasmic Ca^{2+} concentration falls, calmodulin unbinds Ca^{2+} and the IQ motif, thus relieving Ca^{2+}-dependent inactivation. Spatial discrimination of Ca^{2+} concentration by CaM may involve regions in the N-terminus of the channel. A Ca^{2+}-binding EF hand motif in the carboxyl terminus of α_1 appears to be necessary to confer Ca^{2+}-dependent inactivation to the $Ca_V\alpha_1 1.2$-subunit, although not through a direct binding of Ca^{2+} (see Figure 3-6, *bottom*). The I-II interdomain linker has been demonstrated as the site of β-subunit binding as well as a critical structural determinant of VDI. Mutations in this linker have been associated with the highly arrhythmogenic Timothy syndrome.[14]

L-type Ca channels are found in all of the myocytes of the mammalian heart and have several important electrophysiological functions. In SA nodal tissue, both L- and T-type channels contribute to diastolic depolarization and, therefore, impulse formation. Modulation of L-type current by the autonomic nervous system is important in controlling the rate of sinus node discharge. Blockade of the L-type channel underlies the sinus node slowing, which is observed with some Ca channel antagonists. The AV node is the only place in the body where Ca channels (L-type) normally conduct excitatory impulses. Consequently, it is not surprising that modulators of the L-type current have profound effects on SA and AV conduction. In muscle tissue, the L-type Ca current is the major depolarizing current during the action potential plateau, and inhibition of this current reduces the voltage of the plateau and shortens the action potential duration. Downregulation of the L-type current, as seen in atrial myocytes isolated from patients with a history of atrial fibrillation, is thought to promote the maintenance of fibrillation.

Table 3-2 Properties of Calcium Channels

	L-TYPE	T-TYPE
Pore-forming α-subunit	α_{1C}	α_{1H}
Auxiliary subunits	β, α_2-δ	?
Permeability	$Ba^{2+} > Ca^{2+}$	$Ba^{2+} \cong Ca^{2+}$
Activation threshold	>–30 mV	>–60 mV
Inactivation threshold	>–40 mV	>–90 mV
Inactivation		
Rate	Slow	Fast
Calcium-dependent	Yes	No
Voltage-sensitive	Yes	Yes
Recovery	Fast	Slow
Localization in heart	All	Nodal > Purkinje > atria
Blocker sensitivity		
Dihydropyridines	++++	+
Phenylalkylamines	++++	+
Benzothiazepines	++++	+
Tetralols	++	+++
Ni^{2+}	+	+++
Cd^{2+}	+++	+

Ba, *Barium;* Cd, *cadmium;* Ni, *nickel.*

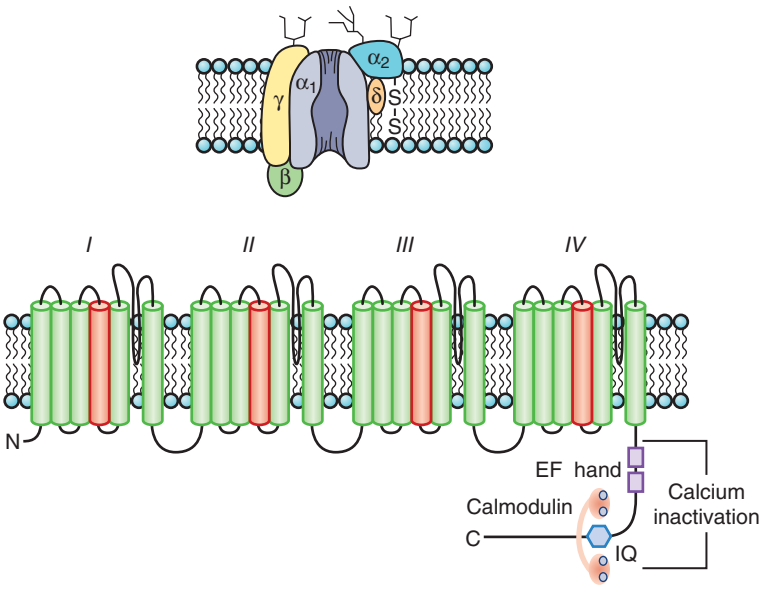

FIGURE 3-6 *Top*, Subunit structure of the cardiac calcium (Ca) channel. The $\alpha_1 1.2$ (α_{1C}) subunit forms the pore and contains drug-binding sites. β_2 and α_2- to δ-subunits coassemble with the α_1 subunit. The intact cardiac L-type Ca channel containing the $\alpha_1 1.2$-subunit is referred to as $Ca_V 1.2$. *Bottom*, The transmembrane topology of the Ca channel is similar to the sodium (Na) channel with four homologous domains, each containing six membrane-spanning repeats. The S4 segments (*dark gray*) are generally conserved, but the molecular basis of inactivation is distinct from Na channels. The Ca channel exhibits both voltage-dependent inactivation and Ca^{2+}-dependent inactivation. Calmodulin (CaM), which is required for Ca^{2+}-induced inactivation of the channel, is tethered to the channel in the carboxyl terminus; with binding of Ca^{2+}, a conformation change occurs in this region of the channel that requires CaM, the CaM binding motif (IQ), and the EF hand motif, and together these constitute the Ca^{2+} inactivation region of the channel.

Calcium Channels: T-type

The other major Ca channel present in the sarcolemma of heart (and prominently in vascular smooth muscle) cells is the T-type channel. The T-type channel has a biophysical fingerprint that is distinct from that of the L-type channel, opening at more negative voltages, inactivating more rapidly, and having a lower conductance than the L-type channel (for reviews, see references 15 and 16). The distribution of the T-type current is more restricted in the heart than is that of the L-type current. The T-type current has been recorded in the SA node, AV node, atrium, and Purkinje cells but not in the normal adult ventricle (see Table 3-2). The T-type current plays a prominent role in phase 4 diastolic depolarization and the action potential upstroke of pacemaking cells. T-type currents play a role in the developing heart and in pathologic remodeling in some species, but this current has not been detected in normal or diseased human ventricular myocytes. Three genes encoding the T-type Ca current α_1-subunits have been cloned. The $Ca_V\alpha_1 3.1$ (*CACNA1G*) cDNA was isolated from neuronal tissue and was the first of this new class of Ca channels cloned. The gene resides on human chromosome 17q22 (see Table 3-1), with a predicted topology similar to that of other Ca channel cDNAs.[16] The gene encoding $Ca_V\alpha_1 3.2$ (I) expressed in human heart resides on chromosome 16p13.3. The gene encoding $Ca_V\alpha 3.3$ (*CACNA1I*) on chromosome 22q13 first appeared as part of the output of the Human Genome Project.[17] Expression of the $Ca_V\alpha_1 3$ cDNAs produces currents with the biophysical hallmarks of the T-type Ca current. Interestingly, $Ca_V\alpha_1 3.2$ lacks a consensus β-subunit–binding motif in the I-II linker of the channel and expresses robustly without the need for other subunits in contrast to L-type channels. The T-type channel genes lack an EF hand or IQ motifs, which suggests modes of inactivation distinct from the L-type channel.

Four chemical classes of compounds have been used to block Ca currents: (1) dihydropyridines, (2) phenylalkylamines, (3) benzothiazepines, and (4) tetralols. Ca channel blockers exhibit significant pharmacodynamic heterogeneity across classes and even within a given chemical class. Drugs of the phenylalkylamine (verapamil) and benzothiazepine (diltiazem) classes are effective antiarrhythmics primarily used to terminate some supraventricular arrhythmias, to control ventricular response in others, and in some forms of idiopathic ventricular tachycardia. Dihydropyridines are more potent vasodilators and are not useful as antiarrhythmic compounds. A number of mechanisms explain these clinical differences. The classes of drugs (dihydropyridines, phenylalkylamines, benzothiazepines) that block the L-type channel have distinct but overlapping binding sites on the $Ca_V\alpha_1 1.2$-subunit. Vascular smooth muscle and cardiac muscle express different splice variants of $Ca_V\alpha_1 1.2$, and the vascular variant is more sensitive to block by dihydropyridines. Perhaps more important than the intrinsic sensitivity of the specific $Ca_V\alpha_1 1.2$ variant to a blocking compound are the voltage dependence and kinetics of channel blockade by the compound. Like Na channel–blocking local anesthetic antiarrhythmic drugs, Ca channel antagonists exhibit use-dependent and voltage-dependent blockade as a result of the preference of the drugs to bind to the inactivated states of the channel. The enhanced sensitivity of vascular Ca channels to blockade by dihydropyridines is predominantly due to the depolarized resting membrane potential of vascular smooth muscle cells (Vm approximately –40 mV), compared with that of cardiac myocytes, and the greater occupancy of the inactivated state. Differences among dihydropyridines, phenylalkylamines, and benzothiazepines in blocking cardiac Ca channels are significantly related to the kinetic of interaction of the drug and the channel. Phenylalkylamines dissociate from the Ca channel very slowly, dihydropyridines do so rapidly, and benzothiazepines recover with intermediate kinetics. T-type channels are less sensitive to blockade by dihydropyridines, phenylalkylamines, and benzothiazepines. Mibefradil is a tetralol Ca channel blocker that is relatively selective for T-type over L-type Ca channels. It was briefly marketed for the treatment of hypertension but was withdrawn because of a high incidence of adverse effects, often occurring as a result of drug interactions.

Potassium Channels

Currents through K channels are the major repolarizing currents in the heart, but the relative importance of any specific channel varies regionally in the heart. K channels are the most diverse subfamily of channel proteins comprising molecules with three distinct molecular architectures (Figure 3-7). The inward rectifier currents (I_{K1}, I_{KACh}, I_{KAdo}), designated *Kir*, are encoded by a K channel that is evolutionarily the most primitive and comprises only two membrane-spanning repeats (analogous to S5 and S6) and a pore, or P, segment. The latter contains the K channel signature sequence (TVGYGDM) that underlies the K^+-selective permeability of the channel. The first K channel gene isolated was from *Drosophilia melongaster*. This mutant fruit fly was called

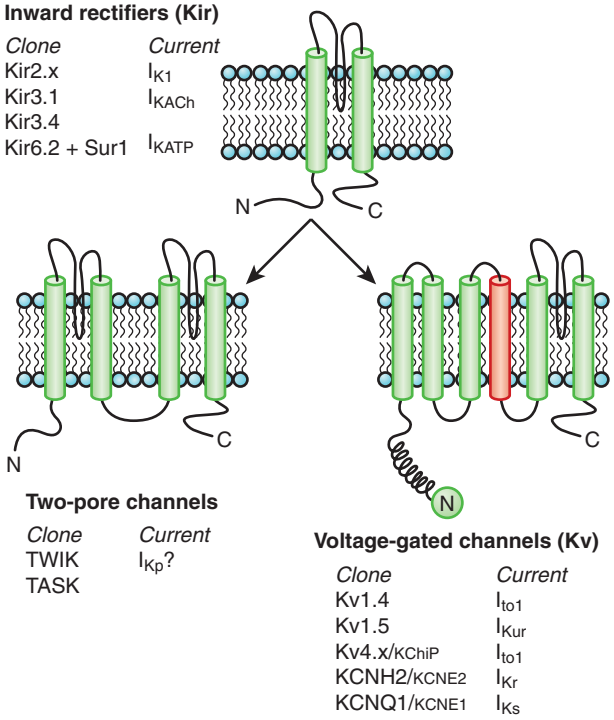

FIGURE 3-7 Evolutionary relationships of families of potassium (K) channels in the mammalian heart. The predicted transmembrane topology of the three subclasses are shown. *Top,* inward rectifier (Kir). *Left bottom,* twin pore K. *Right bottom,* voltage-gated (Kv) channels. Gene duplication events involving Kir channels likely produced the twin-pore and Kv channel gene products in this illustration. Examples of specific channels in each class that are expressed in the human heart are given.

Shaker because of its response to ether anesthesia. The gene that caused the Shaker phenotype was isolated by positional cloning and encoded a voltage-dependent K (Kv) channel.[18] Since the original cloning of the Shaker K channel (Kv1.x), a number of K channel genes in the same or closely related gene families have been isolated (Kv1.x to Kv11.x). The voltage-dependent K channels that have been identified in the mammalian heart are shown in Figure 3-7. The voltage-dependent K channels, which are structurally similar to a single domain of the Na channel or the Ca channel, are composed of six membrane-spanning segments, including a highly basic S4 segment. The cytoplasmic half of the S6 membrane–spanning repeat appears to mediate drug blockade of voltage-gated K channels, analogous to regions of the Na channel that bind local anesthetics. Similar to Kir channels, Kv channels must tetramerize to form the intact channel and are typically associated with ancillary subunits. Within a subfamily of K channels (e.g., Kv1.x), subunits may hetero-multimerize, but it is believed that assembly does not occur across subfamilies. It seems likely that two rounds of gene duplication generated Ca and Na channels from the less complex Kv structure. It is possible that a more straightforward gene duplication of an inward rectifier channel produced the third type of K channel, the two-pore K^+-selective channel (see Figure 3-7).

The cDNAs that encode the α-subunits of the K channel are sufficient to generate K^+-selective currents, but a number of ancillary subunits that modify channel function (Kvβ, KCNE, KChIP) have been identified. A family of related proteins (Kvβ1 to Kvβ3) modulates the function of Kv channels. The β-subunits bind to the amino terminus of Kv α-subunits that modify their function in an isoform-specific fashion (for review see reference 19). The crystal structure of Kvβ2 complexed with the amino terminus of Kv1.1 has been solved,[20] and it has been suggested that it functions as an oxidoreductase. Indeed, Kvβ1.2 has been shown to confer oxygen sensitivity to Kv4.2 channels. A recently described, unrelated family of proteins, KChIPs, that contain Ca^{2+}-binding EF hand motifs modulate the function of the members of the Kv4 family, which suggests the possibility that more than one type of ancillary subunit can interact with Kv4 channels. The molecular details of the interaction of KChIP and Kv4 subunits are still being studied (Figure 3-8, *left*).

Still other K channel ancillary subunits are transmembrane proteins that are predicted to have the ability to not only alter channel gating but, in some cases, also influence channel pore properties. Most relevant to the heart are the gene products of *KCNE1* (minK) and *KCNE2* (MiRP-1), which are thought to coassemble with KvLQT1 (*KCNQ1*)[21,22] and HERG (*KCNH2*) to form

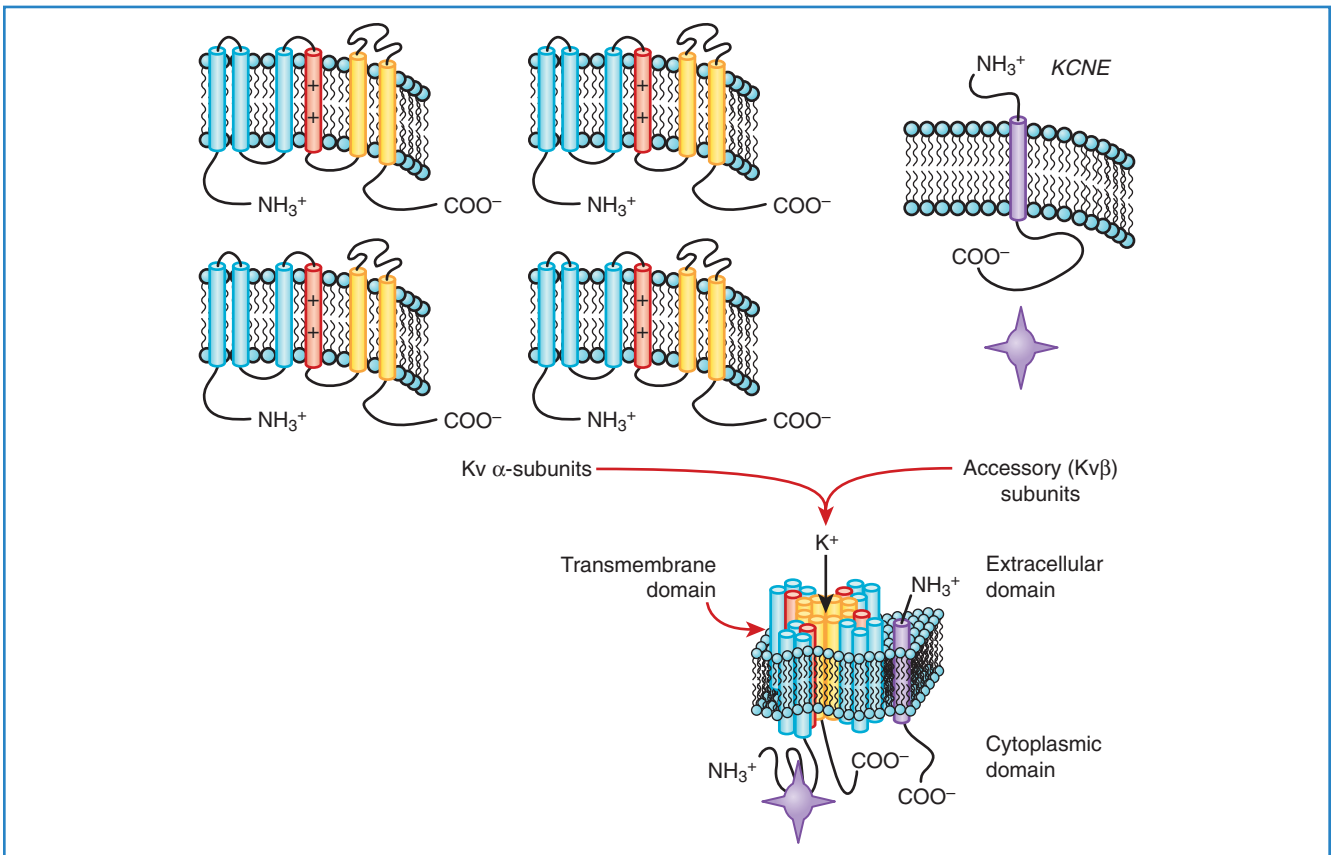

FIGURE 3-8 Potassium (K) channels are multi-subunit complexes. α-Subunits are the major, pore-forming subunits. Transmembrane segments are represented by cylinders; the *red cylinders* are the voltage sensors, and the *yellow cylinders* line the ion conductive pore. At least three types of accessory subunits are found in the heart. Kvβ associates with the amino terminal section of Kv1 α-subunits and the carboxyl terminus of Kv4 α-subunits. KChIPs are Ca^{2+}-binding ancillary subunits that associate with the amino terminus of Kv4 α-subunits. Kvβ- and KChIP-subunits increase the current density when co-expressed with Kvα-subunits and modify gating. The gene products of *KCNE1* (minK) and *KCNE2* (MiRP-1) are believed to be transmembrane proteins. *KCNE1* has been shown to influence the ion-conductive pathway of the I_{Ks} channel. Many other proteins may modulate K channel function.

the two components of the delayed rectifier current I_{Ks} and I_{Kr}, respectively (see Figure 3-8, *right*, and see below). α-Subunits, which by themselves are not functional (e.g., Kv9.x), may modulate the function of other Kv α–encoded channels.

In response to a depolarizing voltage pulse, K channels, like other voltage-gated ion channels, undergo a series of conformational changes that alter function. The S4 membrane–spanning repeats are critical components of the activation gating machinery. Many K channels (like Na and Ca channels) close in the face of continued depolarization; that is, they inactivate. The molecular basis of inactivation, however, is mechanistically heterogeneous. The first type of inactivation to be understood in molecular detail in K channels validated a scheme, referred to as the *ball-and-chain* mechanism, proposed by Armstrong[23] In an elegant series of experiments, Aldrich and coworkers demonstrated the "ball" role of the amino terminus of the Shaker K channel in the inactivation process that they called *N-type* (because it involves the amino terminus).[24,25] After channel activation by a depolarizing stimulus, the amino terminus binds to and plugs the cytoplasmic mouth of the channel pore, thus terminating the K^+ flux (see Figure 3-7, *bottom*). Channels that have the amino terminus removed fail to undergo this type of inactivation, but it can be restored if a peptide that resembles the amino terminal ball is added to the cytoplasm of the cell.[25] A second form of inactivation (carboxyl-terminal, or C-type) involves the outer mouth of the channel pore and amino acid residues in S6 and in the P segment. It has been suggested that C-type inactivation of the channel protein resembles the closing of a camera shutter; that is, it involves constriction of the outer pore of the channel.

K channels serve multiple roles in the maintenance of normal cardiac electrophysiology. Of the multiple subtypes (voltage-gated, inward-rectifier, twin-pore), voltage-dependent K channels underlie both the transient outward (sometimes called *A-type*) current and the delayed rectifier current in the heart. The transient outward K current activates and inactivates rapidly and is a critical determinant of phase 1 repolarization of the ventricular action potential (see Figure 3-1). The two components of the transient outward current in the heart are a Ca^{2+}-independent K current (I_{to1}) and a Ca^{2+}-dependent current (I_{to2}). The latter is a K current in some species and a chloride (Cl) current in others. The channels that encode cardiac I_{to1} not only vary among species but may vary regionally in the ventricle as well. Kv1.4 is a minor, but important, component of I_{to1} in some species, including humans. However, in the human ventricle, I_{to1} is primarily encoded by Kv4.3, which recovers from inactivation much faster than do homomeric Kv1.4 channels. Indeed, the Kv1.4 channel recovers so slowly (2 to 3 seconds) that it cannot be a significant component of the cardiac I_{to1} at physiologic heart rates. However, it is possible that hetero-multimerization of Kv1.4 with other Kv1 family genes and/or coassembly with β-subunits could alter the kinetics of the current. Another argument against Kv1.4 as the major component of cardiac I_{to1} is the insensitivity of expressed Kv1.4 to blockade by low-dose flecainide (10 μM), whereas expressed Kv4 and native cardiac I_{to1} are both flecainide sensitive. The Kv4 family of genes is expressed in relative abundance in the mammalian heart—Kv4.3 in larger mammalian ventricles, such as dog and human, and Kv4.2 in rodent ventricle. Data suggest that Kv1.4 mRNA and protein are also present in mammalian ventricular myocytes and that a physiologic correlate of Kv1.4-based I_{to1} may be a slowly recovering transient outward current in the subendocardium of the human ventricle.

The ultrarapidly activating delayed rectifier current (I_{Kur}), which is primarily found in the atrium in human heart (and throughout rodent heart) is generated by Kv1.5, although other rapidly activating delayed rectifiers may be encoded by genes in the Kv3 family in the atria of some species. A close correspondence exists between the biophysical and pharmacologic properties of I_{Kur} in human atrial myocytes and Kv1.5. Furthermore, Kv1.5 protein and mRNA have been observed in human atrial and ventricular tissues, and Kv1.5-specific antisense oligonucleotides suppress I_{Kur} in atrial myocytes. The restricted expression of Kv1.5 in atrium makes it an attractive pharmacologic target for the treatment of supraventricular arrhythmias.

The delayed rectifier K current (I_K) plays a major role in terminating repolarization in the cells of large mammalian hearts. I_K is a composite current made up of a rapid component (I_{Kr}) and a slow component (I_{Ks}). Definition of the genetics of LQTS clarified the molecular basis of both components of the delayed rectifier. MinK (*KCNE1*) was initially considered a "minimal K channel" that encoded a current that resembled I_{Ks}. Subsequently, positional cloning identified the disease gene in chromosome-11 linked LQTS as *KvLQT1*[26] (Kv7.1), but the current encoded by *KCNQ1* was a functional orphan, not resembling any known cardiac K current. However, the co-expression of *KCNQ1* and *KCNE1* generated a current with a much closer resemblance to native I_{Ks} than to either of the subunits expressed alone.[21,22] An alternatively spliced variant of *KCNQ1* is expressed in the heart and exerts a dominant negative effect on I_{Ks} in vitro; thus, native I_{Ks} may be regulated, in part, by the extent of such alternative splicing.

Long QT genetics identified *KCNQ1* as the gene underlying I_{Ks}, and HERG (Kv11.1) encoded by *KCNH2* underlying I_{Kr}.[27] I_{Kr} exhibits a number of unusual physiologic properties, which when disrupted (by mutations in *KCNH2*, by hypokalemia, or by drug blockade) disrupt normal repolarization. With depolarizations to progressively more positive potentials, activating I_{Kr} actually decreases. This "inward rectification" is a manifestation of the very rapid inactivation that HERG channels undergo once they are open. The extent of this fast inactivation increases at positive potentials and with lower extracellular K^+. The latter explains the decrease in I_{Kr} (causing action potential and QT prolongation) observed in hypokalemia. Further, when the action potential enters phase 3, channels recover from inactivation, transitioning rapidly to an open (conducting) state before closing relatively slowly. Thus, as the action potential begins to repolarize, I_{Kr} increases markedly, further accelerating repolarization. HERG channels are blocked by many drugs, including methansulfonanilide drugs such as dofetilide and sotalol. As with *KVLQT1*, HERG may coassemble with other proteins to produce native I_{Kr}. Database mining for homologs of *KCNE1* uncovered a related gene, *MiRP-1* (encoded by *KCNE2*), in the same locus on chromosome 21 that encodes a topologically similar, small polypeptide with an extracellular amino terminus, a single transmembrane domain, and a cytoplasmic carboxy tail (see Figure 3-8). When *MiRP-1* is co-expressed with HERG voltage-dependent gating, single-channel conductance, regulation by K^+_o, and biphasic blockade by methansulfonanilides are all modified. However, the role of *MiRP-1* in native cardiac I_{Kr} remains uncertain. HERG exists in alternatively spliced forms, but the role that different splice variants play in generating the native current is uncertain. As with *KCNH2* and *KCNQ1*, mutations in *KCNE1* and *KCNE2* have been linked to LQTS.

Another major class of K channel genes expressed in the heart encodes inwardly rectifying currents. The term *inward rectification* is used to describe the fact that these channels pass current more readily into cells than out of them (Figure 3-9). All inward rectifiers share a similar topology, with only two membrane-spanning repeats and a pore loop, and they must tetramerize to form the intact channel. In 1998, a major advance in ion channel biology occurred with the determination of the structure of a bacterial inward rectifier channel from *Streptomyces lividans*, called *KcsA*.[28] The structure is remarkable in that it accounts for a number of the physical principles that underlie K^+-selective permeation.[29] The crystal structure demonstrated that the linker between the two membrane-spanning domains (P segments) form the outer mouth of the channel and that the K channel signature sequence forms the selectivity filter. High rates of ion flux are maintained despite the relatively avid binding of K^+ due to the presence of the two K^+ ions in the selectivity region that repel each other. The second membrane-spanning repeat, analogous to the S6 of Kv channels, forms much of the inner mouth of the channel, where antiarrhythmic drug binding is expected to occur (Figure 3-10). Models of other K channels have since been generated by structural or homology approaches. A *KCNQ1* structural model has been proposed, based on homology to other K channel structures, and this, in turn, has been used to identify the key structural features of interactions between *KCNQ1* and *KCNE1*.

The inward rectifier family of cDNAs is designated Kir, and its members are part of the *KCNJ* superfamily. I_{K1}, the current that is important in maintaining the resting membrane potential and in facilitating terminal repolarization, is encoded by the Kir2.x subfamily (*KCNJ2* and *KCNJ4*). It is likely that Kir2.1 encodes I_{K1} in the human ventricle, but other Kir2 isoforms have been detected in the heart.

The other inward rectifiers in the heart exhibit specialized functions, as in response to neurohormones or metabolic stress. The Kir3 family of inward rectifier channels underlies the K current that is coupled to the M2 muscarinic (I_{KACh}) or A1 adenosine receptors (I_{KAdo}) in nodal cells and atria. I_{KACh} (I_{KAdo}) is a heteromultimer of the products of two different genes in the Kir3 family, initially referred to as *GIRK* (G-protein inwardly rectifying K channel, Kir3.1) and *CIR* (cardiac inward rectifier, Kir3.4) (*KCNJ3* and *KCNJ5*). Kir3.1 and Kir3.4 tetramerize in a 2:2 ratio to form the I_{KACh} channel protein, which encodes a current that is directly activated by the β-subunit and γ-subunit of an inhibitory G-protein (Figure 3-11, *left*). I_{KACh} is the primary mediator of the negative chronotropic and dromotropic effects of parasympathetic activation in the heart.

Another inward rectifier, I_{KATP}, links electrical signaling to the metabolic state of the myocyte. Changes in the activity of I_{KATP} profoundly influence the electrophysiology of the heart in ischemia and play a key role in the endogenous cellular mechanism that limits the injurious effect of myocardial ischemia known as *ischemic preconditioning*.[30] I_{KATP} is believed to be a hetero-multimeric channel complex comprising a tetrameric assembly of Kir6.2 channels (*KCNJ8* and *KCNJ11*) at its core surrounded by four sulfonylurea receptor subunits (SUR2A, Figure 3-11, *right*). SUR2A, encoded by *ABCC9*, is an ATP-binding cassette (ABC) protein that imparts sensitivity to sulfonylureas and K channel openers such as pinacidil and chromakalim to the channel complex.

A third structural class of K channels has been observed in the heart. These channels comprise four transmembrane segments and two pore loops. TASK (twin-pore acid-sensitive K channel) is a member of the twin-pore family of K channel genes that is highly expressed in the heart. The TASK channel exhibits little intrinsic voltage or time dependence and therefore most resembles a background current. The precise role for this channel and other members of the twin-pore family in cardiac myocytes is unknown.

I_f "Funny" or Pacemaker Current

I_f is a current that contributes to diastolic depolarization in pacemaking cells in the heart. The current is found in many cell types, but its features are variable. For example, I_f is present in ventricular myocytes, but its activation voltage is so negative that it is not likely to be of physiologic significance.[31] I_f activates slowly on hyperpolarization and deactivates rapidly with depolarization. I_f supports a mixed monovalent cation (Na^+ and K^+) current with a reversal potential of −20 to −30 mV. The current is highly regulated: β-Adrenergic stimulation increases I_f and hastens diastolic depolarization. A family of genes topologically similar to voltage-dependent K channels and related to cyclic nucleotide–gated channels in photoreceptors in the retina appears to encode I_f. A number of hyperpolarization-activated cyclic nucleotide–gated channels (HA-CNG) have been cloned from the heart, and several exhibit the general features of I_f in cardiac pacemaking cells. It has been suggested that I_f itself is a composite current with fast and slow components encoded by *HCN2* and *HCN4*, respectively. Support for I_f as the pacemaker current in the heart also comes from a genetic model of bradycardia in zebrafish with a dramatically reduced I_f.

Electrogenic Transporters

Na^+-Ca^{2+} Exchanger

The Na^+-Ca^{2+} exchanger is an electrogenic ion transporter that exchanges three Na^+ ions for one Ca^{2+}. The highest levels of exchange activity have been observed in the heart. The cardiac NCX, a transmembrane glycoprotein, was originally proposed to have 11 or 12 transmembrane repeats based on hydropathy analysis. More recent mutagenesis data challenge the original topologic models and instead suggest that there may be only nine transmembrane segments[32] (Figure 3-12). NCX contains two membrane-spanning domains, with the first five transmembrane segments being separated from the remainder by a large cytoplasmic loop that makes up about half of the molecule. The intracellular loop contains domains that bind Ca^{2+} and the endogenous NCX inhibitory domain, XIP.

Na^+-Ca^{2+} exchange is an electrochemical process during which three Na ions are exchanged for one Ca ion. The exchange is thus electrogenic (i.e., generates a current). Ion exchange can occur in either direction. With each heart beat, cytosolic [Ca^{2+}] is released from sarcoplasmic reticulum (SR) stores, primarily by the ryanodine release channel RyR2. [Ca^{2+}]$_i$ rises from the resting level of less than 100 nM to approximately 1 μM with each cardiac cycle. Under normal physiologic conditions, outward Ca^{2+} flux through the NCX (generating an inward current) and Ca^{2+} reuptake into the SR by the SR Ca^{2+}-ATPase (SERCA) are the major mechanisms of restoration of normal diastolic [Ca^{2+}]. NCX is sensitive to the cytoplasmic concentrations of Ca^{2+} and Na^+, which determine the exchanger activity and the potential at which the exchange reverses direction. The NCX current is time independent and largely reflects changes in intracellular Ca^{2+} during the

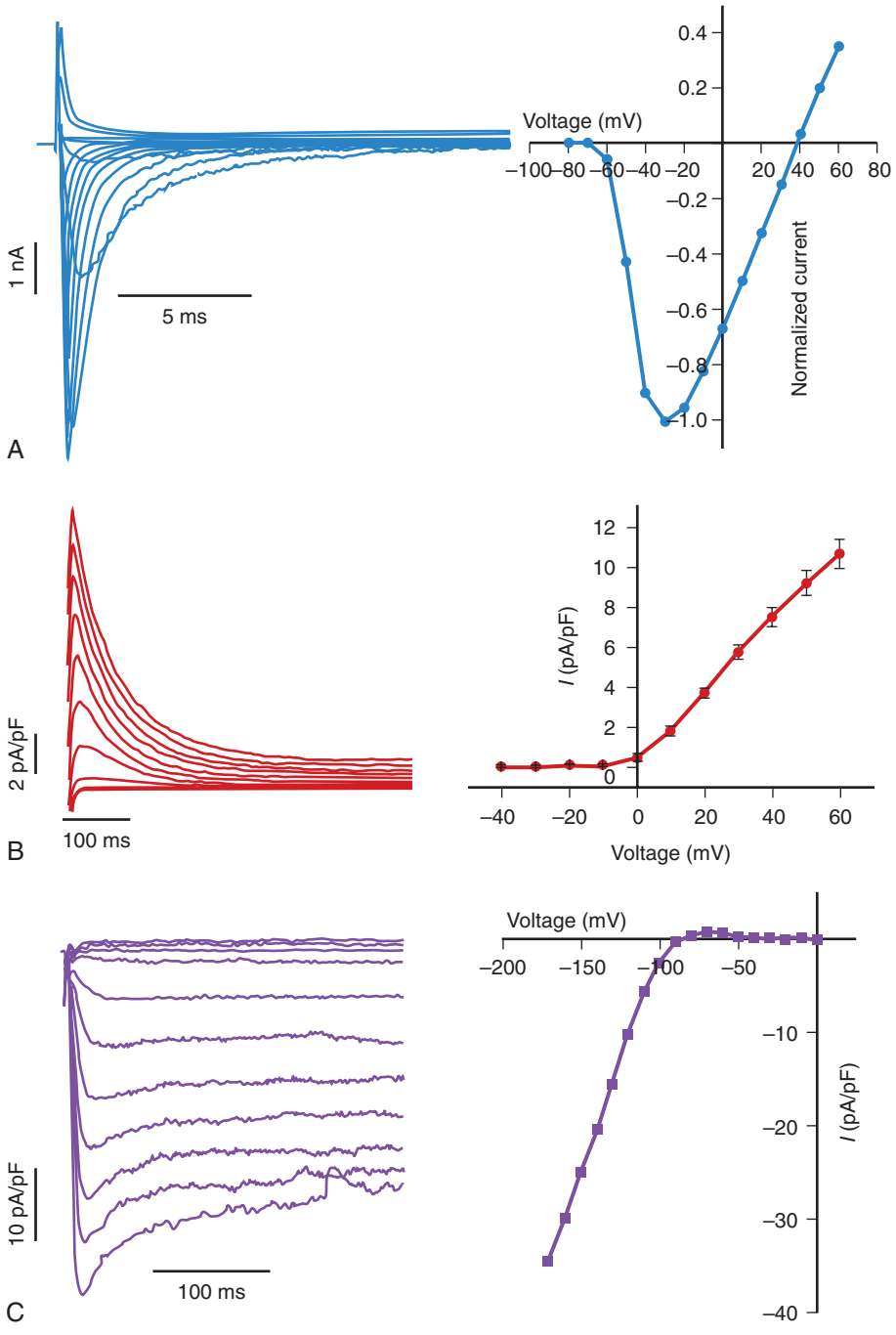

FIGURE 3-9 Properties of ionic currents in the heart. **A,** Whole-cell sodium (Na) currents recorded from mammalian tissue culture cells transfected with the complementary DNA that encodes the human cardiac Na channel (NaV1.5). By convention, the current is inward (Na^+ ions flowing into the cell) and therefore negative. The current activates rapidly on depolarization of the cell membrane and rapidly closes in the face of maintained depolarization of the cell membrane, a gating process referred to as *inactivation*. This channel passes current in both inward and outward directions, depending on transmembrane voltage. **B,** Whole-cell recording of the transient outward K current (I_{to1}) recorded from a human ventricular myocyte. The current activates rapidly with depolarization and then inactivates. The current flow is preferentially in the outward direction (positive current) and is referred to as *outward rectification*. **C,** Whole-cell current flow through inward rectifier potassium (K) current (I_{K1}). I_{K1} channels are activated at rest and close with membrane depolarization. At voltages where the channel prefers to open (voltages negative to the Nernst potential for K^+), there is little time-dependent current decay or inactivation. Current preferentially flows in the inward (negative) direction; thus, this channel and all of the channels in the Kir family are referred to as *inward rectifiers*.

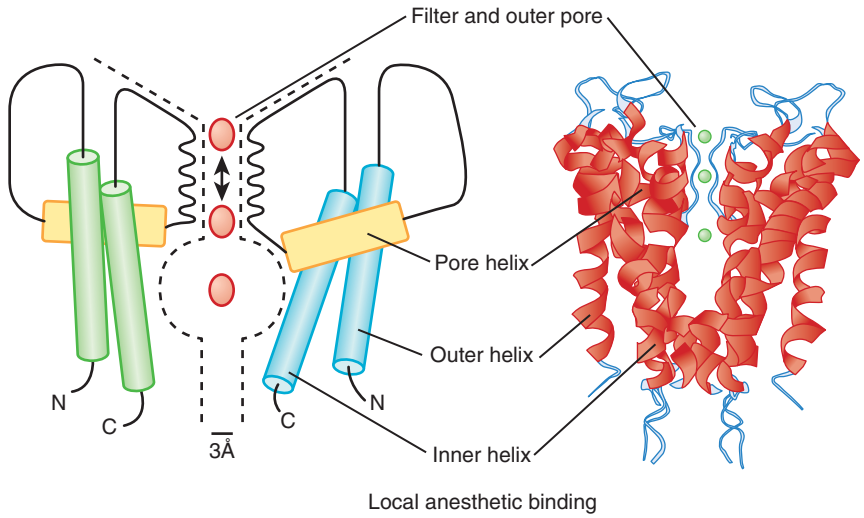

FIGURE 3-10 Crystal structure of the KcsA bacterial inward rectifier potassium (K) channel. *Left*, Representation of the major features of the structure of the bacterial channel, KcsA. Each of the four channel subunits (only two are shown in this figure) contain two α-helical membrane-spanning repeats, a pore helix, and the K channel signature sequence that forms the K^+-selective pore. *Right*, The structure of KcsA. The peptide backbone is rendered in a ribbon format. The features of the permeation pathway include the presence of two to three K^+ ions in the pore with ion-ion repulsion, which facilitates high rates of ion transport and a large inner vestibule comprising the carboxyl terminal portion of the outer, or M2, helix. The M2 helix corresponds to the S6 domains of voltage-dependent K channels that mediate antiarrhythmic drug binding.

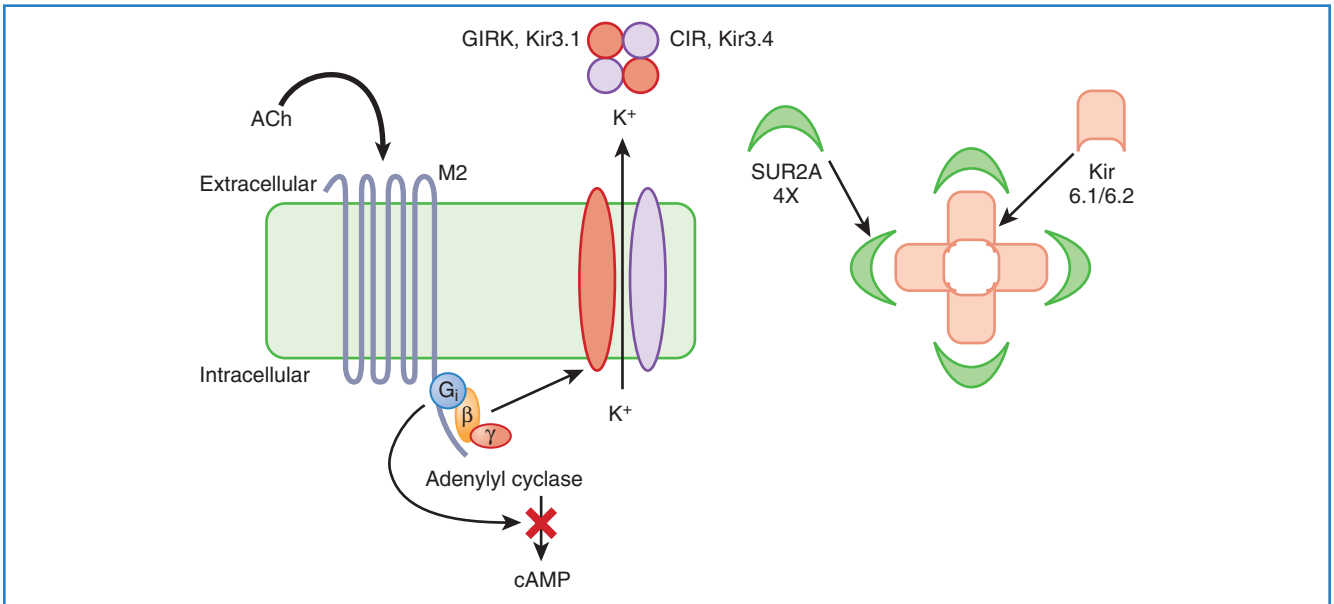

FIGURE 3-11 Subunit structure of I_{KACh} and I_{KATP}. *Left*, IKACh is a glycoprotein-coupled channel that is activated by acetylcholine (*ACh*) binding to M2 cholinergic receptors in the heart. The channel is separate from the receptor and is formed by the heterotetramerization of two inward rectifier potassium (K) channel subunits, Kir3.1 (*GIRK1*) and Kir3.4 (*CIR*), in a 1:1 stoichiometry. *Right*, I_{KATP} is formed by the hetero-octomeric assembly of the adenosine triphosphate–binding cassette protein, the sulfonylurea receptor (*SUR2A*), and the inward rectifier Kir6.2.

action potential. Thus, NCX has an important effect on membrane voltage both at rest and during activation of the myocyte. At highly depolarized potentials, reverse mode Na^+-Ca^{2+} exchange (Ca^{2+} influx, net outward current) can occur; however, the role of reverse mode exchange in initiating SR Ca^{2+} release and contraction is uncertain.

Increases in intracellular Ca^{2+} shift the reversal potential of NCX in the positive direction and therefore increase the driving force for the inward exchanger current. The inward NCX current will depolarize the membrane toward the threshold for firing an action potential and thus is potentially arrhythmogenic. The NCX current is an important component of the inward current (transient inward current, I_{TI}) that underlies delayed afterdepolarizations (DADs). DADs are spontaneous membrane depolarizations from rest after complete repolarization of the action potential. DADs are usually not present under physiologic conditions but are favored by conditions that increase the SR Ca^{2+} load, such as rapid firing rates, digitalis intoxication, or ischemia/reperfusion. Under these conditions, spontaneous SR Ca^{2+} release occurs, which then increases NCX and probably other Ca^{2+}-dependent currents, which, in turn, results in membrane depolarization. DADs may produce arrhythmias in two ways. First, if DADs are of sufficient amplitude, they may trigger an action potential. Second, even if DADs are below the threshold for generation of an action potential, they may affect the excitability of the cell, slowing conduction in the myocardium.

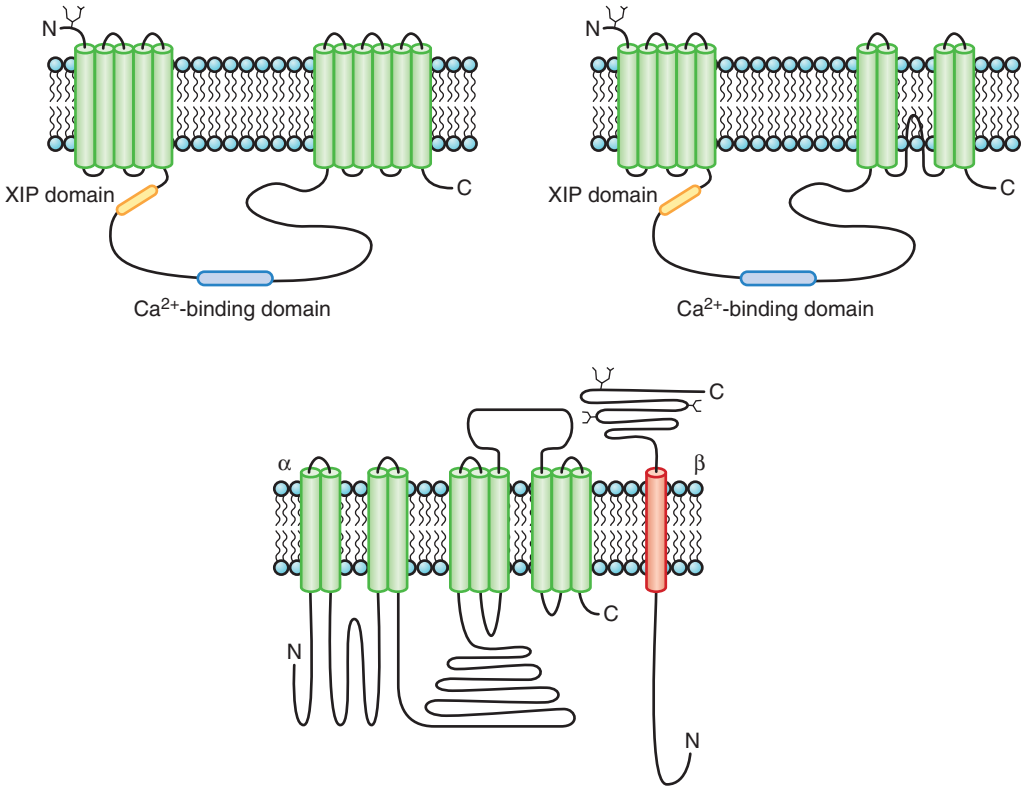

FIGURE 3-12 Subunit structure and transmembrane topology of the sodium-calcium (Na^+-Ca^{2+}) exchanger (NCX) and the sodium-potassium (Na^+-K^+) adenosine triphosphatase (ATPase) (Na pump). *Top*, Two alternative transmembrane topologies for the NCX. A large cytoplasmic loop is a crucial to physiologic regulation of the exchanger and contains Ca^{2+} and inhibitory peptide (*XIP*)–binding domains. *Bottom*, The Na^+-K^+-ATPase is a heteromeric assembly of a large α-subunit and a smaller single membrane–spanning repeat β-subunit.

Na^+-K^+-ATPase

The Na^+-K^+-ATPase, or Na pump, is responsible for establishing and maintaining major ionic gradients across the cell membrane. The Na pump belongs to the widely distributed class of P-type ATPases that are responsible for transporting a number of cations. The P-type designation of this family of enzymes refers to the formation of a phosphorylated aspartyl intermediate during the catalytic cycle. The Na^+-K^+-ATPase hydrolyzes a molecule of ATP to transport two K^+ into the cell and three Na^+ out and is thereby electrogenic, generating a time-independent outward current. The Na^+-K^+-ATPase is oligomeric and consists of α-, β- and, possibly, γ-subunits. There are four different α- and three distinct β-isoforms (for review see reference 38). The evidence that the γ-subunit is part of the complex comes from photoaffinity labeling with ouabain derivatives and immunoprecipitation studies. The γ-subunit belongs to a family of small membrane-spanning proteins, including phospholemman, which support ionic fluxes.

Na^+-K^+-ATPase isoforms exhibit tissue-specific distributions. The $\alpha_1\beta_1$ isoform is broadly distributed, α_2-containing isoforms are preferentially expressed in the heart, skeletal muscle, adipocytes, and brain, α_3 is predominantly a brain isoform, and α_4 is found in abundance in the testis. The structural diversity of the Na^+-K^+-ATPase comes from variations in α- and β-genes, splice variants of α-subunits, and the promiscuity of subunit associations, which are all themes that also underlie the diversity of ion channels, particularly K channels. The α-subunit is catalytic and binds digitalis glycosides in the extracellular linker between the first and second membrane-spanning regions (see Figure 3-12, *bottom*). α_1-, α_2-, and α_3-subunits are found in the human heart. In the rat, α_3-subunits bind glycosides three orders of magnitude greater affinity than do α_1-containing pumps. However, in humans, the binding affinities of the α subunits are far less variable. The β-subunits are essential for normal pump function and influence the Na^+ and K^+ affinities of the α-subunits and also serve as chaperones ensuring the proper trafficking of the α-subunit to the sarcolemma. Only β_2 appears to be present in significant quantities in the human heart.

In heart failure, the density of the Na^+-K^+-ATPase decreases as assessed by ^{3}[H]-ouabain binding. The decrease occurs without any significant impact on the inotropic effect of digitalis glycosides in the human ventricular myocardium. However, the reduction in the density of the Na pump may influence the electrophysiology of cardiac myocytes and their response to an extracellular K^+ load, as might occur in ischemia.

Molecular Basis of Activation and Recovery of the Heart

In normal sinus rhythm, cardiac activation begins in the SA node, the specialized collection of pacemaking cells in the roof of the right atrium between the crista terminalis and the right atrial–superior vena cava (RA-SVC) junction. SA nodal cells undergo spontaneous depolarization, repetitively activating the rest of the heart. As a result of the lower density of the inwardly rectifying K current (I_{K1}) and the presence of a hyperpolarization-activated

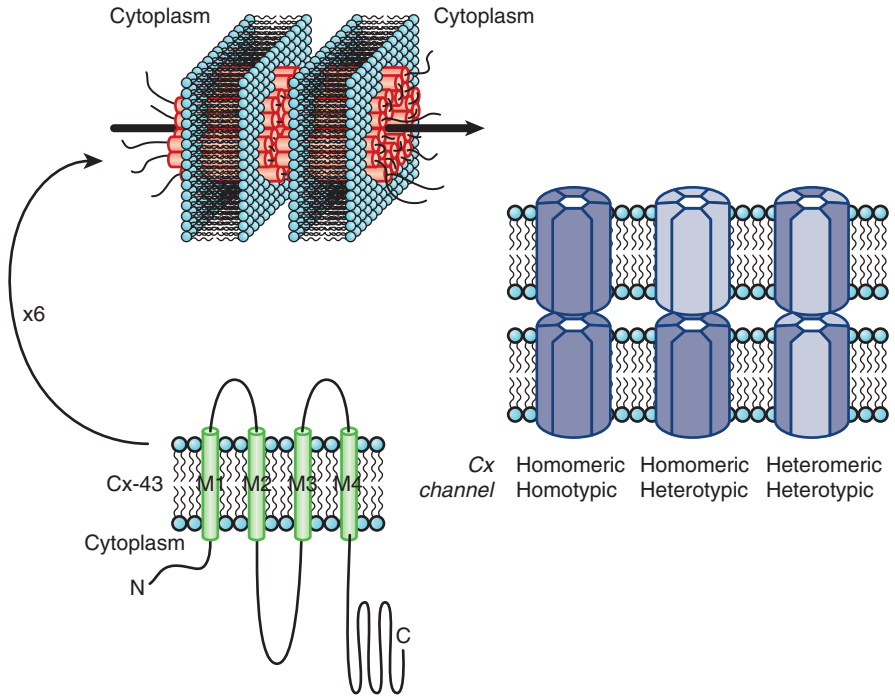

FIGURE 3-13 Subunit structure of the gap junction channels. *Left,* Gap junction channels are intercellular ion channels composed of two hemichannels or connexons in adjacent cells. Each hemichannel is composed of six subunits or connexins composed of four highly conserved membrane-spanning repeats, two conserved extracelluar loops and a more divergent cytoplasmic loop, and amino and carboxyl termini. *Right,* Different subtypes of connexins may assemble to form channels that are homomeric (single type of connexin in each connexon), heterotypic (different connexins in each connexon), or heteromeric heterotypic, in which more than one type of connexin is present in each connexon.

pacemaker current, I_f, the resting membrane potentials of SA and AV nodal cells are considerably less negative than those of atrial or ventricular muscle cells. The result is a continuous, slow depolarization of the membrane potential; thus, nodal cells do not have a true resting potential, but the maximum diastolic potential is never more negative than –60 mV.

The aggregate activity of I_f and diminished I_{K1} slowly depolarizes the nodal cell until ~–40 mV when Ca currents are activated, hastening the rate of rise of the action potential. First, the transient T-type Ca current ($I_{Ca,T}$) is activated, driving the membrane potential toward E_{Ca}; then, the longer-lasting, dihydropyridine-sensitive L-type Ca current ($I_{Ca,L}$) is activated. Simultaneously, the more slowly activating outward K currents (delayed rectifier, I_K) are activated, hindering the movement of the membrane potential toward E_{Ca}. Ultimately, Ca currents inactivate, and the membrane potential moves back toward E_K, turning off I_K and activating I_f and then starting the cycle again. Current continues to flow through the electrogenic Na^+-Ca^{2+} exchanger throughout the cycle, and the magnitude and direction of this current depend on the membrane potential as well as intracellular Ca^{2+} and Na^+ concentrations. It has recently been demonstrated that cyclic variations of submembrane Ca^{2+} concentration drive the activation of the Na^+-Ca^{2+} exchanger during diastole to act in concert with ion channels to confer pacemaking activity on SA node cells, a phenomenon known as the *calcium clock*.[33a]

The synchronization of the somewhat diffuse pacemaking cells that comprise the sinus node is through gap junction channels comprising Cx-40 and Cx-43. The activity of pacemaking cells is synchronized by a process of mutual entrainment, whereby each of the cells in the nodal syncytium constantly modulates the discharge frequency of the other cells.

As in the case of the nodal cell action potential, the highly orchestrated activity of a number of ionic currents inscribes the muscle cell action potential. A prototypical action potential from atrial and ventricular myocytes with a schematic of the trajectory of the underlying ionic currents is shown in Figure 3-13. The action potential is divided into five phases: (1) Phase 0 is rapid upstroke; (2) phase 1 is early repolarization; (3) phase 2 is the plateau; (4) phase 3 is late repolarization; and (5) phase 4 is the resting potential or, in the case of a nodal action potential, diastolic depolarization (see Figure 3-1). Unlike in the case of nodal cells, a true resting potential can be defined in cardiac muscle cells, and it is ~90 mV, close to E_K; thus, at rest, cardiac muscle cells are mostly permeable to K^+ due to the activity of I_{K1}.

Under normal conditions, muscle cells are stimulated by spontaneously occurring impulses generated in pacemaking tissue. When this stimulus moves the membrane voltage positive to threshold (~–65 mV), an action potential is initiated. Depolarization beyond the threshold explosively activates Na channels, producing an enormous (~400 pA/pF) but transient (1 to 2 ms) current, driving the membrane voltage toward E_{Na} (+65 to +70 mV). Although, Na channels are, by far, the most numerous in the myocyte cell membrane, their activity is fortunately short lived, as otherwise the transmembrane Na^+ gradient would be quickly exhausted. The Na current quickly dissipates by inactivation, and the membrane must repolarize to its resting potential before Na channels recover from inactivation and again become available to activate. Thus, the time and the voltage dependence of the availability of the Na current is the basis of refractoriness in cardiac muscle.

The upstroke of an action potential falls short of E_{Na} because of the inactivation of the Na current and the activation of a K current and, additionally, in some cases a Ca^{2+}-dependent Cl^- current (I_{to2}) that in concert produce rapid membrane repolarization to ~+10 mV (phase 1). The Ca^{2+}-independent transient outward K current (I_{to1}) activates as Na channels inactivate. Activation of I_{to1} is rapid (~10 ms), and this current decays over 30 to 40 ms at physiologic temperatures. The density of I_{to1} is less than

5% of the Na current; thus, inactivation of the Na current is the main reason for early repolarization, while I_{to1} is an important determinant of the membrane voltage at the end of phase 1. In canine ventricular myocytes, I_{to2} is a prominent current during phase 1 of the action potential; however, its role in human myocytes is uncertain.

Depolarization of the membrane potential activates a number of other currents, albeit more slowly than in the case of the Na current and I_{to1}. In ventricular myocytes, $I_{Ca,L}$ is activated and accounts for the major depolarizing current during the action potential plateau or phase 2. This current is the main route for Ca^{2+} influx and triggers Ca^{2+}-induced Ca^{2+} release (CICR) from the SR to initiate contraction. $I_{Ca,L}$ tends to depolarize the cell membrane, and delayed rectifier repolarizing K currents that are active during the plateau and phase 3 oppose this action. Activation of delayed rectifier K currents and inactivation of Ca currents serve to terminate the plateau phase and begin phase 3 or late repolarization. In atrial tissue, I_{Kur}, is a prominent delayed rectifier that is an important determinant of the plateau height and aids in the termination of the plateau. Delayed rectifiers (especially I_{Kr}) are important in terminating the plateau but are limited in their ability to restore the normal resting potential because they deactivate at voltages less than −40 mV. Final repolarization is mediated by the outward component of I_{K1} even in atrial cells where the density of I_{K1} is small compared with that of ventricular myocytes.

Cellular and Molecular Basis of Cardiac Electrophysiology

Excitability and Propagation

Many of the electrophysiological properties of the heart are direct consequences of ionic current activity during the action potential. Cardiac cells are excitable because the action potential, which is a typical, regenerative response, is elicited if the membrane potential exceeds a critical threshold. Action potentials are regenerative because they can be conducted over large distances without attenuation. Action potentials generated in the sinus node serve to excite adjacent atrial muscle and, thus, the remainder of the heart under normal conditions.

In atrial and ventricular muscle at rest, the membrane is most permeable to K^+, which is the result of the activity of I_{K1}. Excitability in cardiac muscle is primarily determined by the availability of I_{Na}. In response to an external stimulus, either from adjacent cells or an artificial pacemaker, depolarization of muscle cells occurs. If the depolarization is sufficient and raises the membrane potential above a critical value, known as the *threshold potential*, Na channels open, depolarize the membrane, and initiate an action potential. In pacemaking tissues such as the sinoatrial or AV node, the Na current is absent, and excitability is mediated by activation of Ca currents. The consequence is a higher threshold for activation and a slower rate of rise (~1 to 10 V/sec versus hundreds of V/sec in muscle) of phase 0 of nodal cell action potentials.

Propagation of a wave of excitation in a homogeneous cable-like medium is continuous and obeys the laws of cable theory (see Passive Membrane Properties and Cable Theory). In such a preparation, the maximal upstroke velocity of the action potential $(dV/dt)_{max}$ is an indirect measure of depolarizing ionic current and conduction velocity.[34] A continuous cable model is a structural oversimplification of all cardiac tissue with the possible exception of normal papillary muscles. Continuous propagation of excitation waves is not characteristic of cardiac tissue. Due to the structural and functional complexities of the myocardium, discontinuous conduction (see below) is the rule.

A feedback exists between network properties (cell-to-cell coupling via gap junctions) and active membrane properties (ionic currents) in propagation in cardiac tissue preparations.[3] Under conditions of normal cellular coupling, fluctuations in local conduction velocity, action potential shape, and ionic current flow are small. However, with cellular uncoupling—such as that which accompanies ischemia—the interaction between intercellular conduction and active membrane properties assumes greater significance. In cardiac muscle, the Na current is the main determinant of membrane depolarization and local circuit current. When cells are uncoupled, discontinuity of conduction increases, the delay between activation of cells increases, and the Na current may sufficiently inactivate such that the currents active during the plateau (i.e., L-type Ca current) of the action potential become essential for driving excitatory current through gap junctions. In both experimental models and computer simulations, blocking the L-type Ca current was shown to reduce the safety factor for conduction and to lower the intercellular resistance that produces conduction blockade. Cellular uncoupling and discontinuous conduction has important implications for safety factors for the propagation of the impulse. With moderate cell-to-cell uncoupling in simple models of propagation, conduction is slower but has a higher safety factor. However, with more significant uncoupling, the transmitted current is so small that insufficient Na current is recruited to initiate an action potential.

The most important causes of discontinuous conduction in the heart are macroscopic discontinuities in cardiac tissue. Such anatomic discontinuities exist in all regions of the heart and are especially prominent in the trabeculated portions of the atria and ventricles, the layers of the left ventricular wall, and the Purkinje-muscle junction. Two-dimensional models of macroscopic discontinuities highlight the importance of the change in geometry and, consequently, the dispersion of the local circuit current in the characteristics of propagation and blockade at such sites. Analogous to the feedback between cellular coupling and ionic currents, a feedback occurs between the current to load mismatch produced by the tissue architecture and the ionic current flow. Small current-to-load mismatches (larger strand-to-sheet ratio) are associated with minor conduction delays across the tissue discontinuity. In contrast, tissue architecture characterized by a large current-to-load mismatch (narrow strand into a large sheet) is associated with significant conduction delay and blockade across the discontinuity that can be produced by either Na or Ca channel blockers. Thus, the L-type Ca current is essential for impulse propagation through cardiac tissue with structural discontinuities. Such structural discontinuities are present in the normal heart but may be much more prominent in the aged or diseased (e.g., hypertrophied or infarcted) myocardium.

Repolarization and Refractory Periods

Refractoriness of tissue, a consequence of the long duration of the cardiac action potential, allows only gradual recovery of excitability. Refractoriness is essential to the normal mechanical function of the heart, as it permits relaxation of cardiac muscle prior

to the next activation. Refractoriness of cardiac muscle is classified as either absolute or relative: The former occurs immediately after phase 0 and during the plateau and no stimulus, regardless of its strength, can re-excite the cell; the latter occurs during phase 3, when the cell is excitable but the stimulus strength for activation exceeds that at rest (Figure 3-14). The molecular basis of refractoriness is the lack of availability of depolarizing current (Na current in muscle) because repolarization to negative potentials is required for channels to recover from fast inactivation and thus be available to pass the excitatory current. The duration of refractoriness of any cardiac tissue thus depends on the complement of ion channels (and, in particular, depolarizing currents) expressed. When the depolarizing current becomes available to activate, outward currents (typically delayed rectifier K currents) increase the stimulus strength required to reach the threshold, making the tissue relatively refractory (compared with the rested state).

Under some conditions, some tissues, particularly Purkinje fibers, may exhibit supranormal excitability. This phenomenon occurs at the end of repolarization and is the result of reactivation of Na currents at a time when the membrane potential of the heart cell is closer to the threshold for reactivation than when the cell has fully returned to rest. Supranormal excitability is one contributor to the vulnerable period of the cardiac cycle; it contributes by increasing the likelihood of re-excitation during terminal repolarization (when heterogeneity of action potential durations are most likely to support re-entry).

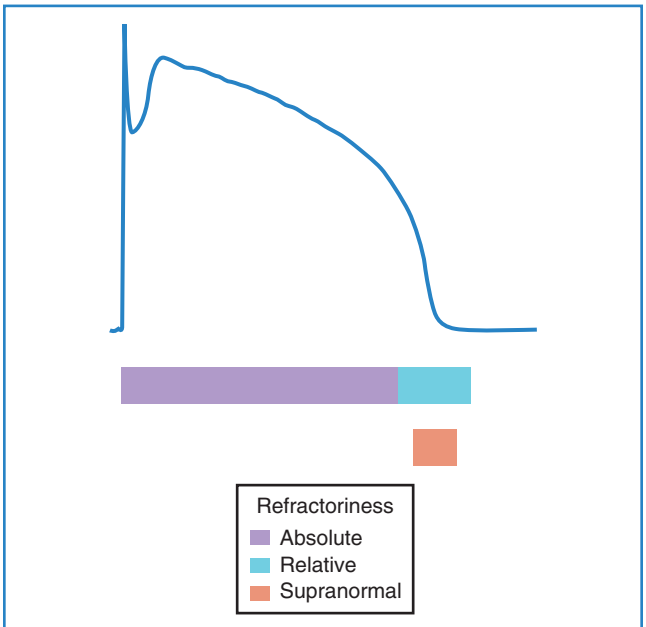

FIGURE 3-14 Absolute and relative refractory periods in the ventricle. Action potential recorded from a ventricular myocyte. The bars underneath the action potential delineate the periods of *absolute refractoriness*, where no stimulus, regardless of amplitude, can elicit another action potential, and *relative refractoriness*, where a subsequent action potential can be initiated with a high-strength stimulus. Under appropriate circumstances, during the period of relative refractoriness, the cell may exhibit supranormal excitability; that is, a stimulus that is normally subthreshold will elicit an action potential.

Cellular and Molecular Mechanisms Contributing to Cardiac Arrhythmias

Cardiac arrhythmias result from abnormalities of impulse generation, conduction, or both. It is, however, difficult to establish an underlying mechanism for many clinical arrhythmias. Criteria such as initiation and termination with pacing and entrainment are used in the clinical electrophysiology laboratory to make the diagnosis of re-entry in some cases. Even fewer specific tools are available to diagnose non–re-entrant arrhythmias. It is clear that molecular changes in the heart predispose to the development of abnormalities of cardiac rhythm. However, an exclusively molecular approach to understanding the mechanisms of arrhythmia is limited by failure to include the cellular and network properties of the heart. We will attempt to place in context the role of cellular and molecular changes in the development of clinically significant rhythm disturbances. A summary of the cellular and molecular changes that underlie prototypical arrhythmias and their putative mechanisms is provided in Table 3-3.

Alterations in Impulse Initiation: Automaticity

Spontaneous (phase 4) diastolic depolarization underlies the property of automaticity, which is characteristic of cells in SA and AV nodes, the His-Purkinje system, the coronary sinus, and, possibly, pulmonary veins. Phase 4 depolarization results from the concerted action of a number of ionic currents, but the relative importance of these currents remains controversial (Figure 3-15). The inwardly rectifying K current (I_{K1}) maintains the resting membrane potential and resists depolarization; thus, the activity of other currents (e.g., Ca currents) or a reduction of I_{K1} (and other K conductances) must occur to permit the cell to reach the threshold for the firing of an action potential. I_f may play a

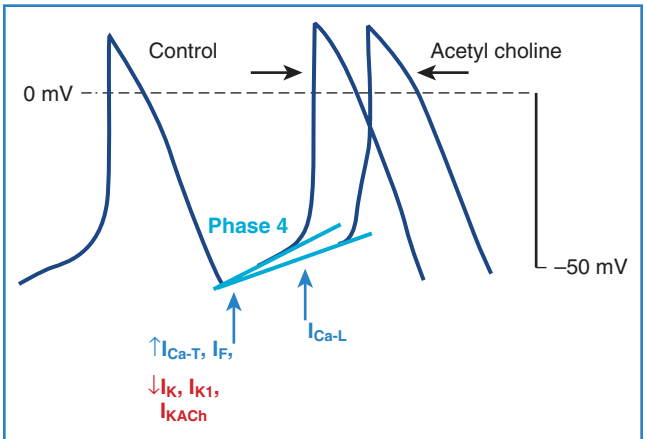

FIGURE 3-15 Nodal action potential and the currents that underlie phase 4 diastolic depolarization. Nodal cells exhibit phase 4 diastolic depolarization that spontaneously brings the cell to threshold, which results in the production of an action potential. Several currents play a role in phase 4, including calcium (Ca) currents (T- and L-types), I_f (or the pacemaker) current, and a reduction in the current flow through several K channels, including I_K, I_{K1}, and I_{KACh}. The rate of phase 4 diastolic depolarization is highly sensitive to the tone of the autonomic nervous system. Cholinergic agonists slow phase 4, whereas sympathomimetics hasten phase 4.

Table 3-3 Arrhythmia Mechanisms

	MOLECULAR COMPONENTS	MECHANISM	PROTOTYPICAL ARRHYTHMIAS
IMPULSE INITIATION			
Automaticity	I_f, $I_{Ca\text{-}L}$, $I_{Ca\text{-}T}$,	Suppression/	Sinus bradycardia
	I_K, I_{K1}	Acceleration	Sinus tachycardia
Triggered automaticity	I_{TI}	DADs	Digitalis toxicity; reperfusion VT, IVR; Idiopathic VT
	$I_{Ca\text{-}L}$, I_K, I_{Na}	EADs	Torsades de pointes
	I_{Na}, $I_{K\text{-}ATP}$		Ischemic VF
EXCITATION			
	$I_{Ca\text{-}L}$	AV conduction block	
	I_{Na}, $I_{Ca\text{-}L}$, K channels	AP prolongation	Polymorphic VT
REPOLARIZATION			
	Ca homeostasis	EADs	Ischemic VT/VF (hypertrophy, HF)
	I_{Na}, $I_{Ca\text{-}L}$, K channels, Ca homeostasis	AP shortening	Atrial fibrillation
MULTICELLULAR			
	Connexins		Uncoupling
	I_{Na}, $I_{K\text{-}ATP}$		Conduction delay or blockade; functional re-entry
CELLULAR COUPLING			
	Extracellular matrix collagen	Re-entry with an excitable gap	Monomorphic VT

DADs, *Delayed after-depolarizations;* EADs, *early after-depolarizations;* VT, *ventricular tachycardia;* IVR, *idioventricular rhythms;* VF, *ventricular fibrillation;* AV, *atrioventricular;* AP, *action potential ;* HF, *heart failure.*

particularly prominent role in the normal automaticity of Purkinje fibers, although this hypothesis is not without controversy. Deactivation of I_K is another mechanism allowing depolarizing currents to move the membrane potential toward the threshold. Ca currents, both the T-type and the L-type, figure prominently in diastolic depolarization and in the upstroke of the action potential in nodal tissue and latent atrial pacemakers. A number of other time-independent currents may play a role in diastolic depolarization and pacemaking activity, including currents through the electrogenic Na^+-K^+-ATPase and the Na^+-Ca^{2+} exchanger and background currents.

The rate of phase 4 depolarization and, therefore, the firing rate of pacemaker cells are dynamically regulated. Prominent among the factors that modulate phase 4 is the tone of the autonomic nervous system. The negative chronotropic effect of activation of the parasympathetic nervous system is the result of the release of acetylcholine that binds to muscarinic receptors, releasing G-protein βγ-subunits that activate a potassium current (I_{KACh}) in nodal and atrial cells (see Figure 3-11). The resultant increase in K^+ conductance opposes membrane depolarization, slowing the rate of rise of phase 4 of the action potential. Agonist activation of muscarinic receptors also antagonizes activation of the sympathetic nervous system through inhibition of adenylyl cyclase, reducing cAMP and inhibiting protein kinase A (PKA). Conversely, augmentation of the tone of the sympathetic nervous system increases myocardial catecholamine concentrations, which activate both α- and β-receptors. The effect of β_1 adrenergic stimulation predominates in pacemaking cells, increasing the L-type Ca current and shifting the voltage dependence of I_f to more positive potentials, thus augmenting the slope of phase 4 and increasing the rate of SA node firing. L-type Ca current density is increased by PKA-mediated phosphorylation, which results in an increase in the rate of rise of phase 4 and the upstroke velocity of the action potential in nodal cells. The positive chronotropic effect of β-adrenergic stimulation has been related to increased subsarcolemmal Ca^{2+} release through the ryanodine receptor (RyR2) accelerating the rate of diastolic depolarization. Enhanced sympathetic nervous system activity can dramatically increase the rate of firing of SA nodal cells producing sinus tachycardia, with rates in excess of 200 beats/min. In contrast, the increased rate of firing of Purkinje cells is more limited, rarely producing ventricular tachyarrhythmia in excess of 120 beats/min.

Normal automaticity may be affected by a number of other factors associated with heart disease. Hypokalemia and ischemia may reduce the activity of the Na–K ATPase, thereby reducing the background repolarizing current and enhancing phase 4 diastolic depolarization. The end result would be an increase in the firing rate of pacemaking cells. Slightly increased extracellular K may render the maximum diastolic potential more positive, thus also increasing the firing rate of pacemaking cells. A greater increase in $[K^+]_o$, however, renders the heart inexcitable by depolarizing the membrane potential and inactivating the Na current.

Sympathetic stimulation explains the normal response of the sinus node to stresses such as exercise, fever, and thyroid hormone excess. Normal or enhanced automaticity of subsidiary latent pacemakers produces escape rhythms in the setting of failure of more dominant pacemakers. Suppression of a pacemaker cell by a faster rhythm leads to an increased intracellular Na^+ load (particularly in cells with a Na^+-dependent action potential) and extrusion of Na^+ from the cell by the Na^+-K^+-ATPase produces an increased background repolarizing current that slows phase 4 diastolic depolarization. At slower rates, the Na^+_i load is decreased as is the activity of the Na^+-K^+-ATPase resulting in a progressively more rapid diastolic depolarization and warm-up. Overdrive suppression and warm-up may not be observed in all automatic tachycardias. For example, functional isolation of the pacemaker tissue from the rest of the heart (entrance blockade) may blunt or eliminate the phenomena of overdrive suppression and warm-up of automatic tissue.

Myocytes in the atrium and the ventricle may exhibit spontaneous activity under pathologic conditions associated with depolarization of the resting membrane potential to levels more positive than –60 mV. The mechanism of spontaneous depolarization in contractile cells is uncertain but is likely to involve the activity of a number of depolarizing and repolarizing currents that, on balance, favor membrane depolarization. Ventricular myocytes do express I_f, although the threshold for activation is well below the resting potential of the cell, so the functional significance of this current is uncertain. Currents that mediate the upstroke of the action potential of abnormally automatic cells depend on the diastolic potential. At more negative diastolic potentials, abnormal automaticity can be suppressed by Na channel–blocking drugs. At more positive diastolic potentials (>–50 mV), Na channel blockers are ineffective, whereas Ca channel blockers suppress abnormal automaticity, implicating the L-type Ca channel in the upstroke in this setting.

Abnormally automatic cells and tissues are less sensitive to overdrive suppression than are cells and tissues that are fully polarized with enhanced normal automaticity. However, in situations where cells may be sufficiently depolarized to inactivate the Na current and limit the intracellular Na^+ load, overdrive suppression may still be observed due to increased intracellular Ca^{2+} loading. Such Ca^{2+} loading may activate Ca^{2+}-dependent K conductances (favoring repolarization) and promote Ca^{2+} extrusion through the Na^+-Ca^{2+} exchanger and Ca channel phosphorylation, increasing Na^+ load and thus Na^+-K^+-ATPase activity. The increase in intracellular Ca^{2+} load may also reduce depolarizing L-type I_{Ca} by promoting Ca^{2+}-induced inactivation of the Ca current.

Abnormal automaticity may underlie atrial tachycardia, accelerated idioventricular rhythms (IVRs), and ventricular tachycardia that is particularly associated with ischemia and reperfusion. It has also been suggested that injury currents at the borders of ischemic zones may depolarize adjacent nonischemic tissue causing predisposition to automatic ventricular tachycardia.

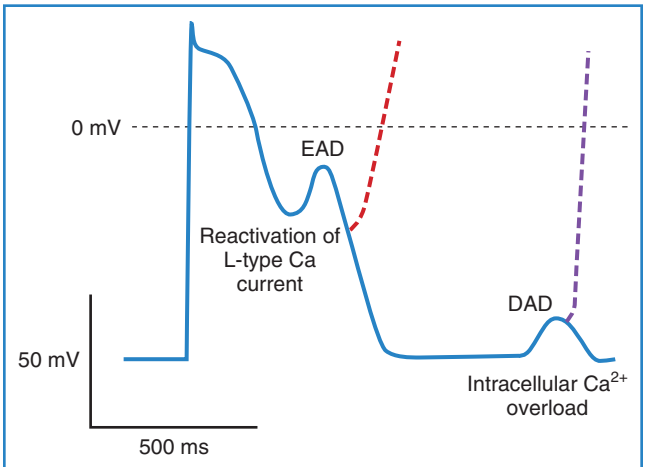

FIGURE 3-16 Early and delayed after-depolarizations. Interruptions of repolarization before its completion are referred to as *early after-depolarizations* (*EADs*). Most EADs, especially phase 2 and early phase 3, are believed to result from reactivation of the L-type calcium (Ca) current and perhaps the sodium-calcium (Na-Ca) exchanger current. Later phase 3 EADs may also involve reactivation of Na currents. After-depolarizations that occur after the completion of repolarization are referred to as *delayed after-depolarizations* (*DADs*). The mechanism of DAD involves intracellular Ca^{2+} overload and oscillatory release of Ca^{2+} from the activation of a number of Ca^{2+}-dependent conductances by the sarcoplasmic reticulum.

After-Depolarizations and Triggered Automaticity

Triggered automaticity or activity refers to impulse initiation that is dependent on after-depolarizations (Figure 3-16). After-depolarizations are membrane voltage oscillations that occur during EADs or following DADs an action potential.[35]

In the early 1970s, DADs were experimentally observed in Purkinje fibers exposed to toxic concentrations of digitalis glycosides. The cellular feature common to the induction of DADs is the presence of increased Ca^{2+} load in the cytosol and SR. Inhibition of the Na-K-ATPase by digitalis glycosides will increase Ca^{2+} load by increasing intracellular Na^+, which is exchanged for Ca^{2+} by the Na^+-Ca^{2+} exchanger. Increased $[Ca^{2+}]_i$ activates a transient inward current, I_{TI}, that depolarizes the cell. The ionic basis of I_{TI} is controversial but likely results from electrogenic currents through the Na^+-Ca^{2+} exchanger and/or Ca^{2+}-activated depolarizing currents.

Inhibition of the Na^+-K^+-ATPase by digitalis glycosides facilitates, but is not necessary for creating, the Ca^{2+} overload that predisposes to DADs. Catecholamines and ischemia sufficiently enhance Ca^{2+} loading to produce DADs. The presumed mechanism of cytosolic Ca^{2+} increase and DADs with catecholamine stimulation is an increase in transmembrane Ca^{2+} flux through L-type Ca^{2+} channels. Catecholamines may also enhance the activity of the Na^+-Ca^{2+} exchanger, thus increasing the likelihood of DAD-mediated triggered activity. Elevations in intracellular Ca^{2+} in the ischemic myocardium are also associated with DADs and triggered arrhythmias. Accumulation of lysophosphoglycerides in ischemic myocardium with consequent Na^+ and Ca^{2+} overload has been suggested as a mechanism for DADs and triggered automaticity. Cells from damaged areas or surviving the infarction may display spontaneous release of Ca from the SR, and this may generate "waves" of intracellular Ca^{2+} elevation and arrhythmias.

The duration of the action potential is a critical determinant of the presence of DADs. Longer action potentials associated with more transarcolemmal Ca^{2+} influx are more likely to be associated with DADs. If I_{TI} underlies at least part of the DAD, then the voltage dependence of the transient inward current should be reflected in the voltage dependence of DADs. Indeed, at membrane voltages where I_{TI} is near its maximum, DADs exhibit the largest amplitude. Importantly, stimulation of the experimental preparation at fast rates increases the size of the DAD and the presence of triggered activity, likely a function of frequency dependent loading of the SR with Ca^{2+}.

Mutations in the cardiac ryanodine receptor (*RYR2*), the SR Ca^{2+} release channel in the heart, have been identified in kindreds with the syndrome of catecholamine-stimulated polymorphic ventricular tachycardia (CPVT) and ventricular fibrillation with short QT intervals. It seems likely that perturbed $[Ca^{2+}]_i$ changes in the relationship between SR Ca^{2+} load and the threshold for Ca^{2+} release, and thus perhaps DADs, contribute to the arrhythmias characteristic of this syndrome. Indeed, murine models of CPVT demonstrate adrenergically mediated arrhythmias, with DADs in vitro. It is likely that some ventricular tachycardias that complicate digitalis intoxication are initiated by triggered activity. It has also been suggested that DADs underlie some forms of

idiopathic ventricular tachycardia, particularly from the right ventricular outflow tract (see Table 3-3). In a recent study, flecainide has been demonstrated to inhibit Ca^{2+} from RyRs in a murine model of CPVT, and preliminary data suggest efficacy in patients with refractory symptoms.

The other type of after-depolarizations, EADs, occur during the action potential and interrupt the orderly repolarization of the myocyte. They have been classified as phase 2 and phase 3, depending on when they occur, and the subclassification may have mechanistic implications. Recent experimental evidence suggests a previously unappreciated interrelationship between intracellular calcium loading and EADs. Cytosolic calcium may rise when action potentials are prolonged. This, in turn, appears to enhance the L-type Ca current (possibly via calcium-calmodulin kinase activation), further prolonging the duration of the action potential as well as providing the inward current driving EADs. Intracellular Ca loading by the prolongation of the action potential may also enhance the likelihood of DADs. The interrelationship among intracellular Ca^{2+} and delayed and early afterdepolarizations may be one explanation for the susceptibility of hearts that are Ca loaded (e.g., in ischemia or congestive heart failure) to develop arrhythmias, particularly on exposure to drugs that prolong the action potential.

The plateau of the action potential is a time of high membrane resistance when there is little current flow. Consequently, small changes in either repolarizing or depolarizing currents can have profound effects on the duration and profile of the action potential. The ionic mechanisms of phase 2 and 3 EADs and the upstrokes of the action potentials they elicit may differ. At the depolarized membrane voltages of phase 2, the Na current is inactivated, and EADs can result from reactivation of the L-type Ca current. Although the available data are inadequate, it has been suggested that current through the Na-Ca exchanger and possibly the Na current may also participate in the inscription of phase 3 EADs. The upstrokes of the action potentials elicited by phase 2 and 3 EADs also differ. Phase 2 EAD-triggered action potential upstrokes are exclusively mediated by Ca currents; these may or may not propagate, but they can substantially exaggerate the heterogeneity of the time course of repolarization of the action potential (a key substrate for re-entry), since EADs occur much more readily in some regions (e.g., Purkinje, midmyocardium) than others (epicardium or endocardium). Action potentials triggered by phase 3 EADs arise from more negative membrane voltages; the upstrokes may be due to both Na and Ca currents and are more likely to propagate.

EAD-triggered arrhythmias exhibit rate dependence. In general, the amplitude of an EAD is augmented at slow rates when action potentials are longer. Pacing-induced acceleration of the heart rate shortens the duration of the action potential and reduces EAD amplitude. Action potential shortening and the suppression of EADs with increased stimulation rate are likely the result of augmentation of delayed rectifier K currents and perhaps the hastening of Ca^{2+}-induced inactivation of L-type Ca currents. Similarly, catecholamines increase the heart rate and decrease the duration of the action potential as well as EAD amplitude, despite the well-described effect of β-adrenergic stimulation to increase L-type Ca current.

A fundamental condition that underlies the development of EADs is action potential prolongation, which is manifest on surface electrocardiogram as QT prolongation. Hypokalemia, hypomagnesemia, bradycardia, and drugs can cause predisposition to the formation of EADs, with drugs being the most common cause.[36] Antiarrhythmics with class IA and III actions produce action potential and QT prolongation intended to be therapeutic but frequently cause proarrhythmia. Noncardiac drugs such as some phenothiazines, some nonsedating antihistamines, and some antibiotics can also prolong the duration of the action potential and cause predisposition to EAD-mediated triggered arrhythmias. Decreased $[K^+]_o$ paradoxically decreases some membrane K currents (particularly I_{Kr}) in the ventricular myocyte, which explains why hypokalemia causes prolongation of the action potential and EADs. Indeed, K infusions in patients with congenital LQTS and drug-induced QT prolongation have been shown to reduce the QT interval.[36a]

EAD-mediated triggered activity likely contributes to the initiation of the characteristic polymorphic ventricular tachycardia—*torsades de pointes*—seen in patients with congenital and acquired forms of LQTS.[36b] In addition, exaggerated dispersion of repolarization is also likely to play a role in both the initiation and the maintenance of torsades de pointes by generating a substrate for functional re-entry (see below). Acquired prolongation of the QT interval most often is the result of drug therapy or electrolyte disturbances, as noted previously. However, structural heart diseases such as cardiac hypertrophy and cardiac failure may also delay ventricular repolarization (so-called *electrical remodeling*) and cause predisposition to arrhythmias related to abnormalities of repolarization.[37,38] The abnormalities of repolarization in cardiac hypertrophy and cardiac failure are often magnified by concomitant drug therapy or electrolyte disturbances.

Abnormal Impulse Conduction: Re-entry

The most common arrhythmia mechanism is re-entry. Re-entry is as much a property of the networks of myocytes as it is a property of individual heart cells. Fundamentally, re-entry is circulation of an activation wave around an inexcitable obstacle. Thus, the requirements for re-entry are two electrophysiologically dissimilar pathways for impulse propagation around an inexcitable region such that unidirectional blockade occurs in one of the pathways and a region of excitable tissue exists at the head of the propagating wavefront.[39] Structural and electrophysiological properties of the heart may contribute to the development of the inexcitable obstacle and of unidirectional blockade. The complex geometry of muscle bundles in the heart and spatial heterogeneity of cellular coupling or other active membrane properties (i.e., ionic currents) appear to be critical.

At the macroscopic level, conduction through normal myocardial tissue is uniformly anisotropic; that is, propagation is continuous or "smooth" but is faster longitudinally than transversely. However, at higher spatial resolution, anisotropy is always non-uniform due to the irregularities of cell shape and gap junction distribution. The conversion of macroscopic anisotropy from being uniform to non-uniform is correlated with an increased predilection to arrhythmias. One well-studied example is the aged human atrial myocardium, in which non-uniform anisotropy, which manifests as highly fractionated electrograms, is associated with lateral uncoupling of myocytes and profound slowing of macroscopic transverse conduction, producing an ideal substrate for the re-entry that may underlie the very common development of atrial fibrillation in older adults.

Anatomically determined, excitable gap re-entry can explain several clinically important tachycardias such as AV re-entry, atrial flutter, and bundle branch re-entry tachycardia. Strong evidence suggests that arrhythmias such as atrial and ventricular

fibrillations associated with more complex activation of the heart are re-entrant. However, this type of re-entry ("functional") is mechanistically distinct from excitable gap re-entry.

Reflection is a type of re-entry that occurs in a linear segment of tissue (e.g., trabecula or Purkinje fiber) containing an area of conduction blockade with re-excitation occurring over the same segment of tissue. If the region of the segment proximal to the area of the blockade is excited, the wave will propagate and generate action potentials up to the area of conduction blockade. Assuming that the area of conduction blockade remains connected to the remainder of the tissue (by gap junctions), it can be electrotonically activated (i.e., by current flow without action potential induction). If the area of conduction blockade is short and the magnitude of the electrotonic current (source) is sufficiently large, the segment of tissue distal to the blocked area (sink) will be excited but with a significant delay. With the appropriate relationship of the electronic current transmitted through the inexcitable segment and the distal excitable tissue, not only can the distal segment be activated, but it can reactivate the proximal segment of muscle by electronic current flow from the distal segment to the proximal segment.

A key feature in classifying re-entrant arrhythmias, particularly for therapy, is the presence and size of an excitable gap. An excitable gap exists when the tachycardia circuit is longer than the tachycardia wavelength (λ = conduction velocity × refractory period), allowing appropriately timed stimuli to reset the propagation in the circuit. Re-entrant arrhythmias may exist in the heart in the absence of an excitable gap and with a tachycardia wavelength nearly the same size as the path length. In this case, the wavefront propagates through partially refractory tissue with no anatomic obstacle and no fully excitable gap. This is referred to as *leading circle re-entry*,[40] which is a form of functional re-entry (re-entry that depends on functional properties of the tissue). Unlike excitable gap re-entry, no fixed anatomic circuit exists in leading circle re-entry, and it may, therefore, not be possible to disrupt the tachycardia with pacing or destruction of a part of the circuit. Furthermore, the circuit in leading circle re-entry tends to be less stable than that in excitable gap re-entrant arrhythmias, with large variations in cycle length and predilection to termination. Atrial flutter represents an example of a re-entrant tachycardia with a large excitable gap not always due to an anatomic constraint but to functional blockade (reflecting the special properties of the crista terminalis discussed above). Experimental data and computer simulations have highlighted the shortcomings of tenets on leading circle re-entry and suggest that spiral waves may better explain some forms of functional re-entry.

Tissue anisotropy is another important determinant of functional re-entrant arrhythmias in ischemic heart disease. Changes in functional and anatomic anisotropy are characteristics of both acute and chronic ischemic heart disease. Within 30 minutes of the onset of myocardial ischemia significant increases in gap junction channel resistance and packing are observed. Further cellular uncoupling and a significant reduction in gap junction protein are observed with 60 minutes of ischemia; this coincides with irreversible cellular damage. These changes exaggerate anisotropic conduction in the ischemic zone.

Chronically ischemic, but not infarcted, myocardium also exhibits ~50% downregulation of gap junction protein (connexin43) with a significant change in the pattern or number of intercalated discs. The suggestion that a 50% reduction in gap junction protein influences anisotropic conduction is supported by measurements of conduction velocities in heterozygous connexin43 knockout mice. The border zones of infarcted myocardium exhibit not only functional alterations of ionic currents but remodeling of tissue and altered distribution of gap junctions in the human ventricle and infarction in canine heart. The alterations in gap junction expression in the context of macroscopic tissue alterations support a role for anisotropic conduction in re-entrant arrhythmias that complicate coronary artery disease. Altered expression of proteins at the intercalated disc is also seen in arrhythmogenic right ventricular dysplasia, a congenital arrhythmia syndrome, and similar mechanisms may thus underlie the development of monomorphic ventricular tachycardia in that entity.

SUMMARY

The science of cardiac electrophysiology, which has its roots in clinical medicine, began, and continues, with descriptions of specific arrhythmia syndromes. Understanding normal and abnormal mechanisms underlying such well-defined syndromes has been a key to the development and widespread implementation of modern therapies such as targeted ablation for focal or re-entrant arrhythmias. Advances in understanding the role of individual current components and their underlying molecular bases in normal and abnormal electrogenesis present us with further opportunities in this direction. Indeed, delineation of specific syndromes such as LQTS or idiopathic ventricular fibrillation, followed by an understanding of their molecular underpinnings, is now poised to further revolutionize arrhythmia therapy: Identification of patients with genetic risk factors for arrhythmias may open the way to effective therapies for patients in these groups. Further understanding of the molecular mechanisms underlying initiation and maintenance of complex and common arrhythmia syndromes such as atrial or ventricular fibrillation may lead to the development of entirely new drugs or nonpharmacologic therapies.

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CHAPTER 4

Mechanisms of Re-entrant Arrhythmias

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The most deadly cardiac arrhythmias result from re-entry, that is, electrical waves that rotate at a high frequency, in a self-sustaining manner. These waves give rise to electrical activity that propagates throughout the ventricles in complex ways. Spontaneous re-entry often occurs as a consequence of a wavebreak produced by the interaction of a propagating wavefront with a functional or anatomic obstacle.[1] It is important to note, however, that the waves that break and initiate re-entry may be generated by electrical pacemaker discharges, triggered activity (i.e., early or delayed after-depolarizations), or another re-entry circuit. The objective of this chapter is to briefly examine the mechanisms of re-entrant arrhythmias. First, the chapter provides a brief historical perspective on the mechanisms of initiation and maintenance of reentry, including those mechanisms thought to underlie tachycardia and fibrillation. Emphasis is placed on the concepts derived from the theory of nonlinear wave of propagation in generic excitable media. This is followed by a summary of the work from the authors' laboratory pertaining to functional re-entry in numerical simulations, engineered mouse models, and larger animals, as well as two-dimensional monolayers of neonatal rat ventricular myocytes. The aim of the chapter is to provide the interested reader with information to enhance didactic, clinical, or research endeavors.

What Is Re-entry?

In its simplest form, re-entry is the circulation of the cardiac impulse around an obstacle; this leads to repetitive excitation of the heart at a frequency that depends on the conduction velocity of the circulating impulse and the perimeter of the obstacle (Figure 4-1).[2] According to the original description by George Mines, which was published in *The Journal of Physiology* in 1913, re-entry occurs around a fixed anatomic obstacle, and the physical disruption of the surrounding circuit will interrupt the activity. As illustrated in Figure 4-1, the initiation of the re-entrant activity depends on the occurrence of a unidirectional block in which activation takes place in only one direction within the circuit.

It is clear from Figure 4-1 that the rotation time around the circuit should be longer than the recovery period of all segments of the circuit. The extra time required for the impulse to successfully complete a rotation may result from a relatively large circuit, a relatively slow conduction velocity of the impulse, or the relatively short duration of the refractory period. Hence, the "wavelength," which may be calculated roughly as the product of the refractory period and the conduction velocity, must be shorter than the perimeter of the circuit. An excitable region will separate the front of the impulse from its own refractory tail (i.e., excitable gap) and re-excitation will ensue.

Re-entry is responsible for various arrhythmias, including supraventricular and ventricular extrasystoles, atrial flutter, atrioventricular (AV) nodal reciprocating tachycardias, supraventricular tachycardias associated with accessory AV pathways, bundle branch ventricular tachycardias, and monomorphic ventricular tachycardias associated with myocardial infarction.

The classic model of anatomically determined re-entry depicted in Figure 4-1 is directly applicable to specific cases of tachyarrhythmias. These include supraventricular tachycardias occurring within the AV node or those using accessory pathways, as well as bundle branch re-entrant tachycardia. However, other types of re-entrant arrhythmias require somewhat different explanations for their mechanisms. For example, the cellular basis of closely coupled ventricular extrasystoles initiated somewhere in the Purkinje fiber network can be explained by the so-called *reflection mechanism* described by Antzelevitch et al in 1980 (Figure 4-2, *A*).[3] Recently, reflection to and from an accessory pathway was shown to be a potential mechanism for the initiation of atrial fibrillation in patients with manifest (pre-excited) Wolff-Parkinson-White (WPW) syndrome.[4]

In the absence of a predetermined obstacle or circuit (Figure 4-2, *B*), however, many tachyarrhythmias that originate in the myocardium (atrial or ventricular) require mechanisms whereby re-entrant activation may occur as vortices of electrical excitation rotating around an area of myocardium. Accordingly, the impulse must circulate around a region of quiescence. In 1977, Allessie et al[5] explained such functionally determined re-entry by proposing the so-called *leading circle hypothesis*, with its two variants of "anisotropic" re-entry described in 1988 by Dillon et al[6] and "figure-of-8" re-entry proposed by El-Sherif[7] in 1985. A somewhat different postulate for vortex-like re-entry, the "spiral wave re-entry" hypothesis, was put forth by Davidenko et al[8] in 1992 and is derived from the theory of wave propagation in excitable media. Spiral wave re-entry attempts to provide a unifying explanation for the mechanisms of monomorphic and polymorphic ventricular tachycardias as well as the mechanism of fibrillation.

Circus Movement Re-entry

Undoubtedly, the concept of circus movement re-entry, in which a cardiac impulse travels around a predetermined circuit or around an anatomic obstacle, may be applied successfully to various clinical situations. Two clear examples of re-entrant

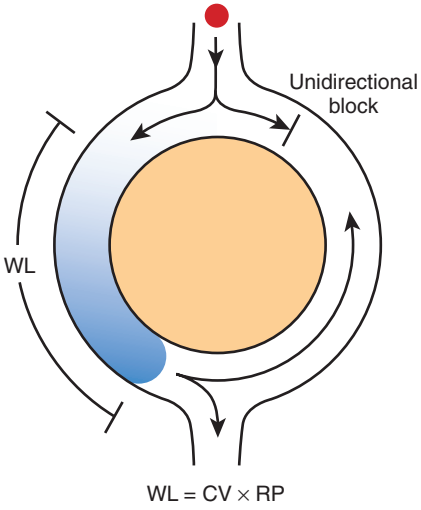

FIGURE 4-1 Circus movement re-entry around a ring of heterogeneous tissue surrounding an anatomic obstacle. re-entry is initiated by the application of a premature stimulus (*red dot*) to the upper branch. As the impulse enters the ring, it encounters tissue recovered on the left side. However, the tissue on the right has not yet recovered from previous excitation (*not shown*), and unidirectional block occurs. As a result, the wavefront begins to rotate around the obstacle. If the pathlength is long enough or the conduction velocity is slow enough, sufficient time is available for recovery on the upper right side of the ring, and sustained re-entry will be initiated. Note that in this hypothetical example, wavelength *(WL)*, which is equal to the product of conduction velocity *(CV)* times refractory period *(RP)*, is much shorter than the path length.

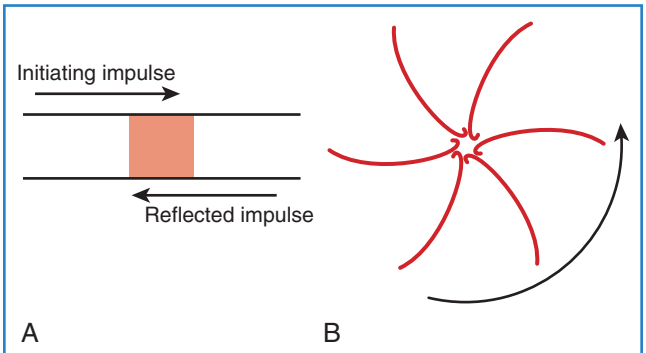

FIGURE 4-2 Two different forms of functional re-entry (i.e., in the absence of an anatomic obstacle). **A,** Reflection, where re-entry occurs over a single pathway in a linear bundle (e.g., a Purkinje fiber) across an area of depressed excitability *(shaded)*. **B,** Functional re-entry in two-dimensional myocardium. *Curved lines* are isochrone lines showing consecutive positions of the wavefront. The *curved arrow* indicates the direction of rotation.

arrhythmias based on the circus movement mechanisms are (1) supraventricular tachycardias observed in patients with WPW syndrome and (2) bundle branch re-entrant ventricular tachycardia, which is more commonly seen in patients with idiopathic dilated cardiomyopathy. All conditions required by the original idea of circus movement re-entry may be found in these two types arrhythmias, as follows:

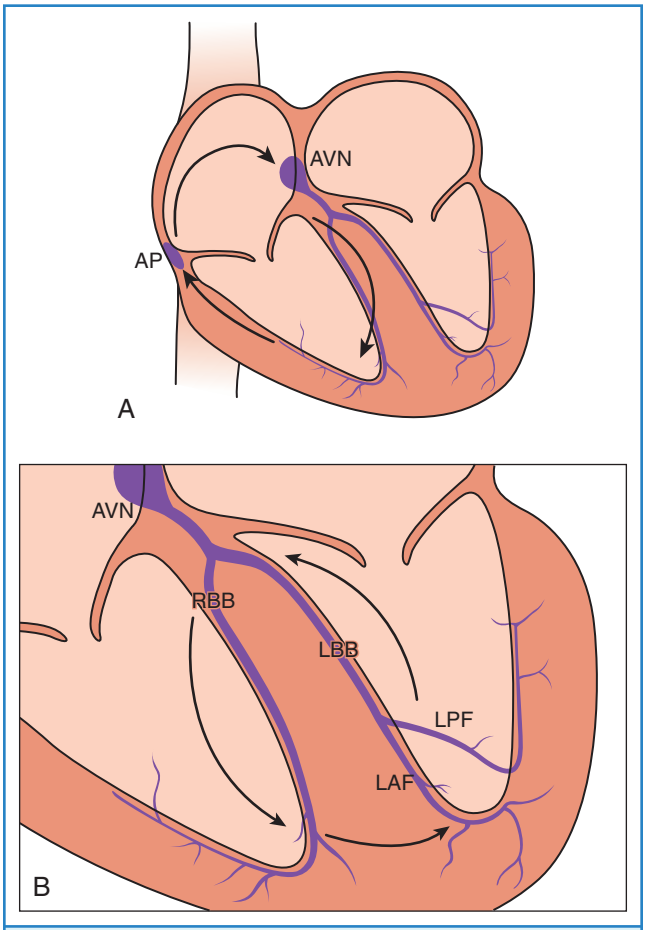

FIGURE 4-3 A, Atrioventricular re-entry in the presence of an accessory pathway *(AP)*. **B,** Bundle branch re-entry using the right bundle branch *(RBB)* and the left anterior fascicle *(LAF)* as the two major components of the circuit. *AVN*, Atrioventricular node; *LBB*, left bundle branch; *LPF*, left posterior fascicle.

1. *An intact predetermined anatomic circuit:* As shown schematically in Figure 4-3, *A*, in the case of WPW syndrome, various types of structures, including the AV node, the His-Purkinje system, ventricular muscle, and an accessory atrioventricular pathway, form the circuit. In the case of bundle branch re-entry (Figure 4-3, *B*), the circuit is composed of the main bundle branches and the interventricular septum. The need for the integrity of the circuit is demonstrated by the fact that its physical interruption at any point leads to the interruption of the arrhythmia.

2. *Unidirectional block before onset of re-entrant activity*: In most cases, unidirectional block occurs in the region of longest refractory period and may occur as a result of various conditions, including the following: (1) increase in sinus rate; (2) rapid or premature atrial pacing; (3) retrograde activation from a ventricular extrasystole; (4) autonomic influences; (5) antiarrhythmic drugs; and (6) ischemia.

3. *Slow conduction in part of the circuit, which facilitates re-entry*: In the case of WPW syndrome, the arrhythmia may begin after significant prolongation of the anterograde AV nodal conduction time. The activation of the ventricles occurs when

both the accessory pathway and atria are recovered. This leads to retrograde activation of the accessory pathway and initiation of re-entrant arrhythmia.

4. *Need for the wavelength of the impulse to be shorter than the length of the circuit*: The presence of an excitable gap has major significance for various reasons: (a) The re-entrant activity will likely be stable in the presence of an excitable gap because the re-entrant wavefront will find only fully recovered tissue in its path; (b) the activity may be entrained or interrupted by means of external stimulation, or both (see later). An externally initiated impulse may invade the circuit during the excitable gap and thus advance the activation front. Depending on the timing or the rate of external stimulation, the wavefront may be premature enough to collide with the repolarizing tail and thus terminate the activity; and (c) agents that prolong the refractory period may not affect the re-entrant process unless the prolongation of refractoriness totally obliterates the excitable gap.

Functionally Determined Re-entry

As Mines noted in 1913, circus movement re-entry results when an electrical impulse propagates around a one-dimensional circuit or ring-like structure. Although the model is entirely applicable to arrhythmias such as those observed in the presence of AV accessory pathways, it may not represent a realistic model for re-entrant arrhythmias occurring in the atria or ventricles. Re-entrant activity may, indeed, occur in the absence of a predetermined circuit—as shown later in 1973 and 1977 by Allessie, Bonke, and Schopman—where the electrical impulse may rotate around a region that is anatomically normal and uniform but functionally discontinuous.

In 1924, Garrey[9] presented in an article in *Physiological Reviews* the first description of re-entrant excitation in the absence of anatomic obstacles in experimental studies on circus movement in the turtle heart. Garrey's observations suggested that point stimulation of the atrium was sufficient to initiate a regular wave of rotation around the stimulus site. Subsequently, in 1946, Wiener and Rosenblueth[10] developed the first mathematical model of circus movement re-entry, which supported waves of rotation around a sufficiently large barrier, but they could not demonstrate re-entry in the absence of an obstacle. This prompted Wiener and Rosenblueth to suggest that perhaps Garrey may have unwittingly produced a transient artificial obstacle near the stimulation site.

The "Leading Circle" Model

In 1973, Allessie, Bonke, and Schopman provided the first direct experimental demonstration that the presence of an anatomic obstacle is not essential for the initiation or maintenance of re-entry. These authors studied the mechanism of tachycardia in small pieces of isolated rabbit left atrium by applying single premature stimuli. Through multiple electrode mapping techniques, they demonstrated, in 1973 and 1977, that the tachycardias were based on rotating waves and suggested that such waves were initiated as a result of unidirectional block of the triggering premature input. Transmembrane potential recordings demonstrated that cells at the center of the vortex were not excited but developed local responses, which led to the development of the "leading-circle" concept of functional re-entry.

According to the leading-circle concept of Allessie and colleagues, in the absence of an anatomic obstacle, the dynamics of re-entry are determined by the smallest possible loop in which the impulse can continue to circulate. Under these conditions, the wavefront must propagate through relatively refractory tissue, in which case no "fully excitable gap" will be present and the wavelength will be very close to the length of the circuit. The leading circle idea paved the way for major advances in the understanding of functional re-entry. It served as a platform for developing a unifying hypothesis (spiral wave re-entry) that explains most of the major properties of functionally determined re-entry, which are commonly observed in normal cardiac muscle in experiments. This includes the phenomenon of re-entry "drift" described by Davidenko et al[8] in 1992 and Pertsov et al[11] in 1993. Re-entry drift results in beat-to-beat changes in the location of the rotation center (see Drifting Vortices and Ventricular Fibrillation).

Anisotropic Re-entry

In 1986, Spach and Dolber[12] implicated microscopic structural complexities of the cardiac muscle in the mechanism of re-entrant activation in both atria and ventricles, particularly in relation to the orientation of myocardial fibers, the manner in which the fibers and fiber bundles are connected to each other, and the effective electrical resistivities that depend on fiber orientation. Because of these structural properties, propagation velocity in the cardiac muscle is three to five times faster in the longitudinal axis of the cells than along the transverse axis. Mapping studies performed by Peters and Wit[13] in 1998, using multiple extracellular electrodes have shown that, in the setting of myocardial infarction, re-entry may occur in the survival epicardial rim of tissue. Under such conditions, the wave circulates around a functionally determined elongated region of block, the so-called *line of conduction block* (Figure 4-4, *A*). Based on the orientation of the line of block, it was thought that anisotropic propagation played a major role both in the initiation as well as in the maintenance of re-entry in ventricular tissue surviving a myocardial infarction (Figure 4-4, *B*). In addition, propagation velocity is exceedingly slow at the edges of the lines of block, which has also been attributed to anisotropic propagation.

Figure-of-8 Re-entry

Figure-of-8 re-entry, described in 1987 by El-Sherif, Gough, and Restivo, has been recognized as an important pattern of re-entry in the late stages of myocardial infarction. In most cases, two counter-rotating waves coexist at a relatively short distance from each other (Figure 4-5). As described for the case of single re-entrant circuits, each wave of the figure-of-8 re-entry circulates around a thin line or arc of block. The region separating the lines of block is called the *common pathway*. A detailed description of the common pathway is of great practical importance, since there is evidence that it could be a strategic region for surgical or catheter ablation in this type of re-entry. In fact, unlike other forms of functionally determined re-entry, figure-of-8 re-entry may, indeed, be interrupted by physical disruption of the circuit. Several studies have attempted to describe the characteristics of propagation in the common pathway. However, the properties of the common pathway are still not clearly defined. It effectively behaves like an isthmus limited by two functionally

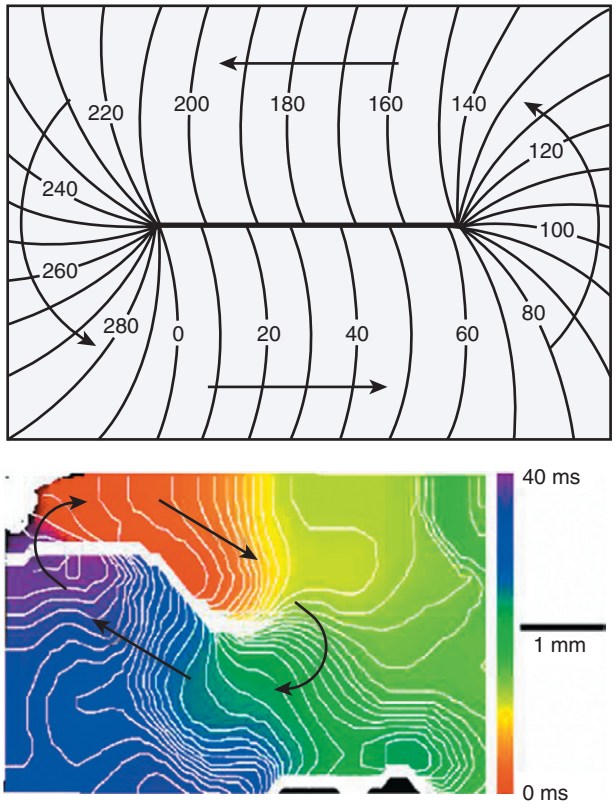

FIGURE 4-4 Anisotropic re-entry around a line of block. *Top panel*, Curved lines are isochrones. The distance between lines denotes velocity of propagation. Velocity is faster in the horizontal direction than around the pivot points. *Bottom panel*, Example of re-entry around a line of block that was recorded in an isolated Langendorff-perfused murine heart with optical mapping. *White lines* are 1-ms isochrones. *Time scale*, 0 to 40 ms.

determined barriers. In addition, there are two wavefronts that interact in the common pathway. As a result, propagation may be determined by a combination of factors other than those analyzed in most experimental studies such as anisotropy. The study of propagation across an isthmus and the influence of wavefront curvature may have significant implications in understanding the properties of the common pathway, as discussed in the next section.

Spiral Wave Re-entry

According to traditional concepts proposed by Allessie and colleagues, circus movement re-entry may be initiated in the heart because block is predetermined by the inhomogeneous functional characteristics of the tissue, whereas spiral waves could be formed in the heart even if cardiac muscle was completely homogeneous in its functional properties as shown by Davidenko et al[8] in 1992, Pertsov et al[11] in 1993, and Winfree[14] in 1998. This is because the initiation of rotating activity may depend solely on transient local conditions (e.g., the conditions created by cross-field stimulation).[1] Moreover, according to the traditional concept of re-entry, the circulation of the activity occurs around an anatomically or functionally predetermined circuit, and the rotating activity cannot drift. In other words, the circuit gives rise to and maintains the rotation. However, spiral waves occur due to initial curling of the wavefront; in fact, the curvature of the wavefront determines the size and shape of the region, called the *core*, around which activity rotates (Figure 4-6). Importantly, the core remains unexcited by the extremely curved activation front and it is readily excitable.[1] This explains the mechanism underlying the drift of spirals.

Modes of Initiation of Spiral Wave Re-entry

In 1946, Weiner and Rosenblueth[10] published a theoretical description of the mechanisms of initiation of flutter and fibrillation in cardiac muscle in the presence as well as in the absence of

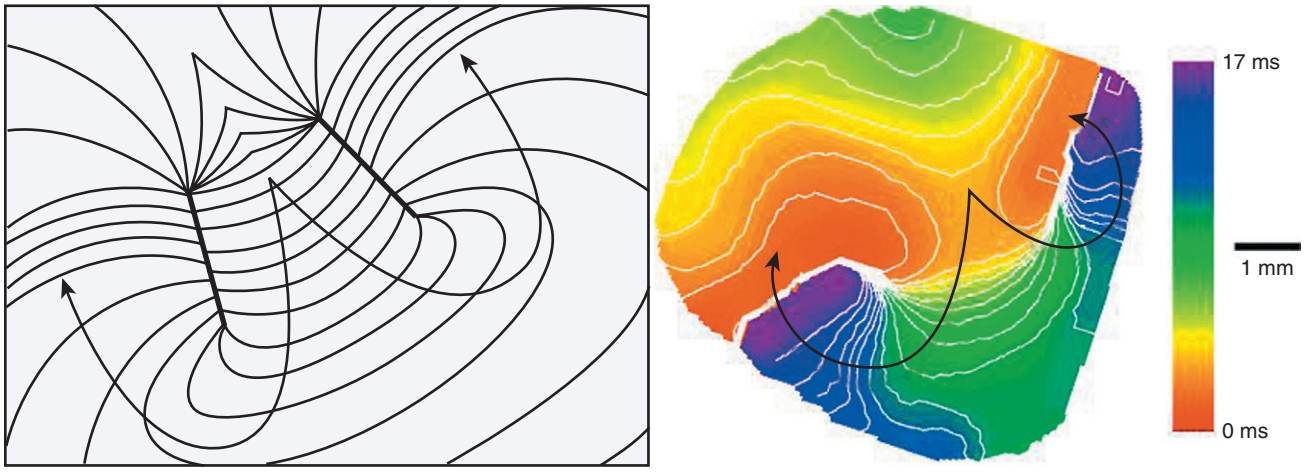

FIGURE 4-5 Figure-of-8 re-entry. *Left panel*, Figure-of-8 re-entry consisting of two counter-rotating wavefronts, one in the clockwise direction and the other in the counterclockwise direction, around their respective lines of block. The wavefronts coalesce in the lower part of the circuits, and they move at varying velocities across the common pathway. *Right panel*, Activation map. Figure-of-8 re-entry recorded in optical mapping of an isolated Langendorff-perfused murine heart. *White lines*, 1-ms isochrones. *Temporal scale*, 0 to 17 ms.

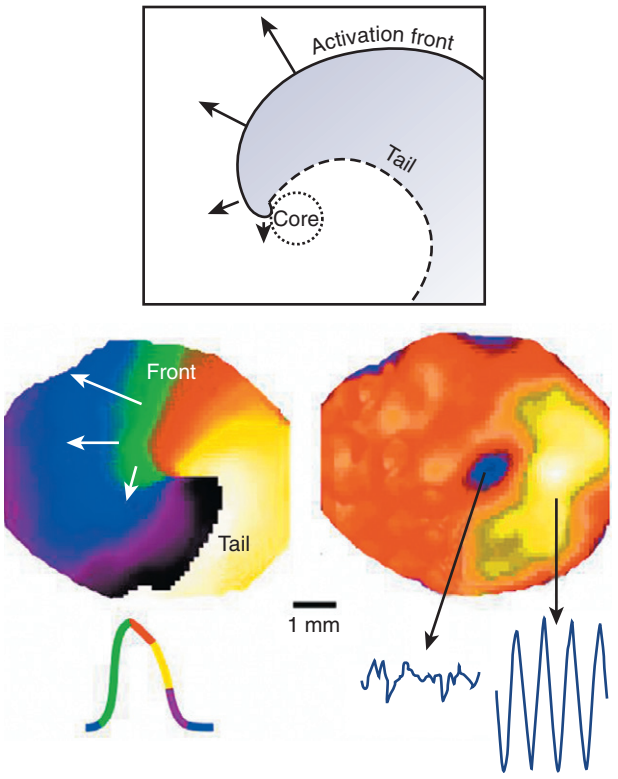

FIGURE 4-6 Spiral wave re-entry. *Top panel*, The activation front has increasing curvature from the periphery to the center. At the tip, the curvature is so extreme that the activation front cannot propagate into the core. Note that the activation front meets its tail of refractoriness (*dotted line*) at a specific point known as the *phase singularity*. *Bottom panel*, *left*, Phase map snapshot of a rotor recorded in an isolated Langendorff-perfused murine heart. The different colors denote the different phases of the action potential: green = upstroke; red, yellow, and purple = repolarization; and blue = resting (*inset*, colored action potential). The site where all the colors converge is the phase singularity. *Bottom panel*, *right*, Fluorescence amplitude map (blue = low, yellow = high) highlighting the core of the rotor of the left panel. The core is delineated in blue, inside which the signal amplitude is much smaller than that recorded away from the core (compare the two 100-ms single-pixel recordings from the core versus those far away).

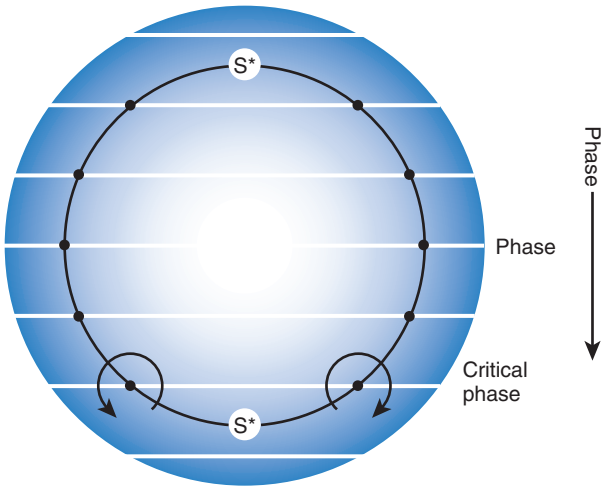

FIGURE 4-7 Winfree's pinwheel experiment. The *circular surface* represents a two-dimensional sheet of cardiac muscle. The *horizontal white lines* indicate different phases of the action potential. The *white circles* represent the critical magnitude *(S*)* of a stimulus applied at the center of the tissue. The *black dots* represent different stimuli occurring at the indicated phases. At the crossing of S* with the critical phase, two counter-rotating vortices emerge.

anatomic obstacles. They proposed that wave rotation around single or multiple obstacles was required for the initiation and maintenance of both types of arrhythmias, which they assumed to result from a single re-entrant mechanism.

More than three decades later, another theory of initiation of vortices in two dimensions was suggested, and it has been supported by experiments in a number of different excitable media. It is based on Winfree's "pinwheel experiment" protocol carried out in 1990.[15] As shown in Figure 4-7, this protocol involves crossing a spatial gradient of momentary stimulus with a spatial gradient of phase (i.e., refractoriness, established by prior passage of an activation front through the medium). In accordance with this theory, when a stimulus of the right size (S*) is given at the proper time, mirror image vortices begin to rotate around crossings of critical contours of transverse gradients of phase and stimulus intensity. On the basis of this theory, a vulnerable domain was described. Its timing occurred just before complete recovery from previous excitation. Thus, with its limits of timing and stimulus intensity, the idea of vulnerable domain was similar to the empirical concept of the vulnerable period. In a 1988 study, Shibata et al[16] demonstrated the application of Winfree's theory to the induction of ventricular fibrillation (VF) in the heart. They concluded that the response to administered shocks during the vulnerable period is a complex one. However, in accordance with theory, during pacing of the ventricles, if a shock of the proper amplitude and delay is applied during the vulnerable period, two counter-rotating vortices can be formed. Thus, as predicted by theory, vortices can be formed even in the normal myocardium. Subsequently, in 1989, Frazier et al[17] used an extracellular recording array with a modification of the pinwheel experiment, the so-called *twin-pulse protocol*, to demonstrate the mechanism of re-entry and fibrillation in the canine heart. They used the term *critical point* to refer to a phase singularity and provided strong support for what is referred to as the *critical point hypothesis for the initiation of vortex-like re-entry and fibrillation.* They also demonstrated that an upper limit of vulnerability for VF exists and that during the vulnerable period, if shock with a strength that is larger than a certain limit is applied, then VF will most likely not be induced.

Another approach for initiating vortices is the cross-field stimulation protocol. This method is different from the pinwheel protocol in that it does not require a large stimulus. As shown in Figure 4-8, in cross-field stimulation, a conditioning stimulus (S1) is used to initiate a plane wave propagating in one direction. Subsequently, a second stimulus, S2, is applied perpendicular to S1 and timed in such a way as to allow interaction of the S2 wavefront with the recovering tail of the S1 wave. The S2 wavefront cannot invade the refractory tissue at the site of the interaction with the S1 wave tail; consequently, a wavebreak or phase singularity is formed at the end of the S2 wave, and rotation about this point occurs.

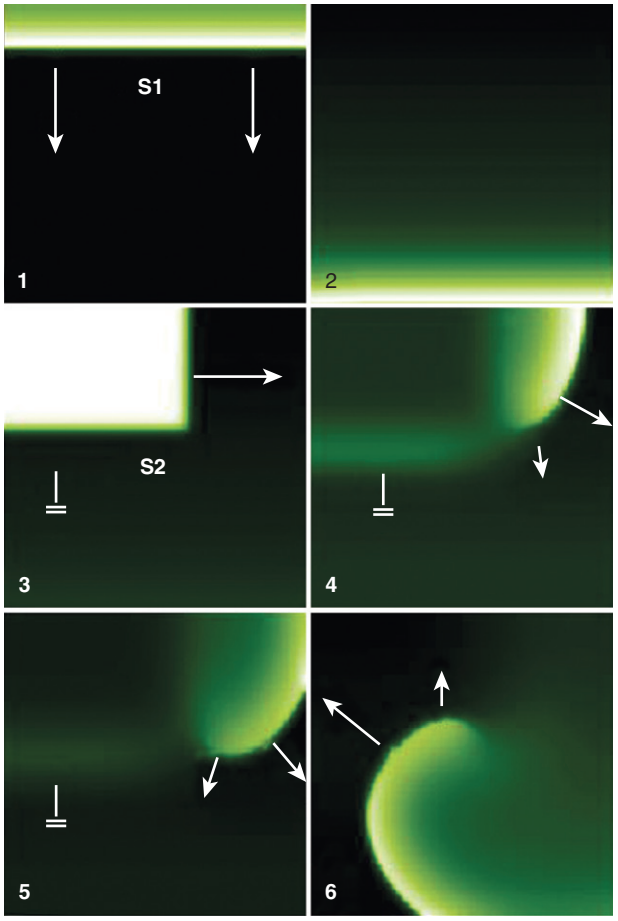

FIGURE 4-8 Cross-field stimulation protocol used to initiate spiral wave (vortex-like) activity in a square sheet of murine action potential model that was generated by the chapter authors. At time 1, an S1 stimulus is applied to the entire upper border of the sheet. At time 2, the wavefront in white reaches the bottom border followed by its tail of refractoriness *(fading green)*. At time 3, an S2 stimulus is applied when the upper border has not yet fully recovered from previous excitation. Consequently, at time 4, the S2 wavefront cannot propagate downward and blocks (*white broken lines*) but propagates from left to right (*white arrow*), developing a pronounced curvature a the tip. At times 5 and 6, the wavefront has curled sufficiently to initiate sustained spiral wave activity. *(From Noujaim SF, Pandit SV, Berenfeld O, et al: Up-regulation of the inward rectifier K+ current (I_{K1}) in the mouse heart accelerates and stabilizes rotors,* J Physiol *578[Pt 1]:315–326, 2007.)*

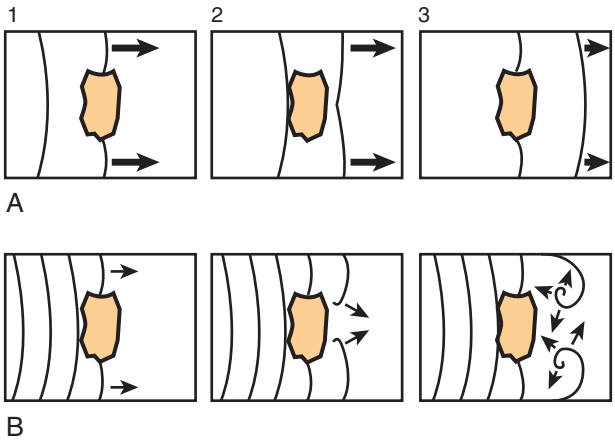

FIGURE 4-9 Initiation of functional re-entry by the interaction of a wavefront with an anatomic obstacle in a rectangular sheet of cardiac muscle. Two conditions of tissue excitability are represented. **A,** Under conditions of high excitability, quasi-planar wavefronts initiated at the left border move rapidly toward the obstacle, break, circumnavigate the obstacle, and then fuse again to continue propagating toward the right border. **B,** When excitability is lower, conduction velocity is slower. After reaching the obstacle, the wavefront breaks. However, in this case, the newly formed wavebreaks detach from the obstacle as they move toward the right border and begin to curl, giving rise to two counter-rotating spirals.

Spontaneous Formation of Rotors

A major contribution of wave propagation theory in excitable media to the understanding of the mechanisms of initiation re-entrant arrhythmias is the concept of wavebreak, which explains how the interaction of a wavefront with an obstacle can lead to wavefront fragmentation and rotor formation.[14] The re-entrant wave can begin as a single vortex, as a pair of counter-rotating vortices, or as two pairs of counter-rotating vortices.

The concept of wavebreak is illustrated schematically in Figure 4-9, which shows the dynamics of the interaction of a wavefront with an anatomic obstacle in a two-dimensional sheet of cardiac tissue with two different excitability conditions. In *A*, when tissue excitability is normal, after circumnavigating the obstacle, the broken ends of the wave join together, the previous shape of the wavefront is regained, and the wave continues. However, in *B*, when excitability is low, the broken ends of the wave do not fuse. Instead, the broken ends rotate in the opposite direction. As illustrated by the diagrams in Figure 4-10, during "normal" propagation, which is initiated by a linear source (planar wave, *A*) or a point source (circular wave, *B*), the wavefront is always followed by a recovery band or wave tail. Under these conditions, the front and tail never meet, and the distance between them corresponds to the wavelength of the excitation. In contrast, as shown in *C*, the broken waves demonstrate a unique feature whereby the front and the tail meet at the wavebreak. In this situation, the wavefront curls, and its velocity decreases toward the wavebreak. In fact, at the wavebreak, the curvature is so pronounced that the wavefront fails to activate the tissue ahead. Consequently, the wavebreak effectively serves as a pivoting point, which forces the wavefront to acquire a spiral shape as it rotates around the core.[1]

Multitudes of obstacles, both anatomic and functional, are present in cardiac tissue. However, the excitation of the heart, which is triggered by signals that originate in the sinus node and subsequently propagate throughout the atria and the ventricles, occurs repeatedly in a rhythmic manner. This process occurs without the induction of arrhythmias because the normal sequence of activation through the His-Purkinje system prevents the formation of wavebreaks. Consequently, the presence of obstacles is not a sufficient condition for the establishment of re-entry. Using a voltage-sensitive dye in conjunction with a high-resolution video imaging system, Cabo et al demonstrated that certain critical conditions must be met in order for unexcitable obstacles to destabilize propagation and produce self-sustained vortices that result in uncontrolled high-frequency stimulation of

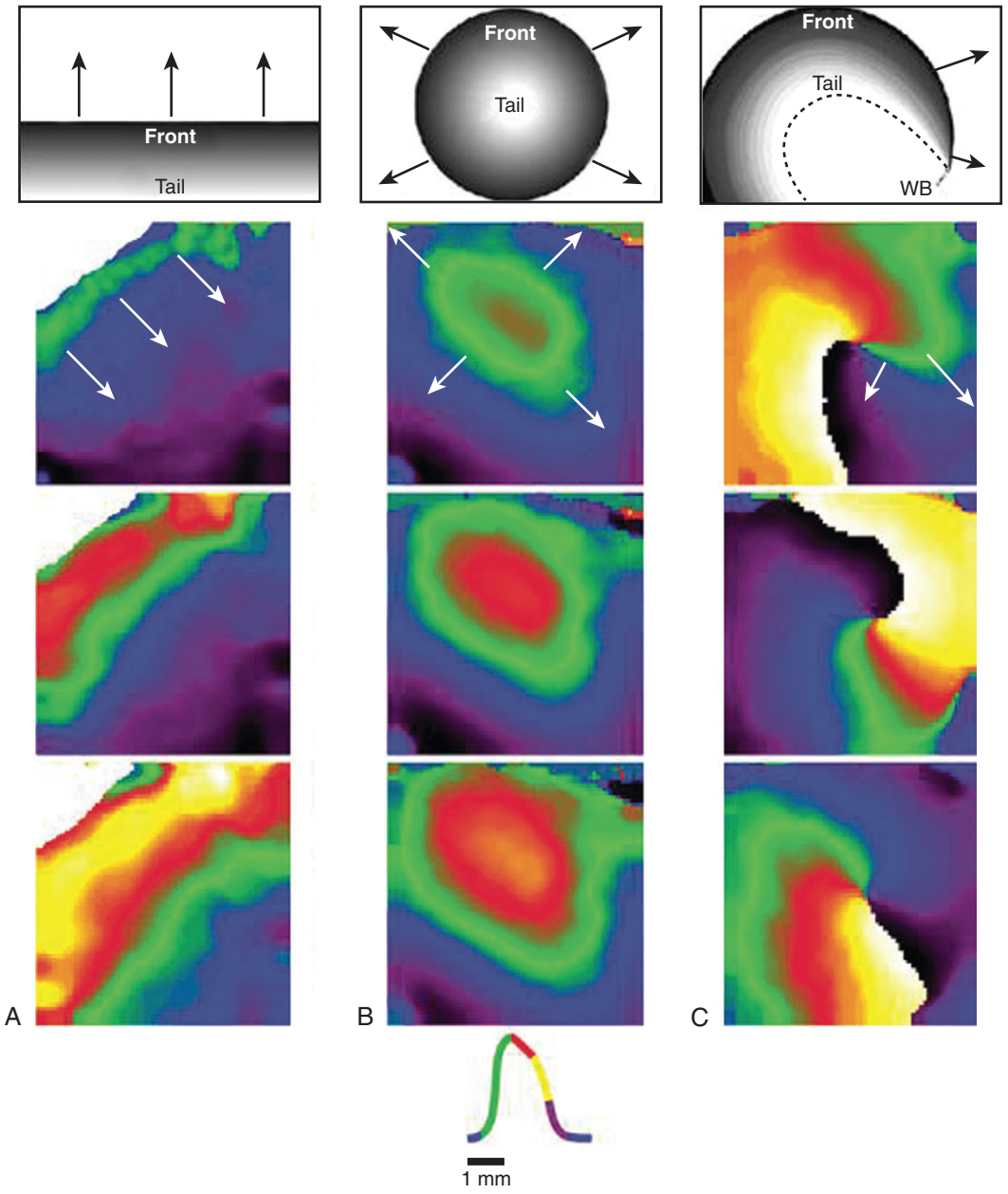

FIGURE 4-10 Expected conditions of propagation of different types of waves in a homogeneous and isotropic sheet of cardiac muscle (*top panels*) and in experiments the chapter authors performed in isolated Langendorff-perfused murine hearts (*bottom panels,* colored phase maps). **A,** Planar wave initiated by stimulation of the entire bottom border of the sheet or the top left corner of the field of view in the optical mapping experiment. **B,** Circular wave initiated by point stimulation in the center of the sheet or the center of the field of view in the optical mapping experiment. **C,** Spiral wave initiated by cross-field stimulation or burst pacing in the experiment. Note that for both planar and circular waves, the wavefront never meets the refractory tail. In contrast, during spiral wave activity, the wavefront and the wave tail meet at the wavebreak *(WB),* or where all the phases of the action potential converge in the experiment. In the phase maps, the wavefront is in green, and the wave tail is in red, yellow, and purple (*inset at bottom,* colored action potential).

the heart.[18] They demonstrated that the critical condition is the excitability of the tissue such that when the tissue excitability is low, a broken wave will contract and vanish (i.e., conduction will be blocked). However, at an intermediate level of excitability, the broken wave detaches from the barrier and forms a vortex in a manner visually similar to the separation of the main stream from a body in a hydrodynamic system, where there is subsequent eddy formation during turbulence. Moreover, Cabo et al demonstrated that high-frequency stimulation, which decreases excitability, also resulted in the detachment of the broken wave and the generation of vortices in the presence of anatomic obstacles. This phenomenon has been termed *vortex shedding*. In summary, the dynamics of wavebreaks are determined by (1) the critical curvature of the wavefront (i.e., the curvature at which propagation fails), (2) the excitability of medium, and (3) the frequency of stimulation or wave succession.

Role of Wavebreaks in Ventricular Fibrillation

Under normal conditions of excitability and stimulation, the interaction of the wavefront with an obstacle does not produce a wavebreak. However, when the excitability is lowered, wavebreaks may be initiated and persist after the collision of the front with the appropriate anatomic or functional obstacles. As predicted by theory, the obstacle size must be equal to or greater than the width of the wavefront for perturbation of propagation to occur. At a propagation speed of 50 cm/s, the wavefront width (i.e., the spatial spread of the action potential upstroke) in normal cardiac muscle is approximately 1 mm.[1] Consequently, obstacles of 1 mm or larger have the potential to generate wavebreaks in the propagating waves and producing vortex-like re-entry.

Clearly, numerous conditions can lead to the formation of wavebreaks. However, what is the relationship between wavebreaks and ventricular fibrillation (VF)? The authors hypothesize that the numerous fragmented wavefronts observed during VF form as the result of the interaction of waves emanating from a high-frequency source with the obstacles present in cardiac tissue.[1] Because of their lateral instability, some waves may shrink and undergo decremental conduction, but other waves may continue unchanged until annihilated by other waves. Still others may undergo curling and form new rotors. The final result is the fragmentation of the mother waves away from the source into multiple short-lived daughter waves that produce a complex pattern of propagation during VF.

Mechanisms of Maintenance of Ventricular Fibrillation

Is Ventricular Fibrillation Random or Organized?

On the basis of his cinematographic studies in 1940, Wiggers[19] concluded that VF could not be adequately described as an asynchronous contraction of myocardial fibers. Wiggers observed that the lack of coordination and asynchrony initially involves comparatively large sections of the myocardium, which progressively multiply and decrease in size as fibrillation continues; however, the study showed that even in the later stages of fibrillation, asynchronous contraction of adjacent fibers does not seem to occur. These observations are in agreement with the notion that VF arises from wandering wavefronts that are ever changing in direction and number. Furthermore, it is possible that the fragmentation of the wavefront into multiple independent wavelets may arise from the interaction of the wavefront with obstacles and with the refractory tails of other waves. As the front breaks, some waves may shrink and cease to exist (i.e., decremental propagation), others may propagate until terminated by the collision with other waves or boundaries, and still others may give rise to new vortices.[1] The product of such phenomena may be the complex patterns of propagation that characterize VF. However, currently, ample evidence in the literature suggests that VF is not entirely a random phenomenon. A summary of the studies that have documented "organization" during VF follows.

In 1981, Ideker and colleagues[20] documented that ventricular activation during the transition to VF arises near the border of the ischemic–reperfused region of the canine heart and is organized as it passes across the nonischemic tissue, but the body surface electrocardiogram (ECG) appears disorganized as judged by the variable spacing between successive, coexistent activation fronts. In 1992, Damle et al[21] demonstrated that epicardial activation during VF in a canine model of healing infarction is not random. Moreover, they showed that during VF, spatial as well as temporal "linking" of activation occurs; in this phenomenon, the same path of conduction is traversed by several consecutive wavefronts in a relatively rhythmic manner.

Garfinkel et al used nonlinear dynamics theory to study fibrillation in a computer model and three stationary forms of arrhythmias: (1) in human chronic atrial fibrillation, (2) in a stabilized form of canine VF, and (3) in fibrillation-like activity in thin sheets of canine and human ventricular tissues.[22] They found that fibrillation arose through a quasi-periodic stage of period and amplitude modulation; thus, they concluded that fibrillation is a form of spatio-temporal chaos. Bayly et al explored several techniques to quantify spatial organization during VF.[23] They used epicardial electrograms recorded from porcine hearts by using rectangular arrays of unipolar extracellular electrodes and concluded that VF is neither "low-dimensional chaos" nor "random" behavior but, rather, a high-dimensional response with a degree of spatial coherence.[23]

The development of an analytic technique by Gray et al, which markedly reduces the amount of data required to depict the complex patterns of fibrillation, has enabled investigators to study the detailed dynamics of wavelets and rotors, including their initiation, life span, and termination.[24] Using a fluorescent potentiometric dye and video imaging, Gray et al recorded the dynamics of transmembrane potentials from a large region of the heart and determined that transmembrane signals at many sites exhibit a strong periodic component. With this analysis, the periodicity is seen as an attractor in two-dimensional phase space, and each site can be represented by its phase around the attractor. Using spatial phase maps at each instant in time, Gray et al revealed the "sources" of fibrillation in the form of topologic defects, or *phase singularities* (a term coined by Winfree in 1990), at several sites.[24] Thus, they demonstrated that a substantial amount of spatial and temporal organization underlies cardiac fibrillation in the whole heart.[24]

The authors of this chapter, using isolated Langendorff-perfused rabbit heart, demonstrated organization during VF in the form of sequences of wave propagation that activated the ventricles in a spatially and temporally similar fashion.[1] Furthermore, the frequency of the periodic activity was shown to correspond to the dominant peak in both the global bipolar electrogram and the optical pseudo-ECG, which suggests that the sources of the periodic activity are the dominant sources that maintain VF in this model. Moreover, quantification of wavelets revealed that during VF, wavebreaks underlie wavelet formation; however, the breakup of rotor waves was not a robust mechanism for the maintenance of VF. Overall, the results suggested that the organized activity of periodic sources is responsible for most of the frequency content of VF and is therefore important for the maintenance of this arrhythmia.[1]

Rotors and Ventricular Fibrillation

Rotors are thought to be the major organizing centers of re-entrant arrhythmias, so much investigation has focused on rotors as the underlying mechanism for VF in the heart. However, two schools of thought have emerged. On one hand, many recently proposed

mechanisms for fibrillation have focused on the transience and instability of rotors. These mechanisms suggest that the breakup of rotors results in the "turbulent" nature of fibrillation. One such mechanism, the *restitution hypothesis*, suggests that fractionation of the rotor ensues when the oscillation of the action potential duration is of sufficiently large amplitude to block conduction along the wavefront.[22,25] Another mechanism for breakup focuses on the fact that propagation within the three-dimensional myocardium is highly anisotropic because of the intramural rotation of fibers; this produces the twisting and instability of the organizing center (filament), which results in multiplication following repeated collisions with boundaries in the heart.[26]

Studies by the authors of this chapter have also focused on rotors as the primary engines of fibrillation. However, here the breakup of the rotor is not regarded as the underlying mechanism of VF. Rather, it is proposed that VF is a problem of self-organization of nonlinear electrical waves with both deterministic and stochastic components.[1,24] This has led to the hypothesis that there is spatial as well as temporal organization during VF in the structurally normal heart, although there is a wide spectrum of behavior during fibrillation. On one end, it has been demonstrated that a single drifting rotor can give rise to a complex pattern of excitation that is reminiscent of VF.[27] On the other end, it has been suggested that VF is the result of a high-frequency, stable source and that the complex patterns of activation are the result of the fragmentation of emanating electrical activity from that source (i.e., fibrillatory conduction).[28,29] In the following sections, these two extremes are examined.

Drifting Vortices and Ventricular Fibrillation

Using optical mapping in the structurally normal isolated Langendorff-perfused rabbit heart, Gray et al studied the applicability of spiral wave theory to VF.[24,27] In that study, they demonstrated the presence of a drifting rotor on the epicardial surface of the heart. Simultaneous recording of a volume-conducted ECG and fluorescence imaging showed that a single, rapidly moving rotor was associated with turbulent polymorphic electrical activity, which was indistinguishable from VF. It was assumed that rotors were the two-dimensional epicardial representation of a three-dimensional scroll wave. In addition, computer simulations incorporating a realistic three-dimensional heart geometry and appropriate model parameters demonstrated the ability to form a rapidly drifting rotor similar to that observed in the experiments.[24,27] Frequency analysis of the irregular ECGs for both experiments and simulations showed spectra that were consistent with previously published data. Furthermore, Gray et al confirmed, through the Doppler relationship, that the width of the frequency spectrum can be related to the frequency of the rotation of the rotor, the speed of its motion, and the wave speed.[30]

Fibrillatory Conduction

Some forms of fibrillation depend on the uninterrupted periodic activity of discrete re-entrant circuits. The faster rotors act as dominant frequency sources that maintain the overall activity. The rapidly succeeding wavefronts emanating from these sources propagate throughout the ventricles and interact with tissue heterogeneities, both functional and anatomic, leading to fragmentation and wavelet formation.[1]

Zaitsev et al,[28] using spectral analysis of optical epicardial and endocardial signals for sheep ventricular slabs, have provided additional evidence suggesting that fibrillatory conduction may be the underlying mechanism of VF. Zaitsev and colleagues presented data showing that the dominant frequencies of excitation do not change continuously on the ventricular surfaces of slabs. Rather, the frequencies are constant over regions termed *domains*; moreover, only a small number of discrete domains are found on ventricular surfaces. Zaitsev and colleagues[28] also demonstrated that the dominant frequency of excitation in the adjacent domains is often related to the fastest dominant frequency domain in 1:2, 3:4, or 4:5 ratios, and this was suggested to be the result of intermittent, Wenckebach-like conduction block at the boundaries between domains.[28] Thus, they concluded that in their model, VF could have resulted from a sustained high-frequency, three-dimensional intramural scroll wave, which created complex patterns of propagation as the result of fragmentation when waves emanating from a high-frequency scroll interacted with tissue heterogeneities.

Samie et al[29] presented new evidence in the isolated Langendorff-perfused guinea pig heart that strongly supports the hypothesis that fibrillatory conduction from a stable high-frequency re-entrant source is the underlying mechanism of VF. Samie et al[29] obtained optical recordings of potentiometric dye fluorescence from the epicardial ventricular surface along with a volume-conducted "global" ECG. Spectral analysis of optical signals (pixel by pixel) was performed, and the dominant frequency (DF, peak with maximal power) from each pixel was used to generate a DF map. Pixel-by-pixel fast Fourier transformation (FFT) analysis revealed that DFs are distributed throughout the ventricles in clearly demarcated domains. The highest frequency domains are always found on the anterior wall of the left ventricle. Correlation of rotation frequency of rotors and the fastest DF domain strongly suggests that rotors are the underlying mechanism of the fastest frequencies. Further analysis of optical recordings has demonstrated that fragmentation of wavefronts emanating from high-frequency rotors occurs near the boundaries of the DF domains. The results demonstrate that in the isolated guinea pig heart, a high-frequency re-entrant source that remains stationary in the left ventricle is the mechanism that sustains VF.

Moreover, experiments and simulations have attributed the stabilization of the high-frequency rotors driving VF in the left ventricle of the guinea pig heart to the presence of a gradient in the inwardly rectifying potassium (K) current (I_{K1}) whereby I_{K1} is larger in the left ventricle compared with that in the right ventricle.[29] I_{K1} is a K current that (1) contributes to the resting membrane potential, (2) controls the approach of the membrane voltage to the range where sodium (Na) channels activate to give rise to the upstroke, and finally (3) modulates the final phase of repolarization. However, in the experiments of Samie et al, there no direct link was demonstrated at the molecular level between the stability of rotors in the left ventricle of the fibrillating guinea pig heart and I_{K1}.[29] As a result, Noujaim and colleagues[31] used a murine model of cardiac-specific Kir2.1 upregulation, where I_{K1} density was consequently increased by about 12-fold to investigate rotor behavior in such a substrate. It was found that the increased I_{K1} serves to stabilize and accelerate rotors responsible for re-entrant VT and VF.[31] The experiments and numerical simulations suggested that during re-entry, the larger I_{K1} accelerates conduction velocity, decreases the core size, and hyperpolarizes the resting membrane potential.[31] The combination of these factors leads to the generation of very fast and stable rotors. As

discussed in earlier sections, wavebreaks and fibrillatory conduction can be characteristics of VF. The authors of this chapter recently examined the role of the slow component of the delayed rectifier K current (I_{Ks}) in wavebreak formation and fibrillatory conduction.[32] In single cells, I_{Ks} has been shown to contribute to repolarization and postrepolarization refractoriness, where because of its slow kinetics of activation and deactivation, I_{Ks} accumulates in a deactivated state in response to fast, repetitive stimuli.[32] As a result, the pool of deactivated channels will serve to oppose a carefully timed depolarization stimulus, even after the myocyte has fully repolarized and the Na channels have recovered from inactivation; this leads to the failure of action potential generation, hence the notion of postrepolarization refractoriness. Using numerical simulations and monolayers of neonatal rat ventricular myocytes expressing I_{Ks} via viral transfer of KvLQT1-minK fusion protein (the respective α- and β-subunits of the channel responsible for carrying I_{Ks}), Munoz et al showed that I_{Ks} is an important player in the formation of wavebreaks and fibrillatory conduction during excitation patterns that closely resemble those recorded during ventricular fibrillation.[32]

Acknowledgment

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CHAPTER 5

Autonomic Nervous System and Cardiac Arrhythmias

David G. Benditt, Scott Sakaguchi, and J. Gert van Dijk

The autonomic nervous system (ANS) comprises the portion of the central nervous system that provides moment-to-moment regulation of the function of the cardiovascular system as well as that of all other organ systems. The ANS continuously monitors afferent neural signals from vascular beds and organ systems and coordinates efferent neural traffic to modify the responses of heart and blood vessels to ever-changing physiological and metabolic requirements. In this context, the sympathetic and parasympathetic components of the ANS are the dominant players (Figures 5-1 and 5-2).[1] However, ANS cardiovascular control also incorporates actions of cardiac and extracardiac neurohumoral agents, intracardiac reflex arcs, and the contributions of certain less well-understood agents such as vasoactive intestinal peptide (VIP), neuropeptide Y, transmitters released by the so-called *purinergic* nerve endings, serotonin, inflammatory cytokines, vasopressin, and nitric oxide.[2] Further, with respect to cardiovascular control, the ANS collaborates with the hypothalamic-pituitary-adrenal (HPA) axis. For its part, the HPA-axis, governed from the hypothalamus, participates by prompting the release of glucocorticoids, mainly cortisol and, to a lesser extent, mineralocorticoids. The HPA theater of operation therefore includes inflammatory, immune, metabolic, and pressor effects.[3] Both systems (ANS and HPA) are involved in stress responses.[2,3]

It is not unexpected that any disturbance of ANS function, given its wide-ranging impact, may lead to clinically important consequences. In terms of cardiac electrophysiology and arrhythmias, common clinical conditions in which ANS effects are evident include acute myocardial ischemia, heart failure, and neurally mediated reflex syncope (particularly the vasovagal faint). Furthermore, it is now widely acknowledged that the nervous system has the capacity to injure the heart acutely (e.g., stress-induced cardiomyopathy); serious acute cerebral disorders such as subarachnoid hemorrhage, intracerebral bleeds, infections, and seizures may induce electrocardiographic changes, myocardial damage, arrhythmias, and even sudden death.[3-7] Perhaps the most publicized direct cardiac effects of presumed autonomic "storms" are the immediate, apparently stress-triggered, increases in the number of cardiovascular events; these include acute myocardial infarctions, sudden cardiac deaths, and presumed stress-induced cardiomyopathy (Table 5-1).[3-5]

This chapter provides a brief overview of current concepts regarding the impact of autonomic innervation as they pertain to cardiac arrhythmias, conduction system disturbances, and related disorders.

Anatomic Nervous System and Cardiac Conduction System Physiology

Sinus Node, Atrioventricular Node, and His-Purkinje System

The sinus node (SN) and the atrioventricular (AV) node appear to be represented by separate cells within the nucleus ambiguus. However, it is uncertain whether the nodes are coordinated centrally; in fact, it seems increasingly likely that local circuits, often positioned within the epicardial fat pads of the heart, participate in the coordination of these structures (Figure 5-3).[4,8]

Sinus Node

In humans, at rest, parasympathetic influence appears to predominate in the case of SN chronotropic state. Of course, multiple factors alter this situation; the most obvious of these is physical exercise, but others include the aging process, drug therapy, and emotional state.

ANS influence is the most important of the many extrinsic factors (e.g., drugs, hormones) affecting SN function. In the healthy heart, fluctuation of the ANS influence results in a normal respiratory-induced variation of sinus cycle length (i.e., respiratory sinus arrhythmia). In the case of respiratory sinus arrhythmia, the variations may be substantial (at times suggesting sinus pauses). Absence of sinus arrhythmia has come to be recognized as a sign of cardiac disease with increased mortality risk.

Age-related changes of sinoatrial function are clinically important, given the prevalence of SN dysfunction in older adults. In terms of ANS contribution, parasympathetic influence on SN chronotropism progressively diminishes with increasing age. However, at the same time, an age-related decrease of "intrinsic" heart rate (i.e., the heart rate in the absence of autonomic influences) also occurs. Thus, maintenance of an appropriate heart rate and chronotropic responsiveness in older individuals is increasingly dependent on the integrity of the sympathetic tone of the ANS.

Atrioventricular Node and Cardiac Conduction System

As a rule, AV nodal dromotropic responsiveness in the resting patient is under relatively balanced sympathetic and parasympathetic neural influence. However, this situation is readily altered by physiological events (e.g., exercise, sleep), the impact of disease

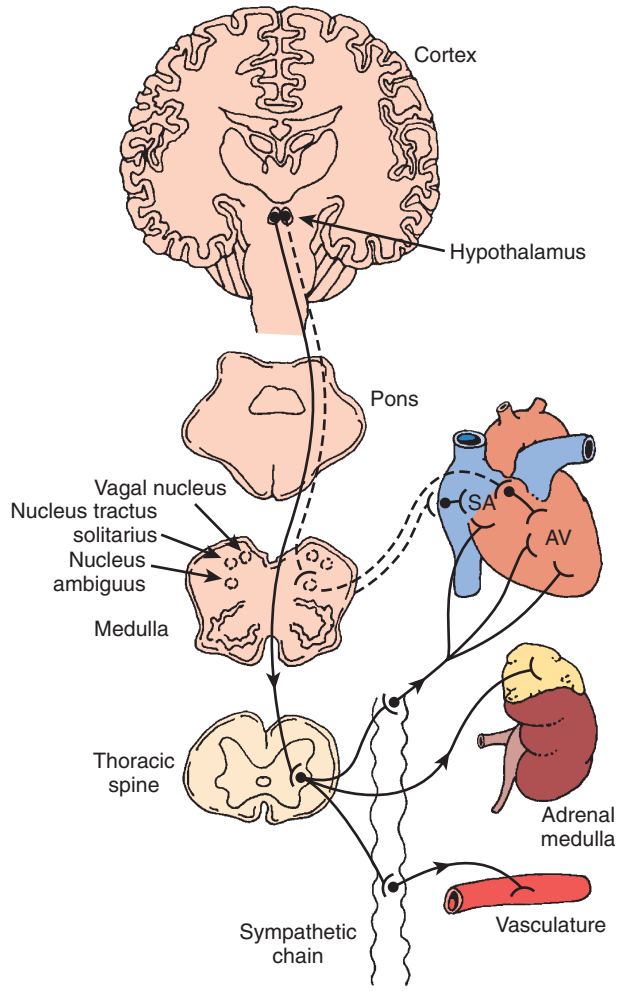

FIGURE 5-1 Schematic illustrating the course of sympathetic (*dashed line*) and parasympathetic (*solid line*) nerve pathways to key cardiac and vascular structures. The manner in which neural control approaches cardiac structures is far more complex than is suggested in this illustration. Further, the important intracardiac neural signaling structures are not shown.

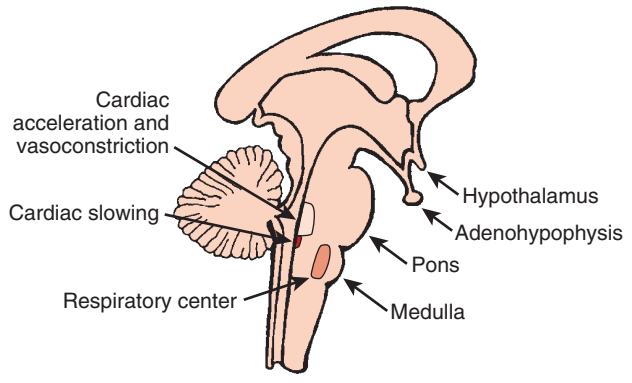

FIGURE 5-2 Schematic illustrating a conventional view of the approximate midbrain sites considered important for basic autonomic nervous system control of cardiovascular function.

Table 5-1 Epidemiologic Associations: Stress and Increased Cardiovascular Event Rates

1. Earthquakes
   - Athens 1981[a]
     Increased cardiovascular mortality
   - Los Angeles 1994[a,b]
     Increased cardiovascular death frequency approximately 2.5 times
     Increased acute MI event rate almost 2 times
   - Japan 2004[a,c]
     Approximately threefold increase in all cardiovascular events and SCD
     Increased tako-tsubo cardiomyopathy 25-fold
   - China (Wenchuan) 2008[d]
     Approximately 10-fold increase in cardiovascular events
2. Sports Events
   - World Soccer Championships, Munich 2006[e]
     Two- to threefold increase in rates of cardiovascular events
   - World Soccer Championships 2002[f]
     Twofold increase in incidence of sudden deaths reported in Switzerland
3. Military/Terror Attack
   - First Iraq War, Israel 1991[g,h]
     Two- to threefold increase of acute MI; twofold increase in sudden death
   - Attack on World Trade Center, New York, September 11, 2001[g,i]
     Two to three times increase in ICD firings
     50% increase in hospitalization for acute MI

MI, *Myocardial infarction;* SCD, *sudden cardiac death;* ICD, *implantable cardioverter-defibrillator.*

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states, drug effects, or during cardiac electrophysiology procedures when certain atrial regions are stimulated. Any tendency toward parasympathetic predominance markedly enhances the decremental properties of the AV node; in the extreme, this can be associated with transient complete AV nodal block (Figure 5-4). The latter is, in fact, a relatively common finding in sleeping patients and in very fit resting subjects. The relationship between ANS control of SN rate and AV conduction properties appears to foster both the maintenance of 1 : 1 AV conduction and a relatively optimal AV conduction interval.

The His bundle and bundle branches comprise cells with larger surface areas, more negative resting membrane potentials, and faster (sodium [Na^+]-dependent) action potentials than those of the AV node. Furthermore, cells that make up the cardiac

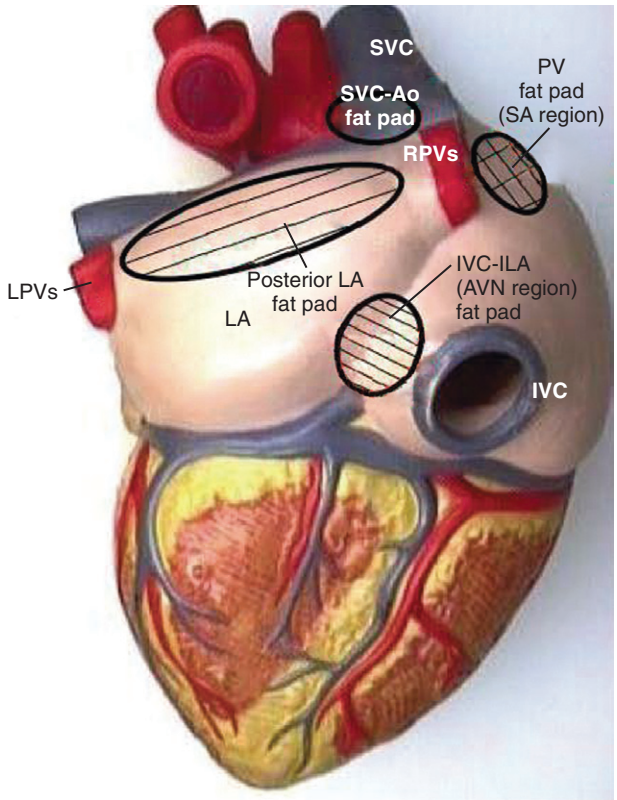

FIGURE 5-3 Diagrammatic representation of the approximate locations of epicardial fat pads; these fat pads are believed to provide sites of intracardiac neural connections and communication. The image depicts the posterior surface of the heart. The principal fat pads are demarcated and labeled. *SVC,* Superior vena cava; *Ao,* aorta; *PV,* pulmonary valve; *SA,* sinoatrial; *RPVs,* right pulmonary veins; *LPVs,* left pulmonary veins; *LA,* left atrium; *IVC,* inferior vena cava; *AVN,* atrioventricular node.

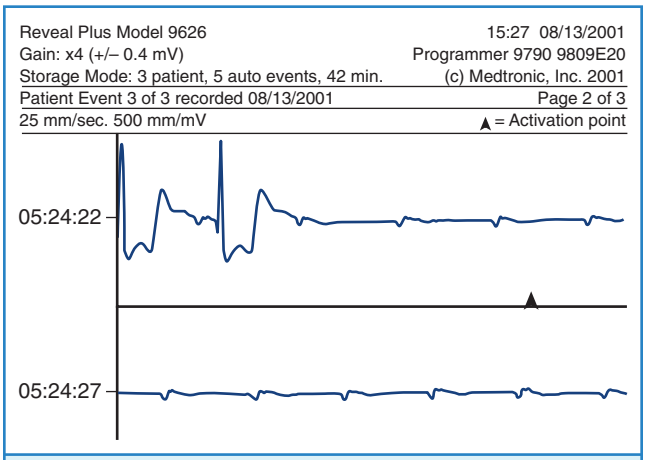

FIGURE 5-4 Electrocardiographic recordings obtained from an implanted loop recorder that had been implanted in a 72-year-old man with recurrent syncope of uncertain cause. The recording documents a transient symptomatic period of high-grade atrioventricular block.

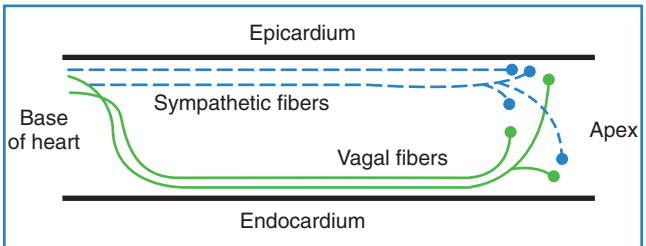

FIGURE 5-5 Diagram depicting the epicardial and endocardial locations of sympathetic and parasympathetic ventricular nerves, respectively. *(Modified from Zipes DP, Inoue H: Autonomic neural control of cardiac excitable properties. In Kulbertus HE, Franck G, editors:* Neurocardiology, *Mount Kisco, NY, 1988, Futura Publishing.)*

conduction system have abundant intercellular connections and are physically arranged in such a way as to promote longitudinal conduction. Consequently, decremental conduction is essentially absent, except in the setting of relatively severe conduction system disease. Sympathetic nerve endings are generally better represented in the distal aspects of the specialized conduction system than are parasympathetic nerves. However, it has become evident that parasympathetic influence penetrates farther than had previously been thought.

Ventricular Myocardium

Ventricular sympathetics tend to lie within the subepicardial layer and follow the large coronary vessels as they spread out over the myocardium.[9,10] The parasympathetics, in contrast, tend to penetrate the myocardium after crossing the AV groove and thereafter are subendocardial in location (Figure 5-5). The parasympathetic vagal efferents to the mycardium terminate not on the muscle cells themselves but on intracardiac ganglia. Evidence suggests that these ganglia not only form relay stations but also subserve certain local integrative functions, including the intracardiac reflex activity discussed earlier.

Heightened adrenergic activation in the ventricular myocardium may be arrhythmogenic by causing enhanced pacemaker activity as well as by increasing the frequency and rate of automaticity. In addition, elevated adrenergic tone is known to increase the likelihood of the generation of early after-depolarizations (EADs) and delayed after-depolarizations (DADs).

Parasympathetic effects, in contrast, are thought to operate mainly as an antiadrenergic action in the setting of increased adrenergic tone. Consideration is being given to vagal nerve stimulation as an antiarrhythmic treatment strategy. The outcome of this activity may be diminished production of adrenergically induced EADs and DADs and an apparently anti-inflammatory action (diminished cytokine release and enhanced glucocorticoid release).

Autonomic Nervous System and Specific Bradyarrhythmias and Cardiac Conduction System Disturbances

Sinus Node Dysfunction

SN dysfunction (sick sinus syndrome) encompasses abnormalities of SN impulse generation, disturbances of impulse emergence into the atrium, abnormal impulse transmission within the atria,

increased susceptibility to atrial tachycardias (particularly atrial fibrillation), chronotropic incompetence, and inappropriate sinus tachycardia. Clinical manifestations vary from seemingly asymptomatic electrocardiogram (ECG) findings to a wide range of complaints, including syncope, shortness of breath, palpitations, fatigue, and premature mental incapacity.

The causes of SN dysfunction are numerous but may be conveniently categorized as conditions that alter the SN, the sinoatrial structure or function directly (so-called *intrinsic* SN disease) or those that operate indirectly to impair sinoatrial function (i.e., extrinsic factors such as autonomic disturbances or drug effects). Ageing-associated idiopathic degenerative changes, fibrotic changes, or both are probably the findings most closely associated with "intrinsic" SN dysfunction. In regard to "extrinsic" SN dysfunction, drugs are the most important non-ANS contributors. β-adrenergic blockers, calcium channel blockers, membrane-active antiarrhythmics, and, to a lesser extent, digitalis are the most frequently implicated. Each of these may alter SN function as a result of direct pharmacologic effects (e.g., flecainide, d-sotalol), or indirectly via the ANS (e.g., β-adrenergic blockers) or both (e.g., quinidine, disopyramide, propafenone, amiodarone, digitalis). In terms of clinical outcomes, cardioactive drugs may initiate or aggravate sinus bradyarrhythmias or induce chronotropic incompetence.

Apart from drug-induced autonomic disturbances, the ANS may also contribute to apparent extrinsic disturbances of SN function. Sinus bradycardia, sinus pauses, sinoatrial exit block, and slow ventricular responses in atrial fibrillation may occur in the setting of parasympathetic predominance despite apparently normal underlying intrinsic SN or atrial function. In some cases, bradyarrhythmias are, in fact, extreme forms of sinus arrhythmia. Perhaps the best example of this is the physically fit individual in whom parasympathetic predominance at both the SN and the AV node levels may be present on a chronic basis. In such cases, sinus pauses and various degrees of AV block have been reported during sleep or at rest. Generally, these are asymptomatic and of little clinical consequence. Nonetheless, their occurrence (often detected inadvertently) may cause alarm. Carotid sinus syndrome and related conditions, in which excessive hypervagatonia is transient, are other instances in which intrinsic conduction system function is usually relatively normal and yet manifests clinically important ANS-induced disturbances. Fortunately, even in the setting of an apparently prolonged asystolic event, spontaneous restoration of the cardiac rhythm occurs in, by far, the vast majority of cases.

The syndrome of persistent or inappropriate sinus tachycardia provides another example of a clinical circumstance in which the ANS appears to play a primary role in *arrhythmogenesis*. The basis for the tachycardia is believed to be abnormal enhanced automaticity within the SN or nearby atrial regions. The cause of inappropriate sinus tachycardia in many cases, excluding those that turn out to be ectopic atrial tachycardias arising in the vicinity of the SN, remains unknown. Diminished parasympathetic control of SN function has been suggested; given the frequent association with recent radiofrequency ablation of cardiac structures (or in former times to surgical ablation of accessory connections), a disturbance of intracardiac vagal reflexes has also been proposed. However, one relatively recent report investigated the prevalence and the functional effects of circulating antiautonomic receptor antibodies in patients with inappropriate sinus tachycardia. Findings suggested a link between inappropriate sinus tachycardia and circulating anti–β-adrenergic receptor antibodies that induce a persistent increment in cyclic adenosine monophosphate (cAMP) production.

The coexistence of periods of bradyarrhythmia and bouts of atrial fibrillation or, less commonly, other paroxysmal primary atrial tachycardias in the same patient is a common manifestation of SN dysfunction (the so-called *bradycardia-tachycardia syndrome*). In bradycardia-tachycardia syndrome, symptoms may be the result of episodes of rapid heartbeats, the bradycardic component, or both. In this case, ANS influences are rarely entirely to blame. Similarly, true chronotropic incompetence is not usually attributable to ANS effects alone. As a rule, patients with parasympathetic predominance may exhibit low resting heart rates but ultimately manifest normal chronotropic responses to physical exertion. True chronotropic incompetence (i.e., inability of the heart to adjust its rate appropriately in response to metabolic need) implies intrinsic SN dysfunction, an undesirable effect of concomitant drug treatment, or both. In this regard, although conventional exercise testing is not generally useful in identifying most forms of SN dysfunction, such testing may be helpful in differentiating patients with resting sinus bradycardia but essentially normal exercise heart rate responses (e.g., physically trained individuals with presumably higher levels of parasympathetic influence on SN automaticity) from patients with intrinsically inadequate chronotropic responses.

Evaluation of SN responses to pharmacologic interventions and neural reflexes (e.g., carotid sinus massage, Valsalva maneuver, heart rate response to upright tilt, or induced hypotension [e.g., by administration of nitroglycerin]) is an important element in the diagnostic assessment of SN function. For example, pharmacologic interventions may assess SN response to β-adrenergic blockade, β-adrenergic stimulation, or parasympathetic muscarinic blockade (i.e., atropine infusion). The most important of these tests is estimation of intrinsic heart rate (IHR, SN rate in the absence of neural control) by pharmacologic autonomic blockade with combined administration of a β-adrenergic blocker and atropine. A normal IHR in a patient with apparent sinus pauses or marked SN bradycardia suggests extrinsic SN dysfunction.

Atrioventricular Conduction Disturbance

First- and second-degree type 1 AV block are most often the result of conduction disturbances at the level of the AV node (i.e., prolonged AH interval) and are frequently attributable to ANS influences. This is especially the case when there is no evidence of underlying cardiac disease, when the QRS morphology is normal, and when the individual is young, physically fit, or both. Of course, drug-induced AV block must also be excluded.

ANS-mediated higher degrees of AV block may also be observed (see Figure 5-4). These episodes of *paroxysmal AV block* are generally benign from a mortality perspective, although they may be associated with dizziness and syncope (e.g., vasovagal faint) and risk of physical injury. Sustained third-degree AV block is, however, not usually attributable to ANS effects. In adults, acquired complete heart block is almost always associated with structural heart disease.

In the setting of acute anterior myocardial infarction, transient or fixed complete AV block is reported to occur in 5% of cases and is typically infranodal. The ultimate poor prognosis in these patients is related to the magnitude of ventricular damage. By contrast, complete AV block occurs in 10% to 15% of patients after inferior wall myocardial infarction. In these instances, however,

the block may often progress through stages beginning with PR interval prolongation, type 1 second-degree AV block, or both; the site of the block is most often within the AV node. The mechanisms eliciting this form of AV block are multiple, including nodal ischemia, adenosine release, and enhanced parasympathetic tone. Often the block can be reversed (at least temporarily) by atropine administration, which supports the importance of the parasympathetic autonomic etiology.

Drug effects are a common cause of AV nodal conduction disturbances. A variety of cardioactive drugs affect the AV node: by direct cellular action, indirectly as a result of their actions on the autonomic nervous system, or both. For example, cardiac glycosides are widely known to affect the AV node by ANS-mediated effects; first- or second-degree type 1 AV block occurs as a result of glycoside-induced enhanced vagal tone at the AV node. β-Adrenergic blockers cause AV nodal conduction slowing, and occasionally block, by diminishing sympathetic neural effects on the AV junction, or both. When certain antiarrhythmic drugs are prescribed, the important ANS effects that they have need to be taken into consideration. Both quinidine and disopyramide manifest prominent vagolytic actions that tend to counterbalance their direct negative dromotropic effects. This vagolytic effect can lead to apparently paradoxical increases of ventricular rate when these drugs are used to treat patients with certain primary atrial tachycardias, especially atrial flutter.

Autonomic Nervous System and Specific Tachyarrhythmias

ANS activity may be implicated to some extent in all tachyarrhythmias. For instance, sympathetic, parasympathetic, and purinergic neural inputs at the AV node may, in large, part determine whether AV node re-entry or AV re-entry supraventricular tachyarrhythmias can be triggered or sustained in patients with known substrates to these arrhythmias. In essence, the ability of a premature atrial or ventricular beat to dissociate conduction pathways and thereby permit re-entry may vary from moment to moment, depending on neural influences.

Atrial Fibrillation

The ANS may play a role both in setting the stage for and in triggering certain forms of atrial fibrillation, or flutter (AF). In addition, the relative balance of ANS input to the cardiac conduction system is a crucial determinant of the ventricular response in AF. Little is known regarding the possibility of ANS elements also participating in the termination of AF. The possibility that reduction of susceptibility to AF, or even AF termination, may be facilitated by ANS manipulations has received relatively little attention until recently. ANS manipulation by catheter ablation is now a topic of interest.

Triggering of Vagally and Adrenergically Mediated Atrial Fibrillation

Vagally mediated (bradycardia or pause-dependent) AF is relatively uncommon. It tends to occur more commonly in men than in women, and the episodes begin at night or in the early morning hours when vagal predominance is greatest. The same individuals may experience post-prandial AF. Clinical recognition of vagally mediated AF is important, given that cardiac glycosides and β-adrenergic blockers are relatively contraindicated.

The ANS also appears to play a role in postoperative AF, although the relationship in this case is largely inferential and not well substantiated. Excluding the probable role played by heightened adrenergic tone in postoperative arrhythmias, true adrenergically mediated forms of paroxysmal AF are less common than is the vagally mediated form. Rarely, adrenergically mediated AF is secondary to a noncardiac disease process such as hyperthyroidism or pheochromocytoma. Most often, the medical history suggests onset during the waking hours (usually in the morning) in association with stress or physical exertion.

Control of Ventricular Rate

The manner in which the AV node responds to a fibrillating atrium remains a subject of conjecture. However, whatever may be the mechanisms at play, it seems clear that the ANS plays an important role in modulating the ventricular rhythm. Increased vagal tone, diminished sympathetic tone, or both are associated with a decrease in average ventricular rate. The converse clearly increases the average ventricular rate.

Supraventricular Tachycardias (Other than Atrial Fibrillation)

Supraventricular tachycardias are typically categorized into whether or not the tachycardia is dependent on AV node conduction. The first group is exemplified by AV nodal re-entry tachycardia (AVNRT) and AV re-entrant tachycardia (AVRT) using accessory AV connections. The AV nodal independent tachycardias include atrial re-entrant arrhythmias as well as those that are thought to be automatic or triggered in origin. In either case, the ventricular rate is determined by the ANS effect on the AV conduction system (particularly the AV node, see earlier). In certain cases, ANS effects may also play a role in terminating tachyarrhythmias, either spontaneously (Figure 5-6) or during medical interventions such as carotid sinus massage.

Ventricular Tachycardia

The importance of the ANS in determining susceptibility to ventricular tachyarrhythmias in certain disease states is well established. Acute ischemic heart disease is the best example.[9,10] However, ANS influences may also be instrumental in triggering tachycardia events in patients with well-established long-standing substrates, such as those with pre-existing fibrotic areas as a consequence of prior myocardial infarction or remote cardiac surgery (e.g., childhood repairs). ANS participation in the triggering of arrhythmias is also almost certainly pertinent in other chronic states in which the arrhythmia substrate is present all the time and yet rhythm disturbances occur only sporadically. Among the best examples of the latter scenario are the abnormal ventricular repolarization syndromes (e.g., long QT syndrome [LQTS], Brugada syndrome).

Ischemic Heart Disease

The ANS contributes importantly to arrhythmogenesis in acute myocardial ischemia.[11,12] In brief, the risk of potentially life-threatening arrhythmias and sudden death appears to increase in response to ischemia-associated increased sympathetic activity.

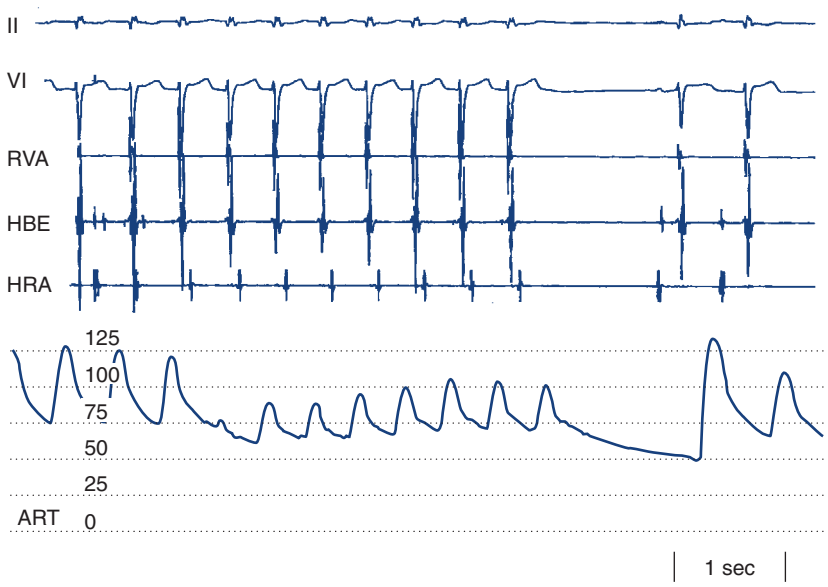

FIGURE 5-6 Electrocardiographic, intracardiac, and arterial pressure traces during a brief episode of re-entry supraventricular tachycardia. Note the initial drop of pressure at onset of the arrhythmia. Thereafter the pressure rebuilds slowly. The pressure recovery may play a role in tachycardia termination.

Conversely, the risk of arrhythmia is diminished by sympathetic blockade, parasympathetic enhancement, and inhibition of the renin–angiotensin system.

Although there is a consensus that β-adrenergic blockade is of value for reducing susceptibility to ischemia-induced arrhythmias, the impact of α-adrenergic blockade is less clear. Evidence both for and against the protective value of α-adrenergic blockade in acute ischemia is available. For the most part, current findings based on canine studies do not support the protective effect of α-adrenergic blockade in most acute ischemic syndromes.

Parasympathetic Neural Influences

Experimental and clinical evidence supports the view that enhanced parasympathetic tone diminishes the risk of arrhythmia in the setting of acute ischemia. In this regard, both neurally mediated heart rate–slowing effects and direct parasympathetic agonist effects contribute to the overall benefit. Furthermore, direct vagal nerve stimulation, by virtue of its anti-sympathetic effects as well as its parasympathetic actions, may become particularly valuable.

Studies of baroreceptor sensitivity (BRS) (a measure of vagal influence on the heart) offer important insights into the potentially protective role played by the parasympathetic nervous system in patients with ischemic heart disease. In a prospective trial of relatively low-risk patients, at 2-year follow-up, BRS values were seen to be lower in those individuals who failed to survive, and the effect appeared to be independent of left ventricular function as assessed by ejection fraction measurement. In this regard, a multicenter trial, Autonomic Tone and Reflexes after Acute Myocardial Infarction (ATRAMI), provided convincing additional evidence.[13] Patients were monitored for 21 ± 8 months. Cardiac mortality was higher (9% vs. 2%; 10% vs. 2%) among individuals with low BRS (<3 ms/mm Hg) or low standard deviation of normal NN intervals (SDNN) (<70 ms) than those with normal BRS or SDNN (>6.1 ms/mm Hg, >105 ms). Combining both indices resulted in recognition of even greater risk. Once again, the effect appeared to be independent of ejection fraction.

The observations related to BRS led to the evaluation of heart rate variation (heart rate variability [HRV]) as an ANS-related means to stratify risk of lethal arrhythmias in patients with ischemic heart disease. The findings suggested that diminished HRV is associated with a much greater mortality risk in post–myocardial infarction patients. Other techniques using markers of ANS status as markers of arrhythmia risk include heart rate turbulence (HRT) and deceleration capacity (DC).

In summary, markers of reduced parasympathetic cardiac control appear to be indicative of increased risk, whereas enhanced parasympathetic control appears to be associated with reduced risk of lethal arrhythmia in patients with ischemic heart disease (at least in the post–myocardial infarction group). Consequently, enhancing parasympathetic predominance through exercise has become part of the overall approach to reducing mortality risk in patients with ischemic heart disease.

Long QT Syndrome, Brugada Syndrome, and Other Channelopathies

Disturbances of ventricular repolarization have been the subject of considerable interest in recent years, partly because of the recognition that they are a common cause of potentially life-threatening arrhythmias (Figure 5-7) but even more as a result of rapid progress in better understanding of why they occur.[14] Currently, it is believed that underlying susceptibility to arrhythmia (primarily torsades de pointes ventricular tachycardia) is based on one or more genetically determined disturbances of the structure of cardiac membrane ionic channels, and/or disturbances of their function, or trafficking to the cell membrane.

The initial recognition of these conditions was based on overt ECG manifestations (e.g., long QT interval, typical Brugada pattern). However, it is now suspected that many more individuals manifest a less overt form of channelopathy; in such cases, the ECG signature may become apparent only after exposure to a trigger, particularly certain drugs or electrolyte disturbances, and, in some cases, acute neurologic injury (e.g., subarachnoid bleed). These latter circumstances are considered acquired,

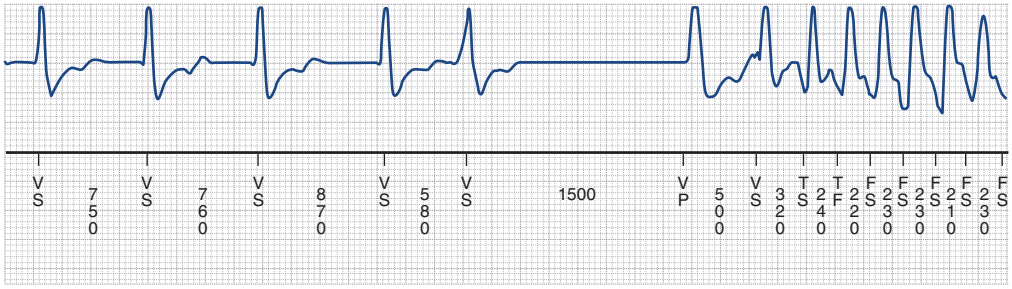

FIGURE 5-7 Recording obtained on interrogation of an implantable cardioverter-defibrillator (ICD) after a 53-year-old patient with long QT syndrome reported feeling light-headed followed by a "shock." Findings revealed a premature ventricular contraction–induced cardiac pause followed by a rapid ventricular tachyarrhythmia (pause-dependent ventricular tachyarrhythmia). The arrhythmia was terminated by administering an ICD shock (*not shown*).

although a concealed congenital predisposition may well be present.

QT Interval and Sympathetic Inputs to the Heart

The clinical observations that syncopal spells and sudden death could be triggered under conditions of physical or emotional stress and that they could be ameliorated with β-adrenergic blockade provided clues to the importance of ANS in LQTS. More direct, anatomic evidence became available subsequently. Using a canine model, it was shown that QT prolongation could be produced either with stimulation of the left stellate ganglion or with right stellectomy. Subsequently, a variety of surgical procedures have been used to selectively reduce or abolish left-sided sympathetic innervation to the heart. Collectively, these procedures have been called *left cardiac sympathetic denervation* (LCSD), a term used in this chapter. As a rule, the favored approach for this procedure is high thoracic left sympathectomy, in which ablation is limited to the lower portion of the left stellate ganglion and the first four or five thoracic ganglia. This technique provides adequate cardiac sympathetic denervation but largely avoids Horner's syndrome as a complication by sparing the upper portion of the stellate ganglion.

Genotype and Phenotype: Differences in Response to the Autonomic Nervous System in Long QT Syndrome

With the identification of specific genotypes for LQTS, it has become apparent that there are clinically significant differences in the expression of their phenotypes. Particularly striking is the observation that patients with LQT1 are especially prone to lethal cardiac arrest during exercise, whereas sudden death during exercise appears to be distinctly unusual in patients with LQT2 and LQT3. In contrast, patients with LQT3 and, to a somewhat lesser extent, those with LQT2 are more prone to lethal events during sleep or at rest.

Jervell and Lange-Nielsen, generally considered to be the earliest to report on LQTS, had noted that one of their subjects exhibited an increase in the QT interval in response to adrenaline and exercise. More recently, catecholamines such as isoproterenol or epinephrine have been used in various protocols trying to determine if an increase in the QT interval could be a tool in the diagnosis of LQTS. It has since become clear that the response to catecholamines cannot be generalized to all genotypes. During epinephrine infusion, the absolute QT interval increased in patients with LQT1 and decreased in those with LQT2 and LQT3. Similarly, the QTc increased during exercise stress testing in patients with LQT1 and decreased in those with LQT2. In effect, patients with LQT1 fail to appropriately shorten their QT interval in response to adrenergic stimulation that occurs during exercise or other types of stress.

More than one factor may make patients with LQT1 especially vulnerable to sudden death during exercise. The slow deactivation kinetics of the normal I_{ks} channel produces an increase in the I_{ks} current at fast heart rates; this shortens ventricular repolarization, which would be protective against torsades de pointes at fast rates, as has been demonstrated in guinea pig ventricular myocytes. A similar contribution of I_{ks} appears to be present in human ventricular muscle in the setting of sympathetic stimulation. The loss of function of I_{ks} that defines LQT1 renders these patients at risk for sudden death during exercise, whereas the presence of a normally functioning I_{ks} channel in LQT2 and LQT3 appears to be protective against lethal cardiac events during exercise. Conversely, patients with LQT3 appear to be particularly vulnerable to sudden death at slow heart rates and more protected at fast heart rates.

Autonomic Responses and Treatment Considerations in Long QT Syndrome

Standard treatment for patients with LQTS has consisted of four principal options, singly or in combination: (1) β-adrenergic blockers, (2) pacing, (3) implantable defibrillators, and (4) LCSD. β-adrenergic blockers have reduced mortality, even though they slow the heart rate, presumably by reducing after-depolarizations and triggered activity postulated to underlie torsades initiation. Cardiac pacing prevents long cycle lengths that prolong the QT interval and lead to torsades. Implantable defibrillators are indicated for protection from sudden cardiac death in patients with prior cardiac arrest, ventricular tachycardia, or syncope. Before the development and acceptance of implantable cardioverter-defibrillators (ICDs), LCSD was considered a last-line option for patients refractory to β-blockers and pacing. LCSD is now considered an option for those with refractory symptoms and may be useful in patients with frequent ICD discharges.

Understanding the molecular basis of LQTS has opened the possibility of therapies targeted at the specific molecular mechanisms underlying an individual form of channelopathy. Even as these are being developed and tested, the traditional treatment options can be reassessed. A particular type of LQTS may respond well to one form of therapy, while other traditional options may be less effective or even undesirable. Patients with LQT1, having an impaired ability to shorten QT at faster heart rates and having a higher risk of death during periods of sympathetic hyperactivity

such as exercise, might be expected to respond well to β-blockade, which limits heart rate increase and decreases after-depolarizations. In one clinical study, 81% of patients with LQT1 were able to avoid syncope, cardiac arrest, or sudden death with β-blocker therapy. In contrast, the symptom-free rate was 59% and 50% in patients with LQT2 and LQT3, respectively.

According to the International Long-QT Syndrome Registry, patients with LQT3 have a higher incident of lethal cardiac events than those with LQT1 or LQT2.[14] Patients with LQT3 are at a particularly high risk of a cardiac event during sleep when EADs may result from a slow heart rate rather than from sympathetic activation. In these patients, β-blockers may be relatively unfavorable, whereas pacing may be particularly desirable. Besides pacing, patients with LQT3 may benefit from LCSD, which will diminish norepinephrine release without slowing the heart rate.

Acquired Long QT Syndrome

Acquired LQTS is far more common than is congenital LQTS and is most frequently the result of QT interval–prolonging drugs. The impact of the ANS on initiating torsades in drug-induced LQTS is not well established, but circumstantial evidence clearly indicates an important link. Torsades in this setting is most often seen during periods of bradycardia (e.g., sleep) or following pauses in the cardiac rhythm (e.g., post–premature ventricular contraction long-short sequence) that accentuates the QT interval. Some of the best-known offending drugs are listed in Table 5-2. The majority of these drugs act by antagonizing outward (i.e., repolarizing) potassium (K^+) currents (e.g., class 1A and class 3 antiarrhythmic drugs). Other agents in this list are reported to interfere with the metabolism of drugs that directly prolong the QT interval.

Table 5-2 Partial List of Drugs Known to Prolong the QT Interval

ANTIARRHYTHMIC AGENTS
Class IA
Disopyramide
Procainamide
Quinidine
Class III
Amiodarone
Dofetilide
d-Sotalol
Ibutilide
N-acetylprocainamide (NAPA)
Sotalol
ANTIANGINAL AGENTS
Bepridil
PSYCHOACTIVE AGENTS
Phenothiazines
Thioridazine
TRICYCLIC ANTIDEPRESSANTS
Amitriptyline
Imipramine
ANTIBIOTICS/ANTI-INFECTIVES
Erythromycin
Pentamidine
Fluconazole
Pentamidine
Ciprofloxacine
Chloroquine
NONSEDATING ANTIHISTAMINES
Terfenadine
Astemizole
OTHERS
Cisapride
Methadone
Droperidol
Haloperidol

Brugada Syndrome

Brugada syndrome is caused by a genetic defect of the cardiac sodium (Na^+) channel gene leading to susceptibility to life-threatening ventricular arrhythmias. The relationship between Brugada syndrome and ANS effects is suggested by sudden death episodes in this setting often occurring during sleeping hours, possibly implicating sleep-related bradycardia as a trigger factor.

Other Forms of Idiopathic Ventricular Tachycardia

ANS activity is suspected to trigger or sustain arrhythmic events in patients with other forms of idiopathic ventricular tachycardia, but this has not been sufficiently investigated. However, a relationship has been seen in the electrophysiology laboratory in certain cases in which parenterally administered β-adrenergic agonists are often needed to induce and β-adrenergic blockade has been used to terminate both ventricular tachycardia of right ventricular outflow tract origin and ventricular tachycardia considered to be of left ventricular fascicular origin.

Autonomic Nervous System and Syncope

Syncope is best viewed as a syndrome characterized by transient loss of consciousness, usually associated with concomitant loss of postural tone and spontaneous recovery. (Table 5-3).[15] Mechanistically, syncope is most often the result of transient disturbances of cerebral blood flow. In this regard, maintenance of cerebral blood flow is normally facilitated by several factors, all of which are, to some extent, significantly influenced by the ANS. Certain of these factors include (1) cardiac output, (2) baroreceptor-induced adjustments of heart rate and systemic vascular resistance, (3) cerebrovascular autoregulation (which is, in part, contributed to by the status of systemic arterial pressure as well as by local metabolic factors, particularly pCO_2), and (3) regulation of vascular volume by the kidneys and by hormonal influences.

Neurally Mediated Reflex Syncope

Of the many causes of syncope, ANS effects are of greatest importance in the various forms of neurally mediated syncope; the *vasovagal* faint and carotid sinus syndrome are the most common among these. Other conditions in this group (e.g., postmicturition syncope, cough syncope, swallow syncope) are relatively uncommon. However, ANS effects are crucial contributors to syncope associated with orthostatic stress and are also believed to play an important contributory role in certain tachyarrhythmias and cases of valvular heart disease.

Table 5-3 Classification of the Principal Causes of Syncope

NEURALLY MEDIATED REFLEX SYNCOPE
- Vasovagal faint
- Carotid sinus syncope
- Cough/swallow syncope and related disorders
- Gastrointestinal, pelvic, or urologic origin (swallowing, defecation, postmicturition)

ORTHOSTATIC SYNCOPE
- Primary autonomic failure, Parkinson's disease
- Secondary autonomic failure (e.g., diabetic and alcoholic neuropathy)
- Drug effects

CARDIAC ARRHYTHMIAS AS PRIMARY CAUSE OF SYNCOPE
- Sinus node dysfunction (including bradycardia/tachycardia syndrome)
- Atrioventricular conduction system disease
- Paroxysmal supraventricular tachycardias
- Paroxysmal ventricular tachycardia (including torsades de pointes)
- Implanted pacing system malfunction (pacemaker syndrome)

STRUCTURAL CARDIOVASCULAR OR CARDIOPULMONARY DISEASE
- Cardiac valvular disease/ischemia
- Acute myocardial infarction
- Obstructive cardiomyopathy
- Subclavian steal syndrome
- Pericardial disease/tamponade
- Pulmonary embolus
- Primary pulmonary hypertension

CEREBROVASCULAR
- Vertebrobasilar transient ischemic attack

In the so-called *vasovagal faint*, and especially faints associated with stress or emotional upset, primary central nervous system stimuli are believed to be responsible for the trigger signals.[4] However, receptors in any of the organ systems may contribute. For instance, mechanoreceptors and, to some extent, chemoreceptors located in the atrial myocardium and in the ventricular myocardium may participate in certain neurally mediated events by initiating afferent neural signals when subjected to increased wall tension or changes in the chemical environment (e.g., myocardial ischemia). Similarly, mechanoreceptors and chemoreceptors in the central great vessels and lungs may contribute, which accounts for the reported occurrence of vasovagal faints in heart transplant recipients. The basis for apparent variations in susceptibility to vasovagal syncope among seemingly otherwise well individuals and the factors causing a faint to occur at a certain point in time still remain unknown.

Bradycardia in neurally mediated reflex syncope is primarily the result of increased efferent parasympathetic tone mediated via the vagus nerve. It may manifest as asystole, sinus bradycardia, or even paroxysmal AV block. If the bradyarrhythmia is sufficiently severe, it may be the principal cause of the faint (i.e., *cardioinhibitory* syncope). However, most patients also exhibit a *vasodepressor* picture comprising inappropriate ANS-induced vasodilatation (Figure 5-8). The mechanism of the vasodilatation is believed to be mainly the result of abrupt peripheral sympathetic neural withdrawal, although potential contributions of excess β-adrenergic tone caused by frequently associated elevated circulating epinephrine levels or altered epinephrine-norepinephrine balance are certainly considerations.

Orthostatic Syncope

The ANS participates importantly in the ubiquitous presyncopal or syncopal symptoms associated with abrupt postural changes.

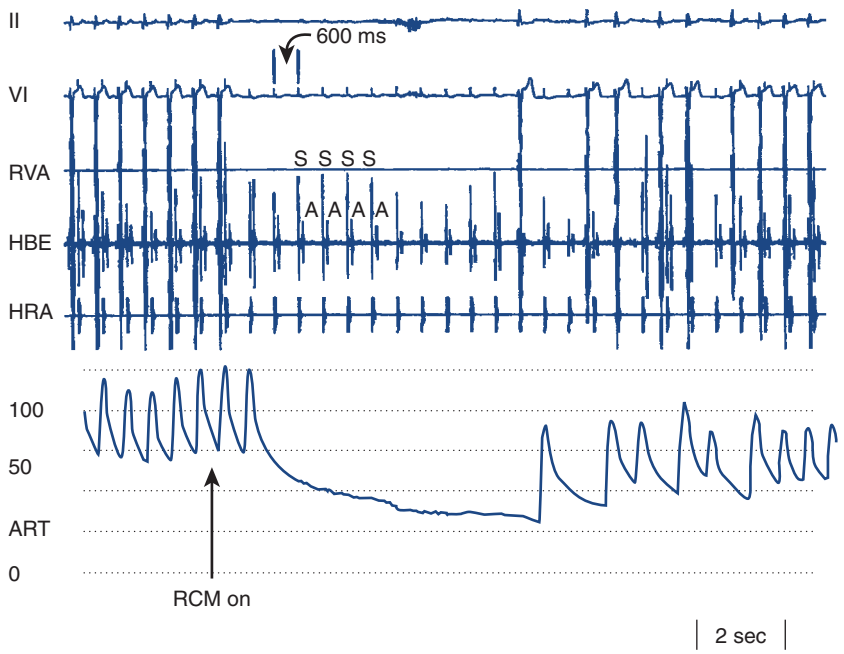

FIGURE 5-8 Electrocardiographic, intracardiac, and blood pressure tracings illustrating the development of a paroxysmal atrioventricular (AV) block during right-sided carotid sinus massage (*RCM*) of approximately 5 seconds duration. In this case, the atria (*A*, atrial electrocardiogram) are being paced (*S*, stimulus) to prevent atrial bradycardia and thereby "unmask" the AV block. Note that following return to conducted rhythm, the blood pressure remains relatively low. The latter implies the concomitant presence of a clinically significant vasodepressor component to reflex in this patient.

For the most part, these symptoms result from actual or relative central vascular volume depletion caused by inadequate or delayed peripheral vascular compensation in the presence of a change in gravitational stress (e.g., moving to upright posture). The outcome is posture-related symptomatic hypotension. Iatrogenic factors such as excessive diuresis or overly aggressive use of antihypertensive agents are important contributors.

Primary ANS disturbances are relatively rare but increasingly recognized causes of abnormal vascular control leading to syncope. Parkinsonism is perhaps the most commonly encountered neurologic disease in which ANS disturbances are associated with orthostatic hypotension as a prominent feature. ANS dysfunction may also occur in association with multiple system involvement (i.e., formerly called *Shy-Drager syndrome*). However, symptoms of orthostatic hypotension also occur in the absence of other apparent neurologic disturbances, and subtle forms may be easily overlooked. Furthermore, ANS diseases in which orthostatic hypotension is secondary in nature are far more common than those in which it is primary in nature. Examples include neuropathies of alcoholic or diabetic origin, dysautonomias occurring in conjunction with certain inflammatory conditions (e.g., Guillain-Barré syndrome), or paraneoplastic syndromes.

Primary Cardiac Arrhythmias

Primary cardiac arrhythmias imply rhythm disturbances associated with intrinsic cardiac disease or other structural anomalies (e.g., accessory conduction pathways) and are among the most frequent causes of syncope. The role played by the ANS in SN dysfunction, conduction system disturbances, and certain tachyarrhythmias has been discussed earlier. However, when syncope occurs in these settings, the basis is usually multifactorial. For instance, recent studies have implicated neural reflex vasodepression as a potential cause of syncope in patients with SN dysfunction, particularly those with paroxysmal atrial fibrillation. The same seems to be the case for other paroxysmal supraventricular tachycardias and possibly even ventricular tachyarrhythmias.

Structural Cardiovascular Disease or Cardiopulmonary Disease

The most common cause of syncope attributable to left ventricular disease is that which occurs in conjunction with acute myocardial ischemia or infarction. In such cases, the contributory factors are multiple and include not only transient reduction of cardiac output and cardiac arrhythmias but also important neural reflex effects, as previously discussed. Other acute medical conditions occasionally associated with syncope include pulmonary embolism, acute aortic dissection, and pericardial tamponade. Again, the basis of syncope is multifactorial with neural-reflex contributions probably playing an important role.

Syncope as a result of obstruction to left ventricular outflow is infrequent but carries a poor prognosis if the underlying problem is not recognized and addressed promptly (e.g., aortic stenosis, hypertrophic obstructive cardiomyopathy). The basis for the faint may, in part, be inadequate cerebrovascular blood flow caused by mechanical obstruction, but, once again (especially in the case of valvular aortic stenosis), ventricular mechanoreceptor-mediated reflex bradycardia and vasodilatation are also thought to contribute significantly.

Table 5-4 Conditions That Mimic Syncope

METABOLIC/ENDOCRINE DISTURBANCES
• Hyperventilation (hypocapnia)
• Hypoglycemia
• Volume depletion (Addison disease, pheochromocytoma)
• Hypoxemia
• Intoxication
PSYCHIATRIC DISORDERS
• Panic attacks
• Somatoform disorder (conversion reaction)
CENTRAL NERVOUS SYSTEM SUBSTRATES
• Seizure disorders (epilepsy)*
• Stroke*
• Subarachnoid hemorrhage*
• Cataplexy/Narcolepsy
**Potential nervous system–mediated cardiac damage and sudden death.*

Noncardiovascular Conditions

Noncardiovascular causes result in *syncope mimics* (Table 5-4) rather than true syncope. However, temporal lobe seizures may induce neurally mediated reflex bradycardia and hypotension (i.e., a vasovagal faint). Furthermore, certain central nervous system syncope mimics may cause worrisome ECG changes and even myocardial damage, as discussed earlier.

Metabolic or endocrine disturbances do not often cause true syncope. Acute hyperventilation provoked by or associated with panic attacks or anxiety attacks, and thus perhaps ANS related, is the most important exception. In these cases, abrupt reduction of pCO_2 levels have been suggested to result in sufficient cerebral vasoconstriction to cause syncope. However, the evidence for hyperventilation causing frank syncope is weak at best.

The role of the ANS in the so-called *chronic fatigue syndrome* has been the source of some controversy following publication of findings suggesting an overlap with tilt-induced hypotension–bradycardia. It is most likely that ANS effects do play a role, but the magnitude of the impact is probably quite variable, and the evidence supporting a close connection between chronic fatigue syndrome and neurally mediated reflex syncope is far from convincing at this stage.

SUMMARY

The ANS has an impact on cardiac electrophysiology and the risk of arrhythmia through a variety of direct and indirect effects. For the most part, current understanding of these effects remains superficial. Nonetheless, progress has been made in terms of the following:

1. Better understanding of central nervous system sites responsible for cardiac effects in certain disease conditions
2. The multiple neurotransmitters and neuromodulators contributing to arrhythmogenesis
3. The potential role of spinal and neural stimulation for modifying ANS impact on susceptibilty to arrhythmia

4. The possible impact of neural ablation at the cardiac level with respect to arrhythmogenicity as well as antiarrhythmic potential

5. The role of certain pharmacologic agents in moderating the risk of arrhythmia through (at least in part) their modulation of ANS effects on the heart

This chapter has presented only some of the more important known relationships between cardiac arrhythmias and ANS effects. Space constraints precluded an in-depth review of the topic, and much still remains unknown. However, the authors hope that some readers will be prompted to delve further into the important, but still underappreciated, field of brain–heart interaction.

Acknowledgment

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CHAPTER 6

Genomics and Principles of Clinical Genetics

David J. Tester and Michael J. Ackerman

The molecular millennium has provided researchers with the essential tools to identify the underlying genetic substrates for thousands of genetic disorders, most of which are rare and follow Mendelian inheritance patterns. Through advances in molecular cardiology research, the genetic underpinnings of potentially lethal electrical diseases of the heart or cardiac *channelopathies*, including long QT syndrome (LQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT), Brugada syndrome (BrS), short QT syndrome (SQTS), Andersen-Tawil syndrome (ATS), progressive cardiac conduction disease, familial atrial fibrillation, and idiopathic ventricular fibrillation have been identified. Additionally, the molecular basis for cardiomyopathic processes susceptible to sudden arrhythmic death—dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), left ventricular noncompaction syndrome (LVNC), and arrhythmogenic right ventricular cardiomyopathy (ARVC)—are now better understood.

Marked genetic and clinical heterogeneity are hallmark features of these disorders with multiple genes and allelic variants being responsible for their fundamental pathogenic mechanisms. To date, hundreds of gene mutations at the single-nucleotide level have been elucidated in genes responsible for this consortium of divergent electrical disorders of the heart. Most epitomize pathogenic disease-causing mutations only discovered in disease cohorts, and some are common or rare genetic polymorphisms identified in disease and in health that may or may not bestow an increased risk for arrhythmias in certain settings. Genetic testing for several of these heritable channelopathies and cardiomyopathies is currently available through expert clinical-based laboratories, research-based laboratories, or both.

The purpose of this chapter is to provide the reader with a foundational understanding of genomics and clinical genetic principles. We present a primer on essential molecular genetics, review some principles of genetic testing, explore laboratory techniques used in genetic testing, and examine some of the future directions in genomics-related research in cardiac electrophysiological diseases.

Elementary Understanding of Molecular Genetics

General Organization and Structure of the Human Genome

Ushering in the molecular millennium, the original draft of the Human Genome Project was completed in February 2001 through a multinational effort and has provided the architectural blueprints of essentially every gene in the human genome.[1,2] The human genome embodies the total genetic information, or the deoxyribonucleic acid (DNA) content of human cells, and is dispersed among 46 units of tightly packaged linear double-stranded DNA called *chromosomes* (22 autosomal pairs and the 2 sex chromosomes X and Y).[3–5] The 24 unique chromosomes are differentiated visually by chromosome-banding techniques (karyotype analysis) and are classified mainly according to their sizes. Each nucleated cell in a living organism normally has a complete and exact copy of the genome, which is largely made up of single-copy DNA with specific sets of DNA sequences represented only once per genome. The remainder of the genome consists of several classes of either perfectly repetitive or imperfectly repetitive DNA elements. The human genome contains nearly three billion base pairs of genetic information containing the molecular design for approximately 35,000 genes whose highly orchestrated expression renders us human.[1,2] Through the mechanism of alternative splicing of the coding sequences within the genes, these approximately 35,000 genes are thought to produce more than 100,000 proteins.[6]

Basic Structure of DNA and the Gene

In 1953, Watson and Crick described the basic structure of DNA as a polymeric nucleic acid macromolecule comprising deoxyribonucleotides or "building blocks," of which there are four types: (1) adenine (A), (2) guanine (G), (3) thymine (T), and (4) cytosine (C) (Figure 6-1).[3-5] DNA is a double-stranded molecule made up of two anti-parallel complementary strands (sense and antisense strands) that are held together by noncovalent (loosely held) hydrogen bonds between complementary bases, where G and C always form base pairs and T and A always pair (see Figure 6-1). In the literature, typically only the DNA sequence of the sense strand (the strand that transcribes the genetic message in the form of messenger RNA [mRNA]) is provided, and the antisense sequence is inferred through these complementary base pairing rules such that if the sense strand reads AGCCGTA, the antisense strand would be TCGGCAT. DNA natively forms a double helix that resembles a right-handed spiral staircase. DNA elements that store genetic information in the form of a genetic code are called *genes* (Figure 6-2, *A*).

Gene sequences account for approximately 30% of the genome; however, less than 2% of the genomic DNA is actually made up of protein-encoding sequences within genes called *exons*. Between the exons are intervening DNA sequences called *introns*, which are not a part of the genetic code but may host gene regulatory elements. The approximately 35,000 genes of the genome range

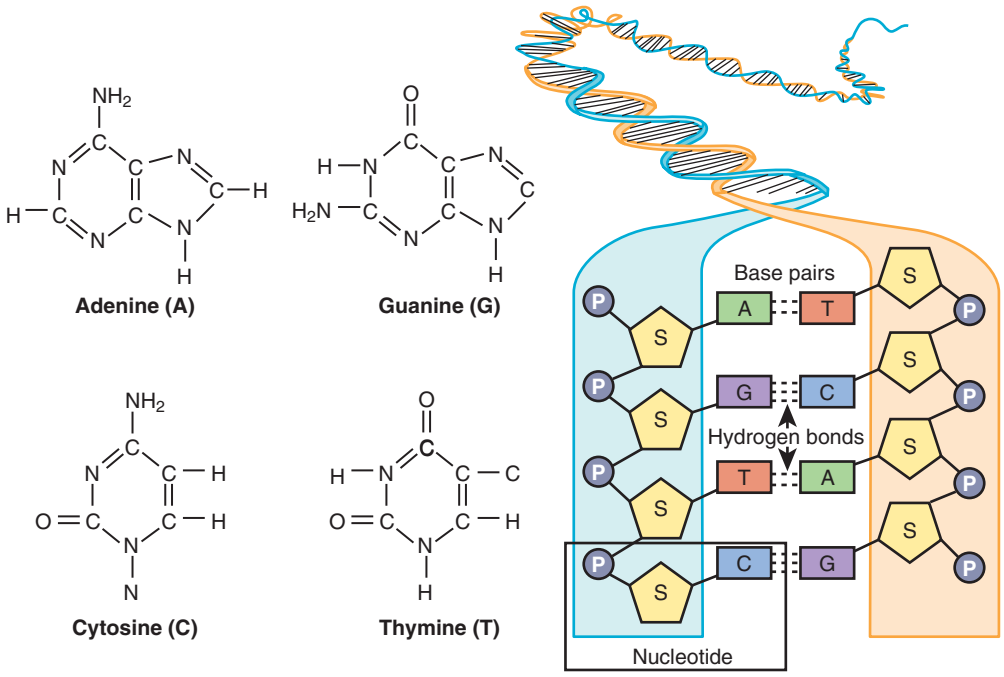


FIGURE 6-1 The chemical structure of adenine (A), guanine (G), cytosine (C), and thymine (T) and the general organization of DNA, illustrating complimentary base pairing via hydrogen bonds between C and G and between A and T. As defined by the box, a single nucleotide consists of a phosphate (P) group, deoxyribose sugar (S), and a base (A, C, G, or T).

in size from one of the smallest of human genes *IGF2* (which contains 252 nucleotides and encodes insulin-like growth factor II) to the largest gene *DMD* (which consists of 2,220,223 nucleotides and encodes dystrophin). The *DMD* gene consists of over 2 million nucleotides, but only 0.5% of the gene (11,055 nucleotides spanning 79 exons) actually encodes for the dystrophin protein. Typically upstream (20 to 100 bp) from the first exon is a regulatory element called the *promoter*, which controls transcription of the hereditary message as determined by the gene sequence. Proteins known as *transcription factors* bind to specific sequences within the promoter region to initiate transcription of the genetic code. The first and last exons of the gene usually consist of an ***u****n****t***ranslated ***r***egion (5′ and 3′ UTR, respectively) that is not a part of the genetic code but may host additional sequence elements that regulate gene expression.[4]

Transfer of the Genetic Code: The Central Dogma of Molecular Biology

DNA sequences in the form of genes contain an encrypted genetic message for the assembly of polypeptides or proteins that serve the biologic function of the cell. This inherited genetic information is transferred to a completed product (protein) through a two-step process.[5] First, *transcription*, which is the process by which the genetic code is transcribed into mRNA, begins with the dissociation of the double-stranded DNA molecule and the formation of a newly synthesized complementary ribonucleic acid (RNA) molecule (Figure 6-2, *B*). Of note, instead of thymine (T), the nucleotide uracil (U) is in its place on the newly transcribed RNA strand; like thymine, uracil pairs with adenine. The initial mRNA molecule (pre-mRNA) matures into a transferable genetic message by undergoing RNA splicing to expunge the noncoding intronic sequences from the transcript. The vast majority of introns begin with the di-nucleotides GT and end with the di-nucleotides AG. These highly conserved splicing recognition sequences at the beginning and end of the exon-intron and intron-exon boundaries are referred to as the *splice donor sites* and *splice acceptor sites*, respectively. These nucleotides allow the RNA splicing apparatus to know precisely where to cleave the sequence in order to excise the noncoding regions (introns) and bring the coding sequences (exons) together. Normal alternative splicing provides the inclusion or exclusion of specific exonic sequences from the mature mRNA transcript to potentially produce several partially unique gene products (proteins) from a single gene that may have unique biologic functions, tissue specificity, or cellular locations. If normal splice recognition sites are disrupted, splicing errors may occur and result in abnormal protein product formation and consequently create a pathogenic substrate for disease. While all cells of the human body, except red blood cells, contain a copy of the genome, not all genes are expressed in all cells. While some genes are ubiquitously expressed, others have exclusive tissue specificity.

The second process, *translation*, involves the decoding of the mRNA-encrypted message and the assembly of the intended polypeptide (protein) that will serve a biologic role (Figure 6-2, *C*). Polypeptides are polymers of linear repeating units called *amino acids*. The assembly of a polypeptide or protein is directed by a triplet genetic code, or codon (three consecutive bases); 64 codons encode for 20 distinct amino acids or the termination of protein assembly. One codon, AUG (ATG on DNA) encodes for the amino acid methionine and is always the first codon (start codon) to start the message and signifies the beginning of the open reading frame (ORF) of the mRNA. Each codon in the linear mRNA is decoded sequentially to give a specific sequence of

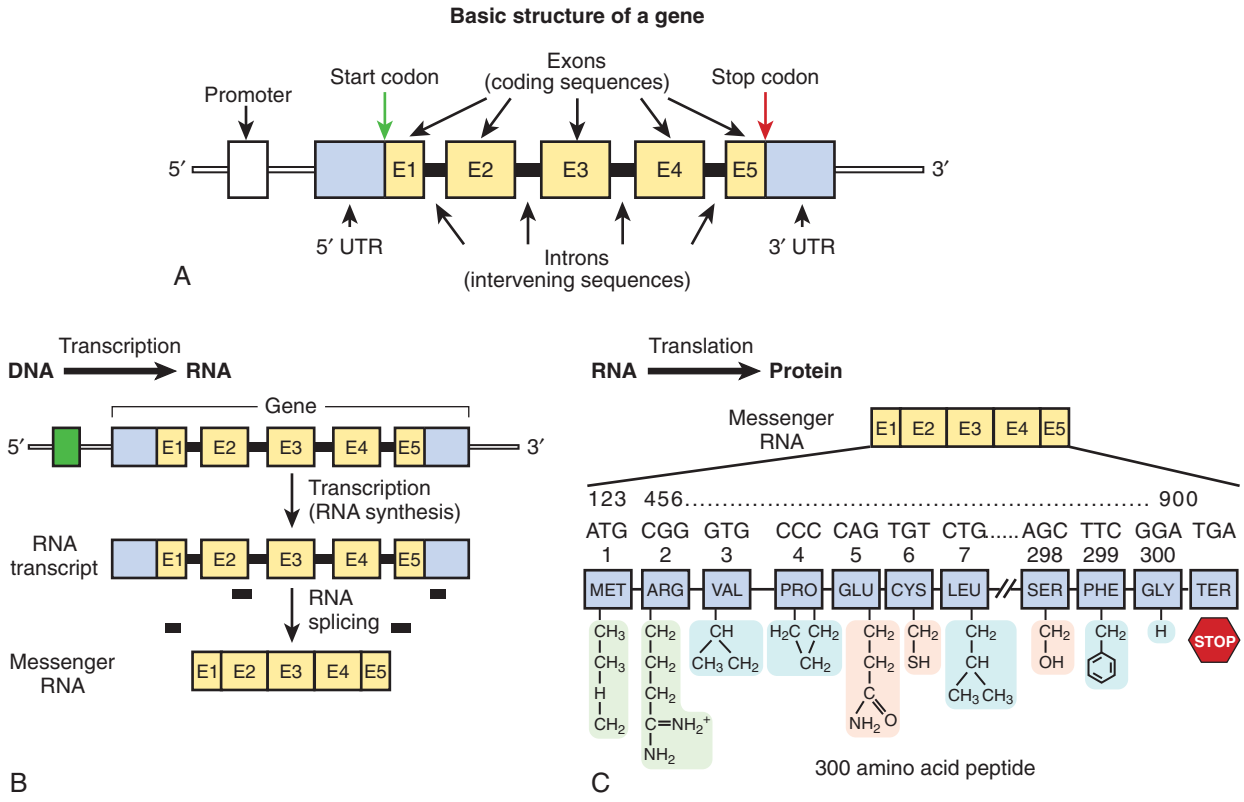


FIGURE 6-2 A, The basic structure of a gene consisting of DNA segments (exons) that encode for a protein product. Between the exons are intervening sequences called *introns*. At the 5′ end of the gene is a regulatory element called the *promoter*, which initiates transcription. At the 5′ and 3′ ends are "untranslated" regions that are considered parts of the first and last exons, respectively. These sequences are not a part of the genetic code but may contain additional regulatory elements. A start codon begins the translation of the genetic message, as encoded by the gene, and a stop codon terminates the message. **B,** Transcription. **C,** Translation. **B** and **C** depict the two-step process of the transfer of genetic information from DNA to RNA to protein.

amino acids that are covalently linked through peptide bonds and ultimately make up a protein. Three codons, UAA, UAG, and UGA, serve as termination codons that stop the linearization of the peptide and signal a release of the finished product. The genetic code is said to be "degenerate" in that specific amino acids may be encoded by more than one codon. For example, when varying the nucleotide in the third position of a codon, often the message does not become altered (the codons GUU, GUC, GUA, and GUG all encode for the amino acid valine).

Each of the 20 amino acids has a unique side chain that provides for its characteristic biochemical properties. Some amino acids are negatively charged and have acidic properties, and some others are positively charged and have basic properties. Some amino acids are considered polar and hydrophilic (water loving), and others are nonpolar and hydrophobic (water fearing). Some amino acids of the same property have different-sized side chains. It is the unique amino acid sequence occurring within a protein that dictates its three-dimensional structural and biologically functional properties. If amino acids of different chemical properties and steric sizes were exchanged, this might alter the overall structure and function of that protein and provide a pathogenic substrate for disease.

The accepted nomenclature for naming and numbering nucleotides and codons typically uses the DNA sense strand of the gene and begins with the A of the start codon (ATG) representing nucleotide 1 and ATG as codon 1. Usually, only consecutive nucleotides within the coding region of the gene are numbered. Intronic nucleotides are typically numbered relative to either the first or last nucleotide in the exon preceding or following the intron. For example, the LQT2-associated KCNH2 splice error mutation L799sp (exon 9, nucleotide substitution: 2398 +5 G > T), results from a G-to-T substitution in the intron, five nucleotides from exon 9, where nucleotide 2398 is the last nucleotide in the ninth exon. This substitution results in a splicing error following the last codon of the exon [codon 799 encoding for leucine (L)].[7]

Non–protein-coding genes are transcribed as well. MicroRNAs (miRNAs) are small ~22 nucleotide-long RNAs that function to inhibit gene expression of targeted genes by binding in a partially complementary fashion to miRNA recognition sequences within the 3′ UTR of target mRNA transcripts and negatively regulate protein-encoding gene mRNA stability or translation into protein.[8-10] Each miRNA is thought to regulate the expression of hundreds of target genes at the post-transcriptional mRNA level. To date, hundreds of human miRNAs have been described, three (miR-1, miR-133, and miR-208) of which are abundant in the heart and serve as key regulators of heart development, contraction, and conduction.[8]

Modes of Inheritance: Genetics of Disease

On average, two unrelated individuals share 99.5% of their approximately three billion nucleotide genomic DNA sequence, and yet their genomic DNA sequences may vary at millions of single nucleotides or small sections of DNA nucleotides dispersed throughout their genomes.[2,11] It is this inherited variation in the genome that is the basis of human and medical genetics. Reciprocal forms of genetic information at a specific locus (location) along the genome are called *alleles*.[3] An allele can represent a segment of DNA or even a single nucleotide. The normal form of genetic information is often considered the *wild-type* or *normal* allele, and the allele at variance from the normal is often referred to as the *mutant* allele.

These normal variations at specific loci in the DNA sequence are called *polymorphisms*. Some polymorphisms are very common, and others represent rare genetic variants. In medical genetics, a disease-causing mutation refers to a DNA sequence variation that embodies an abnormal allele and is not found in the normal healthy population but subsists only in the diseased population and produces a functionally abnormal product. An individual is said to be *homozygous* when he or she has a pair of identical alleles, one paternal (from father) and one maternal (from mother). When the alleles are different, then that individual is said to be *heterozygous* for that specific allele. The term *genotype* refers to a person's genetic or DNA sequence composition at a particular locus or at a combined body of loci, and the term *phenotype* refers to a person's observed clinical expression of disease in terms of a morphologic, biochemical, or molecular trait.[5]

Genetic disorders are described by their patterns of familial transmission (Figure 6-3). The four basic modes of inheritance are (1) autosomal dominant, (2) autosomal recessive, (3) X-linked dominant, and (4) X-linked recessive.[3] These modes, or patterns, of inheritance are based mostly on the type of chromosome (autosome or X-chromosome) the gene is located on and whether the phenotype is expressed only when both maternal-derived and paternal-derived chromosomes host an abnormal allele (recessive) or if the phenotype can be expressed even when just one chromosome of the pair (maternal or paternal) harbors the mutant allele (dominant).

Many monogenic-appearing genetic disorders are often found to be genetically heterogeneous once analyzed completely. Genetically heterogeneous disorders have a related clinical phenotype but arise from multiple different genotypes. Genetic heterogeneity may be a consequence of different mutations at the same locus (gene), a result of mutations at different loci (genes), or both. For example, hundreds of unique gene mutations now identified in 12 different genes have been shown to be pathogenic for LQTS (LQT1–LQT12).

In many genetic disorders, the abnormal phenotype can be clearly distinguished from the normal one. However, in certain disorders, the abnormal phenotype is completely absent in some individuals (asymptomatic, with no discerning clinical markers) harboring the disease-causing mutation, while some others show significant variations in the expression of the phenotype in terms of clinical severity, age at onset, and response to therapy. *Penetrance* is the probability that an abnormal phenotype, as a result of a mutant gene, will have any expression at all. When the frequency of phenotypic expression is less than 100%, the gene is said to show *reduced* or *incomplete penetrance* (Figure 6-4).

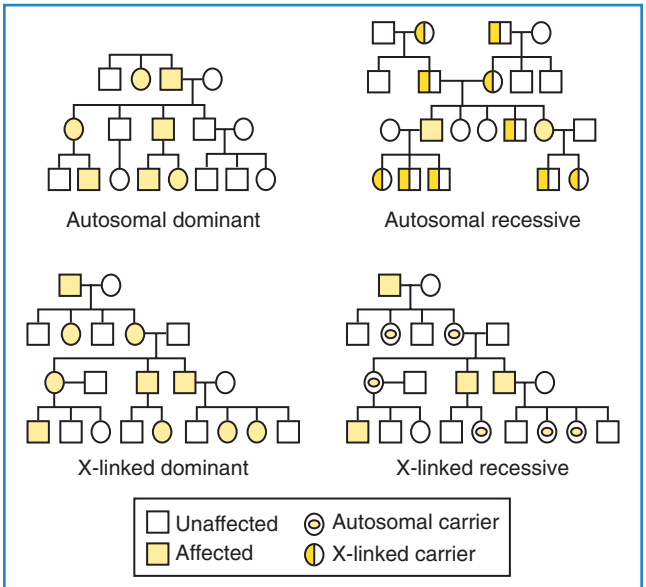


FIGURE 6-3 Pedigrees exemplifying four different modes of inheritance: autosomal dominant, autosomal recessive, X-linked dominant, and X-linked recessive.

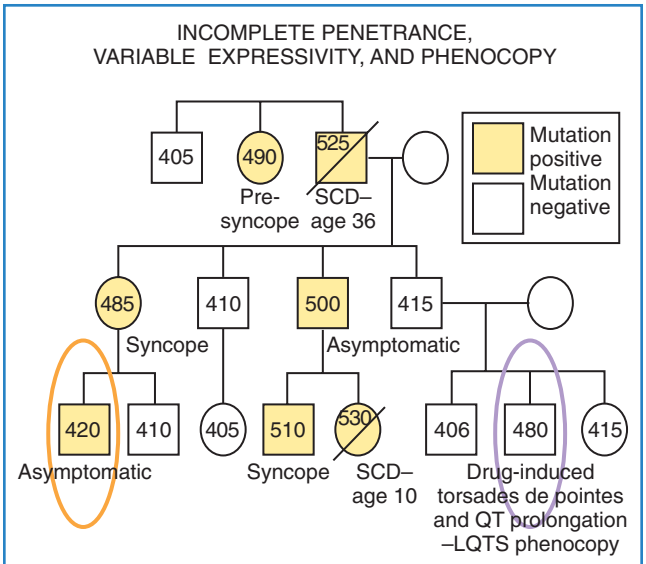


FIGURE 6-4 A hypothetical long QT syndrome pedigree demonstrating incomplete or reduced penetrance (mutation-positive host with absence of a clinical marker for the disease; asymptomatic with a nondiagnostic QTc—*orange oval*) and variable expressivity (expression of the disorder ranging from symptom-free to sudden cardiac death [SCD] at a young age). The *purple oval* highlights a case of LQTS phenocopy, where a mutation-negative relative has experienced torsades de pointes and a prolonged QTc in the setting of a medication known for this unwanted or adverse drug response. The numbers provided represent the QTc as measured in milliseconds. (*Modified from Tester DJ, Ackerman MJ: Genetic testing. In Gussak I, Antzelevitch C, editors:* Electrical diseases of the heart: Genetics, mechanisms, treatment, prevention, *London, 2008, Springer.*)

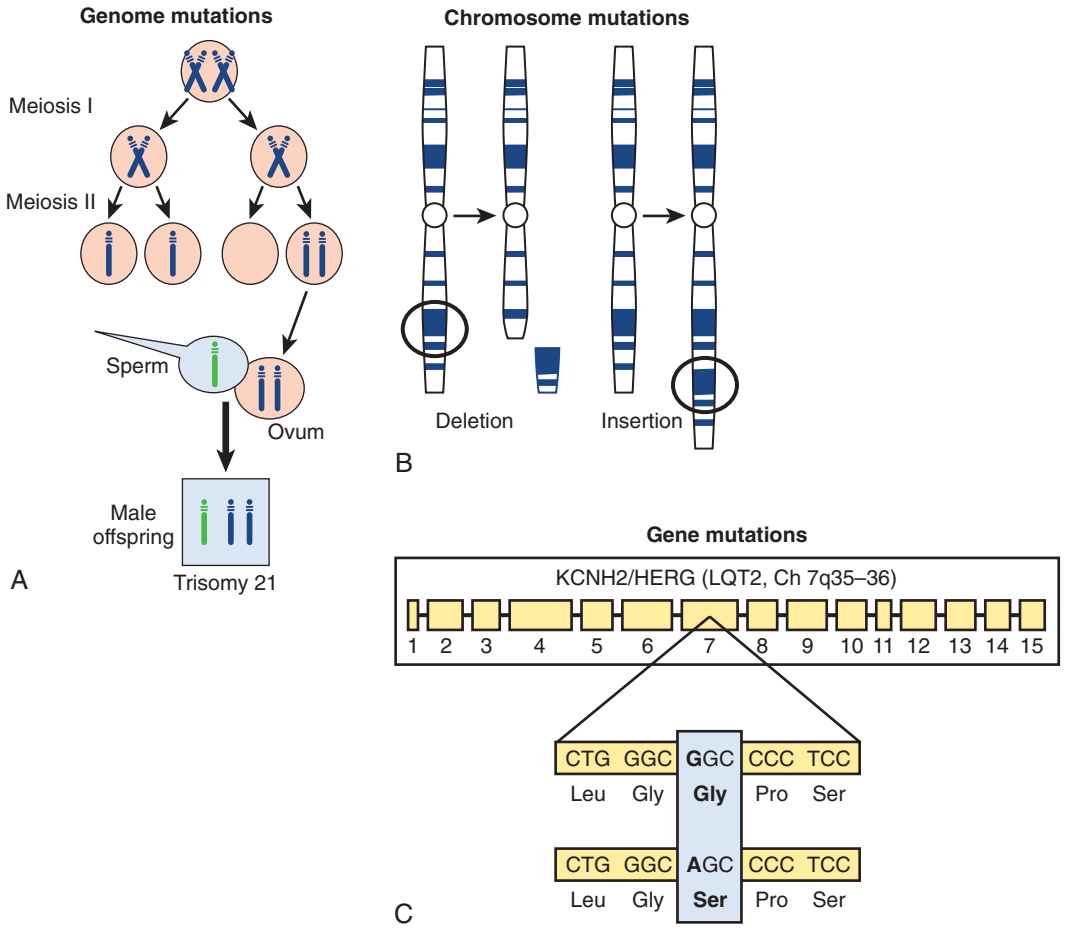


FIGURE 6-5 A, Genome mutations involve the abnormal segregation of chromosomes during cell division. **B,** In chromosome mutations, major portions of chromosomes may be deleted or duplicated. **C,** Gene mutations involve changes at the nucleotide level and disrupt the normal function of a single gene product. (*Modified from Tester DJ, Ackerman MJ: Genetic testing. In Gussak I, Antzelevitch C, editors:* Electrical diseases of the heart: Genetics, mechanisms, treatment, prevention, *London, 2008, Springer.*)

Expressivity refers to the level of expression of the abnormal phenotype, and when the manifestations of the phenotype in individuals who have the same genotype are diverse, the phenotype is said to exhibit *variable expressivity* (see Figure 6-4). A *phenocopy* represents an individual who displays the clinical characteristics of a genetically controlled trait but whose observed phenotype is caused by environmental factors rather than determined by his or her genotype (see Figure 6-4). For example, an individual experiencing drug-induced *torsades de pointes*, a prolonged QT interval on ECG, or both may represent a phenocopy of LQTS. Reduced penetrance, variable expressivity, and observed phenocopies create significant challenges for the appropriate diagnosis, pedigree interpretation, and risk stratification of some genetic disorders, particularly those involving electrical disorders of the heart.

Mutation Types in Human Genetic Disease

The DNA of the human genome is highly stable from generation to generation but not immutable. Instead, it is vulnerable to an array of different types of germline (heritably transmitted) and somatic mutations. In general, mutations can be classified into three categories: (1) genome mutations, (2) chromosome mutations, and (3) gene mutations (Figure 6-5).[3,5] Genome mutations are caused by the abnormal segregation of chromosomes during cell division and are illustrated by trisomy 21 (Down syndrome), which results from abnormal cells containing three copies of chromosome 21 instead of the two copies found in a normal cell (see Figure 6-5, *A*) and Turner's syndrome (XO), in which the Y chromosome is omitted.

Chromosome mutations involve the structural breakage and rearrangement of chromosomes during cell division, when major portions of a particular chromosome may be missing (deleted) or inserted (Figure 6-5, *B*). For example, patients with chromosome 22 microdeletion syndrome have variable size deletions involving the long arm of chromosome 22 (22q11.2). Large deletions and duplications of hundreds to thousands of base pairs may lead to copy number variations of genetic material, which may serve as a pathogenic basis for disease. Such gene rearrangements may involve the deletion or duplication of many genes, single genes, or even single exons within specific genes.

Gene mutations involve alterations at the nucleotide level that disrupt the normal function of a single gene product (Figure 6-5, *C*). Such mutations are classified into three basic categories:

(1) nucleotide substitutions, (2) deletions, and (3) insertions. If a single nucleotide substitution, which is the most common, occurs in the coding region (exon), the result may be either a synonymous (silent) mutation in which the new codon still specifies the same amino acid or a nonsynonymous mutation in which the altered codon encodes for a different amino acid or terminates further protein assembly (i.e., introduces a premature stop codon) (Figure 6-6, *A*). The term *missense mutation* is also used to indicate a single nucleotide substitution that results in the exchange of a normal amino acid in the protein for a different one (see Figure 6-6, *A*). Importantly, a missense mutation may or may not result in a functionally perturbed protein that leads to a disease phenotype. The functional consequence of a missense mutation may depend on the differences in biochemical properties between the amino acids that are being exchanged, the location in the protein at which the exchange occurs, or both. A *nonsense mutation* is a nonsynonymous mutation resulting in a substitution of an amino acid for a stop codon (see Figure 6-6, *A*). A nonsense mutation results in a truncated (shortened) gene product at the location of the new stop codon. The functional effects could range from no appreciable difference to functional lethality (a nonfunctioning protein), depending on where in the protein a nonsense mutation occurs.

Intronic (noncoding) base substitutions may also result in an altered gene product. The normal process by which intronic sequences are excised from newly transcribed RNA to create a mature mRNA product relies on specific nucleotide sequences located at the intron-exon (acceptor site) and exon-intron (donor site) boundaries. Base substitutions within these highly conserved sequences can result in abnormal splicing of the immature RNA. In some cases, entire exons can be skipped (deleted), or entire introns may be included in the mature mRNA.

Gene mutations may also involve insertions and deletions of nucleotides that can be as small as a single nucleotide or as large as several hundreds to thousands of nucleotides in length. Most of these insertions and deletions occurring in the exon alter the "reading frame" of translation at the point of the insertion or deletion and produce a new sequence of amino acids in the finished product, the so-called *frame-shift mutation* (Figure 6-6, *B*). Many frame-shift mutations often result in a different product length from the normal gene product by creating a new stop codon, which produces a shorter or longer gene product, depending on the location of the new stop codon. In-frame insertions and deletions occur when three nucleotides are affected (see Figure 6-6, *B*) and result in a single amino acid or multiple amino acids being removed or added without affecting the remainder of the transcript.

Notably, not all nucleotide alterations (mutations) create a new gene product that causes or modifies a clinical disease state. A DNA sequence variation that may (nonsynonymous) or may not (synonymous) alter the encoded protein is called a *common polymorphism* if present in at least 1% of the normal population. Although not pathogenic or disease causing, nonsynonymous single nucleotide polymorphisms can, indeed, be *functional* polymorphisms and exert a significant effect on how endogenous and exogenous triggers are handled. Functional polymorphisms are sought to explain the variations observed in humans with regard to therapeutic and side-effect profiles of pharmaceutical agents (*pharmacogenomics*) or to rationalize the heterogeneous expression of disease in families harboring the same, presumptive disease-causing mutation (i.e., *modifier genes*).

Principles of Genetic Testing

Currently, nearly 1500 genetic tests (www.GeneTests.org) are clinically available and are offered by nearly 600 diagnostic laboratories worldwide. In addition, many genetic tests are available on a research basis. Most current genetic tests are performed to identify gene mutations in rare genetic disorders that follow Mendelian inheritance patterns (such as cystic fibrosis, Huntington chorea, sickle cell anemia, and Tay-Sachs disease) or for more complex conditions (such as breast, prostate, and colon cancers). In cardiology, clinical genetic testing is available for most of the cardiac channelopathies and cardiomyopathies.

General Techniques Used in Genetic Testing at the Single Gene Level

Typically, 5 to 15 mL whole blood obtained from venipuncture placed in ethelenediaminetetraacetic acid (EDTA)–containing tubes ("purple top") is requested as the genomic DNA source for either research-based or clinic-based genetic testing.[5] DNA isolated from a buccal (mouth cheek) swab does not provide a sufficient amount of DNA for comprehensive genetic testing, but it may be adequate for mutation-specific confirmatory testing of family relatives. Umbilical cord blood may be acquired at the time of birth for newborn screening. For autopsy-negative cases of sudden unexplained death, a cardiac channel genetic test can be completed on DNA isolated from EDTA blood, a piece of frozen ventricle myocardium tissue, or tissue from any other organ (liver, spleen, thymus) with a high nucleus to cytoplasm ratio.[12] DNA from paraffin-embedded tissue, however, remains an unreliable source.[13] Both research-based and clinical genetic testing typically

FIGURE 6-6 Compared with the depicted normal DNA, the amino acid (single-letter abbreviation) sequence and the resulting peptide sequence are examples of nucleotide substitutions and deletion mutations. The amino acids of the peptide sequence are color coded to represent their unique biophysical properties, in which yellow represents nonpolar hydrophobic amino acids, green represents polar hydrophilic amino acids, pink represents negatively charged acidic residues, and blue represents positively charged basic amino acid residues. A nucleotide change results in a new codon that encodes for the following: **A,** The same amino acid as the normal sequence is a silent mutation. **B,** A different amino acid is a missense mutation. **C,** A termination codon is a nonsense mutation. **D,** A deletion of a single nucleotide (G) that results in a shift of the open reading frame of the transcript, thus representing a frame-shift mutation. Note how the sequence of amino acids has been altered from this point forward. Although not illustrated here, frame-shift mutations as a result of a deletion or insertion of nucleotides often lead to a premature stop codon and thus a truncated protein. **E,** The deletion of three nucleotides (GAC) produces an in-frame deletion of a single amino acid (aspartic acid, Asp) in the protein. The remaining amino acid sequence is unaltered. Three nucleotide insertions (not shown) can have a similar effect in which an amino acid is inserted into the protein product.

Single nucleotide substitutions

Normal

ATG CCG GAC TCG TTT CTC GGG

M P D S F L G

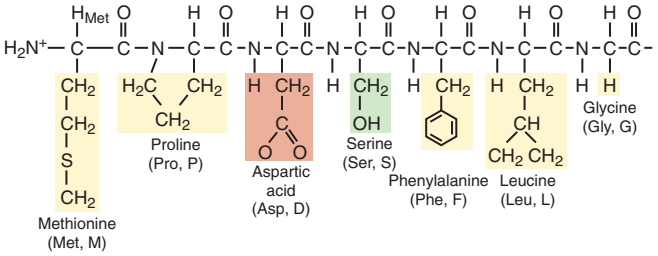
Silent

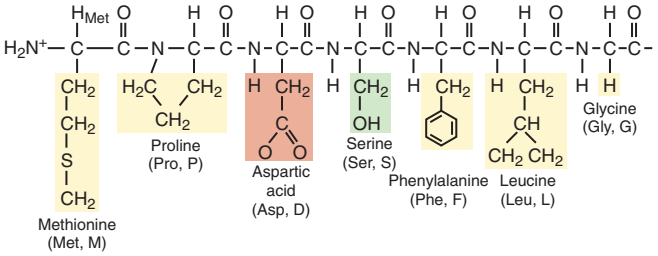
(G>A, Ser to Ser)

ATG CCG GAC TCA TTT CTC GGG

M P D S F L G

A





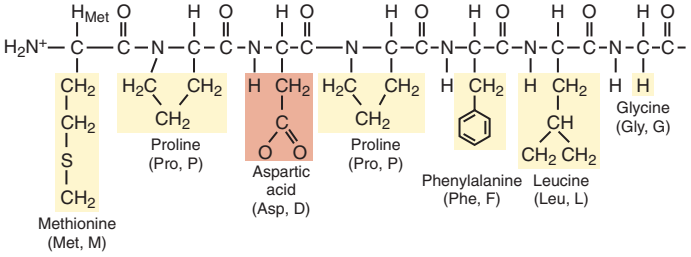
Missense

(T>C, Ser to Pro)

ATG CCG GAC CCG TTT CTC GGG

M P D P F L G

B



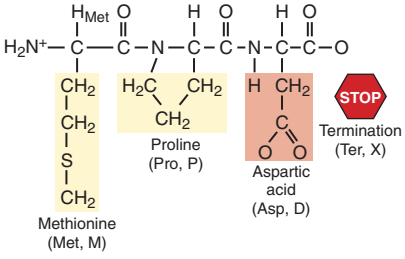
Nonsense

(C>A, Ser to Ter)

ATG CCG GAC TAG TTT CTC GGG

M P D X F L G

C



Deletions/insertions

Frame shift

Deletion of a "G"

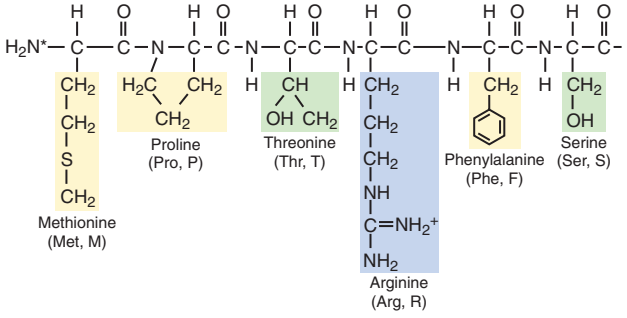
ATG CCG ACT CGT TTC TCG GGT

M P T R F S G

G

(Met, M)

D



In-frame deletion

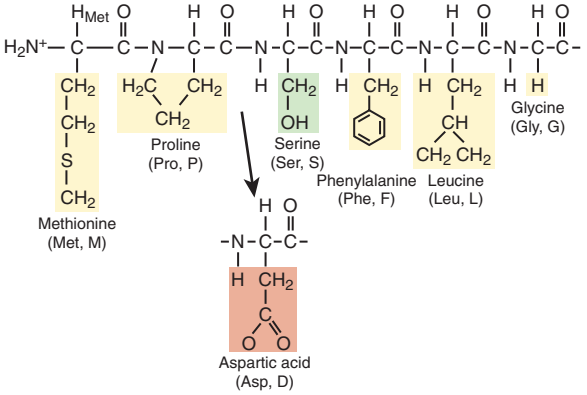
Deletion of a "GAC"

ATG CCG TCG TTT CTC GGG

M P S F L G

GAC D

E



require signed and dated informed consent to accompany the samples to be tested.

In genetic testing, the identification of gene mutations usually involves the polymerase chain reaction (PCR) technique. PCR is used to amplify many copies of a specific region of DNA sequence within the gene of interest. Typically, 20 to 25 base pair (bp) forward and reverse single-stranded DNA oligonucleotide primers are designed to be complementary to reciprocal intronic DNA sequences flanking the exon of interest to produce PCR products (200 to 400 bp in length) containing the desired DNA sequence to be analyzed. A well-optimized PCR reaction will yield millions of copies of *only* the specific sequence of interest.[14]

PCR amplification is often followed by the use of an intermediate mutation detection platform such as single-stranded conformational polymorphism (SSCP), denaturing gradient gel electrophoresis (DGGE), or denaturing high-performance liquid chromatography (DHPLC). These methods are used to inform the investigator of the presence or absence of a DNA sequence alteration in the samples examined. DHPLC is currently one of the most sensitive and accurate technologies to discover unknown gene mutations.[15,16] DHPLC is based on the creation and separation of double-stranded DNA fragments containing a mismatch in the base pairing between the wild-type and mutant DNA strands, known as *heteroduplex DNA*. This mismatch in base pairing creates a weakness in the double-stranded DNA complex. PCR products are injected onto a solid phase column and eluted by using a linear acetonitrile gradient. Samples containing heteroduplex DNA (as a result of a heterozygote DNA alteration) will elute from the column faster than will normal homoduplex (perfect match) DNA fragments, thus providing an abnormal elution chromatogram profile.[14]

While intermediate mutation detection platforms help the investigator identify which samples (PCR products) contain mutations, direct DNA sequencing must be used to determine the precise underlying DNA alteration(s). Review and comparison of the resulting sequence chromatograms and the published wild-type DNA and amino acid sequence for the gene or protein of interest will allow for the determination of whether the underlying DNA change is protein altering and potentially pathogenic or a nonpathogenic normal variant.

In some cases, the use of an intermediate mutation detection platform is bypassed for direct DNA sequencing of all samples examined; this is typically the case in clinical genetic testing. Though this direct approach to mutational analysis is presently more expensive, it may accelerate the detection of mutation.

Together, these techniques provide excellent precision and accuracy to detect (1) single nucleotide substitutions that produce missense, nonsense, and splice site mutations and (2) small insertions and deletions. However, large whole-gene, multiple-exon, or single-exon deletions or duplications elude detection by this approach. Another technique, *multiple ligation probe analysis* (MLPA), however, will allow for the identification of such large gene rearrangements, which have recently been reported to account for as much as 5% to 10% of patients with LQTS with an otherwise negative genetic test.[17-19] In contrast to the traditional PCR/DHPLC/DNA sequencing approach to mutation detection, MLPA relies on specifically engineered probes that are designed to bind to gene sequences (typically exonic sequences) and allows for the detection of copy number changes of the target sequence.[19] Large deletion mutations, for example, will result in a loss of copy number of the target (exon), and duplications are represented as an increase in copy number.

Since first described in 1977 by Sanger and colleagues, advances in DNA sequencing methodologies and technical instrumentation have rapidly evolved DNA sequencing capacity and genetic information output. Massively parallel sequencing or *next-generation sequencing technology* is on the verge of allowing investigators to go well beyond the current capacity of generating DNA sequence reads of 600 to 800 nucleotides for 96 samples per instrument run to the ability to process from hundreds of thousands to tens of millions of base sequence reads in parallel. Through the use of next-generation sequencing and multiplex exon amplification, the possibility exists for molecular interrogation of an individual's complete library of annotated protein-coding sequences in a single reaction or a few reactions with remarkable cost-effectiveness.[20,21]

Genetic Testing: Benefits, Limitations, and Family Matters

Genetic testing may have diagnostic value for symptomatic individuals by elucidating the exact molecular basis for the disorder, by establishing a definitive molecular diagnosis or disease prediction when the clinical probability of the disorder is inconclusive, by confirming or excluding the presence of a disease-causing mutation in presymptomatic individuals with a family history of a genetic disorder, and by helping personalize treatment recommendations and management of a patient's specific disorder by characterization of the precise genotype.[22,23] Genetic testing may also prove carrier status in those concerned about recessively inherited disorders such as cystic fibrosis.

While benefits such as certainty of diagnosis, increased psychological well being, and greater awareness of prophylactic treatment and risk stratification may be achieved, genetic testing may also contribute to an increase in risk for depression, anxiety, guilt, stigmatization, discrimination, family conflict, and unnecessary or inappropriate use of risk-reducing strategies.[24] Patients therefore need to be well informed on the implications of genetic testing and should not be coerced into providing a DNA sample for analysis. Full disclosure should be given as to the intent of the research or clinical genetic test, the results of the analysis, and who will have access to the results.[5]

Genetic information must be considered private and personal information that has the potential to be mishandled.[25,26] Disclosure of confidential information to third parties such as insurance companies or employers can have negative consequences for the patient in the form of genetics-based discrimination. In May 2009, the Genetic Information Nondiscrimination Act (GINA) was signed into federal law prohibiting employers and health insurers from denying employment or insurance to a healthy individual on the basis of genetic test results.[27]

Genetic testing is appreciated now as a family as well as an individual experience.[24] Even though genetic testing is performed on an individual's genetic material, the individual's decision to undergo genetic testing and the test results may have substantial implications for other family members, especially for those with disorders associated with sudden cardiac death. However, under current guidelines, only the individual tested or the legal guardian in the case of a minor may be informed of the genetic test results, and the decision or responsibility to inform unsuspecting relatives of the potential for genetic predisposition for sudden cardiac death rests exclusively on the informed patient.[5]

Interpretation of Genetic Test Results

The patient and family suspected of having genetic heart disease should be evaluated and managed by a cardiologist with specific expertise in heritable channelopathies or cardiomyopathies.[5] Because of issues associated with incomplete penetrance and variable expressivity, the results of the genetic test must be interpreted cautiously and incorporated into the overall diagnostic evaluation for these disorders. The assignment of a specific variant as a true pathogenic disease-causing mutation requires vigilant scrutiny. To illustrate this requirement, recently a comprehensive determination of the spectrum and prevalence of rare nonsynonymous single nucleotide mutations (amino acid–altering variants) in the five LQTS-associated cardiac ion channel genes was performed in approximately 800 ostensibly healthy subjects from four distinct ethnic groups. The study showed that approximately 2% to 5% of healthy individuals are found to host rare amino acid–altering missense variants.[28,29] Some of the variants observed in this healthy population may represent subclinical disease modifiers and others simply represent benign background "genetic noise." This observation of background nonpathogenic missense variants is certainly not confined to the LQTS genes alone but may extend to virtually any gene in the human genome. Therefore, rather than being viewed as a binary yes-or-no test result, genetic testing results more appropriately should be considered as probabilistic in nature. Algorithms based on mutation location, species conservation, and the biophysical nature of the amino acid substitution may assist in distinguishing pathogenic mutations from otherwise rare variants of uncertain significance (VUS) and perhaps allow for the assignment of estimated predictive values to the probability of pathogenicity of each novel mutation identified within a specific gene.[30]

Future Directions in Cardiovascular Genetics

Genome-Wide Association Studies

Since the completion of the Human Genome Project's final draft in 2003 and the International HapMap Project in 2005 and with the advent of novel high-throughput genotyping methods, an explosion of genome-wide association studies (GWAS) has taken place. GWAS are large, population-based (involving thousands of individuals), hypothesis-free association studies of common genetic variants and observed phenotypic diversity of complex traits; these studies are conducted through large-scale genotyping of hundreds of thousands of SNPs located across the genome and compare the allelic frequencies of SNPs in cases and controls.[31,32] To date, several hundred genetic loci and specific polymorphisms have been found to be associated with a number of complex traits for many diseases categories, including neurodegenerative, neuropsychiatric, metabolic, autoimmune, and musculoskeletal diseases; several forms of cancer; and cardiovascular diseases.[31,32]

GWAS have been performed recently for electrocardiographic traits that have been associated with risk for ventricular arrhythmias and sudden cardiac death, including the PR interval and QRS duration as measures of cardiac conduction and the QT interval duration as an index of cardiac repolarization.[33-35] A GWAS for atrial fibrillation, a disease of irregular rhythm of the heart's upper chambers and significantly associated with an increased risk for stroke, heart failure, and death, has been completed.[36] Cardiovascular GWAS have not only isolated associations between specific genetic variants and complex disease-defining traits but have shed light on novel biologic mechanistic pathways. For example, an initial GWAS and subsequently several replication studies have identified a strong association between variants in the *NOS1AP* (capon) gene and QT interval duration, thus highlighting the importance of nitric oxide synthase pathway in myocardial function and action potential repolarization that had not been previously known and providing novel physiological information.[37] Recently, two large independent GWAS meta-analysis studies identified significant associations with 10 loci that appear to modulate or influence the QT interval duration, including loci mapping near the monogenic LQTS-associated genes *KCNQ1*, *KCNH2*, and *SCN5A*.[33,34] Whether or not these novel loci represent the location of additional candidate LQTS-causing or disease-modifying genes remains to be investigated.

Micro-RNAs as Pathogenic Contributors to Electrical Diseases of the Heart

miRNA represent one family of small noncoding RNA molecules, which function as *micromanagers* of gene expression, as genetic on-off switches to eliminate mRNAs that should not be expressed in a particular cell type or at a particular moment, or as a finetuning mechanism adjusting the physiological levels of gene expression in response to environmental factors. In mammals, miRNAs mediate post-transcriptional gene silencing usually by binding to the 3′ UTR region of mRNAs of their target transcripts and may individually regulate tens to hundreds of gene transcripts.[10]

Recently, the dysregulation of specific miRNAs has been linked to the development and pathogenesis of numerous disease states, including those of the heart.[8,9] For example, miRNA expression array studies have shown upregulation, and/or downregulation of miRNAs in morphologic pathologies of the heart, including aortic stenosis, hypertrophic cardiomyopathy, dilated cardiomyopathy, and ischemic cardiomyopathy, compared with the normal condition of the heart. Additionally, cardiac electrophysiology may be altered by perturbations in miRNA expression profiles, as numerous cardiac action potential repolarizing K^+ ion channels, including the LQTS-associated *KCNQ1-*, *KCNH2-*, and *KCNJ2*-encoded channels, are under the finetuning control of miRNAs in maintaining gradients in ion channel density that are critical for the correct chronologic excitation of cardiomyocytes.[9] Often, after cardiac infarction, the surviving heart muscle hypertrophies and undergoes *electrical remodeling* that is associated with continuous alterations in the electrical properties of cardiomyocytes and may prolong the action potential, slow cardiac conduction, and provide a proarrhythmic milieu.

Of the several hundred miRNAs that have been identified, *miR-1* and *miR-133* are thought to be muscle specific. In a recent study, *miR-1* was found to be overexpressed in patients with coronary heart disease; when overexpressed in normal and infarcted rat hearts, *miR-1* aggravated cardiac arrythmogenesis through conduction slowing and membrane depolarization by post-transcriptionally repressing the *KCNJ2* gene (encoding the K^+ channel subunit kir2.1, which is responsible for Andersen-Tawil syndrome) and the *GJA1* gene (which encodes for connexin43, which is responsible for intracellular conductance in ventricles).[38] Interestingly, the elimination of *miR-1* by an antisense inhibitor

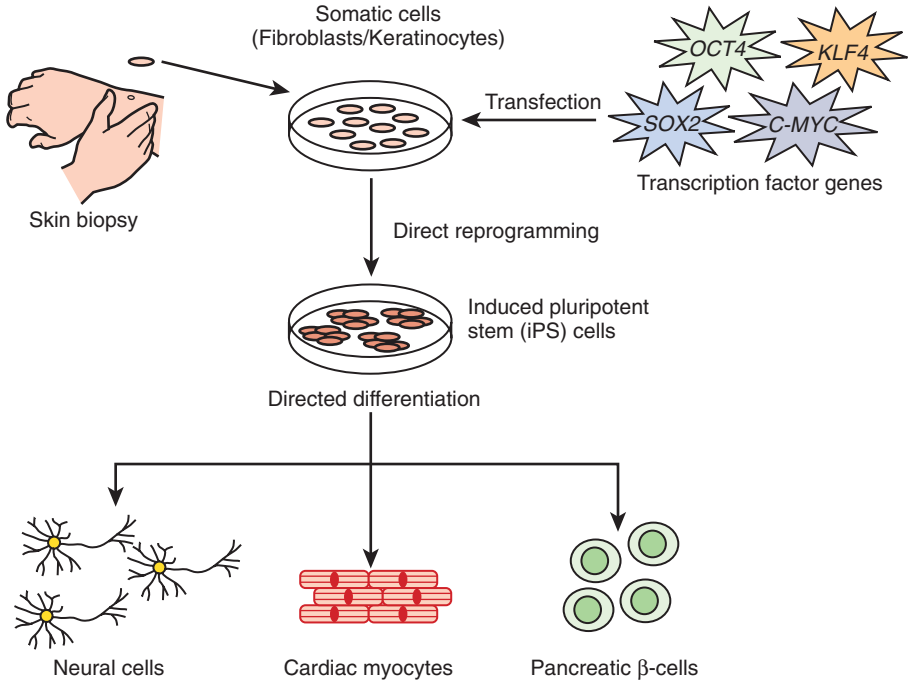


FIGURE 6-7 The biomedical promise of regenerative medicine and of human-specific and patient-specific disease models derived from human induced pluripotent stem (iPS) cells is enormous. Fibroblasts or keratinocytes, containing the patient's own complete library of genetic information, can be obtained at the time of a simple skin biopsy and may be reprogrammed to a pluripotent state by introducing and overexpressing specific transcription factor encoding genes (direct reprogramming). Through directed differentiation, these iPS cells have the potential to generate virtually any cell type.

in infarcted rat hearts was antiarrhythmic, suggesting that therapeutic inhibition of *miR-1* following myocardial infarction may reduce the proarrhythmic response and the occurrence of sudden death. Whether or not perturbations to *miR-1* or other heart-specific miRNAs in the form of single nucleotide substitutions resulting in mishandling of proper miRNA expression or maturation can lead to a monogenic cardiac electrical disorder or if specific miRNA therapeutic inhibition may be used to repress potentially life-threatening arrhythmias remains to be seen and will certainly be a part of the next decade of cardiovascular genetic and pharmacologic research.

Induced Pluripotent Stem Cell–Derived Cardiomyocytes

In 2006, Takahashi and Yamanaka showed that murine embryonic fibroblast and adult fibroblast acquired embryonic stem cell–like properties following retroviral induction of four transcription factor (Oct3/4, Sox2, Klf4, and c-Myc)–encoding genes.[39,40] These newly transformed cells were referred to as *induced pluripotent stem cells* or *iPS cells*. In 2007, the application of this groundbreaking technology to human cells was rapidly realized with the generation of iPS cells derived from human fibroblast using either the same cocktail of transcription factors or an independently determined mixture.[41,42] The iPS technology allows for the potential to overcome important obstacles that are currently associated with embryonic stem (ES) cells, such as immune rejection of ES-derived tissues after transplantation and the profound ethical concerns associated with destroying human embryos. The biomedical promise of human iPS cells derived from the patient's own skin biopsy (fibroblast) is enormous and may hugely benefit regenerative medicine, drug or toxicology research, and disease model generation efforts (Figure 6-7). In fact, disease-specific iPS cell lines from patients are now beginning to emerge.

In 2009, Zhang and colleagues showed for the first time that human iPS cells derived from fibroblast could be differentiated into functional cardiomyocytes.[43] This holds significant promise for the application of iPS cell–derived cardiomyocytes in cardiac research on disease models, in drug development, and as an autologous source of cells for myocardial repair. In the study of electrical diseases such as LQTS, for example, researchers may be able to take a skin biopsy from a patient with LQTS and subject iPS cell–derived cardiomyocytes to candidate drugs to determine the best therapy for that particular individual. iPS cell–derived cardiomyocytes from mutation-positive patients with LQTS would permit the functional electrophysiological study of that patient's specific ion channel mutation in its most native environment, rather than using the currently available technology of heterologous overexpression studies that only partially recapitulate the true macromolecular ion channel complex. Such studies may allow for a more precise in vitro characterization of variant channels to assist in deciphering truly pathogenic mutations from benign VUS. This technology may also allow investigators to answer key questions surrounding the observed reduced penetrance and variable expressivity that are common among cardiac electrical disorders; this may be accomplished by generating iPS cell–derived cardiomyocytes from multiple family members who show variable disease expression ranging from an asymptomatic course to a severe symptomatic course. Such studies may further elucidate particular genetic or environmental factors that may

contribute to the overall risk of experiencing a cardiac event, including sudden death.

Conclusion

Advances in genomics and molecular medicine are rapidly propelling the electrophysiological and cardiomyopathic disorders of the heart into the realm of clinical genetic testing. As novel disease genes and mechanisms are discovered and new genotype-phenotype correlates are derived, the compendium of available genetic tests and gene-guided therapies are bound to increase. As new technologies such as iPS cell generation and cardiomyocyte derivation are refined, personalized clinical cardiovascular medicine will be further enhanced. It is hoped that through discoveries of the underlying mechanisms of disease and further advances in our existing knowledge of these genetic disorders, we can, in the words of Dr. Charles W. Mayo, "*heal the sick and advance the science.*"

Conflicts of Interest

Dr. Ackerman is a consultant for Transgenomic with respect to the FAMILION genetic test for cardiac ion channel mutations. Intellectual property derived from M.J. Ackerman's research program resulted in license agreements in 2004 between Mayo Clinic Health Solutions (formerly Mayo Medical Ventures) and PGxHealth (formerly Genaissance Pharmaceuticals), which was acquired by Transgenomic in 2010.

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CHAPTER 7

Ion Channelopathies: Mechanisms and Genotype-Phenotype Correlations

Charles Antzelevitch and Jonathan M. Cordeiro

Recent years have witnessed an explosion of knowledge contributing to the understanding of ion channelopathies associated with inherited cardiac arrhythmia syndromes that are responsible for the sudden death of infants, children, and young adults. These ion channelopathies are the consequences of genetic variations giving rise to primary electrical diseases, including long QT syndrome (LQTS), short QT syndrome (SQTS), and Brugada syndrome (BrS), as well as catecholaminergic ventricular tachycardia (VT) (Table 7-1).[1-3] This review focuses on the molecular, genetic, cellular, and ionic mechanisms underlying the arrhythmogenesis associated with these syndromes and the genotype-phenotype correlation.

Brugada Syndrome

Arrhythmogenesis in BrS is believed to be the result of amplification of heterogeneities in the action potential characteristics among the different transmural cell types in the right ventricular (RV) myocardium.[4,5] A decrease in sodium (Na^+) or calcium (Ca^{2+}) channel current, I_{Na} or I_{Ca}, or augmentation of any one of a number of outward currents, including rapidly activating delayed rectifier potassium (K^+) current (I_{Kr}) or transient outward current (I_{to}), can cause preferential abbreviation of the right ventricular epicardial action potential; this, in turn, leads to the development of spatial dispersion of repolarization and, thus, the substrate and trigger for VT, which is usually polymorphic and less frequently monomorphic.[6-12]

BrS displays an autosomal dominant mode of inheritance. For many years, the only gene linked to BrS was *SCN5A*, the gene encoding for the α-subunit of the cardiac Na^+ channel gene.[6] However, recent evidence has shown that mutations in other genes are linked to the development of BrS.

BrS1, *SCN5A*

Mutations in *SCN5A* were the first to be associated with BrS.[6] Over 293 mutations in *SCN5A* have now been linked to the syndrome.[13] About three dozen of these have been studied in expression systems and shown to result in loss of function of the Na^+ channel because of the following reasons: (1) failure of the sodium channel to express; (2) a shift in the voltage dependence and time dependence of I_{Na} activation, inactivation, or reactivation; (3) entry of the Na channel into an intermediate state of inactivation from which it recovers more slowly, or (4) accelerated inactivation of the Na^+ channel.[14-16] Premature inactivation of the Na^+ channel has been observed at physiological temperatures but not at room temperature.[17] Because this characteristic of the mutant channel is exaggerated at temperatures above the physiological range, it was suggested that the syndrome may be unmasked and that patients with BrS may be at an increased risk during a febrile state.[17]

BrS2, *GPD1L*

Weiss et al described a second locus on chromosome 3, close to but distinct from *SCN5A*, linked to the syndrome in a large pedigree in which the syndrome is associated with progressive conduction disease, a low sensitivity to procainamide, and a relatively good prognosis. The gene was recently identified as the *glycerol-3-phosphate dehydrogenase 1-like* (*GPD1L*) gene, and the mutation was found in this gene.[18-20] Interestingly, it was also found that both *GPD1L* RNA and protein are abundant in the heart. Furthermore, the mutation was present in all affected individuals and absent in more than 500 control subjects. Coexpression studies of mutant *GPD1L* (A280V) with *SCN5A* in human embryonic kidney (HEK) cells resulted in a reduction in the magnitude of I_{Na} by approximately 50%.[19] These studies provided evidence that mutations in *GPD1L* lead to a reduction in I_{Na} and cause BrS.[19] Valdivia et al recently demonstrated that mutations in *GPD1L* related to BrS and sudden infant death syndrome (SIDS) cause a loss of enzymatic function, which results in glycerol-3-phosphate PKC-dependent phosphorylation of *SCN5A* at serine 1503 (S1503) through a *GPD1L*-dependent pathway. The direct phosphorylation of S1503 markedly decreases I_{Na}. These findings therefore show a function for *GPD1L* in cellular physiology and a mechanism linking mutations in *GPD1L* to sudden cardiac arrest. Because the enzymatic step catalyzed by *GPD1L* depends on nicotinamide adenine dinucleotide (NAD), this *GPD1L* pathway links the metabolic state of the cell to I_{Na} and excitability and may be important more generally in cardiac ischemia and heart failure.[21]

BrS3 and BrS4, *CACNA1c* and *CACNB2b*

The third and fourth genes associated with BrS were recently identified and were shown to encode the α_1-subunit (*CACNA1c*) and the β-subunit (*CACNB2b*) of the L-type cardiac Ca channel.[8] This new clinical entity, which exhibits electrocardiogram (ECG) and arrhythmic manifestations of both BrS and SQTS, was shown to be associated with loss of function mutations in the α_1-subunit (*CACNA1c*) and the β-subunit (*CACNB2b*) of the L-type cardiac Ca^{2+} channel.[8] Alterations in L-type Ca^{2+} current have been implicated in the development of BrS both clinically and

Table 7-1 Genetic Disorders Causing Cardiac Arrhythmias in the Absence of Structural Heart Disease

		RHYTHM	INHERITANCE	LOCUS	ION CHANNEL GENE	GENE
LQTS	(RW)	TdP	AD			
	LQT1			11p15	I_{Ks}	*KCNQ1, KvLQT1*
	LQT2			7q35	I_{Kr}	*KCNH2, HERG*
	LQT3			3p21	I_{Na}	*SCN5A, $Na_v1.5$*
	LQT4			4q25		*ANKB, ANK2*
	LQT5			21q22	I_{Ks}	*KCNE1, minK*
	LQT6			21q22	I_{Kr}	*KCNE2, MiRP1*
	LQT7 (Andersen-Tawil syndrome)			17q23	I_{K1}	*KCNJ2, Kir 2.1*
	LQT8 (Timothy syndrome)			6q8A	I_{Ca}	*CACNA1C, $Ca_v1.2$*
	LQT9			3p25	I_{Na}	*CAV3, Caveolin-3*
	LQT10			11q23.3	I_{Na}	*SCN4B, Na_vb4*
	LQT11			7q21–q22	I_{Ks}	*AKAP9, Yotiao*
	LQT12			20q11.2	I_{Na}	*SNTA1, α_1-syntrophin*
LQTS (JLN)	TdP		AR	11p15	I_{Ks}	*KCNQ1, KvLQT1*
				21q22	I_{Ks}	*KCNE1, minK*
BrS	BrS1	PVT	AD	3p21	I_{Na}	*SCN5A, $Na_v1.5$*
	BrS2	PVT	AD	3p24	I_{Na}	*GPD1L*
	BrS3	PVT	AD	12p13.3	I_{Ca}	*CACNA1C, $Ca_V1.2$*
	BrS4	PVT	AD	10p12.33	I_{Ca}	*CACNB2b, $Ca_v\beta_{2b}$*
	BrS5	PVT	AD	19q13.1	I_{Na}	*SCN1B, $Na_v\beta1$*
	BrS6	PVT	AD	11q13–14	I_{Ca}	*KCNE3, MiRP2*
	BrS7	PVT	AD	11q23.3	I_{Na}	*SCN3B, Navb3*
SQTS	SQT1	VT/VF	AD	7q35	I_{Kr}	*KCNH2, HERG*
	SQT2			11p15	I_{Ks}	*KCNQ1, KvLQT1*
	SQT3		AD	17q23.1-24.2	I_{K1}	*KCNJ2, Kir2.1*
	SQT4			12p13.3	I_{Ca}	*CACNA1C, $Ca_V1.2$*
	SQT5		AD	10p12.33	I_{Ca}	*CACNB2b, $Ca_v\beta_{2b}$*
CPVT	CPVT1	VT	AD	1q42-43		*RyR2*
	CPVT2	VT	AR	1p13-21		*CASQ2*

AD, *Autosomal dominant;* AR, *autosomal recessive;* BrS, *Brugada sydrome;* CPVT, *catecholaminergic polymorphic ventricular tachycardia;* JLN, *Jervell and Lange Nielsen;* LQTS, *long QT syndrome;* PVT, *polymorphic ventricular tachycardia;* RW, *Romano-Ward;* SQTS, *short QT syndrome;* TdP, *torsades de pointes;* VF, *ventricular fibrillation;* VT, *ventricular tachycardia.*

experimentally.[5,8] In both of those studies, the BrS phenotype was the result of a loss in peak I_{Ca}. More recently, a study identified a case of BrS in which the disease phenotype was observed as a result of accelerated inactivation of the L-type Ca^{2+} current without significantly affecting peak current.[9] The accelerated inactivation was caused by a mutation in *CACNB2b,* which encodes the β-subunit of the cardiac L-type Ca^{2+} current. The carrier of this mutation exhibited ST-segment elevation in only one precordial lead and converted to a more typical BrS phenotype with a procainamide challenge. VT/VF (ventricular fibrillation) was inducible and subsequently detected on interrogation of the implanted implantable cardiac defibrillator (ICD), corroborating the diagnosis of a potentially life-threatening syndrome.

BrS5 and BrS7, *SCN1B and SCN3B*

Genes that encode cardiac channel β-subunit proteins have long been appealing candidates for the treatment of ion channelopathies such as BrS because of their significant role in modulating channel expression and function.[22] The role of β_1-subunits has been studied most extensively. Wild-type (WT) β_1 coexpression has been reported to have no observable effect on *SCN5A* function, result in increased Na^+ current density with no detectable effects on channel kinetics or voltage-dependence, modulate channel sensitivity to lidocaine blockade with subtle changes in channel kinetics and gating properties, and shift the voltage dependence of steady-state inactivation or alter the rate of recovery from inactivation.[23-31] Coexpression of *SCN5A* with WT β_3 results in either (1) increased current density, a depolarizing shift in the voltage-dependence of inactivation, and an increased rate of recovery from inactivation in *Xenopus* oocytes or (2) a hyperpolarizing shift of inactivation, slowed recovery from inactivation, and reduced late Na^+ channel current.[30,31]

Mutations in *SCN1B* and *SCN3B* have recently been identified as the fifth and seventh genes associated with BrS. Mutations in β_1-subunits ($Na_v\beta_1$ and $Na_v\beta_{1b}$) have been shown to be associated with combined BrS and cardiac conduction disease phenotype in humans.[32] Another recent study by the authors of this chapter provided evidence that *SCN3B* is a BrS-susceptible gene.[33] An L10P missense mutation in a highly conserved residue was shown to produce a major reduction in I_{Na} secondary to both functional and trafficking defects in cardiac Na^+ channel expression. These results indicate that a mutation in the extracellular domain can impair trafficking of *SCN5A* to the membrane. These results suggest that WT β_3 plays a role in facilitating *SCN5A* transport to the plasma membrane, since a mutation in the extracellular domain of β_3 is capable of disrupting trafficking of *SCN5A* to the plasma membrane.[33]

BrS6, *KCNE3*

The role of the transient outward K^+ current (I_{to}) is thought to be central to the development of BrS. This hypothesis comes from several lines of evidence. First, since BrS is characterized by ST-segment elevations in the right precordial leads, a more prominent I_{to} in RV epicardium has been suggested to underlie the much greater prevalence of the Brugada phenotype in males.[34] The more prominent I_{to} causes the end of phase 1 of the RV epicardial action potential to repolarize to more negative potentials in tissue and arterially perfused wedge preparations obtained from male patients; this facilitates the loss of the action potential dome and the development of phase 2 re-entry and polymorphic VT. A link between mutations in genes responsible for the I_{to} current and the development of BrS was recently reported by Delpón and coworkers. *KCNE3* was identified as the seventh gene associated with BrS.[11] *KCNE3* normally interacts with $K_v4.3$ to suppress I_{to}; and a mutation in *KCNE3* was shown to result in a gain of function in I_{to}.[11,35] Experimentally, the Brugada phenotype can be produced in arterially perfused wedge preparations by the I_{to} activator NS5806. This compound has been shown to increase peak I_{to} amplitude and slow inactivation in isolated cardiomyocytes, which results in a more prominent phase 1 repolarization and loss of the action potential (AP) dome in mid- and epicardial cells.[36] The results of the study using the I_{to} activator are consistent with the clinical observations that an enhancement of I_{to} can lead to the development of BrS.

Table 7-2 lists the seven genotypes thus far associated for BrS and their yields. Four of the genes identified produced a loss of function of Na^+ channel current; two led to a reduction in Ca^{2+} channel current; and one gene was associated with a gain of function of transient outward current. *SCN5A* mutations were identified in 11% to 28% of probands (average of 21%).[13] Ca^{2+} channel mutations are found in approximately 12% to 15% of probands.[8,37] Variations in the other genes were relatively rare.

Genotype-Phenotype Correlation

Patients with *SCN5A*-positive BrS exhibit conduction slowing characterized by prolonged PR intervals and QRS duration.[38,39] PR interval and QRS duration are prolonged more prominently, and the QRS axis deviates more to the left with aging in those patients with BrS with *SCN5A* mutations. Smits et al observed significantly longer conduction intervals at baseline in patients with *SCN5A* mutations (PR and HV interval) and greater prolongation after the administration of Na^+ channel blockers.[38] These results concur with the observed loss of function of mutated BrS-related Na^+ channels.

Patients with BrS who have calcium channel mutations are phenotypically distinct from those with mutations in other genes.[8] A large fraction of *CACNA1c*- and *CACNB2b*-positive patients display a shorter-than-normal QTc interval (<360 ms) in addition to an ST-segment elevation in the right precordial leads, thus manifesting a combination of BrS and SQTS. Patients with mutations in Ca^{2+} channel genes also exhibit a diminished rate adaptation of QT interval.[8,40]

Table 7-2 Yield of Brugada Syndrome Genotypes

		ION CHANNEL	GENE	% OF PROBANDS	REFERENCE
BrS1	I_{Na}	↓	*SCN5A*	11–28	116
BrS2	I_{Na}	↓	*GPD1L*	Rare	19, 21, 117
BrS3	I_{Ca}	↓	*CACNA1C*	6.6–7.6	8, 37
BrS4	I_{Ca}	↓	*CACNB2b*	4.8–6.8	8, 9, 37
BrS5	I_{Na}	↓	*SCN1B*	1.1	32
BrS6	I_{to}	↑	*KCNE3*	Rare	11
BrS7	I_{Na}	↓	*SCN3B*	Rare	33

Mechanism of Arrhythmia in Brugada Syndrome

The arrhythmogenic substrate responsible for the development of extrasystoles and polymorphic VT in BrS is believed to be secondary to the amplification of heterogeneities intrinsic to the early phases (phase 1–mediated notch) of the action potential of cells residing in different layers of the right ventricular wall of the heart. Rebalancing of the currents active at the end of phase 1 is thought to underlie the accentuation of the action potential notch in the right ventricular epicardium, which is responsible for the augmented J wave and ST segment elevation associated with BrS (see[41–43] for references). The presence of an I_{to}-mediated spike and dome morphology, or *notch*, in the ventricular epicardium but not in the endocardium creates a transmural voltage gradient that is responsible for the inscription of the electrocardiographic (ECG) J wave (Figure 7-1, *A*).[5,44] The ST segment is normally isoelectric because of the absence of transmural voltage gradients at the level of the action potential plateau. Accentuation of the right ventricular action potential notch under pathophysiological conditions leads to exaggeration of transmural voltage gradients and thus to accentuation of the J wave or to J point elevation (Figure 7-1, *B*). If the epicardial action potential continues to repolarize before that of the endocardium, the T wave remains positive, giving rise to a saddleback configuration of the ST-segment elevation. Further accentuation of the notch is accompanied by a prolongation of the epicardial action potential causing it to repolarize after the endocardium, thus leading to inversion of the T wave. The down-sloping ST segment elevation, or accentuated J wave, observed in experimental wedge models often appears as an R, mimicking a right bundle branch block (RBBB) morphology of the ECG, largely because of early repolarization of the right ventricular (RV) epicardium, rather than major delays in impulse conduction in the right bundle.[45] Despite the appearance of a typical Brugada sign, the electrophysiological changes shown in Figure 7-1, *B*, do not give rise to an arrhythmogenic substrate. The arrhythmogenic substrate may develop with a further shift in the balance of current leading to loss of the action potential dome at some epicardial sites but not others (Figure 7-1, *C*). A marked transmural dispersion of repolarization develops as a consequence, creating a vulnerable window, which can trigger a re-entrant arrhythmia when captured by a premature extrasystole. Because loss of the action potential dome in epicardium is generally heterogeneous, epicardial dispersion of repolarization develops as well. Conduction of the action potential dome from sites at which it is maintained to sites at which it is lost causes local re-excitation via phase 2 re-entry (Figure 7-1, *D*); this leads to the development of a closely coupled extrasystole that is capable of capturing the vulnerable window across the ventricular wall, thus triggering a circus movement re-entry in the form of VT/VF (Figures. 7-1, *E* and *F*).[4,46] Support for these hypotheses

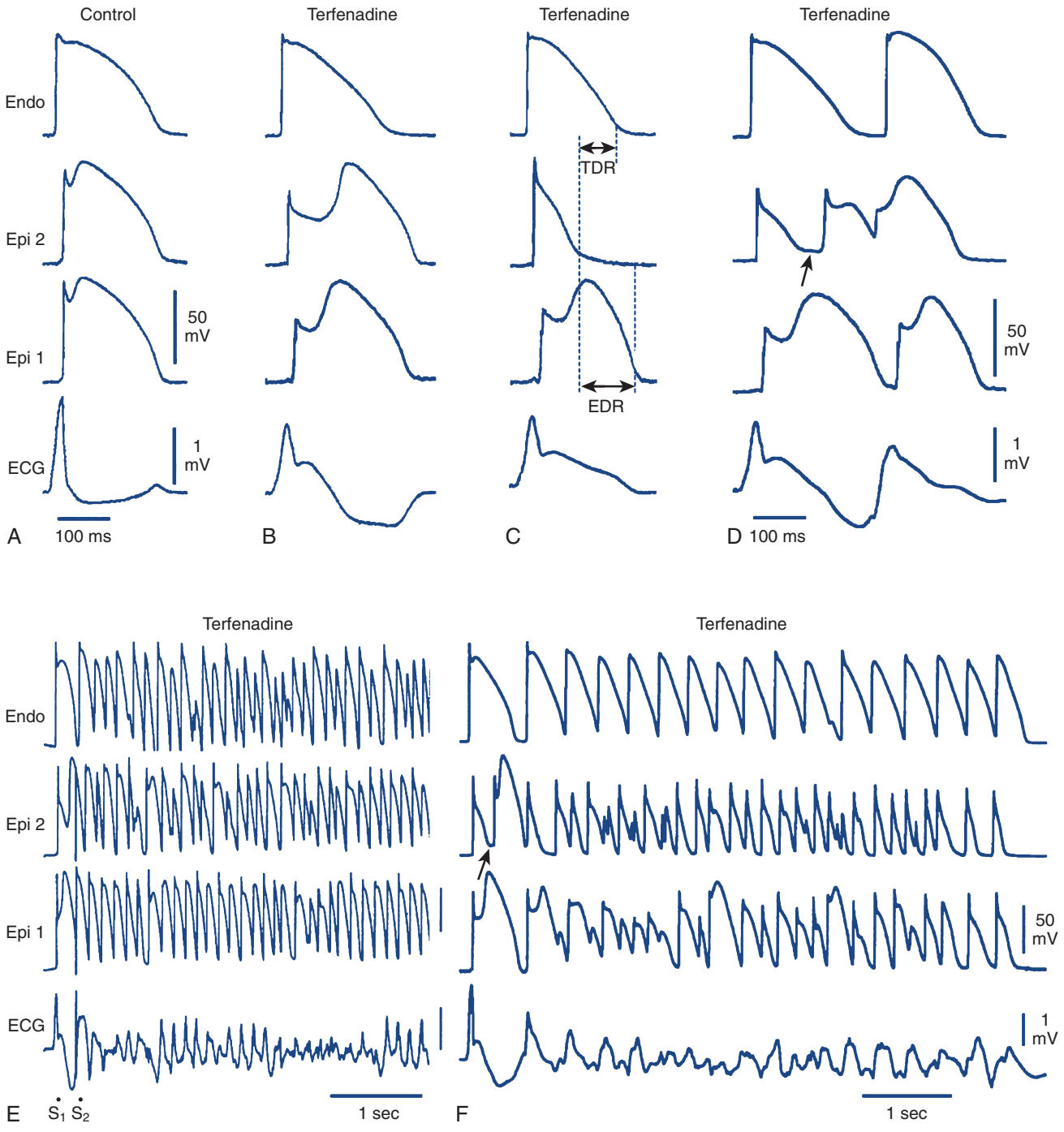

FIGURE 7-1 Cellular basis for electrocardiographic and arrhythmic manifestation of BrS. Each panel shows transmembrane action potentials from one endocardial (*top*) and two epicardial sites together with a transmural electrocardiogram (ECG) recorded from a canine coronary-perfused right ventricular wedge preparation. **A,** Control (basic cycle length [BCL] 400 ms). **B,** Combined sodium and calcium channel block with terfenadine (5 μM) accentuates the epicardial action potential notch, creating a transmural voltage gradient that manifests as an ST-segment elevation or exaggerated J wave on the ECG. **C,** Continued exposure to terfenadine results in all-or-nothing repolarization at the end of phase 1 at some epicardial sites but not others, creating a local epicardial dispersion of repolarization (*EDR*) as well as a transmural dispersion of repolarization (*TDR*). **D,** Phase 2 re-entry occurs when the epicardial action potential dome propagates from a site where it is maintained to regions where it has been lost, giving rise to a closely coupled extrasystole. **E,** Extrastimulus (S_1-S_2 = 250 ms) applied to the epicardium triggers a polymorphic ventricular tachycardia. **F,** Phase 2 re-entrant extrasystole triggers a brief episode of polymorphic ventricular tachycardia. *(Modified from Fish JM, Antzelevitch C: Role of sodium and calcium channel block in unmasking the Brugada syndrome,* Heart Rhythm *1:210–217, 2004.)*

comes from experiments involving the arterially perfused RV wedge preparations and from recent studies in which monophasic action potential (MAP) electrodes were positioned on the epicardial and endocardial surfaces of the right ventricular outflow tract (RVOT) in patients with BrS.[4,5,41,47-51]

Long QT Syndrome

LQTS is characterized by the appearance of long QT intervals on the ECG, an atypical polymorphic VT known as *torsades de pointes* (TdP), and a high risk for sudden cardiac death.[52-54] A reduction of net repolarizing current secondary to loss of function of outward ion channel currents or a gain of function of inward currents underlies the prolongation of the myocardial action potential and QT interval that attend both congenital and acquired LQTS.[55,56]

Here again, amplification of spatial dispersion of repolarization is thought to generate the principal arrhythmogenic substrate. The accentuation of spatial dispersion is secondary to an increase of transmural and trans-septal dispersion of repolarization. Early after-depolarization (EAD)–induced triggered activity also contributes to the development of the substrate and provides the triggering extrasystole that precipitates TdP arrhythmias observed under LQTS conditions (Figures 7-2 and 7-3).[57,58] In vivo and in vitro models of LQTS have contributed to the understanding of the mechanisms involved in arrhythmogenesis.[59,60] Models of the LQT1, LQT2, and LQT3 forms of LQTS have been developed by using arterially perfused left ventricular (LV) wedge preparations (see Figure 7-2) in canine models.[61] These models have shown that in these three forms of LQTS, preferential prolongation of the M cell action potential duration (APD) leads to an increase in the QT interval as well as an increase in the transmural dispersion of repolarization (TDR), the latter providing the substrate for the development of spontaneous as well as stimulation-induced TdP.

LQT1, *KCNQ1*

LQT1 is the most prevalent of congenital LQTS.[62] Loss of function of the slowly activating delayed rectifier (I_{Ks}) underlies congenital LQT1. Inhibition of I_{Ks} using chromanol 293B leads to uniform prolongation of APD in all three cell types (epicardial, endocardial, and M cell) in the wedge, causing little change in TDR. Although the QT interval is prolonged, TdP never occurs under these conditions, nor can it be induced. Addition of isoproterenol results in abbreviation of epicardial and endocardial APD, and the M cell APD either prolongs or remains the same. The dramatic increase in TDR provides the substrate for the development of spontaneous as well as stimulation-induced TdP.[63] These results support the thesis that the problem with LQTS is not the long QT interval but, rather, the increase in TDR that often accompanies the prolongation of the QT interval. The combination of I_{Ks} block and β-adrenergic stimulation creates a broad-based T wave in the perfused wedge, similar to that observed in patients with LQT1. These findings provide an understanding of the great sensitivity of patients with LQT1 to sympathetic influences (see Figures 7-2, *A* and *D*).[52,64]

LQT2, *KCNH2*

The second most prevalent form of congenital LQTS is LQT2, which is caused by loss of function of the rapidly activating delayed rectifier (I_{Kr}). I_{Kr} inhibition is also responsible for most cases of acquired LQTS. In the wedge, inhibition of I_{Kr} with d-sotalol produces a preferential prolongation of M cells, resulting in accentuation of TDR and spontaneous as well as stimulation-induced TdP. If I_{Kr} block is accompanied by hypokalemia, a deeply notched or bifurcated T wave is observed in the wedge preparation, similar to that seen in patients with LQT2. Isoproterenol further exaggerates TDR and increases the incidence of TdP in this model, but only transiently (see Figures 7-2, *B* and *E*).

LQT3, *SCN5A*

LQT3, which is encountered far less often, is caused by a gain in the function of the late Na^+ current (late I_{Na}). Augmentation of late I_{Na} using the sea anemone toxin ATX-II also produces a preferential prolongation of the M cell action potential in the wedge, which results in a marked increase in TDR and development of TdP. Because epicardial APD is also significantly prolonged, delay in the onset of the T wave in the wedge occurs, as observed in the clinical syndrome.[65] β-Adrenergic stimulation abbreviates APD of all cell types under these conditions, reducing TDR and suppressing TdP (see Figures 7-2, *C* and *F*).[66]

Sympathetic activation displays a very different time course in the case of LQT1 and LQT2, both in experimental models (see Figure 7-2) and in the clinic.[58,67] In LQT1, isoproterenol produces an increase in TDR that is most prominent during the first 2 minutes but which persists, although to a lesser extent, during the steady state. TdP incidence is enhanced during the initial period as well as during the steady state. In LQT2, isoproterenol produces only a transient increase in TDR that persists for less than 2 minutes. TdP incidence is therefore enhanced only for a brief period. These differences in time course may explain the important differences in the autonomic activity and other gene-specific triggers that contribute to events in patients with different LQTS genotypes.[62,64]

While β-blockers are considered the first line of therapy in patients with LQT1, they have not been shown to be beneficial in LQT3. Preliminary data suggest that patients with LQT3 might benefit from Na^+ channel blockers, such as mexiletine and flecainide, but long-term data are not yet available.[68,69] Experimental data have shown that mexiletine reduces transmural dispersion and prevents TdP in LQT3 as well as in LQT1 and LQT2, which suggests that agents that block the late Na^+ current may be effective in all forms of LQTS.[63,65] Clinical trial data are not currently available.

LQT7, *KCNJ2*

Andersen-Tawil syndrome (ATS1), also known as *LQT7*, is a clinical disorder consisting of K-sensitive periodic paralysis, prolonged QT intervals, ventricular arrhythmias, and dysmorphic features caused by mutations in the *KCNJ2* gene.[70,71] An experimental model of this syndrome has been developed.[72]

LQT8, *CACNA1c*

Timothy syndrome, also known as *LQT8*, is a multisystem disease secondary to mutations in the Ca^{2+} channel $Ca_v1.2$ encoded by the *CACNA1c*. Because the Ca channel $Ca_v1.2$ is present in many tissues, patients with Timothy syndrome have many clinical manifestations, including congenital heart disease, autism,

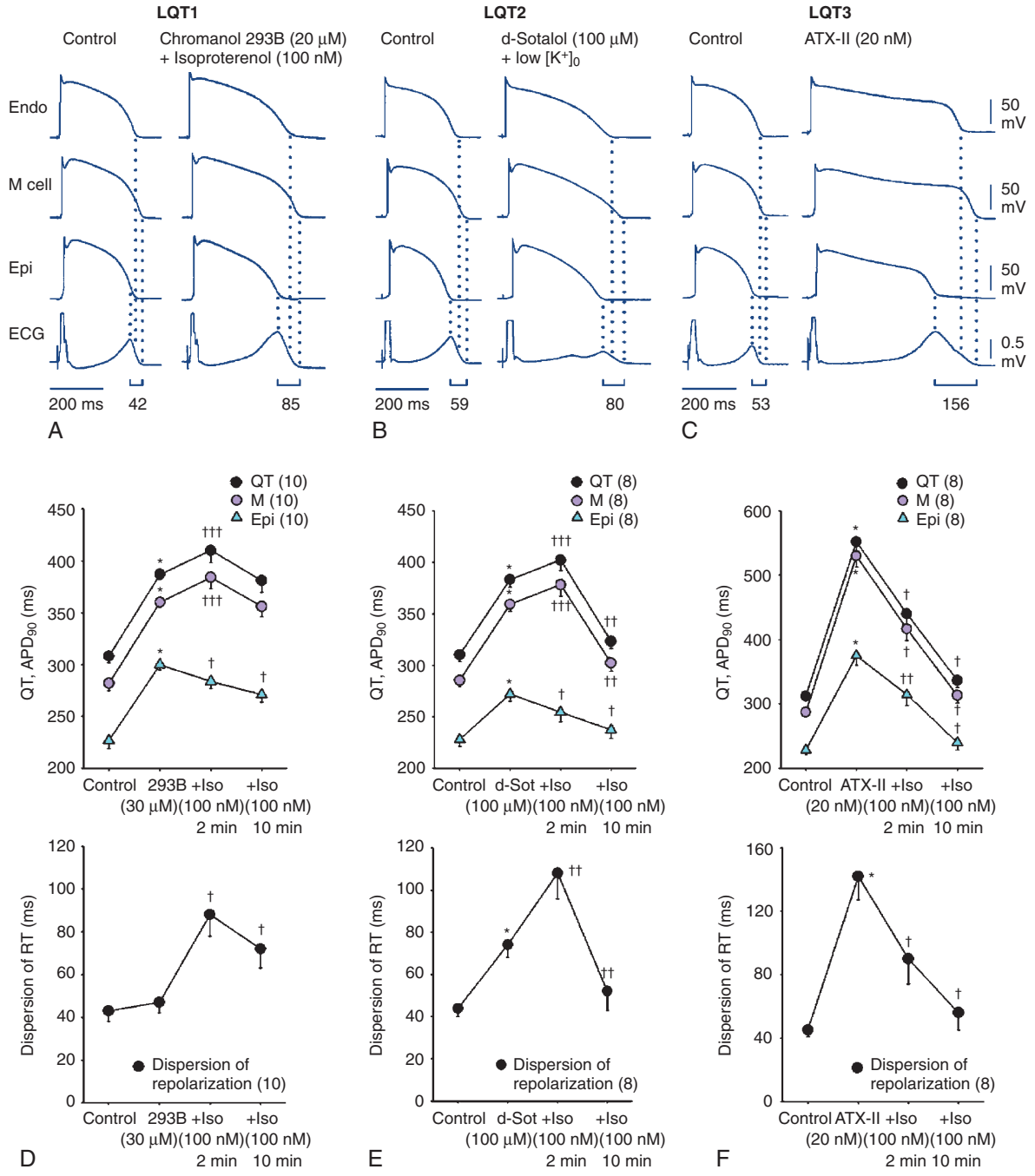

FIGURE 7-2 Transmembrane action potentials and transmural electrocardiograms (ECG) in control and LQT1 (**A**), LQT2 (**B**), and LQT3 (**C**) models of LQTS (arterially perfused canine left ventricular wedge preparations). Isoproterenol + chromanol 293B (an I_{Ks} blocker), d-sotalol + low $[K^+]_o$, and ATX-II (an agent that slows inactivation of late I_{Na}) are used to mimic the LQT1, LQT2, and LQT3 syndromes, respectively. **A** to **C,** Action potentials simultaneously recorded from endocardial (*Endo*), M, and epicardial (*Epi*) sites together with a transmural ECG. BCL = 2000 ms. Transmural dispersion of repolarization (TDR) across the ventricular wall, is denoted below the ECG traces. **D** and **F,** Effect of isoproterenol. In LQT1, isoproterenol (*Iso*) produces a persistent prolongation of the action potential duration measured at 90% repolarization (APD_{90}) of the M cell and of the QT interval (at both 2 and 10 minutes), whereas the APD_{90} of the epicardial cell is always abbreviated, resulting in a persistent increase in TDR (**D**). In LQT2, isoproterenol initially prolongs (2 minutes) and then abbreviates the QT interval and the APD_{90} of the M cell to the control level (10 minutes), whereas the APD_{90} of epicardial cell is always abbreviated, resulting in a transient increase in TDR (**E**). In LQT3, isoproterenol produced a persistent abbreviation of the QT interval and the APD_{90} of both M and epicardial cells (at both 2 and 10 minutes), resulting in a persistent decrease in TDR (**F**). **P* < .0005 vs. control; †*P* < .0005; ††*P* < .005; †††*P* < .05; vs. 293B, d-Sotalol (d-Sot) or ATX-II. *(Modified from Shimizu W, Antzelevitch C: Cellular basis for the ECG features of the LQT1 form of the long QT syndrome: Effects of β-adrenergic agonists and antagonists and sodium channel blockers on transmural dispersion of repolarization and torsades de pointes,* Circulation *98:2314–2322, 1998; Shimizu W, Antzelevitch C: Sodium channel block with mexiletine is effective in reducing dispersion of repolarization and preventing torsades de pointes in LQT2 and LQT3 models of the long-QT syndrome,* Circulation *96:2038–2047, 1997; Shimizu W, Antzelevitch C: Differential effects of beta-adrenergic agonists and antagonists in LQT1, LQT2 and LQT3 models of the long QT syndrome,* J Am Coll Cardiol *35:778–786, 2000.)*

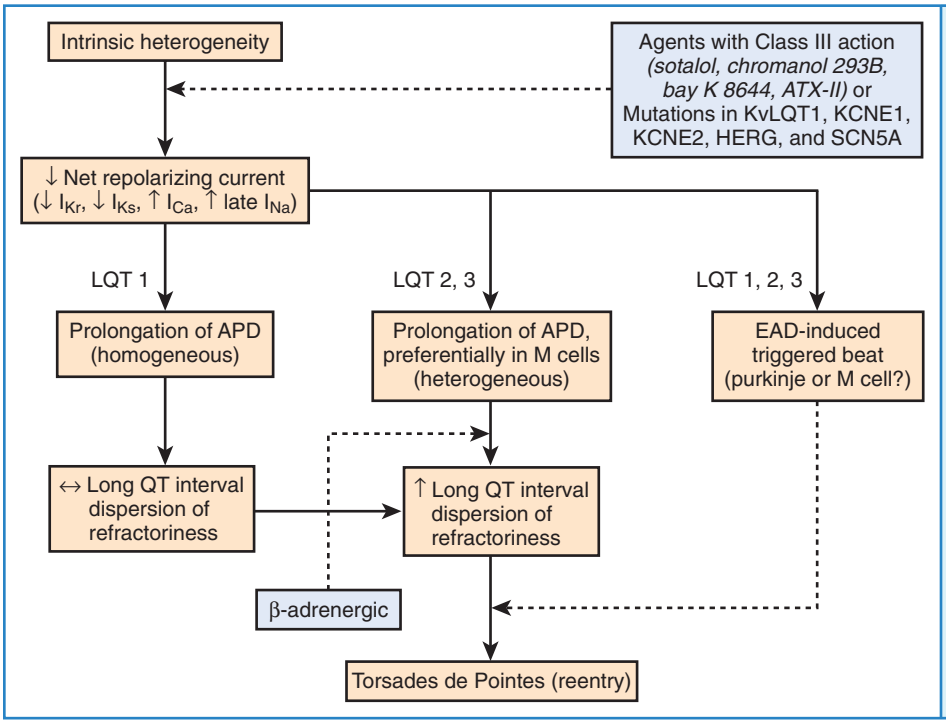

FIGURE 7-3 Cellular mechanism for the development of torsades de pointes in long QT syndrome.

syndactyly, and immune deficiency.[73,74] An experimental model of this syndrome has been developed.[75]

Mutations in seven other genes have been associated with LQTS in recent years (see Table 7-1). These genetic variations, which include structural proteins as well as other ion channel proteins, are thought to be fairly rare.

Genotype-Phenotype Correlation

Genotype–phenotype studies have demonstrated that there are significant differences among patients with LQT1, LQT2, and LQT3 forms of LQTS, which account for 95% of all genotyped patients. Gene-specific ECG patterns have been identified (see Figure 7-2), and the trigger for cardiac events has been shown to be locus specific.[62] Patients with LQT1 experience 97% of cardiac events during physical activity as opposed to those with LQT3 who experience the majority of cardiac events at rest or during sleep. Auditory stimuli and arousal have been identified as relatively specific triggers for patients with LQT2 while swimming has been identified as a predisposing setting for cardiac events in those with LQT1.[76-79]

The first risk stratification scheme based on genotype was proposed by Priori et al in 2003.[80] QT interval, genotype, and gender were significantly associated with outcome. A QTc interval longer than 500 ms in LQT2 or LQT3 indicated a worse prognosis. In 2004, the same authors reported that the response to β-blockers is also affected by the genotype, and patients with LQT1 showed greater protection by response to β-blockers than did those with LQT2 and LQT3.[81]

Patients with LQT2 harboring pore mutations were shown to exhibit a more severe clinical course and to experience a higher frequency of arrhythmia-related cardiac events occurring at an earlier age than do subjects with nonpore mutations.[82] *KCNH2* missense mutations located in the transmembrane S5-loop-S6 region were again shown to be associated with the greatest risk in a recent study.[83]

Mechanism of Arrhythmia in Long QT Syndrome

Accentuation of spatial dispersion of refractoriness within the ventricular myocardium, secondary to exaggerated transmural or trans-septal dispersion of repolarization, has been identified as the principal arrhythmogenic substrate in both acquired and congenital LQTS.[84,85] This exaggerated intrinsic heterogeneity and triggered activity induced by EADs and delayed afterdepolarizations (DADs), both caused by a reduction in net repolarizing current, underlie the substrate and trigger for the development of TdP arrhythmias observed under LQTS conditions.[58,86] Experimental models of LQTS suggest that preferential prolongation of the M cell APD leads to an increase in the QT interval as well as an increase in transmural dispersion of repolarization (TDR), which contributes to the development of spontaneous as well as stimulation-induced TdP (Figure 7-3).[63,65,66,85,87,88] The spatial dispersion of repolarization is further exaggerated by sympathetic influences in LQT1 and LQT2, which accounts for the great sensitivity of patients with these genotypes to adrenergic stimuli (see Figure 7-2).

Short QT Syndrome

SQTS, a clinical entity recently described in 2000, is characterized by a short QT interval on the ECG, episodes of paroxysmal atrial fibrillation, and sudden cardiac death (SCD) in patients with structurally normal hearts.[89] A distinctive ECG feature of SQTS is the appearance of tall peaked symmetrical T waves. The

augmented T_{peak} to T_{end} interval associated with this ECG feature of the syndrome suggests that here, as in LQTS, a transmural dispersion of repolarization underlies the arrhythmogenic substrate in the ventricles. To date, three different K^+ channel genes and two different Ca^{2+} channel genes have been linked to SQTS.[8,90-92]

SQT1, *KCNH2*

The *KCNH2* gene (HERG) encodes for the rapidly activating delayed rectifier K^+ channel (I_{Kr}). The authors of this chapter and their group identified two different missense mutations in the same residue in *KCNH2* in two unrelated families.[90] Both mutations resulted in the same substitution of asparagine for lysine at codon 588 (N588K), an area at the outer mouth of the channel pore. Patch clamp studies of N588K channels expressed in TSA201 mammalian cells revealed that the mutation abolished the inactivation, thereby increasing the I_{Kr} current. Analysis of the current–voltage relation showed that N588K channels failed to rectify over a physiological range of voltages.[93,94] During action potential clamp experiments, N588K currents were larger during all phases of the action potential compared with WT *KCNH2* channels.[93] The biophysical analysis therefore showed that the mutation induced a "gain of function" in the I_{Kr} current, thus shortening the action potential. The presence of paroxysmal atrial fibrillation in some affected patients suggests that the increased heterogeneity would also be present at the atrial level and may be responsible for the arrhythmia. Experimental studies support this observation as well.[95,96] In one family, the N588K mutation is associated only with atrial fibrillation with no occurrence of ventricular arrhythmias in any of the family members displaying short QT intervals.[97]

SQT2, *KCNQ1*

A second inherited form of SQTS (SQT2) has been linked to a gain of function in the slow delayed rectifier K^+ current (I_{Ks}) secondary to mutations in *KCNQ1*.[92] This form of SQTS appears to be quite rare. The *KCNQ1* gene encodes the α-subunit responsible for I_{Ks}. The mutation was first identified in a 70-year-old man with ventricular fibrillation and a QT interval of 290 ms after resuscitation.[92] Biophysical analysis showed that mutation in the *KCNQ1* gene produced an outward K^+ current of comparable magnitude compared with WT channels. However, since the half-activation voltage was markedly shifted to negative potentials, the mutated channel activated at more negative potentials and displayed accelerated activation kinetics.[92] These observations demonstrate a gain of function of I_{Ks}, which explains the SQTS phenotype.

A second mutation in *KCNQ1* was found in a female infant born at 38 weeks. Delivery was induced because the infant was experiencing bradycardia and an irregular rhythm.[98] The ECG revealed atrial fibrillation with slow ventricular response and a short QT interval. Genetic analysis identified a de novo missense mutation in the *KCNQ1* gene. Voltage clamp experiments to characterize the physiological consequences of this mutation revealed an instantaneous and voltage-independent K^+-selective current. Mathematical modeling experiments confirmed a shortening of the action potential duration in ventricular myocytes.[98] A recent preliminary report has identified another novel *KCNQ1* mutation (R259H) associated with SQT2.[99]

SQT3

Finally, mutations in the *KCNJ2* gene have also been associated with SQTS. The *KCNJ2* gene encodes a protein (Kir2.1) responsible for the inward rectifier K^+ current (I_{K1}). The proband and her father, in whom the mutation was discovered, displayed short QT correction intervals of 315 and 320 ms, respectively, and ECG recordings showed asymmetrical T waves with an abnormally rapid terminal phase. Expression of the mutant channel in a mammalian cell line revealed that the mutated Kir2.1 channels generated ionic currents in which rectification was reduced, compared with WT channels. The hallmark of I_{K1} is a region of outward current and negative slope conductance at membrane potentials between −80 mV and −30 mV. Because rectification was reduced in the mutant Kir2.1 channel, a larger outward current was observed over this range of potentials. Functionally, I_{K1} is responsible for terminal repolarization of the ventricular action potential.[100,101] Mathematical modeling of the effects of the mutated channel on the ventricular action potential showed an increase of terminal repolarization and shortening of the APD.

SQT4 and SQT5

The fourth and fifth genes associated with BrS were recently identified and shown to encode the α_1-subunit (*CACNA1c*) and the β-subunit (*CACNB2b*) of the L-type cardiac Ca^{2+} channel.[8] This new clinical entity, which exhibits ECG and arrhythmic manifestations of both BrS and SQTS, was associated with loss of function mutations in the α_1-subunit (*CACNA1c*) and the β-subunit (*CACNB2b*) of the L-type cardiac Ca^{2+} channel.[8]

Mechanism of Arrhythmia in Short QT Syndrome

An increase in net outward current caused by either a reduction in inward depolarizing current such as I_{Na}, I_{Ca}, an augmentation of outward repolarizing current like I_{to}, I_{K1}, $I_{K\text{-}ATP}$, I_{ACh}, I_{Kr}, I_{Ks}, or a combination of both favors early repolarization leading to abbreviation of the action potential and the QT interval (Figure 7-4). Experimental studies suggest that abbreviation of the action potential in SQTS is heterogeneous with preferential abbreviation of either the epicardium or the endocardium, giving rise to an increase in TDR. Dispersion of repolarization and refractoriness serves as the substrate for re-entry in that it promotes unidirectional block. Marked abbreviation of wavelength (product of refractory period and conduction velocity) is an additional factor promoting the maintenance of re-entry. Mutations giving rise to a gain of function of outward K^+ currents has been identified in SQT1–SQT3 and a loss of function in inward I_{CaL} have been identified in SQT4-SQT5 (see Table 7-1).[8,90-92] Moreover, the T_{peak} to T_{end} interval and the T_{peak} to T_{end}/QT ratio, an electrocardiographic index of spatial dispersion of repolarization, and perhaps TDR, are significantly augmented in cases of SQTS.[102,103] This ratio is larger in patients who are symptomatic.[104]

Evidence supporting the role of augmented TDR in arrhythmogenesis in SQTS comes from the experimental models involving use of the K_{ATP} activator pinacidil or the selective I_{Kr} agonist PD-118057 to abbreviate repolarization time and thus mimic the cellular conditions created by the of gene mutation responsible for SQT1.[105-107]

Abbreviation of APD, and effective refractory period (ERP), and amplification of spatial dispersion of repolarization have also

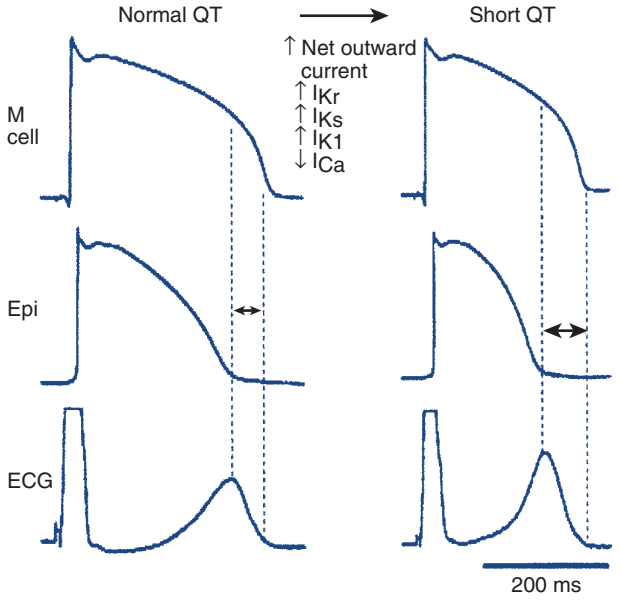

FIGURE 7-4 Proposed mechanism for arrhythmogenesis in short QT syndrome. An increase in net outward current due to a reduction in late inward current or augmentation of outward repolarizing current serves to abbreviate the action potential duration heterogeneously, which leads to an amplification of transmural dispersion of repolarization and the creation of a vulnerable window for the development of re-entry. Re-entry is facilitated both by the increase in transmural dispersion of repolarization and abbreviation of refractoriness. *(Modified from Antzelevitch C: The role of spatial dispersion of repolarization in inherited and acquired sudden cardiac death syndromes,* Am J Physiol Heart Circ Physiol *293:H2024–H2038, 2007.)*

been shown to predispose to the development of atrial fibrillation by creating the substrate for re-entry.[96]

Transmural Dispersion of Repolarization as a Common Link in the Development of Arrhythmias

The three inherited sudden cardiac death syndromes thus far discussed differ with respect to the characteristics of the QT interval (Figure 7-5). In LQTS, QT increases as a function of disease or drug concentration. In SQTS, the QT interval decreases as a function of disease or drug, whereas in BrS, the QT interval remains largely unchanged. What these three syndromes have in common is an amplification of TDR, which results in the development of polymorphic VT and fibrillation when dispersion of repolarization and refractoriness reaches the threshold for re-entry. When polymorphic VT occurs in the setting of long QT, it is referred to as TdP. The threshold for re-entry decreases as APD and refractoriness are reduced and the pathlength required for establishing a re-entrant wave is progressively reduced.

Catecholaminergic Polymorphic Ventricular Tachycardia

Catecholaminergic, or familial, polymorphic ventricular tachycardia (CPVT) is a rare, autosomal dominant inherited disorder, predominantly affecting children or adolescents with structurally normal hearts. It is characterized by bidirectional VT (BiVT), polymorphic VT (PVT), and a high risk of sudden cardiac death (30% to 50% by the age of 20 to 30 years).[108,109] Molecular genetic studies have identified mutations in genes encoding for the cardiac ryanodine receptor 2 (*RyR2*) or calsequestrin 2 (*CASQ2*) in patients with this phenotype.[110-113]

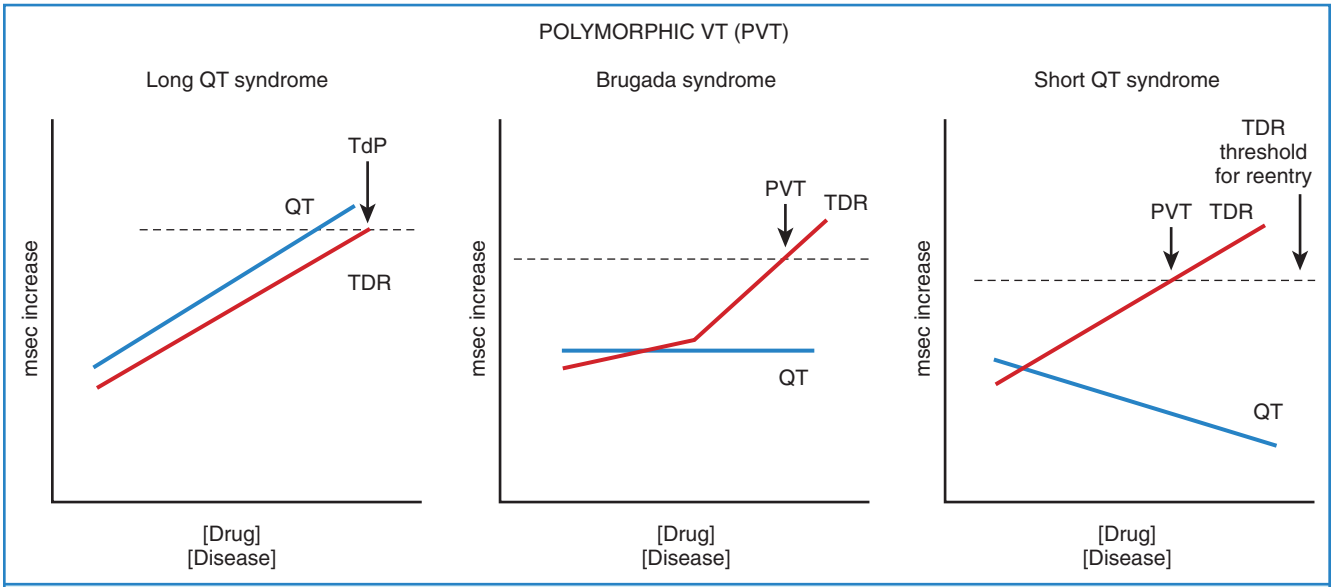

FIGURE 7-5 The role of transmural dispersion of repolarization (*TDR*) in channelopathy-induced sudden cardiac death. In long QT syndrome, QT increases as a function of disease or drug concentration. In Brugada syndrome, it remains largely unchanged, and in short QT syndrome, the QT interval decreases as a function of disease or drug. The three syndromes have in common the ability to amplify TDR, which results in the development of torsades de pointes (*TdP*), when dispersion reaches the threshold for re-entry. The threshold for re-entry decreases as action potential duration and refractoriness are reduced. *(Modified from Antzelevitch C, Oliva A: Amplification of spatial dispersion of repolarization underlies sudden cardiac death associated with catecholaminergic polymorphic VT, long QT, short QT and Brugada syndromes,* J Intern Med *259:48–58, 2006.)*

Mechanisms of Arrhythmias in Catecholaminergic Polymorphic Ventricular Tachycardia

Several lines of evidence point to DAD-induced triggered activity (TA) as the mechanism underlying monomorphic or bidirectional VT in patients with CPVT. These include the identification of genetic mutations involving Ca^{2+} regulatory proteins, a similarity of the ECG features to those associated with digitalis toxicity, and the precipitation by adrenergic stimulation. The cellular mechanisms underlying the various ECG phenotypes and the transition of monomorphic VT to polymorphic VT or VF were recently elucidated with the help of the wedge preparation.[114] The wedge was exposed to low-dose caffeine to mimic the defective Ca^{2+} homeostasis encountered under conditions that predispose to CPVT. The combination of isoproterenol and caffeine led to the development of DAD-induced TA arising from the epicardium, the endocardium, or the M region. Migration of the source of ectopic activity was responsible for the transition from monomorphic to slow polymorphic VT. Alternation of epicardial and endocardial sources of ectopic activity gave rise to a bidirectional VT. Epicardial VT was associated with an increased T_{peak} to T_{end} interval and transmural dispersion of repolarization caused by reversal of the normal transmural activation sequence; thus, this created the substrate for re-entry, which permitted the induction of a more rapid polymorphic VT with programmed electrical stimulation. Propranolol or verapamil suppressed arrhythmic activity.[114]

Recently, Cerrone and coworkers used a transgenic murine model to demonstrate that the His–Purkinje system is an important source of DAD-induced triggered activity that gives rise to focal arrhythmias in CPVT.[115]

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CHAPTER 8

Disorders of Intracellular Transport and Intercellular Conduction

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Disorders of Intercellular Trafficking

The cardiac action potential is formed by stringent coordination of ion channel and gap junction channel functions. Ion channels pass ions that generate current, and gap junctions play a major role in propagating this current through the myocardium. The ability for either of these channel types to play a role in normal electrical propagation is dependent on their presence at cell membranes in normal locations and quantity. Ion channels and gap junction channels are formed by proteins specific for each type of channel. This normally occurs through the process of protein translation from ribonucleic acid (RNA), followed by protein folding and trafficking to cell membranes. As membrane proteins, the subunits that form ion channels and gap junction channels follow a carefully regulated pathway from formation of the protein within the endoplasmic reticulum (ER) of the cell to their final destination within the cell membranes. Disruption of any of the trafficking steps leads to intracellular retention of the protein subunits and a subsequent loss of function at the cell membrane. Because of the dependence of normal cardiac electrical propagation on the presence of these functional channels, this loss can lead to cardiac arrhythmias.

Formation of Protein Subunits

Following the transcription of RNA from deoxyribonucleic acid (DNA), individual protein monomers are formed via translation on the ribosomes. For proteins destined for the cell membrane, this process occurs only on ribosomes that are attached to the ER, where every three RNA molecules code for an individual amino acid. The generalized pattern is messenger RNA (mRNA) binds to the ribosomes attached to the ER, and transcription proceeds with the nascent polypeptide inserting into the ER membrane. Under normal conditions, protein subunits are folded into their appropriate configuration as the protein is being formed. In some cases, individual monomers interact with other monomers forming channel subunits while still in the ER. These channels leave the ER in membrane-bound vesicles that pinch off as individual packets, sending the individual channels to the Golgi apparatus for post-translational modifications such as glycosylation. From here, channels are delivered to myocyte membranes for insertion and eventual function.

As membrane proteins are formed in the ER, they undergo folding to their correct functional conformation. Occasionally, this process does not work correctly. In order to ensure that nonfunctional proteins are not targeted to the myocyte membrane, a process called *unfolded protein response* occurs. ER-associated degradation (ERAD) is responsible for the elimination and control of the buildup of aberrant proteins, preventing the aggregation of toxic nonfunctional proteins.[1] These misfolded proteins are recognized by chaperones such as Hsp70/Hsp40, which interact directly with the misfolded protein and aid in its translocation into the cytoplasm for degradation by the proteasome. Evidence is now beginning to accumulate that the ERAD pathway participates not only in the removal of proteins that are not folded correctly but also in the rapid degradation of excess proteins. Thus, a protein is made from RNA in larger quantities than needed under normal conditions but is degraded via the ERAD pathway prior to insertion into cell membranes. When a cell needs a rapid increase of a particular protein, the ERAD system is turned off and more of the protein is trafficked to the cell membrane for use. An example of this is the adenosine-5′-triphosphate (ATP)–sensitive potassium (K[ATP]) channel, whose biogenesis and surface expression are controlled by ERAD. This is thought to be a mechanism for rapid increase in the availability of K(ATP) channels during cellular stress.[2]

In some cases, actual channel formation from multiple monomers does not occur until after the monomers leave the ER and are within the Golgi apparatus. Here, the monomers form channels (or, in the case of gap junctions, half the channels) and undergo post-translational modifications, which may include glycosylation, acetylation, and interactions with protein partners. In any of these cases, the coordination of this multiple-step process is tightly regulated, and the need for this to work perfectly is underscored by the fact that dysfunction in any of the above steps leads to a loss of ion channel function or gap junction function, altered electrical propagation, and formation of an arrhythmogenic substrate.

Genetic Disorders of Trafficking

Normal trafficking of membrane proteins is exquisitely dependent on having particular amino acid sequences within the protein sequence. These sequences allow for the interaction of the channel protein with molecular motors, cytoskeletal elements, and scaffolding proteins, which are all important for protein movements throughout the cell. Changes in the nucleotide sequence of DNA will translate into RNA missense errors, which, in turn, lead to the production of incorrect amino acid sequences within the proteins. Thus, errors within the genome may produce proteins that are missing part or all of the appropriate trafficking sequences, thus causing genetic trafficking disorders. Since the normal cardiac rhythm is dependent on ion channels and gap junctions, abnormal ion channel and gap junction function underlie a

number of cardiac rhythm disturbances. Alteration in individual channel gating function was thought to cause much of the loss of function of mutated channels, but analysis of many of the proarrhythmic mutations indicates that the true cause is the loss of trafficking to the membrane surface. For example, an alteration in the trafficking of ion channels to the cell's surface has been shown to occur in some forms of atrial fibrillation (AF), long QT syndrome (LQTS) types 1 and 2, Brugada syndrome, and Anderson syndrome (Table 8-1).

One of the more common forms of changes within protein sequences occurs when a coding change produces a protein with alternative amino acids at a given position within the protein. This shift, known as *polymorphism*, has two possible amino acids at particular loci within a protein but leaves the remaining amino acids in the correct location within the protein sequence. In many cases, no phenotypic change associated with polymorphisms occurs, but in rare cases, the changes at a single site can lead to the production of a protein that is nonfunctional. For example, in *SCN5A*, a mutation at amino acid 1053 from glutamic acid (E) to lysine (K) leads to a trafficking disorder of the sodium (Na^+) channel. Written as I1053K, this mutation prevents the *SCN5A* protein from localizing to cell membranes by interrupting the ability of the *SCN5A* protein to interact with the scaffolding protein ankyrin G, which normally maintains the protein subunit at the cell membranes (see Chapter 2 and Table 8-1). This simple substitution of a single amino acid thus causes the Brugada syndrome phenotype.

Frame shift mutations may also occur. In these mutations, a coding error causes the initial RNA triplet to have either an extra nucleotide or a lost nucleotide, shifting the reading frame in a manner that causes a novel amino acid to be produced at that site. The produced protein will then have a scrambled or "nonsense" sequence of amino acids. These errors are very severe and often lead to proteins that are trafficking deficient; in addition, if the trafficking deficiency is rescued pharmacologically, these proteins are unable to form a channel with normal function. One example of this is the LQTS type 1 (LQT1) mutation that results from a frame shift at position 178 in the α-subunit of the channel that underlies the slow component of the delayed rectifier current, I_K. In this case, the alanine normally found at position 178 is lost, which leads to the formation of an abnormal amino acid sequence; this sequence ends 105 amino acids later when, by chance, the combination of nucleotides forms a stop codon and the protein translation is terminated. This type of mutation, written as A178fs/105 in this case, causes the formation of a truncated form of the protein that is trafficking deficient and leads to the LQT1 phenotype (see Table 8-1).

Sodium Channels

The primary phenotype found in patients with mutations that cause loss of trafficking of sodium (Na^+) channels to the cell membranes is Brugada syndrome. This phenotype is associated with high risk for sudden cardiac death. Voltage-gated Na^+ channels are responsible for the rapid upstroke of the cardiac action potential and persistence of some Na^+ current after rapid depolarization participates in the early phase of repolarization. Conduction velocity is, in part, dependent on both the amplitude and the rate of activation of these channels, and repolarization is normally slowed by the persistence of Na^+ inward current during the early plateau phase. Therefore, decreased Na^+ current leads to a shortened action potential duration. This exaggerates the normal heterogeneity of the outward current found in the heart. This heterogeneity is usually masked by the inward Na^+ current leading to a voltage gradient across the ventricular wall, which is evident on the ECG as the classic Brugada's ST-segment elevations in leads V1 through V3.[3] Brugada syndrome can also result from mutations in the channel proteins that cause changes in channel function rather than a trafficking defect. Thus, loss of properly functioning Na^+ channels at the cell membranes—either because of direct Na^+ channel mutations or through loss of interaction of the Na^+ channel with trafficking or scaffolding partners—leads to reduced Na^+ current, increased heterogeneity in repolarization, and the subsequent production of re-entrant arrhythmias leading to sudden cardiac death.

Potassium Channels

Potassium (K^+) channel mutations that decrease total channel expression at cell membranes are an important cause of LQTS types 1 and 2 in addition to other mutations that cause loss of function of channels that are trafficked to the membranes. The primary current affected in LQTS is the delayed outward rectifier K^+ current, I_K. Depending on the channel in which a mutation resides, the subtypes of K^+ current affected (I_{Kr} or I_{Ks}) may vary, but the overall effect that manifests as LQTS is a loss of outward K^+ current. This loss leads to a delay in ventricular cell repolarization and the duration of the QT interval. As with Brugada syndrome, this leads to an increase in transmural repolarization gradients. The mechanism for ventricular tachycardia (torsades de pointes, TdP) associated with LQTS has been postulated to be the occurrence of early after-depolarizations (EADs) and triggered activity caused by the action potential prolongation, which leads to re-entry facilitated by the heterogeneities of repolarization.[3]

An additional K^+ channel trafficking mutation associated with cardiac arrhythmias and sudden cardiac death is Andersen-Tawil syndrome (see Table 8-1). This pleiotropic disorder is caused by a primary mutation in the gene *KCNJ2*. This gene codes for the Kir2.1 channel, which underlies the inwardly rectifying K^+ channel. As with other K^+ channel trafficking mutations, the primary ECG manifestation is a longer than normal QT interval, a dispersion of repolarization, and an increase in the propensity for ventricular arrhythmias likely triggered by EADs. While Andersen-Tawil syndrome has electrocardiographic similarities to LQTS, the pleiotropic nature of the disorder (periodic paralysis and dysmorphic features) helps distinguish it from other LQTSs.

Calcium Channels

Unlike Timothy syndrome, which is a gain of function mutation, a trafficking mutation in the calcium (Ca^{2+}) channel Cav1.2 is an example of a loss of function mutation leading to a decrease in the L-type Ca^{2+} current. This current normally functions in phase 2 of the action potential causing a sustained depolarization of the cardiac action potential (the plateau phase, mainly ventricular and Purkinje). Thus, loss of this channel leads to loss of the action potential dome, shortening of the action potential, and alterations in the rate of repolarization and duration. As with all cardiac ion channels, the L-type Ca^{2+} channel is heterogeneously expressed with a transmural gradient of expression from the epicardium to the endocardium (high to low current density). Complete channel loss leads to greater dispersion of repolarization across the

Table 8-1 Examples of Known or Suspected Trafficking Mutations Associated with Arrhythmias

CHANNEL	MUTATION	EFFECT	HUMAN DISORDER	REFERENCES
SCN5A (I_{Na})	K1578fs/52* L325R R367H	No current; possible trafficking defect	Brugada syndrome	Makiyama et al: *J Am Coll Cardiol* 46(11):2100, 2005. Keller et al: *Cardiovas Res* 67(3):510, 2005. Hong et al: *J Cardiovasc Electrophysiol* 15(1):64, 2004.
SCN5A (I_{Na})	T353I	Trafficking defect; mexitelene rescue unmasks persistent Na^+ current	Brugada syndrome; masking persistent Na^+ current associated with long QT syndrome	Pfahnl et al: *Heart Rhythm* 4:46, 2007.
SCN5A (I_{Na})	G1743R	Trafficking defect; mexitelene rescues this defect	Brugada syndrome; rescue gives normal Na^+ current	Valdiva et al: *Cardiovasc Res* 62:53, 2004.
SCN5A (I_{Na})	E1053K	Trafficking defect caused by loss of interaction with the scaffolding protein ankyrin G	Brugada syndrome	Mohler et al: *PNAS* 101:17533, 2004.
GPD1L (affects I_{Na})	A280V	Trafficking of GPD1L is increased, causing a decrease in *SCN5A* trafficking to the membrane	Brugada syndrome	London et al: *Circulation* 116:2260, 2007.
KCNH2 (I_{Kr})	T65P F463L N470D A558P A561V G572S G601S Y611H V612L T613M L615V F640V R752W N8611I R805C V822M R823W	Trafficking defect	LQT2	Delisle et al: *Circ Res* 94:1418, 2004.
KCNQ1 (I_{Ks})	A178fs/105 L191P* F275S	Trafficking defect	LQT1	Aizawa et al: *FEBS Lett* 574:145, 2004. Pan et al: *Cell Signal* 21(2):349, 2009. Li et al: *Biochem Biophys Res Commun* 380:127, 2009.
KCNJ2 (Kir)	V302M	Trafficking defect	Andersen-Tawil syndrome	Bendahhou et al: *J Biol Chem* 278:51779, 2003.
CaV1.2	A39V	Trafficking defect	Brugada phenotype with shorter than normal QT	Antzelevitch et al: *Circulation* 115(4):442, 2007.
Cx40 (GJa5)	P88S	Trafficking defect with a dominant negative effect on wild-type Cx40 as well as on Cx43	Atrial fibrillation	Gollob et al: *N Engl J Med* 354(25):2677, 2006.
Cx40	G38D	Trafficking defect	Atrial fibrillation	Gollob et al: *N Engl J Med* 354(25); 2677, 2007.

**fs indicates a frame shift mutation that causes formation of a scrambled sequence of amino acids that ends after a stop codon is accidentally made; the number after the slash describes how many scrambled amino acids are made in this particular protein before the aberrant stop codon truncates the protein.*

ventricular wall, manifested as an ST elevation on the ECG, and leads to the formation of the arrhythmogenic substrate. The distinguishing factor between this mutation and other Brugada syndrome mutations is that in patients with this mutation, the QT interval is shorter than normal because of the rapid repolarization of the myocardium.

Gap Junction Channels

Although deficiencies in gap junction function are associated with many different cardiac arrhythmias (see below), to date, the only arrhythmia associated with trafficking deficient mutations of gap junction proteins is AF. In some patients with AF, a subset of trafficking deficient mutations is found in connexin40 (Cx40), a primary gap junction protein in the atria.[4] Interestingly, these mutations also cause a dominant negative effect on the trafficking of connexin43 (Cx43), the other connexin isoform found in the atria, leading to very low levels of cell–cell coupling between the atrial myocytes. The mechanism for this transdominant effect is not clear, but the overall effect is loss of cell–cell coupling, which leads to slowed conduction and a propensity for the formation of re-entrant arrhythmias. Trafficking mutations in Cx43, which is the major gap junction protein in the ventricular myocardium, have not been found to be associated with ventricular arrhythmias. This is primarily because Cx43 is vital for normal cardiac development and function; thus, trafficking mutations would likely cause embryonic lethality.

Intercellular Communication

The ability for the heart to pump efficiently is dependent on the syncytial nature of the myocardium. Coordination of the contraction is maintained by passage of the electrical current through gap junctions, which are specialized membrane channels.[5] Gap junctions are formed from half, or hemi-, channels inserted into the plasma membranes of individual myocytes. These hemichannels (connexons) localize to the intercalated disc and meet head-to-head across the extracellular space with a connexon from an adjacent cell. This forms a longitudinally oriented conduit, which rapidly spreads excitation throughout the heart (Figure 8-1). The importance of gap junctions in maintaining conduction is underscored by the fact that their loss has been associated with slowed conduction and the formation of re-entrant arrhythmias.

Connexons are formed from the oligomerization of proteins from the connexin family in the Golgi apparatus. These proteins form four transmembrane domain-spanning units (see Figure 8-1). Overall, there are 21 isoforms of connexin in the human genome, five of which are found in the heart (Table 8-2).[5] The most abundant connexin in the heart is Cx43, which localizes to both the atrial and the ventricular myocytes. The second most abundant connexin is Cx40, which is found in the atrial myocytes, largely co-localizing with Cx43 but is also a predominant isoform within the nodes of the heart. It is found more sparsely within the specialized conduction system in conjunction with connexin45 (Cx45). Low levels of this connexin have been reported in both the atria and the ventricles, although the physiological relevance Cx45 in these regions is unclear. The nodes of the human heart also contain connexin31.9 (Cx31.9), a low-conductance gap junction channel. Connexin37 (Cx37) occurs in the endothelial lining of the cardiac vasculature in conjunction with Cx43.[5]

Table 8-2 Connexins in the Heart

Cx31.9	Sinoatrial node Atrioventricular node (although found only in animal models to date)
Cx37	Endothelial cells of vessels
Cx40	Atria Sinoatrial node Atrioventricular node
Cx43	Atria Ventricles
Cx45	Conducting system and nodes Atria and ventricles (very low levels)

Connexins follow the general pattern of membrane protein trafficking outlined above, with some interesting additions. The threading of the connexin protein into the membrane occurs, as with all membrane proteins, as it is being formed in the ER, but then the six connexins that form the connexon oligomerize, most likely beginning this process in the ER but finalizing the connexon formation within the Golgi apparatus.[6] Thus, the protein subunits form the channel prior to insertion into the membrane of the cell and must be regulated to stay closed to ensure that the intracellular compartments do not exchange components.

Once the connexons are formed, they traffic out to the plasma membrane within vesicles and in some cases, such as Cx43, within caveolae with the aid of microtubules.[7,8] For nonpolarized cells such as epithelial cells, a nondirected movement of connexons occurs, when connexons are trafficked outward to any region of the cell membrane. Polarized cells such as cardiomyocytes show directionality in the trafficking, with connexons being shuttled to the membrane domains in which they will reside and function. In the cardiac myocyte, this is the intercalated disc. From here, connexons move through the lipid bilayer and accumulate at the edges of gap junctional plaques, increasing the size of the plaque. As the protein is added, older protein that is designated to be removed from the plaque coalesces in the center of the plaque, and removal occurs from there.[9] This turnover is rapid, occurring within a few hours, giving an exquisite regulatory control to the level of junctional coupling between cells.

To maintain proper levels of cell-cell coupling, regulation of connexon function is vital. As such, connexins are subjected to multiple layers of regulation. In addition to the regulation by connexon turnover, connexins in the heart are both pH and voltage dependent. Connexin proteins also contain multiple sites for regulation by kinases, phosphatases, and scaffolding proteins, many of which are altered during cardiac dysfunction, which leads to aberrant regulation of gap junction channels.

Abnormalities in Intercellular Communication Causing Cardiac Arrhythmias

Cardiac arrhythmias are an expression of the abnormal electrophysiological properties of the heart. These abnormalities are

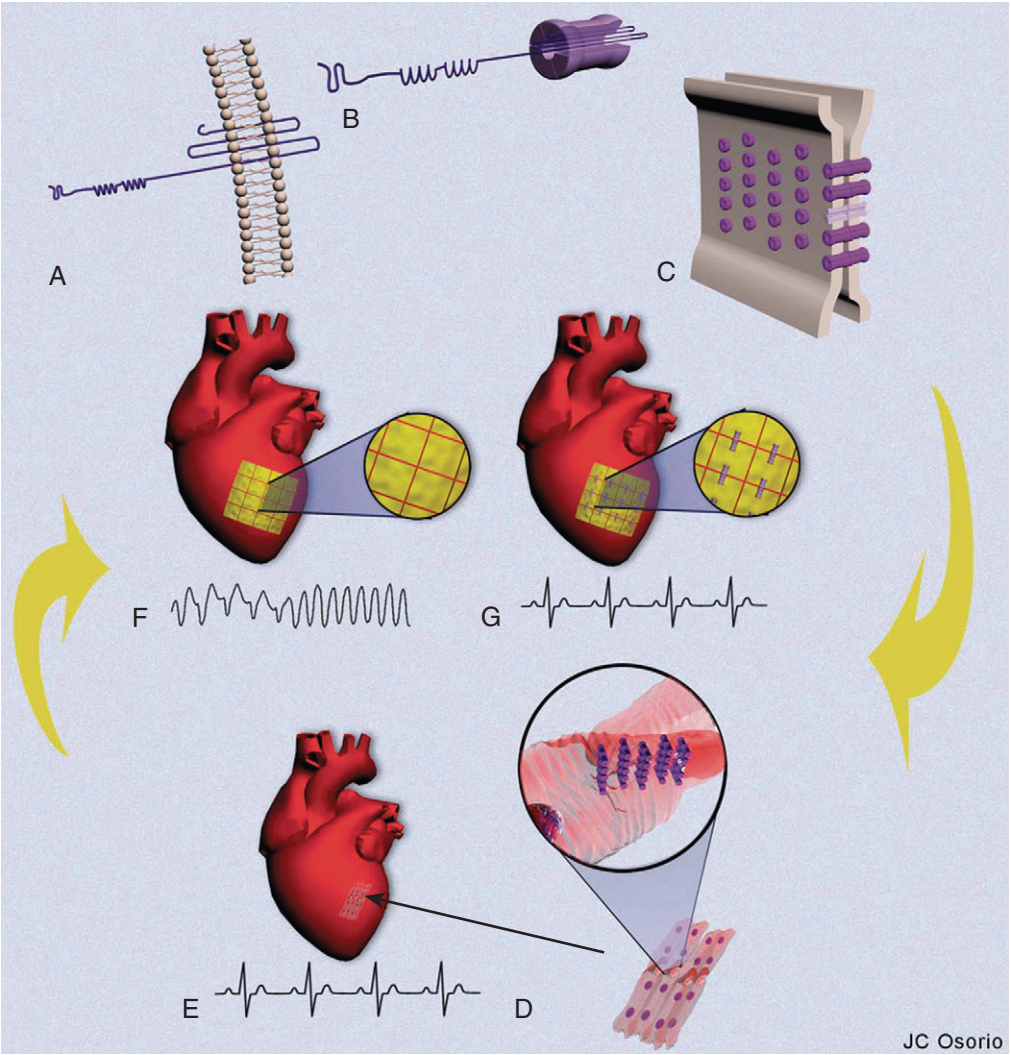

FIGURE 8-1 Connexins, connexons, and gap junctions in the heart. **A,** Connexin proteins, which form gap junctions, are four transmembrane domain proteins with intracellular amino and carboxyl terminal domains. **B,** Six individual connexin proteins oligomerize to form a half of a gap junction channel, known as a *connexon* (or *hemi-channel*). The connexon is shown here with one of its connexins visible for clarification. **C,** Connexons from adjacent cells are inserted into the membranes in a plaque where they meet head-to-head across the extracellular space to form a full channel. **D,** In healthy cardiac tissue, these gap junctional plaques are found at intercalated discs allowing for direct myocyte-to-myocyte coupling. **E,** Cell coupling in the heart underlies normal electrical propagation. **F,** Loss of gap junctions under pathologic conditions underlies, in part, the formation of an arrhythmogenic substrate. **G,** Animal models have shown that replacement of gap junction in the injured myocardium can decrease the formation of arrhythmias, although increased coupling in the face of an infarct has been shown to increase overall infarction size and thus may add risk for future arrhythmias.

mainly dependent on the aberrant function of sarcolemmal ion channels and gap junction channels in intercalated discs, often localized to a diseased area. Along with any structural changes associated with pathology, such as fibrosis, apoptosis, and necrosis, they form the arrhythmogenic substrate, that is, the electrophysiological environment that promotes arrhythmias. Remodeling of connexins causes loss of gap junction function that may lead to arrhythmias. Remodeling of connexins may occur in three forms: (1) changes in the function of connexin-formed gap junction channels without changes in the quantity or location of connexins, (2) changes in the quantity of connexins, and (3) location of connexins in membrane regions where they are not normally located (outside intercalated discs). The common feature is that they all lead to a decrease in gap junction conductance between myocytes.

Changes in Gap Junction Conductance Without Changes in Connexin Amount or Location

The gap-junctional membrane provides low-resistance pathways for current flow between myocardial cells as well as for the passage of small molecules (up to 1 kDa). The permeability of a gap junction to the flow of ions that carry current (i.e., junctional conductance) is determined by the number of junctional channels, the proportion of the channels that are in the open state, and the permeability (conductance) of the open

channel. The permeability of the gap junction channel in the open state, or *unitary conductance*, is determined by the particular connexin isoform or combination of isoforms that form the channel.[5]

The conductance of gap junctional channels may change under pathophysiological conditions without any change in the quantity or location of the connexin protein, through a change in the average conductance of gap junction channels. An important cause of reduction in Cx43 gap junction coupling that can occur in the ventricular ischemic arrhythmogenic substrate is low intracellular pH (below 6.5), an effect that can be facilitated by high intracellular Ca^{2+}. Effects of Ca^{2+} and pH are caused by a change in the open probability of the gap junction channel rather than by single-channel conductance. pH becomes an important direct influence at the low pH (<6.5) associated with hypoxia and ischemia by directly closing the channels, but ischemia and hypoxia may also lead to changes in connexon configuration that contribute to decreased gap junction conductance.[6]

Changes in the phosphorylation state of connexins during remodeling can change gap junction channel function.[6] For example, Cx43 is normally phosphorylated at multiple serine residues. Phosphorylation plays a number of roles. It might be necessary for maintaining hemi-channels in their closed state until docking occurs in the membrane of the intercalated disc. It also appears to be necessary for the normal opening and closing of gap junction channels. Changes in the phosphorylation state during acute ischemia can decrease the open probability of gap junction channels, probably prior to the change in Cx43 quantity that occurs following approximately 15 minutes of ischemia.

Changes in Quantity of Connexin Protein

Gap-junctional plaques have half-lives in the order of 3 hours, which allows for rapid turnover of connexins (synthesis and degradation; see above). This rate of turnover may be altered in pathophysiological states, thus affecting connexin quantity and myocyte coupling. A decrease in the quantity of connexin protein has been documented in a number of different cardiac diseases. Although quantifying connexins may not be an adequate indicator of what is happening to levels of gap junctional communication, it can give some determination as to the likelihood of loss of cell coupling and formation of the arrhythmogenic substrate.

Atrial Remodeling

The atria, including the sleeves of the thoracic veins, contain Cx40, Cx43, and Cx45.[10] Cx40 is expressed two- to threefold higher in the right atrium than in the left.[11] Distribution is heterogeneous, with areas containing large amounts of Cx40 adjacent to regions with minimal or no Cx40. Cx43 is more homogeneously distributed in the atria, although some reports have suggested an increased level of Cx43 in the right atrial free wall, as compared with the left atrial free wall. The functional significance of this difference in expression is unknown. The presence of multiple connexin isoforms in the atria may result in the formation of gap junction channels that have multiple isoform configurations with different regulatory and physiological characteristics. Gap junctions may comprise Cx40 alone, Cx43 alone, or Cx45 alone (homomeric and homotypic). The channels may also be homomeric but heterotypic; for example, homomeric Cx40 connexons may be coupled with homomeric Cx43 or Cx45 connexons. Channels may also be heteromeric but heterotypic; that is, a single connexon may be composed of different connexins such as Cx40 and Cx43, and coupled with another connexon comprising different connexins.[6]

Remodeling of gap junctions in the atrial myocardium has been documented in atrial fibrillation, an arrhythmia often associated with aging.[10] Fibrosis associated with aging and fibrillation occurs in the form of fine longitudinally oriented collagenous microsepta and diminishes intercellular connections.[12] It might decrease connexin quantity, although the relationships of connexin quantity to this kind of gap junction remodeling have not been determined. More extensive fibrosis that occurs in other atrial pathologies is often associated with decreased connexin as well (see below) and may play a larger role in the formation of the atrial arrhythmogenic substrate.

Studies on quantification of Cx43 and Cx40 have been done mostly in right atrial tissue from human and animal models of atrial fibrillation.[10] Connexin quantification in the left atrium has rarely been done. This represents a significant problem in relating connexin remodeling to fibrillation, which often originates in the left atrium or pulmonary veins. Increase, decrease Cx40, and no change in the quantity of Cx40 have been reported.[10] A common finding that is unrelated to quantitative changes in humans or animal models has been an increased heterogeneity in Cx40 distribution manifested as increased regions, in which Cx40 containing myocytes are located adjacent to myocytes mostly lacking Cx40. Cx43 may increase, decrease, or not change in quantity.[10] Cx45, which has only been measured in postoperative AF, does not change. No quantitative data indicates how heteromeric or heterotypic gap junction channels might be affected. Together, these disparate data suggest that changes in connexins are variable. Their relationship to the occurrence of AF is uncertain but has been supported by some studies in transgenic murine models (see below).

Ventricular Remodeling

A decrease in total Cx43 occurs in the ischemic region as early as 15 minutes after experimental coronary occlusion (Figure 8-2). A change in the phosphorylation state of Cx43 that accompanies acute ischemia also occurs.[13,14] Total phosphorylation is markedly decreased such that the ratio of dephosphorylated Cx43 to phosphorylated Cx43 increases. Dephosphorylation occurs at sites at S325, S328, S330, or in all three, which may contribute to decreased cell coupling by decreasing the number of functional gap junctions in intercalated discs.[13,14] After more than 6 hours of ischemia resulting from coronary occlusion, Cx43 disappears from the necrotic infarct core but remains in reduced amounts in surviving myocytes that form border zones and then remains decreased (5% to 30% of normal) for days to months.[15]

In the border zones of healed infarcts, significant interstitial fibrosis is present. Collagen fibrils separate myofibers and distort the interconnections between cells. Fewer gap junctions per unit of intercalated disc length are present, and the long transversely oriented gap junctions in the interplicate regions are essentially absent.[16] As a result, the number of cells connected to an individual ventricular myocyte is reduced with side-to-side contacts selectively affected. Normal organization of gap junctions as a prominent ring enclosing small spots is no longer discernible in some border zone myocytes adjacent to the necrotic core.[15] Comparatively fewer labeled gap junctions are organized in discrete intercalated discs, and many are spread laterally over the cell (see

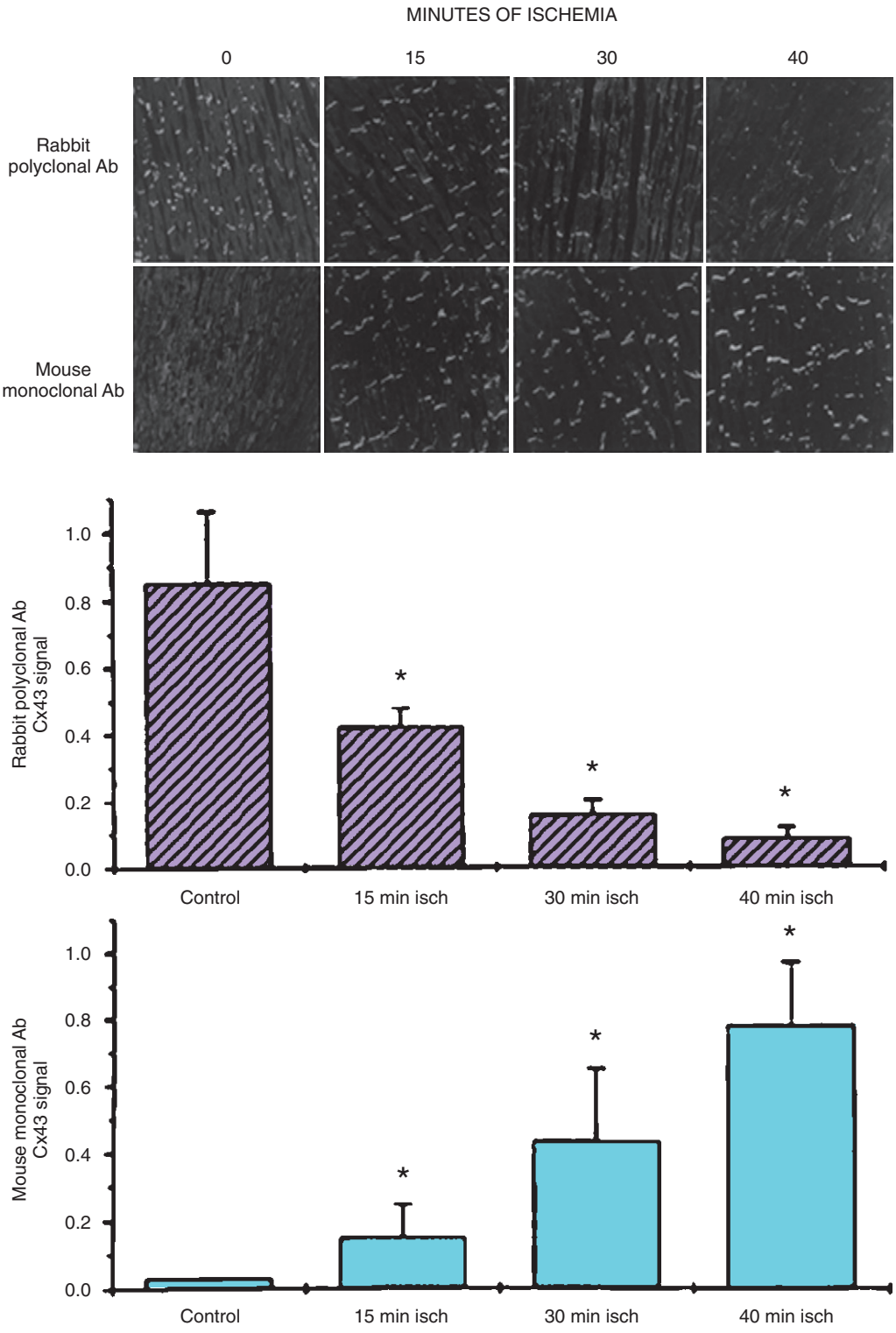

FIGURE 8-2 Remodeling of Cx43 expressed as a reduction of total Cx43 and an increase in dephosphorylated Cx43. *Top panels*, Representative confocal images of rat ventricles subjected to selected intervals of ischemia and immunostained with either polyclonal (stains both phosphorylated and dephosphorylated Cx43) or monoclonal (stains only dephosphorylated Cx43) anti-Cx43 antibodies. Immunoreactive signal is concentrated in discrete spots at sites of intercellular apposition. In normal rat, ventricle immunofluorescence from polyclonal antibody is plainly seen representing mainly the phosphorylated antibody, and little staining from monoclonal antibody represents dephosphorylated antibody. With time, after onset of ischemia, total Cx43 decreases, and the inactive dephosphorylated Cx43 increases. *Bottom panel*, Quantitative digital image analysis of rat ventricles subjected to ischemia (*isch*) and immunostained with polyclonal or monoclonal anti-Cx43 antibodies. Cx43 signal is expressed as a percentage of the total area occupied by tissue. *$P < .05$ compared with the 0-minute time point for each antibody. *(From Beardslee MA, Lerner DL, Tadros PN, et al: Dephosphorylation and intracellular redistribution of ventricular connexin43 during electrical uncoupling induced by ischemia,* Circ Res *87:656–662, 2000.)*

section on lateralization).[15] A reduction of Cx43 expression by more than 50% has been measured in experimental and clinical heart failure and hypertrophy, although quantitative data differ, depending on the cause, the duration, and the regions of the ventricle sampled.[17,18]

Upregulation of Cx45 in conjunction with downregulation of Cx43 at the end stage of human failing ventricles has been reported.[19] An increase or no change in the quantity of Cx45 in the face of a decrease in Cx43 levels would increase the Cx45/Cx43 ratio, potentially promoting the formation of more heterotypic gap junctions with lower conductance than in normal hearts. As in ischemia, a decrease in the phosphorylated form and an increase in the dephosphorylated form of Cx43 are evident in experimental as well as clinical heart failure, with a substantial decrease in both pS365 as well as in pS325/328/330, which would also be expected to decrease conductance.[20]

Cx43 gap junctions within the intercalated discs of the hypertrophied myocardium are reduced.[21] In hypertrophic cardiomyopathy, intercalated discs in regions of myocyte disarray do not show the standard stepwise morphology but are abnormally enlarged and show abundant Cx43 immunostaining. In areas of myofiber disarray, Cx43 gap junctions are no longer confined to intercalated discs but are dispersed over the surfaces of myocytes (see next section).

Normal gap junction amount and localization in ventricular myocytes likely depend on normal mechanical coupling via cell–cell adhesion junctions.[22] Carvajal syndrome is caused by a recessive mutation in desmoplakin, a protein that links desmosomal adhesion molecules in intercalated discs, to the myocyte cytoskeleton. Naxos disease is caused by a recessive mutation in plakoglobin (γ-catenin), that links N-cadherins in the discs to actin and desmosomal cadherins to desmin. In Naxos disease, Cx43 is expressed abundantly but fails to localize to gap junctions. Both diseases are associated with a reduction in Cx43.[22]

Changes in Location of Connexin Protein: Lateralization

Connexin remodeling in ventricles is often associated with Cx43 dispersion over the cell surface outside the intercalated disc, a process called *lateralization*. Lateralization is not as prevalent in the atria as in the ventricles, although it has been described in AF.[10] Lateralization appears to be intimately related to remodeling that leads to a decrease in connexin protein at intercalated discs. After acute ischemia, some of the Cx43 rapidly moves to lateral nonintercalated disc membranes within 30 minutes.[13,23] In chronic ischemia and infarction, lateralization of Cx43 occurs in infarct border zones mainly in the surviving myocytes that are adjacent to the necrotic regions (Figure 8-3).[15] The amount of

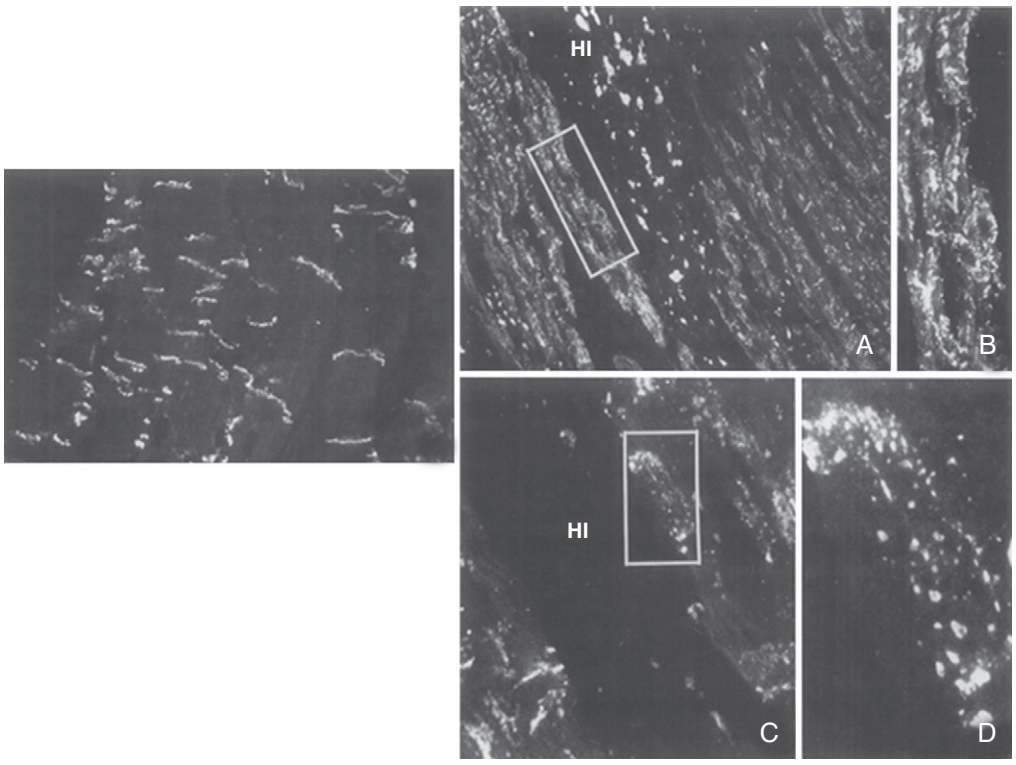

FIGURE 8-3 *Left*, Immunostained gap junctions from human left ventricle as observed by laser scanning confocal microscopy (transplant patient). The immunofluorescence labeling is at the ends of the myocytes showing the normal distribution of Cx43 in the intercalated discs. *Right*, Gap junction distribution in myocytes bordering healed infarcts in the left ventricle of a transplant patient, as viewed by immunostaining and laser scanning confocal. The normal segregation of gap junctions into intercalated discs is retained by some cells (*arrow* in **B**), and myocytes in **A, C,** and **D** show labeling on lateral membranes outside intercalated discs. **A** and **C,** Composite images prepared from multiple optical sections. **B** and **D,** Single optical sections. *Magnification*: **A,** x143; **B,** x780; **C,** x355; **D,** x2520. *(From Smith JH, Green CR, Peters NS, et al: Altered patterns of gap junction distribution in ischemic heart disease. An immunohistochemical study of human myocardium using laser scanning confocal microscopy,* Am J Pathol *139[4]:801–821, 1991.)*

lateralized Cx43 is not commensurate with lateralized gap junctions. In a canine model, at 5 days after occlusion, very few lateral gap junctions were detected by ultrastructure analysis despite abundant lateral immunofluorescent antibody to Cx43 (Heather S. Duffy, unpublished observation). In chronic infarcts, lateral gap junctions have been detected, but they are not as numerous as would be expected if most of the lateralized Cx43 formed gap junctions.[15] Gap junctions are still present in intercalated discs after lateralization. However, the normal organization as a prominent ring around the myocyte enclosing small regions of gap junctional plaques within the intercalated disc is no longer discernible.[15] The long ribbon-shaped junctions in the interplicate disc appear to be reduced in conjunction with the widening of the intercellular space.[16] Lateralization of Cx43 also occurs in heart failure and hypertrophy.[17,18] The amount of lateralized Cx43 as detected by immunofluorescence is much greater than any increase in identifiable gap junctions**.** Decreases in transverse conduction velocity following coronary occlusion argue against lateralized gap junctions forming functional channels between adjacent myocytes.

Electrophysiological Mechanisms of Cardiac Arrhythmias

Arrhythmias result from critical alterations in cellular electrophysiology. The two general causes of arrhythmias are (1) abnormalities in impulse initiation (automaticity and triggered activity) and (2) abnormalities in impulse conduction (re-entry). Gap junction remodeling may play a role in both.

Role of Gap Junction Remodeling in Re-entrant Excitation

Slowed conduction facilitates the occurrence of re-entry. During conduction of the impulse, the transmembrane current during the depolarization phase (0) of the action potential results in axial current flow along the cardiac fiber through the cytoplasm and the gap junctions connecting the myocytes. A decrease in this inward current, an increased resistance to axial current flow (effective axial resistance), or both decreases the magnitude and spread of axial current and decreases conduction velocity. Thus, the extent, distribution, and conductance of gap junctions influence axial resistance and conduction.

Conduction velocity decreases monotonically with a reduction in intercellular coupling as would occur with gap junction remodeling.[24] Conduction becomes discontinuous, and the safety factor increases, which differs from the fall in safety factor that occurs with a reduction of I_{Na}. Conduction can slow to about one fifteenth of normal at gap junction coupling, which is reduced by a factor of approximately 100, whereas minimum possible conduction velocity with reduced I_{Na} is by about a factor of 3.[24] Therefore, gap junction uncoupling can cause the necessary slowed conduction that enables re-entry. Decreased gap junction coupling during remodeling also can alter the anisotropic properties of the myocardium, an important factor in arrhythmogenesis. A uniform reduction of transverse and longitudinal gap junction conductance causes a uniform longitudinal and transverse reduction of conduction velocity with an increase in the anisotropic ratio, since transverse conduction decreases more than longitudinal conduction does.[25] Changes in the characteristics of anisotropic propagation from uniform to nonuniform may also be a consequence of gap junction remodeling.[12]

Gap junction coupling influences the refractory properties of the myocardium as well. Significant differences in refractory periods (heterogeneity) between closely adjacent regions predispose the myocardium to conduction block of premature impulses in those regions with longer refractory periods and allows conduction in those regions with shorter refractory periods, which can initiate re-entrant excitation.[26] The time courses of repolarization of myocytes in different regions of the ventricles and atria are different because of intrinsic differences in repolarizing membrane currents. These intrinsic differences in the ventricles are expressed in the action potentials of isolated myocytes, in which the time course of repolarization is longest in the deep subepicardial/midmyocardial myocytes (M cells) of the left ventricular free wall and the deep endocardial layers of the septum and papillary muscles and shorter in the epicardial and subendocardial myocytes.[27] However, a significant transmural gradient does not occur in situ, likely caused by current flow through gap junctions when cells are well coupled.[28] Current flows from myocytes repolarizing early to myocytes repolarizing late because of the intrinsic differences in the time course of repolarization, lengthening the repolarization in cells with a shorter time course and shortening the repolarization in cells with a longer time course. Decreased gap junction coupling with gap junction remodeling decreases homogeneity (increases heterogeneity) by enabling the differences in intrinsic membrane properties to be expressed.[28]

Re-entry Caused by Changes in Gap Junction Channel Conductance Without Changes in Connexin Amount or Location

Ventricular arrhythmias that occur within the first minutes of coronary artery occlusion (phase 1a) are mostly caused by re-entrant excitation with slow conduction resulting from membrane depolarization, before conduction slowing caused by gap junction uncoupling. A second phase of arrhythmias that occurs later (phase 1b) may also be caused by re-entry at a time when uncoupling occurs because of the effects of hypoxia, acidification, and dephosphorylation on gap junction channel function.[26] Uncoupling causes a substantial increase in internal longitudinal (axial) resistance and conduction velocity over a period of about 30 minutes before conduction block occurs.[29,30] Alterations in the configuration of connexon channels in gap junctions over a slightly longer time course, up to 3 hours, may also contribute to the decreased conductance before irreversible cell damage occurs.[23] Increased heterogeneity of refractoriness that contributes to conduction block during both phases may be partly related to uncoupling. Cx43 quantity begins to decrease shortly after coronary occlusion, probably contributing to more long-term slowing of conduction during phase 1b arrhythmia.[14]

Re-entry Caused by Gap Junction Remodeling Characterized by Changes in Connexin Quantity

The decrease in connexin protein that accompanies atrial and ventricular pathology is often associated with the occurrence of arrhythmias. Although a re-entrant mechanism is a likely cause, it has not always been directly demonstrated. A decrease in connexin protein should decrease the number of functioning gap junctions, intercellular coupling, and conduction velocity and also increase heterogeneity of refractoriness. The exact quantitative relationship between reduction of connexin protein levels and changes in conduction velocity and refractoriness is uncertain.

This problem of relating connexin reduction to changes in conduction has been addressed in studies of transgenic murine models. For example, in the atria of transgenic murine models with downregulation of Cx40 in the absence of changes in Cx43 and Cx45, almost complete reduction of Cx40 was shown to result in decreased atrial conduction velocity of 30% to 36%.[31] The decrease in Cx40 is heterogeneous, as is the decrease in conduction, likely causing block in some regions devoid of most Cx40. Such heterogeneities also occur in animal models as well as in patients with AF.[10] Refractory periods have not been measured in the transgenic murine models but are heterogeneous in both animal models and patients, which is a possible result of heterogeneous gap junction remodeling. Some slowing of atrial conduction also occurs with decreased Cx43. The presence of Cx43, therefore, may be maintaining conduction in the absence of Cx40. In a clinical study, it was found that the ratio Cx43/[Cx43+Cx40] was directly related to propagation velocity and that the Cx40/[Cx43+Cx40] ratio was inversely related to propagation velocity.[32] This suggests that changing the ratio of homomeric channels to heteromeric channels will have effects on propagation velocity, reflecting the functions of individual channels. As described above, in some clinical studies on AF, an upregulation of Cx40 has been demonstrated.[10] Its effects on conduction or other electrophysiological properties are unknown, but it may contribute to the occurrence of heterogeneities in conduction and refractoriness.

The link between atrial gap junction remodeling and arrhythmias is circumstantial. An increased occurrence of spontaneous and induced atrial arrhythmias in transgenic models of reduced Cx40 has been demonstrated, although re-entrant circuits have not been mapped.[33] Induction and termination by pacing is suggestive of a re-entrant mechanism. Re-entry has been shown to cause rapid atrial arrhythmias in both animal models and clinical cases.[10] The relative contributions of gap junction remodeling and other properties of the arrhythmogenic substrate have not been determined.

In the ventricles, reduction of Cx43, either by targeting the genes that control Cx43 formation or the genes controlling other proteins related to gap junction location in intercalated discs, causes a significant decrease in gap junction coupling and ventricular arrhythmias related to abnormal conduction and refractoriness, which are likely to be re-entrant (Figure 8-4). Reduction of Cx43 in the ventricles by as much as 50% by disruption of one allele of the Cx43 gene does not significantly slow conduction.[34] However, it does predispose the myocardium to the effects of "second hits" on gap junctions to slow conduction such as

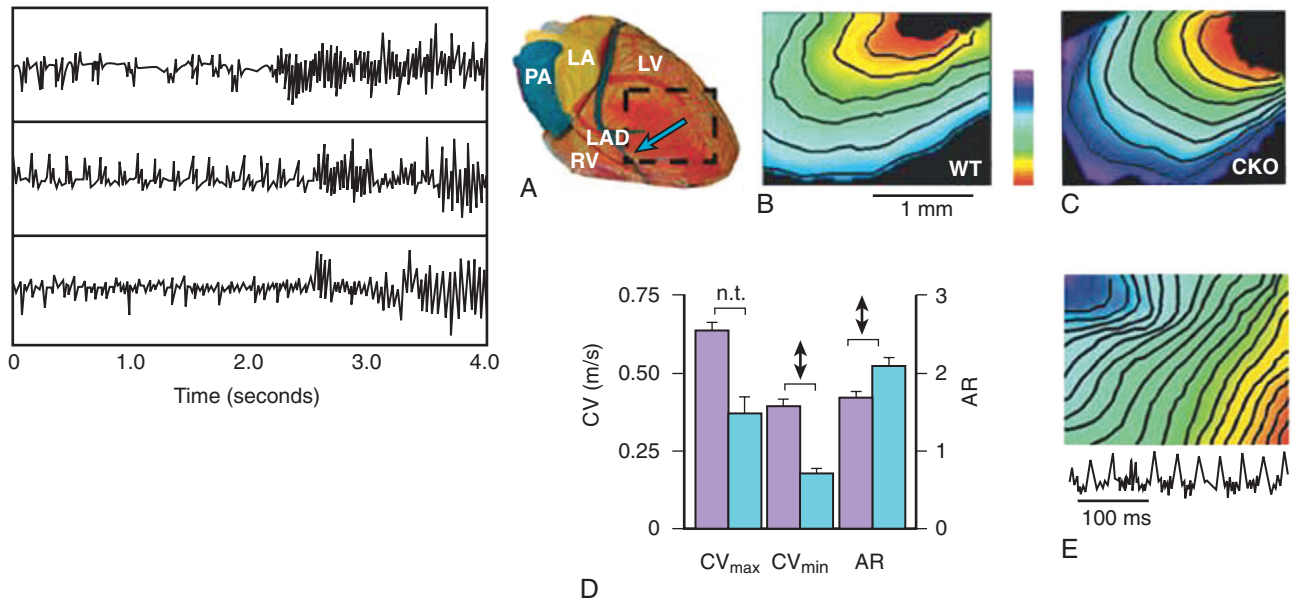

FIGURE 8-4 *Left*, Continuous electrocardiographic recordings from miniaturized implanted transmitter devices in three MHC-CKO mice at 5 (top), 8 (middle), and 7 (bottom) weeks of age. The recordings show normal sinus rhythm initially, followed by ventricular tachycardia. The arrhythmias quickly degenerated into ventricular fibrillation. *Right*, Optical-mapping studies in MHC-CKO mice. **A,** Schematic of the anterior surface of the heart showing the approximate area imaged and used to calculate conduction velocities. Hearts in this study were paced at the left ventricular lateral wall, and the epicardial activation pattern was recorded as it spread across the anterior wall toward the ventricular septum, as indicated by the *arrow*. **B,** Anterior view of a control littermate heart showing the expected smooth epicardial activation pattern from the site of pacing at the lateral wall and spreading toward the ventricular septum. C_{Vmax} in this control heart is 0.58 m/s, and C_{Vmin} is 0.32 m/s. **C,** Representative epicardial activation pattern of an age-matched MHC-CKO mouse heart paced in the same fashion as the control heart. C_{Vmax} in this MHC-CKO heart is 0.42 m/s, and CVmin is 0.15 m/s. **D,** C_{Vmax}, C_{Vmin}, and anisotropic ratio (*AR*) for the control (n = 56) and MHC-CKO (n = 54) mice. **E,** Epicardial activation pattern in an MHC-CKO mouse with incessant ventricular tachyarrhythmia. The bottom trace shows a pseudo-electrocardiogram that summarizes the activity recorded during the episode. Color scale bars in **B** and **C** indicate 0 (red) to 4 ms (purple) and in **E** from 0 to 10 ms. *LA*, Left atrium; *LV*, left ventricle; *LAD*, left anterior descending artery; *RV*, right ventricle; *WT*, wild type. *(From Gutstein DE, Morley GE, Vaidya TH, et al: Conduction slowing and sudden arrhythmic death in mice with cardiac-restricted inactivation of connexin43,* Circ Res *88:333–339, 2001.)*

ischemia (see below). A very large reduction of Cx43, by more than 75%, significantly slows conduction by approximately 50% in the transverse and approximately 20% in the longitudinal direction, and increases the anisotropic ratio (see Figure 8-4).[35,36] Conduction slowing does not seem to be commensurate with the marked reduction in Cx43 in transgenic murine models, and it is not certain if this quantitative relationship applies to the human heart (see below).

Since remodeling of Cx43 associated with a decrease in quantity is usually heterogeneous, regions of the myocardium nearly devoid of Cx43 may occur both in pathology and in transgenic murine models. These regions cause very slow conduction or conduction block and may be the critical feature leading to re-entry. Although the upregulation of other connexins must be considered as an explanation for the unexpected maintenance of conduction in the face of a marked reduction of Cx43 in transgenic models, this has not been demonstrated. Another important factor concerning gap junction control of conduction in murine ventricles is the very small size of the myocytes and the concomitant high resistance of the intracellular compartment in relation to gap junction resistance and an upregulation of Na^+ channels, both rendering conduction less dependent on gap junction coupling than it might be in humans.[24]

Beyond the observation that arrhythmias are associated with Cx43 remodeling, direct proof that remodeling of gap junctions is the cause of re-entry caused by slow conduction in pathology is sparse. The diseased heart in which gap junction remodeling occurs usually has alterations in sarcolemmal ion channel function as well as structural changes such as fibrosis, making it difficult to define the relative role of gap junction remodeling in the arrhythmogenic substrate. In a canine model of myocardial infarction, in which there is a decrease in Cx43 and lateralization (see below), re-entrant circuits causing ventricular tachycardia have been mapped in the epicardial border zone.[36] It is likely that interaction between the reduced Na^+ current in border zone myocytes with reduced gap junction coupling causes the slow conduction and block necessary for re-entry. Re-entrant circuits have also been mapped in border zones of healed human infarcts which have gap junction remodeling.[21,26] Although gap junction remodeling can influence the refractory period, re-entry dependent on heterogeneities in the effective refractory period has only been shown in a canine model of pacing-induced heart failure.[37]

Additional evidence to show the relationship between conduction slowing caused by Cx43 reduction and re-entrant arrhythmias comes from studies on transgenic murine models of gap junction remodeling, in which changes in sarcolemmal ion channel function and myocardial structure changes do not occur. Cx43 heterozygous mice are abnormally susceptible to the development of ventricular tachycardia in response to acute ischemia, despite the minimal effects of the reduction in Cx43 by itself (~50%) on conduction.[38] The effects of ischemia to reduce gap junction coupling may be enhanced and thus cause more severe conduction slowing leading to re-entrant excitation, although re-entrant circuits have not been mapped. This has important implications for clinical arrhythmias, since hearts with chronic pathology causing reduction of Cx43 (e.g., failure and hypertrophy) that, in itself, may not be sufficient to cause arrhythmias may be more susceptible following an ischemic event.

Murine hearts with conditionally inactivated Cx43 genes, resulting in Cx43 expression reduced by up to 90% with extensive areas completely devoid of Cx43, exhibit spontaneously occurring ventricular tachycardia/fibrillation and sudden cardiac death as well as inducible ventricular arrhythmias indicative of a re-entrant mechanism.[35] Arrhythmias do not occur if Cx43 is not reduced to less than 40%.[39] Other transgenic murine models with reduction of Cx43 also have demonstrated ventricular tachyarrhythmias.[40] Re-entrant circuits that have been mapped have the characteristics of anisotropic re-entry with conduction velocity more rapid in the longitudinal direction and functional lines of conduction block of transversely conducting wavefronts.[39] Small rotors may also form in regions with inexcitable obstacles formed by myocytes devoid of Cx43. Abnormal impulse initiation (see below) cannot be excluded.

Although the evidence is limited, Cx45 may be upregulated in heart failure.[19] Transgenic mice overexpressing Cx45, without changes in Cx43 gap junctions, exhibit enhanced spontaneous or induced ventricular arrhythmias suggesting a re-entrant mechanisms.[41] Overexpression of Cx45 in cells normally expressing Cx43 significantly reduces intercellular coupling, since Cx43 and Cx45 may form low-conductance heteromeric channels.

Gap Junction Remodeling Characterized by Changes in Gap Junction Location

Lateralization of connexin protein may be part of the process that leads to a reduction of connexins. In most instances, a decrease in total connexins occurs despite an increase on nondisc lateral membranes. Lateralized Cx43, sometimes but not always, is dephosphorylated, which may be part of the mechanism for lateralization. The expected increase in transverse conduction velocity that would occur if new lateral gap junctions were formed has usually not been seen (Figure 8-5), and an increase in lateral gap junctions commensurate with increased lateralized connexin demonstrated by immunofluorescent studies is absent.[36]

Effects of Gap Junction Remodeling on Abnormal Impulse Initiation

Automaticity

The sinus node provides an example of the influence of gap junction coupling on automaticity. The sinus node is poorly coupled with the surrounding atrial myocardium through transitional cells with gap junctions formed by connexins 40, 45, 31.9, or all of them. If the two regions were well coupled, hyperpolarizing current flow from the well-polarized atrial myocardium would prevent sinus node impulse initiation. The weak coupling allows propagation from the small mass of the sinus node to the larger mass of the atrium.[42] The effect of gap junction coupling on sinus node automaticity and conduction also applies to the interaction of subsidiary pacemakers with surrounding nonpacemakers. In well-coupled cells, flow of the hyperpolarizing current from nonpacemaker cells to pacemaker cells would slow spontaneous firing or even inhibit it, depending on the coupling resistance, while preventing impulses initiated in a relatively small region from propagating into the larger surrounding region. Partial uncoupling caused by gap junction remodeling would allow subsidiary pacemakers to fire and possibly drive the heart as an arrhythmia.[43] Such arrhythmias might occur in any of the pathologic situations that result in atrial or ventricular gap junction remodeling, particularly in situations of heterogeneous decreases in connexin.

Conversely, the flow of current between partially depolarized regions and well-polarized regions may induce spontaneous

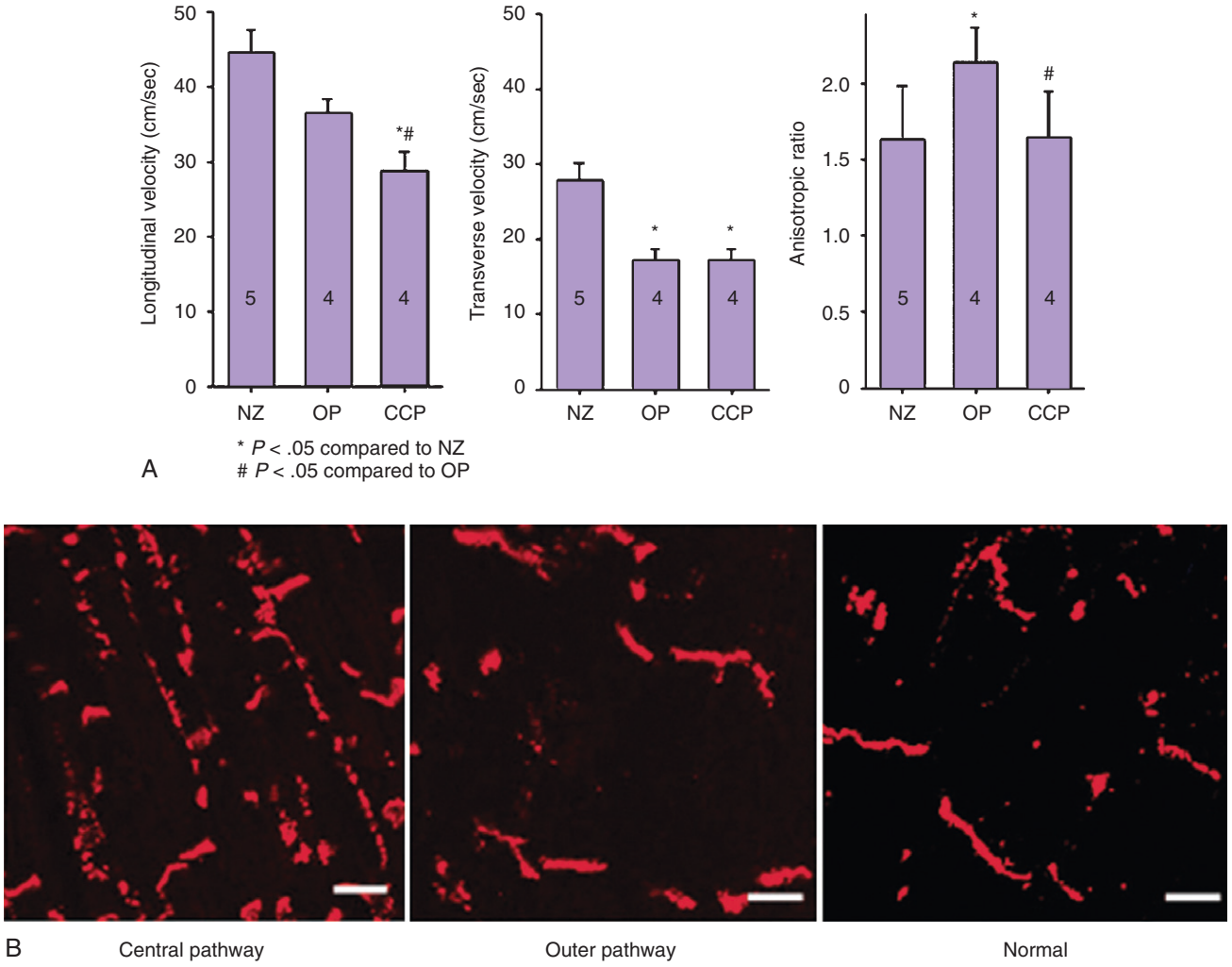

FIGURE 8-5 A, Conduction velocities (ordinates) in normal (*NZ*), central common pathway (*CCP*), and outer pathway (*OP*) (abscissa) of re-entrant circuits in 5-day-old canine infarct epicardial border zone. Longitudinal velocities are at the *left*, transverse velocities in the *center*, and anisotropic ratios at the *right*. Numbers in bars indicate number of experiments in each group. **B,** Immunofluorescence images of epicardial border zone of the CCP and OP of a mapped re-entrant circuit. Location of Cx43 shown by red fluorescence. In the central pathway, significant amounts of Cx43 are located along lateral membranes, at the same time maintaining a presence at the ends of the myocytes. Nevertheless, both transverse and longitudinal conduction velocities are decreased. In the normal and outer pathway tissues, fluorescence is seen only at the intercalated disc regions of the myocytes. *Scale bars*: 25 μm. *(From Cabo C, Yao J, Boyden PA, et al: Heterogeneous gap junction remodeling in re-entrant circuits in the epicardial border zone of the healing canine infarct,* Cardiovasc Res *72[2]:241–249, 2006.)*

(automatic) firing under special circumstances. In ischemic regions with decreased membrane potential adjacent to normally polarized myocytes either in nonischemic subendocardial Purkinje system or muscle, an injury current flows from the ischemic myocytes with low membrane potentials to myocytes with higher membrane potentials, which results in depolarization-induced impulse initiation (abnormal automaticity) in the latter.[26] When there is normal coupling, the flow of the injury current is too large to permit spontaneous activity, since it "clamps" the cells at the low membrane potential. If uncoupling is too severe, insufficient injury current occurs to depolarize the myocytes to the level of membrane potential necessary for abnormal automaticity.[44] The cause of the uncoupling is likely the low pH and elevated Ca^{2+}, which occur during acute ischemia; however, by this time, some dephosphorylation and reduction of Cx43 have occurred (see above).

Triggered Activity

Since the occurrence of EADs is favored by the prolongation of repolarization in the presence of inciting influences such as β-adrenergic stimulation or class III antiarrhythmic drugs, gap junction remodeling leading to uncoupling and the increase in action potential duration described above, can lead to EAD formation and triggered activity, particularly in myocytes with long intrinsic action potential durations such as M cells.[26] However, even in the face of moderate uncoupling, EADs may be prevented by the flow of repolarizing current from the neighboring

myocardium.[45] The amount of current required is dependent on the size of the EAD focus, and this, in turn, influences the degree of uncoupling that allows EAD expression. If the uncoupling is sufficient to allow the expression of EADs and triggered activity, the coupling must still be sufficient to allow the propagation of the triggered activity to the surrounding myocardium.[46] In the case of acute ischemia and partial uncoupling, the flow of injury current, particularly at junctions of partially depolarized ventricular muscle with more normally polarized Purkinje fibers, can prolong repolarization time course and lead to the formation of EADs. The effects of coupling on DAD-induced triggered activity has not been specifically addressed, but the same influences of well-polarized cells on automaticity and EADs described above would be expected.

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CHAPTER 9

Fundamentals of Regenerative Medicine and Its Applications to Electrophysiology

David H. Lau and Michael R. Rosen

The adult human heart has long been accepted as an end organ having no regenerative properties. In contrast, nonmammalian species such as zebrafish recover completely after ventricular apical resection thereby manifesting cardiac regeneration.[1] Regenerative medicine builds on such observations, with the aim to replace or regenerate cells, tissues, and organs to restore or establish normal function.

Despite previous wisdom, recent evidence suggests that (1) adult human cardiomyocytes have mitotic potential, (2) cardiac progenitor cells can be isolated, (3) cardiomyocyte turnover occurs, and (4) human embryonic stem cells can differentiate into cardiomyocyte-like cells in culture.[2-7] These discoveries have sparked excitement about the idea of repopulating the heart with healthy cardiomyocytes after a myocardial infarction, an idea that only recently was considered science fiction.[4] Part of the effort in regenerative medicine has focused on cardiac arrhythmias. This effort has drawn on knowledge of the molecular and biophysical properties of the ion channels and signaling molecules that contribute to the initiation and propagation of the action potential. The effort has gained impetus from continued disappointment with the performance of antiarrhythmic drugs.

Gene- and cell-based strategies to treat cardiac arrhythmias offer several potential advantages over traditional drugs. First, gene- and cell-based therapies can be site selective; that is, they can be delivered by catheter to exert their effects selectively on the tissue of interest. Second, these therapies have the potential to have durable effects, which obviates daily dosing with medications. Lastly, these therapies can deliver almost any therapeutic protein, or proteins, toward achieving normal physiology. The therapeutic agent may be a construct that is native or foreign to cardiac cells, chimeric, or mutated to enhance therapeutic efficacy.

Gene Transfer by Viral Vectors

A successful gene therapy strategy must be safe, easy to deliver, and predictable in expression, efficacy, and duration of effect. Viral vectors have been widely used for gene transfer. Several factors need to be considered in choosing a viral vector: (1) the size of the gene it can incorporate; (2) the ease of genetic manipulation; (3) the ability to infect the target cell type; (4) replication deficiency; (5) lack of inflammatory and oncogenic potential; and (6) reliability of expression. Adenovirus and adeno-associated virus are favored for proof of concept studies because they are easily manipulated and have high expression levels. Durability of expression is the major limitation of adenovirus. Adeno-associated virus can mediate expression in the heart for months, if not longer, but the packaged gene size is limited to under five kilobases. Retroviruses such as lentivirus are incorporated into the genome and have the potential for long-term expression of the therapeutic gene.[8-10]

Major concerns regarding the clinical administration of viral vectors include infection potential, carcinogenesis, and inflammation potential of long-term viral protein expression. Ex vivo gene transfer strategies involve harvesting a patient's own cells, transducing them with the gene of choice, and implanting them back into the donor-patient. The use of autologous cells in ex vivo gene therapy circumvents immunologic rejection. Furthermore, laboratory verification of therapeutic protein expression can be performed prior to implantation, which may be important to dosage calculations.

Stem Cell–Based Therapy

Embryonic stem cells and cardiac progenitor cells have raised the possibility of regenerating and replacing the functional myocardium. The majority of cardiac cell therapy research has focused on restoring myocardial function after infarction. Recently, cell-based therapeutic strategies to treat arrhythmias have been demonstrated (see below).

The multipotency of progenitor cells and pluripotency of embryonic stem cells are the fundamental properties that make them attractive for regenerative medicine, but they also raise safety questions. Undesirable differentiation and proliferation of stem cells may cause tumor formation. Also, stem cells migrate and home to specific biochemical signals. These homing properties can be exploited to target them to specific areas of disease.[11] Alternatively, stem cells may migrate and lose their effect if they detect a chemoattractant located elsewhere. While autologous progenitor cells are ideal for limiting rejection, some stem cells (e.g., mesenchymal stem cells) appear to be immunoprivileged and have potential application in allogeneic therapy. Genetic engineering of stem cells can be accomplished by various techniques that use viruses, electroporation, or liposomes. Stem cells also represent a platform for "designer" therapeutics.

Treatment Strategies for Bradyarrhythmias: Biologic Pacemakers

Properties of an Ideal Biologic Pacemaker

Advances in microcircuitry and battery technology have miniaturized the modern electronic pacemaker such that implantation is now a routine procedure done outside a surgical operating suite. However, electronic pacemaker therapy has some shortcomings, such as the requirement for permanent hardware implantation, limited battery life, potential for malfunction, and a foreign body that may serve as a nidus for infections. The extraction of an infected pacemaker (especially an infected lead) is a complex undertaking that has a significant risk of mortality. The placement of pacemaker leads and the activation of the myocardium may impact unfavorably on cardiac contractility and electrophysiology. Furthermore, electronic pacemakers are not responsive to autonomic stimulation, especially that related to a physical activity or an emotional state. In the pediatric patient, electronic pacemaker hardware must be selected taking physical growth into consideration. Lastly, the function of the electronic pacemaker is prone to interference from common consumer electronic devices as well as medical equipment such as magnetic resonance imaging (MRI) equipment. These limitations have led to interest in the development of biologic pacemakers.[12,13]

In the normal heart, the sinoatrial node serves as the natural cardiac pacemaker. The hyperpolarization activated current, I_f, is a critical component of sinoatrial pacemaking, initiating diastolic depolarization after membrane repolarization. The sodium-calcium (Na^+-Ca^{2+}) exchanger contributes to diastolic depolarization, and when the sinoatrial action potential threshold is reached, T- and L-type calcium currents activate. Repolarizing potassium (K^+) currents return the membrane to a hyperpolarized state, and the cycle repeats. Circulating catecholamines increase I_f activity and automaticity. An ideal biologic pacemaker does not need to recreate the sinoatrial node to be successful. However, it must have certain characteristics before it can be a feasible clinical alternative to the modern electronic pacemaker.

The ideal biologic pacemaker must (1) provide stable, continuous cardiac rhythm at physiologic rates; (2) have chronotropic responsiveness to neurohormonal signals reflecting physical activity and emotions; (3) offer durability that at least matches that of electronic pacemakers and, ideally, persists for the lifetime of the patient; (4) have no potential for neoplasia, inflammation, or infection; (5) not migrate from the site of implantation; and (6) have no proarrhythmic consequences.

Strategies to Create Biologic Pacemakers

Gene Therapy

The initial proof-of-concept studies to create biologic pacemakers used gene transfer to modulate native cardiomyocyte electrophysiology. Several strategies have provided convincing evidence of biologic pacing, as follows.

Overexpression of β-Adrenergic Receptors

Glycoprotein (G-protein)–coupled β-adrenergic receptors regulate chronotropic and ionotropic responses to circulating catecholamines. The first successful gene transfer experiment resulting in biologic pacemaking used plasmids to overexpress the human β_2-adrenergic receptor in the murine atrium.[14] Edelberg et al then demonstrated that gene transfer was feasible by using catheter-based injection of plasmid into the procine right atrium. Overexpressing the human β_2-adrenergic receptor was shown to increase heart rate by about 50% 2 days after plasmid injection.[15] Further application of these studies was limited because the plasmid-based gene delivery system conferred only short-lived expression.

Inhibition of Diastolic Repolarization Current, I_{K1}

Ventricular cardiomyocytes possess the necessary ion channels for pacemaker function, but their activity is normally repressed by the inward-rectifier K^+ current (I_{K1}). I_{K1} is encoded by the *Kir2* gene family. I_{K1} is robustly expressed in adult atrial and ventricular myocytes, where it stabilizes the negative resting potential and suppresses cellular excitability. It is nearly absent in nodal pacemaker cells.

Mutations within the pore regions of channels can dramatically affect channel conductance. Miake et al introduced an adenovirus packaged with the *Kir2.1AAA* mutant and green fluorescent protein (GFP) into the guinea pig left ventricle cavity.[16] Transfected myocytes showed 80% suppression of I_{K1}. The *Kir2.1AAA*-expressing myocytes exhibited two electrophysiological behaviors: (1) They lacked spontaneous activity with elicited prolonged action potentials, or (2) they expressed spontaneous activity remarkably similar to that of sinoatrial pacemaker cells. The electrocardiograms (ECGs) of transfected animals showed that half of them remained in sinus rhythm with QT prolongation, and the other half showed spontaneous ventricular rhythms that were at times faster than sinus.

However, the *Kir2.1AAA* strategy raised the question of proarrhythmia, as I_{K1} suppression may prolong action potential duration and promote dispersion of repolarization. Indeed, these investigators subsequently showed that an electrophysiological profile mimicking Andersen's syndrome results from this approach.

Overexpression of I_f

Ion channels encoded by the *HCN* (hyperpolarization-activated, cyclic nucleotide–gated) gene family underlie the pacemaker current, I_f, which initiates depolarization during phase 4 of the sinoatrial action potential (Figure 9-1). Because I_f only activates on hyperpolarization, it does not have the potential to prolong the duration of the action potential and initiate proarrhythmia on this basis. Qu et al injected adenovirus carrying the mouse *HCN2* gene (one of four *HCN* isoforms), into the canine left atrial appendage.[17] A spontaneous cardiac rhythm originated from the left atrium in all four dogs studied during sinus arrest (induced by right vagal stimulation). Patch-clamping of isolated *HCN2*-expressing atrial myocytes showed I_f current magnitude 500 times greater than that in control atrial myocytes.

Plotnikov et al used catheter-based endocardial injection to deliver the adenovirus expressing *HCN2* into the canine proximal left bundle branch, an ideal site for providing organized left ventricular activation when the distal conducting system is functional.[18] Two days later, a left ventricular rhythm was observed during sinus arrest induced by vagal stimulation. Subsequently, stable pacemaker function was demonstrated following *HCN2* injection into the left bundle branch of dogs with complete heart block.[19] Expression with this adenoviral construct lasted 2 weeks.

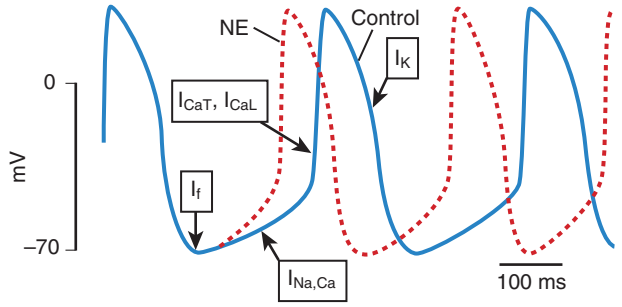

FIGURE 9-1 The role of I_f in the generation of pacemaker potentials in the sinoatrial node. Pacemaker potentials in the sinoatrial nodal cells under control conditions and after β-adrenergic stimulation with norepinephrine (NE). The major currents that control oscillatory pacemaker potentials are indicated. I_f current (produced by hyperpolarization-activated cyclic nucleotide-gated [HCN] channels), T-type (I_{CaT}) and L-type (I_{CaL}) calcium currents, sodium-calcium exchange current ($I_{Na,Ca}$), and repolarizating potassium currents (I_K). *(Modified from Biel M, Schneider A, Wahl C: Cardiac HCN channels: Structure, function, and modulation*, Trends Cardiovasc Med *12[5]: 206–212, 2002.)*

Ion Channel Mutations

Structure-function studies of *HCN2* channels have revealed that certain amino acids are critical to defining the channel's operating characteristics. A point mutation (glutamic acid to alanine at position 324, E324A) in *mHCN2* positively shifted the voltage dependence of activation and deactivation gating kinetics. The positive shift in voltage dependence of E324A channels generates a faster pacemaker rate and increased sensitivity to catecholamines than native *HCN2*. When adenovirus expressing E324A was injected into the canine left bundle branch, dogs receiving E324A were significantly more responsive to catecholamines.[19] During epinephrine infusion, all E324A-injected dogs had their heart rate increase by at least 50%, whereas only a third of the *HCN2*-injected dogs and a fifth of the control dogs had a similar response. The E324A study also illustrates that gene therapy is not limited to using endogenous genes but that mutations can be tailored to function.

A chimeric approach to creating an *HCN*-based biologic pacemaker with faster basal rates was undertaken by Plotnikov et al.[20] A channel with the N and C terminals of *HCN2* and the transmembrane domains of *HCN1* was created (HCN212) that would have *HCN2's* superior catecholamine response with the favorable activation kinetics of *HCN1*. The HCN212 chimera had similar electrophysiological characteristics to *HCN2* when expressed in isolated ventricular myocytes; however, the mean time constant of activation was faster in HCN212. An HCN212-based biologic pacemaker would likely result in a faster basal rate than an *HCN2*-based one, as more current would pass earlier during diastolic depolarization. Expression of HCN212 into the left bundle of dogs with complete heart block resulted in rapid ventricular tachycardia originating from the adenoviral injection site that was responsive to the I_f-blocking drug, ivabradine. Additional work to fine tune an *HCN*-based biologic pacemaker is needed. If I_f-associated arrhythmias occur with *HCN*-based pacemakers, I_f-blocking drugs maybe useful in the suppression of these arrhythmias.

Tse et al working with an *HCN1* mutant (*HCN1*-ΔΔΔ) with a deletion in the S3-S4 linker (position 235 to 237) created a biologic pacemaker in the procine atrium.[21] The *HCN1*-ΔΔΔ mutation favors channel opening, and its expression in ventricular myocytes has been shown to result in automaticity with rates greater than 200 beats/min. In a porcine model of sick sinus syndrome, *HCN1*-ΔΔΔ was transduced with an adenoviral vector into the left atrium, and an electronic pacemaker was implanted. The *HCN1*-ΔΔΔ–injected pigs exhibited atrial pacemaking activity originating from the left atrium, which increased with catecholamines. The approach of Tse et al relies on normal atrioventricular (AV) nodal conduction to activate the ventricle. In a heart with impaired AV conduction, biologic pacemakers in the atrium will not effectively pace the ventricle.

Kv1.4 is a member of the *Shaker K* channel gene family. When expressed in heterologous systems, *Kv1.4* channels express depolarization-activated delayed rectifier potassium currents. Furthermore, *Kv1* gene family members are not expressed significantly in cardiac tissue. Kashiwakura et al created an ion channel based on *Kv1.4*, but functionally similar to *HCN* channels.[22] This synthetic I_f-like channel was made via three point mutations within the voltage sensor in S4 (R447N, L448A, R453I): The channel was hyperpolarization activated and had a point mutation in the pore region (G528S), conferring permeability to K^+ and Na^+. Because the genes of *Kv* and *HCN* channels produce tetrameric ion channel complexes, hetero-multimerization with products from genes of the same family can occur. One advantage of a *Kv1.4*-based, I_f-like channel is that hetero-multimerization with native I_f channels (*HCN* genes) will not occur. A disadvantage of the synthetic Kv channel is that the cyclic adenosine monophosphate (cAMP) binding that is essential to the autonomic responsiveness of *HCN* channels is not replicated. Three to five days after injecting the synthetic *Kv1.4* channel into guinea pig hearts, pacemaker function was detected. Patch clamp records of isolated myocytes revealed a robust hyperpolarization-activated inward current, and the myocytes also exhibited spontaneous action potentials.

Cell Therapy Approaches

Human Mesenchymal Stem Cells Overexpressing HCN2

Human mesenchymal stem cells (hMSC) are readily available, are easily harvested, and can be maintained in culture. They appear to be immunoprivileged, a property that facilitates allogeneic transplantation without significant rejection. The rationale for using hMSC to build a biologic pacemaker is shown in Figure 9-2.

Potapova et al showed that robust I_f is present in hMSC transfected via electroporation with the murine *HCN2* gene and that they possess the cellular machinery required to respond to neurohumors.[23] In co-cultures of *HCN2*-hMSC with canine ventricular myocytes, dual whole-cell recording of hMSC and myocyte pairs demonstrated electrical coupling. Furthermore, ventricular myocytes co-cultured with *HCN2*-hMSC had more positive maximum diastolic potentials and faster spontaneous rates than had myocytes cultured with hMSC expressing GFP alone. Dogs implanted with *HCN2*-hMSC had significantly faster idioventricular rates originating from the implant site than did controls (Figure 9-3). hMSC were identified histologically, and immunostaining revealed connexin43 in junctions between the hMSC and canine ventricular myocytes in vivo. No inflammation or rejection was seen, underscoring the immunoprivileged status of hMSC. Moreover, *HCN2*-hMSC provided reliable biologic pacing for up to 6 weeks without wandering, rejection, or apoptosis.[24]

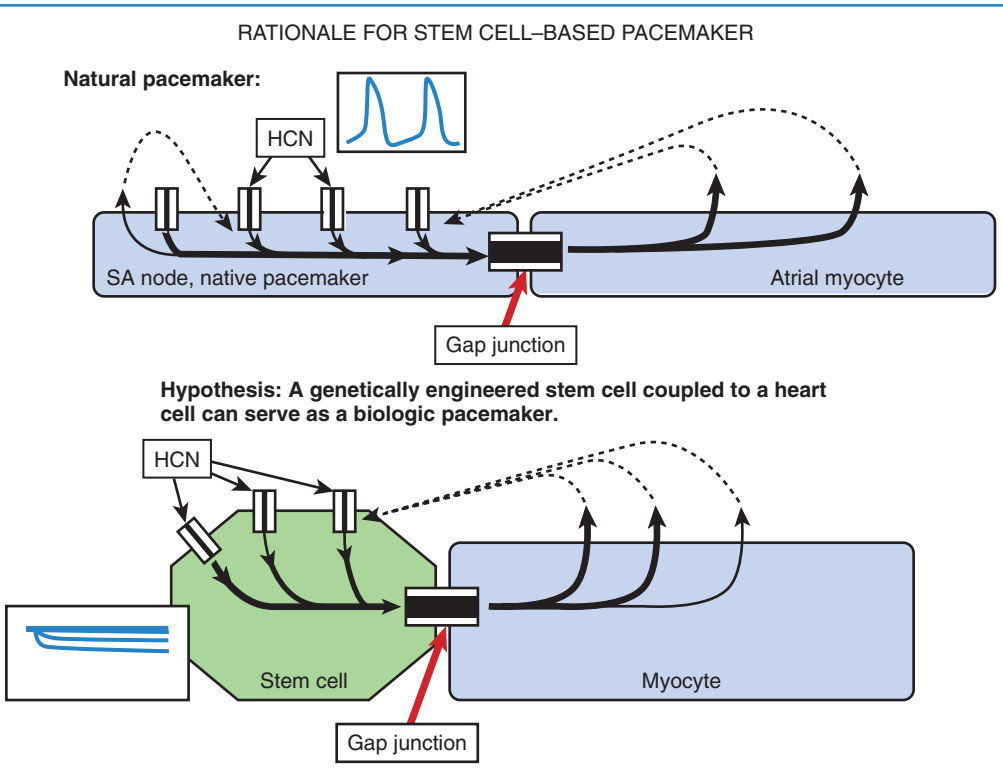

FIGURE 9-2 Pacemaker activity initiated from genetically engineered native pacemaker cells or myocytes and genetically engineered stem cells. *Top,* In native pacemaker cells or myocytes that express pacemaker current via gene transfer, action potentials are initiated by inward current through hyperpolarization-activated cyclic nucleotide–gated *(HCN)* channels. Current flowing through gap junctions results in depolarization and action potential propagation in neighboring cardiomyocytes. *Bottom,* A stem cell engineered to express *HCN* channels. Electrical coupling via gap junction formation between the stem cell pacemaker and native myocytes is critical. *HCN* channels in the normally nonexcitable stem cell require membrane hyperpolarization to open. The electrical coupling with a myocyte provides the requisite hyperpolarization to open *HCN* channels, and in return, the *HCN* inward current in the stem cell will depolarize the myocyte and initiate the next action potential. The *HCN*-expressing stem cell and the host myocyte work as one functional unit. *(From Rosen MR, Brink PR, Cohen IS, Robinson RB: Genes, stem cells, and biological pacemakers,* Cardiovasc Res *64[1]:12–23, 2004.)*

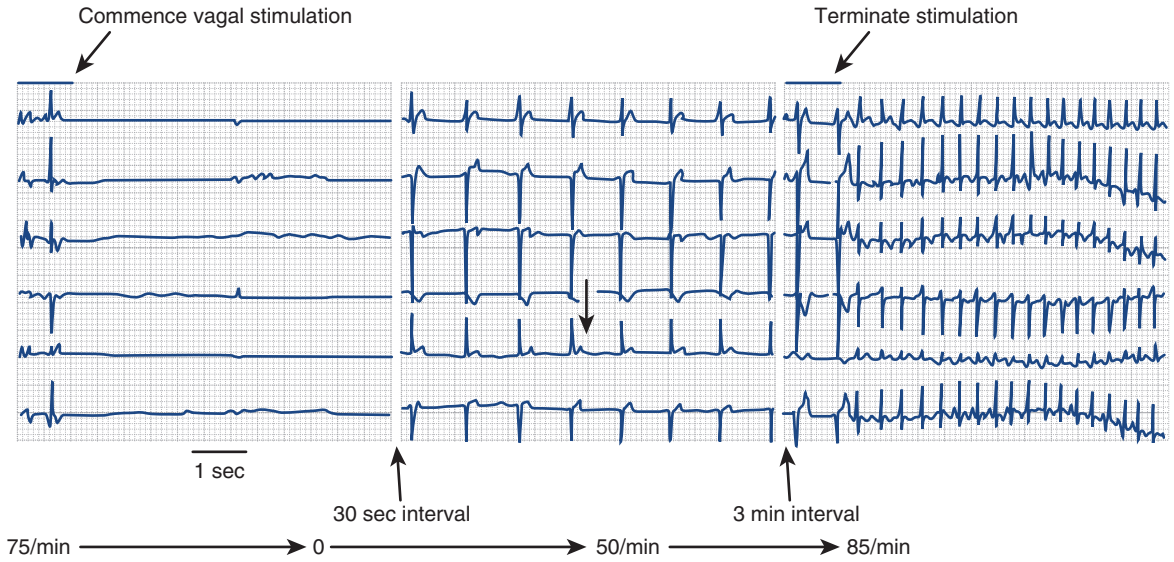

FIGURE 9-3 Pacemaker function in canine heart in situ. *Top* to *bottom,* Electrocardiogram leads I, II, III, AVR, AVL, and AVF. *Left panel,* Last two beats in sinus rhythm and onset of vagal stimulation (*arrow*) causing sinus arrest in a dog studied 7 days after implanting mHCN2-transfected human mesenchymal stem cells in left ventricular anterior wall epicardium. *Middle panel,* During vagal stimulation, an idioventricular escape focus emerges, having a regular rhythm. *Right panel,* On cessation of vagal stimulation (*arrow*), postvagal sinus tachycardia occurs. *(From Potapova I, Plotnikov A, Lu Z, et al: Human mesenchymal stem cells as a gene delivery system to create cardiac pacemakers,* Circ Res *94:952–959, 2004.)*

Human Embryonic Stem Cell–Derived Cardiac Pacemaker

Human embryonic stem cells (hESC) are derived from blastocysts, are pluripotent, and can be maintained in culture in the undifferentiated state for prolonged periods. hESC can be directed down the cardiomyocyte lineage in culture, raising the possibility of producing biologic pacemakers.[7] These cells have spontaneous action potentials, large sodium current, and I_f. Kehat et al injected the spontaneously beating embryoid bodies into the left ventricular wall in 13 pigs with complete heart block.[25] Eleven had ventricular rhythms that originated from the injection site. Histologic examination revealed the hESC-derived cardiomyocytes and gap junction formation with neighboring porcine cardiomyocytes. Xue et al had similar findings using an hESC line stably expressing GFP after lentiviral gene transduction.[26] Following implantation of hESC into guinea pig heart, optical mapping revealed membrane depolarizations propagating from the injection site to the surrounding myocardium.

The use of hESC in biologic pacemaker development will likely become more widespread as embryonic stem cell and induced pluripotent cell biology are better understood. With better knowledge of the signals directing hESC to differentiate down the cardiac lineage and specifically into SA node-like cells, , genes that express I_f or I_f-like currents can be introduced to tune the frequency of hESC cardiomyocytes and thus to engineer better pacemakers.

Chemically Induced Fusion of *HCN1* Expressing Fibroblast with Cardiomyocytes

An alternative approach to couple biologic pacemakers to the myocardium is direct fusion of the cell-based pacemaker with resident cardiomyocytes. Cho et al explored chemically induced fusion between a cell-based pacemaker and the host myocardium to achieve electrical integration.[27] In this study, a guinea pig lung fibroblast cell line stably expressing *HCN1* channels was established. These fibroblasts were mixed with isolated guinea pig ventricular myocytes in the presence of polyethylene glycol in vitro. Cell fusion occurred rapidly and formed heterokaryons, which exhibited spontaneous action potentials having phase 4 depolarization. *HCN1*-expressing fibroblasts suspended in polyethylene glycol (PEG) solution were then directly injected into the cardiac apex of the guinea pigs. More than a third of them exhibited an idioventricular rhythm pace mapped to the apex for up to 3 weeks. Such use of a local chemical fusion agent could be expected to anchor biologic pacemaker therapy at a specific site and minimize pacemaker cell migration.

Treatment Strategies for Tachyarrhythmias

Atrioventricular Nodal Conduction Inhibition

Rapid ventricular rates during atrial fibrillation can often be difficult to control medically. AV nodal modification by gene-based and cell-based methodologies has been explored as an alternative therapy. In the AV node, β-adrenergic effects on adenylyl cyclase speed conduction and are countered by Gαi, which is coupled to muscarinic M2 and adenosine A1 receptors. Gαi binds and inactivates adenylyl cyclase counteracting the actions of β-adrenergic stimulation and slowing AV nodal conduction. In a porcine model of atrial fibrillation (AF), adenovirus encoding Gαi2 was arterially infused into the AV nodal region; it reduced ventricular rates during acutely induced AF. A follow-up study using an adenovirus carrying a constitutively active mutant of Gαi2 (Gαi2-Q205L) provided continuous heart rate control; similar results were obtained when a Ca^{2+} channel–inhibiting G-protein, GEM, was delivered by gene transfer to the AV node.[28,29]

A study with a cell-based approach to modifying AV nodal conduction used autologous fibroblasts pretreated with transforming growth factor-β (TGF-β), a fibroblast stimulant.[30] Injections were targeted at the peri-AV node. Marked increases in AH interval and average RR interval during pacing-induced AF were noted in the fibroblast+TGF-β group with lesser increases in a fibroblast-alone group, compared with saline controls and a TGF-β–alone group. Complete heart block was never observed. Histologic examination showed the presence of fibroblastic proliferation in all the fibroblast-alone group as well as in the fibroblast+TGF-β–injected dogs.

Suppression of Myocardial Infarction–Related Ventricular Arrhythmia

Dominant Negative *KCNH2*

The majority of ventricular tachycardias (VTs) are infarct associated and re-entrant tachycardias. Because of limitations in the management of VT and sudden death with antiarrhythmic drug therapy and implantable devices, gene-based approaches have created great interest. They offer several distinct advantages: (1) Expression vectors can be precisely delivered to an area of interest, such as the infarct border zone, to directly modify the arrhythmogenic substrate while minimizing systemic side effects with currently available technology (coronary catheterization, percutaneous endocardial injection); (2) inappropriate painful defibrillation from an implantable cardioverter-defibrillator (ICD) can be avoided; (3) they do not require permanent hardware; (4) durable expression can obviate antiarrhythmic medications, some of which require frequent monitoring.

In their study, Sasano et al created myocardial infarctions in pigs and assessed VT inducibility by programmed stimulation after 3 weeks of recovery. Monomorphic VT was induced in all the pigs.[31] Adenovirus expressing a dominant negative *KCNH2 (hERG)* K^+ channel (G628S) was locally infused into the mid left anterior descending artery. VT was no longer inducible in all pigs treated with G628S (Figure 9-4). The duration of the monophasic action potential and the effective refractory period increased only in the anterior septum (gene transfer zone) but not in other areas of the heart. Patch clamping of isolated myocytes from the anterior septum also exhibited prolonged action potential durations. G628S gene transfer was not proarrhythmic. Three pigs with infarcts were treated with dofetilide, a known *KCNH2*-blocking drug. Unlike G628S, dofetilide increased the QT interval and prolonged the effective refractory period (ERP) globally, and the pigs still had inducible VT.

Overexpression of SkM1

The native cardiac Na^+ channel, SCN5a, has a $V_{1/2}$ of inactivation of −84 mV. In the relatively depolarized cardiomyocyte of the myocardial infarct border zone, inactivated *SCN5A* channels accumulate and contribute to low action potential upstroke, slow conduction, and re-entry. A Na^+ channel with a more positive $V_{1/2}$ of inactivation, such as the skeletal muscle Na^+ channel, SkM1 ($V_{1/2}$ inactivation −62 mV), operates more efficiently at depolarized diastolic membrane potentials. Modeling studies

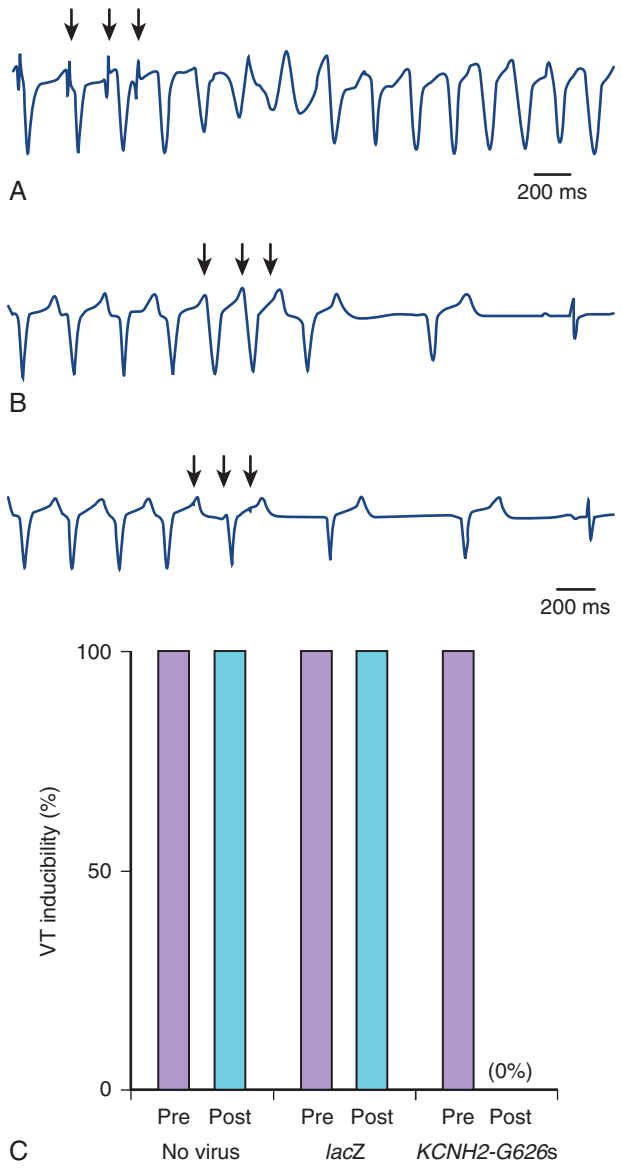

FIGURE 9-4 Expression of a dominant negative *KCNH2 (G628S)* in a porcine myocardial infarction model prevents inducible ventricular tachycardia. **A,** Prior to gene transfer, premature stimulation reproducibly induced sustained ventricular tachycardia (*VT*). *Arrows* indicate S2–S4 stimuli. **B,** In the same pig, 1 week after gene transfer, programmed stimulation did not induce VT. The upper trace shows the tightest possible coupling interval of S2-S4 with ventricular capture, and the lower trace shows refractory stimulation. **C,** Summary data from all pigs. No change in VT induction was seen in the no-virus group or the adenovirus-with-LacZ group. Prior to *G628S* gene transfer, all pigs had inducible VT. After *G628S* gene transfer, none of the *G628S* subjects had inducible VT. *(From Sasano T, McDonald AD, Kikuchi K, Donahue JK: Molecular ablation of ventricular tachycardia after myocardial infarction,* Nat Med *12:1256–1258, 2006.)*

have demonstrated that SkM1 expression permits action potential generation at diastolic membrane potentials as positive as –60mV but that *SCN5A* overexpression does not.[32]

Adenovirus-expressing SkM1 was injected into the epicardial border zone after left anterior descending artery ligation of canine hearts. A week after the injection, local electrograms from the epicardial border zone were significantly broader and fragmented in the controls (adenovirus-expressing GFP) compared with SkM1-injected dogs (Figure 9-5, *A*). The infarct sizes were similar between SkM1-injected and control dogs. Programmed premature stimulation induced sustained VT or VF in 6 of 8 controls versus 2 of 12 SkM1-injected dogs (Figure 9-6). No difference was seen in the duration of the maximum diastolic potential or of the action potential between the SkM1-expressing myocytes and control myocytes in microelectrode studies of myocardium isolated from the canine hearts. However, action potentials recorded from SkM1-injected sites had significantly higher V_{max} than did those of the controls at all membrane potentials tested (Figure 9-5, *B*).

Current antiarrhythmic strategies focus on slowing conduction, prolonging refractoriness, or inducing conduction block by ablation, but SkM1 expression preserves conduction at depolarized membrane potentials and can be delivered focally to areas of slow conduction. The SMASH-VT study showed a significant decrease in ICD discharges in patients with ischemic cardiomyopathy, who underwent left ventricular ablation at endocardial sites showing fractionated electrograms.[33] SkM1 gene therapy may be targeted to areas with fractionated electrograms, to normalize activation without inducing myocardial injury with ablation.

Overexpression of SERCA2a

Abnormal Ca^{2+} handling occurs during ischemia and may lead to after-depolarizations with significant consequences in the development of arrhythmias. SERCA2a, the sacroplasmic reticulum (SR) Ca^{2+} adenosine triphosphatase (ATPase), plays an important role in intracellular Ca^{2+} regulation by pumping Ca^{2+} from the cytosol into the SR. Prunier et al hypothesized that overexpression of SERCA2a in the porcine heart may be antiarrhythmic.[34] Adenovirus-expressing SERCA2a was delivered into the porcine heart by intracoronary infusion. Seven days after gene delivery, the pigs were subjected to transient left anterior descending artery (LAD) balloon occlusion (ischemia-reperfusion) or complete LAD occlusion and observed over 24 hours for the development of spontaneous ventricular arrhythmias. In the complete occlusion group, no difference was seen in VT or VF incidence between the SERCA2a-injected pigs compared with control pigs. However, among the ischemia-reperfusion pigs, SERCA2a-overexpressing pigs had substantially reduced episodes of VT. Regulation of post-ischemia Ca^{2+} handling may be an antiarrhythmic strategy.

Fibroblasts Expressing *Kv1.3*

In a fibroblast-based approach to modify ventricular excitability, *Kv1.3*, a voltage-gated K^+ channel with very slow deactivation kinetics, was stably transfected into a fibroblast cell line.[35] Computer simulations showed that depolarizing a cardiomyocyte would depolarize the gap junction–coupled, *Kv1.3*-expressing fibroblast and activate the *Kv1.3* K channel. The outward *Kv1.3* current would hyperpolarize the fibroblast; through electrotonic interaction, the fibroblast, acting as a current sink, would decrease phase 0 depolarization of the myocyte, hyperpolarize the diastolic membrane potential, increase the refractory period, and depress conduction. This outcome was clearly demonstrated in neonatal cardiomyocyte cultures focally seeded with *Kv1.3* fibroblasts. In

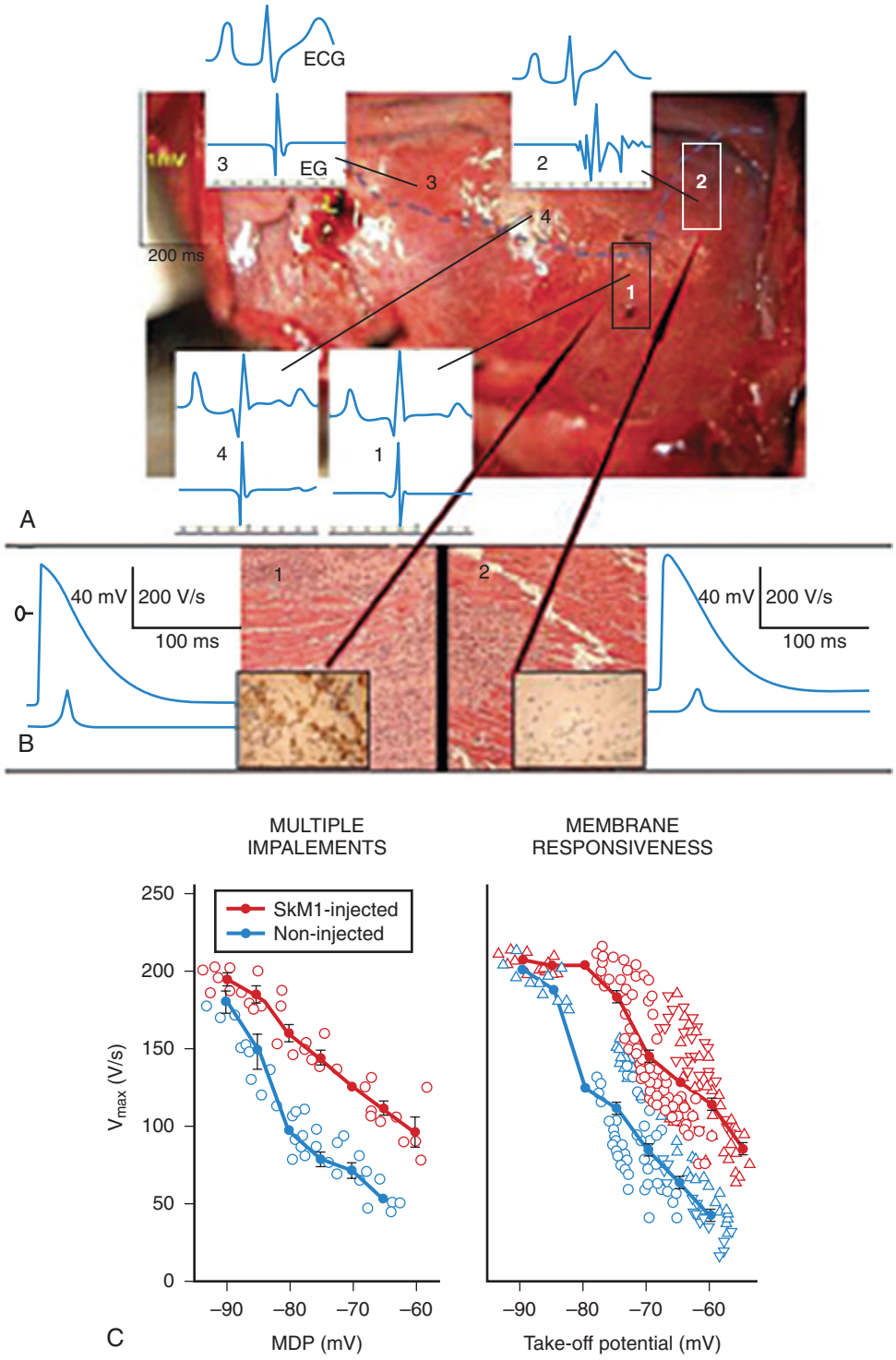

FIGURE 9-5 Effect of epicardial border zone expression of SkM1. **A,** Canine heart injected with adenovirus-expressing SkM1 at site 1 7 days earlier. Each small panel displays a surface electrocardiogram (ECG) (*top*) and a bipolar local ECG (*bottom*). The *broken blue line* demarcates infarcted (*bottom*) and noninfarcted myocardium (*top*). Site 2, an infarcted area not injected, exhibits a marked fragmented local electrogram. Site 1, within the infarction and injected with SkM1, shows a normal local ECG similar to noninfarcted site 3 and site 4. **B,** Hematoxylin and eosin staining of site 1 (with SkM1) and site 2 (no SkM1) shows evidence of infarcted myocardium and green fluorescent protein (GFP)–positive in site 1 and GFP negative in site 2. Representative action potentials recorded at site 1 have higher V_{max} and amplitude than from site 2. **C,** *Left*, Multiple impalements from SkM1-injected (*red*) and SkM1-noninjected (*blue*) zones show higher V_{max} in action potentials from SkM1-injected sites ($P < .05$). The same is true for membrane responsiveness (*right*, $P < .05$). *(Reprinted with permission from Lau DH, Clausen C, Sosunov EA, et al: Epicardial border zone overexpression of skeletal muscle sodium channel SkM1 normalizes activation, preserves conduction, and suppresses ventricular arrhythmia: An in silico, in vivo, in vitro study,* Circulation *119[1]:19–27, 2009.)*

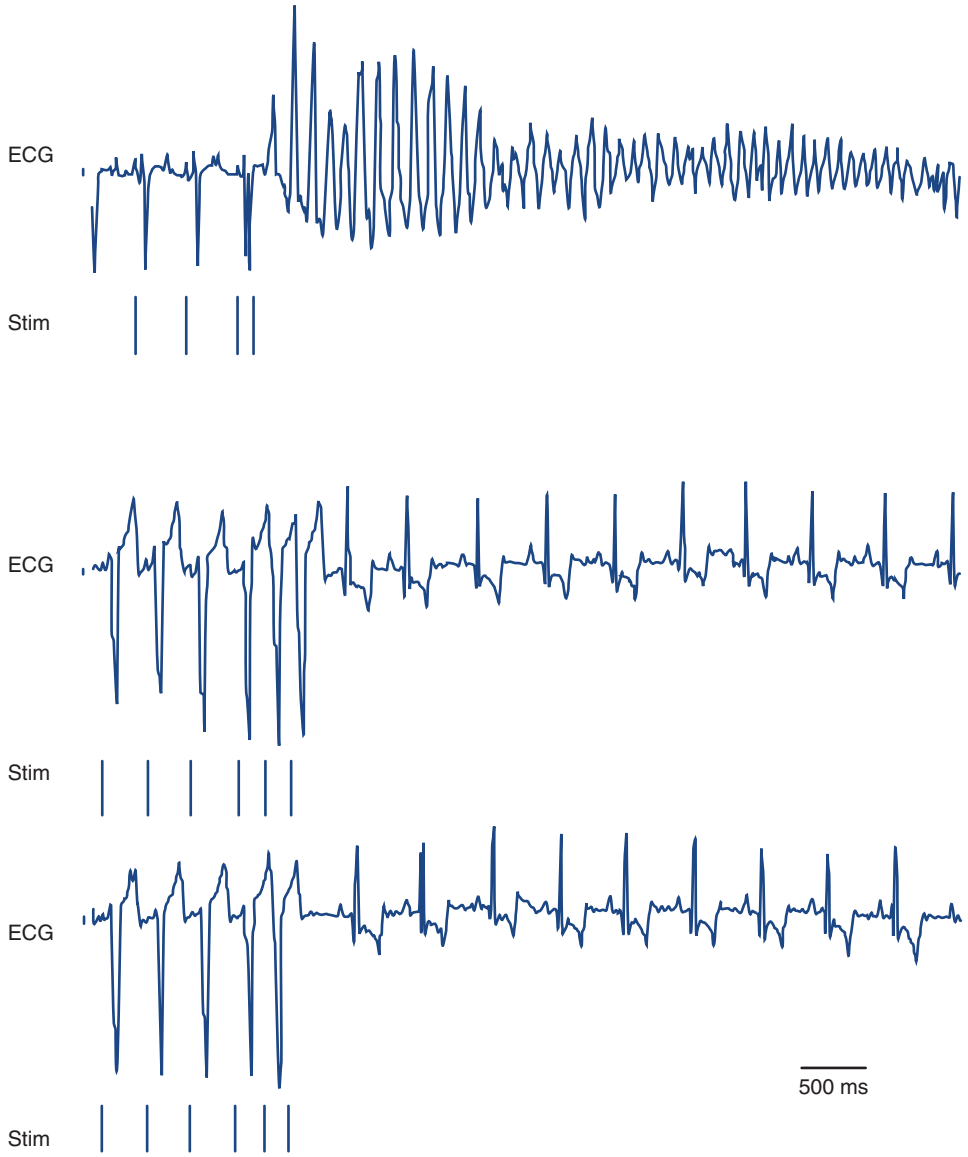

FIGURE 9-6 Overexpression of SkM1 in the canine epicardial border zone is antiarrhythmic. **A,** Programmed extrastimulus pacing in a dog with an anterior wall myocardial infarction injected with adenovirus-expressing green fluorescent protein induces a polymorphic ventricular tachycardia that degenerates into ventricular fibrillation. The stimulus train is shown below the surface electrocardiogram (*ECG*). **B,** In a SkM1-overexpressing dog, programmed pacing with two extrastimuli does not induce ventricular extrasystoles. The upper trace shows the tightest possible coupling interval of S2-S3 with ventricular capture, and the lower trace shows refractory stimulation. *(From Lau DH, Clausen C, Sosunov EA, et al: Epicardial border zone overexpression of skeletal muscle sodium channel SkM1 normalizes activation, preserves conduction, and suppresses ventricular arrhythmia: An in silico, in vivo, in vitro study,* Circulation *119[1]:19–27, 2009.)*

vivo studies grafting the *Kv1.3* fibroblasts into rat and pig ventricles demonstrated significant prolongation of local event-related potential 1 week after implantation. No ventricular arrhythmias were noted with Kv1.3 fibroblast grafting; programmed premature stimulation did not induce any ventricular arrhythmias in four pigs.

Arrhythmic Potential of Stem Cell–Based Cardiac Regeneration Strategies

Thus far, we have focused on the use of cell therapy to carry constructs to an arrhythmic and diseased heart. However, an ultimate therapy would replace diseased, arrhythmogenic tissues with healthy tissue and normal rhythm. Regenerative approaches to heart disease have mainly focused on the improvement of ventricular function after myocardial infarction. Preclinical studies have used skeletal myoblasts, embryonic stem cells, mesenchymal stem cells, and early cardiomyocytes derived from stem cells.[5] Early clinical testing with skeletal myoblasts has underscored the potential for arrhythmic consequences of certain cell-based regenerative therapies.[36] In a study where ischemic cardiac patients received intracardiac skeletal myoblasts, the myoblast group did not differ in ventricular function or mortality at 4-year follow-up compared with the placebo group. However, 87% of the skeletal-myoblast group had appropriate automatic ICD

discharges compared with 13% of controls.[37] In contrast, the Myoblast Autologous Grafting in Ischemic Cardiomyopathy (MAGIC) trial of skeletal myoblasts injected around ventricular scar tissue at the time of coronary artery bypass surgery but did not report a significantly higher arrhythmia incidence.[38]

The clinical problem encountered with skeletal myoblast therapies is that they do not appear to form gap junctions with host cardiomyocytes in vivo. Moreover, studies mapping the co-cultures of skeletal myoblasts with rat cardiomyocytes showed a lack of electrical coupling between the two cell types and resultant spiral-like waves of depolarization.[37] When skeletal myoblasts were transfected with connenix43, the co-cultures revealed functional coupling, more homogenous wavefronts of activation, and less re-entrant activity.[39]

Functional electrical integration does occur when fetal cardiomyocytes and stem cell–derived cardiomyocytes are introduced into the adult myocardium. Cardiomyocytes derived from embryoid bodies co-cultured with neonatal cardiomyocytes exhibit synchronous contraction.[25] Furthermore, the embryoid body–derived cardiomyocytes provide biologic pacemaking. Evidence of electrical coupling between fetal cardiomyocytes grafted to adult myocardium has been obtained by microelectrode recording and with two-photon microscopy visualizing Ca^{2+} transients.[40,41] Mesenchymal stem cells have also been shown to express sufficient levels of gap junctional proteins to couple to host myocardium and provide a delivery platform.[23,42]

Conclusion

Gene therapies and cell therapies for cardiac arrhythmias are in their infancy. Biologic-based strategies may not only be effective treatments but also hold the possibility of providing definitive cures. Proof-of-concept studies have demonstrated biologic strategies to be effective in animal models, but the delivery vectors were not clinically applicable. Viral vectors with durable expression are available for long-term animal studies and are in clinical testing. As the knowledge of stem cell biology grows, stem cells or cells derived from them may be the platform of choice to base therapeutics for arrhythmias.

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CHAPTER 10

Basic Electrocardiography

Galen Wagner

Historical Perspective

We have passed the hundredth anniversary of the introduction of the clinical electrocardiogram (ECG). The initial three leads have been expanded to 12 to provide six views of cardiac electrical activity in the frontal plane and six in the horizontal (transverse) plane. During this century of development of more sophisticated and expensive cardiac diagnostic tests, the standard 12-lead ECG has had increasingly expanded its clinical importance, particularly in the evaluation of patients with ischemic heart disease.

In the early 1900s, Einthoven and colleagues placed recording electrodes on the right and left arms and the left leg and an additional electrode on the right leg to ground the "elektrokardiogramme" (EKG).[1] Three leads (I, II, and III) were produced; each used a pair of limb electrodes, one serving as the positive pole and one as the negative pole. Each lead can be considered to provide two "views" of the cardiac electrical activity: one view from the positive pole and an inverted or "reciprocal" view from the negative pole. The positive poles of these leads are located either to the left or inferiorly so that "normal" cardiac waveforms typically appear primarily upright on the recording. For lead I, the left arm electrode is the positive pole, and the right arm electrode is the negative pole. Lead II, with its positive pole on the left leg and its negative pole on the right arm, provides a view of the electrical activity along the long (base to apex) axis of the heart. Finally, lead III has its positive pole on the left leg and its negative pole on the left arm (Figure 10-1, *A*).

These three leads form the Einthoven triangle, a simplified model of the true orientation of the leads in the frontal plane. Consideration of these three leads as they intersect in the center of the frontal plane while retaining their original orientation provides a triaxial reference system for viewing cardiac electrical activity (Figure 10-1, *B*).

The 60-degree angles among leads I, II, and III create wide gaps among these three views of cardiac electrical activity. Wilson and coworkers developed a method for filling these gaps by creating a central terminal, connecting all three limb electrodes through a 5000-ohm resistor.[2] A lead using this central terminal as its negative pole and an exploring electrode at any site on the body surface as its positive pole is termed a *V lead*. When the central terminal is connected to an exploring electrode on an extremity, the electrical signals are small. The amplitude of these signals in the frontal plane may be augmented by disconnecting the attachment of the central terminal to the explored limb. Such an augmented V lead is termed an *aV lead*. For example, aVF measures the potential difference between the left leg and the average of the potentials at the right and left arms. The gap between leads I and II is filled by lead aVR, between leads II and III by lead aVF, and between leads III and I by lead aVL. Leads aVR, aVL, and aVF were introduced in 1932 by Goldberger and colleagues. The positive poles of aVL and aVF are located to the left or inferiorly so that "normal" cardiac waveforms typically appear primarily upright on the recording; however, the positive pole of lead aVR is located to the right and superiorly so that "normal" cardiac waveforms typically appear primarily downward.

Addition of these three aV leads to the triaxial reference system produces a hexaxial system for viewing the cardiac electrical activity in the frontal plane with the six leads separated by angles of only 30 degrees. This provides a perspective of the frontal plane similar to the face of a clock, as discussed later in Section III and illustrated in Figure 10-2. Using lead I (located at 0 degrees) as the reference, positive designations increase at 30-degree increments in a clockwise direction to +180 degrees, and negative designations increase at the same increments in a counterclockwise direction up to −180 degrees. Lead II appears at +60 degrees, aVF at +90 degrees, and III at +120 degrees, respectively. Leads aVL and aVR have designations of −30 degrees and −150 degrees, respectively. The negative poles of each of these leads complete the "clock face." Most modern electrocardiographs use digital technology. They record leads I and II only and then calculate the remaining limb leads in real time based on Einthoven's law: I + III = II.[1] The algebraic outcome of the formulas for calculating the aV leads from leads I, II, and III are:

$$aVR = -1/2\,(I + II)$$

$$aVL = I - 1/2\,(II)$$

$$aVF = II - 1/2\,(I)$$

thus,

$$aVR + aVL + aVF = 0$$

Today's standard 12-lead ECG includes these six frontal plane leads plus six leads relating to the transverse plane of the body. These leads, introduced by Wilson, are produced by connecting the central terminal to an exploring electrode placed at various positions across the chest wall.[3-7] Since the positive electrodes of these leads are close to the heart, they are termed *precordial*, and the electrical signals have sufficient amplitude so that no augmentation is necessary. However, because leads must be bipolar, they should not be termed "precordial" because they also provide electrical information from the opposite (postcordial) aspect of the heart. Indeed, by the laws of physics, the negative electrode could be considered to be at the location on the posterior thorax that

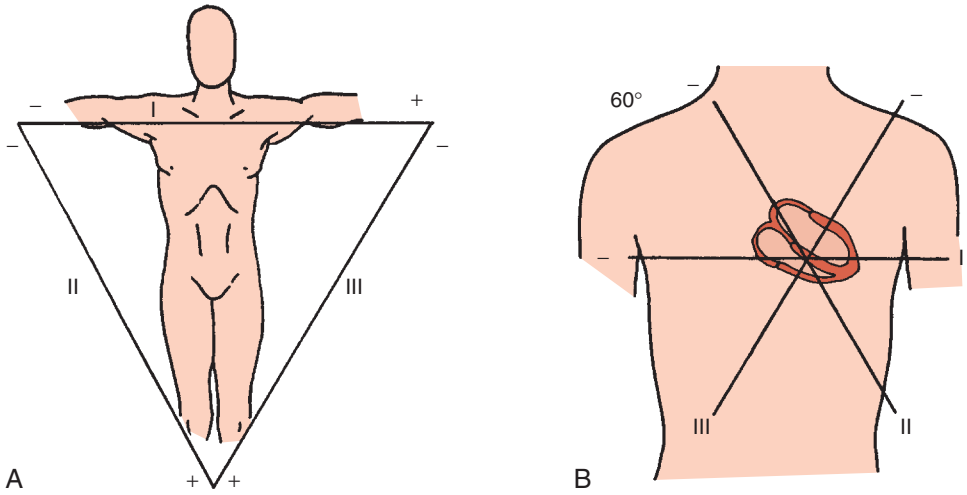


FIGURE 10-1 **A,** The equiangular (60-degree) Einthoven triangle formed by leads I, II, and III is shown with positive (I, II, III) and negative poles (–) of each of the leads indicated. **B,** The Einthoven triangle is shown in relation to the schematic view of the heart, and the three leads are shown to intersect at the center of the cardiac electrical activity.

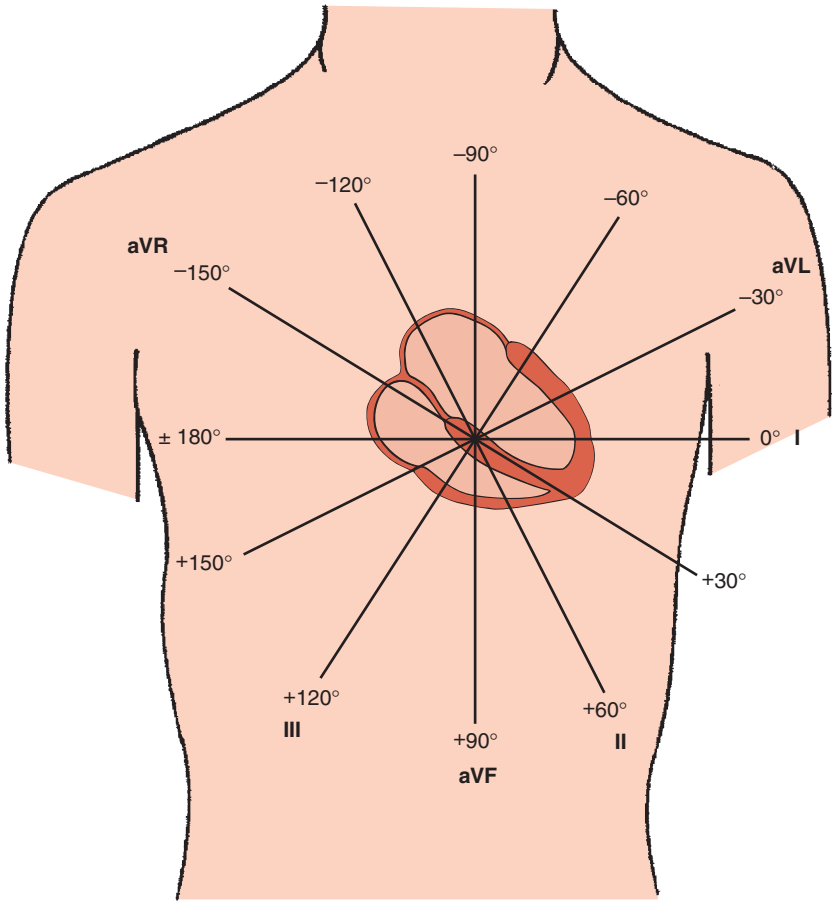


FIGURE 10-2 The locations of the positive and negative poles of each lead around the 360 degrees of the "clock face" are indicated, with the names of the six leads appearing at their positive poles.

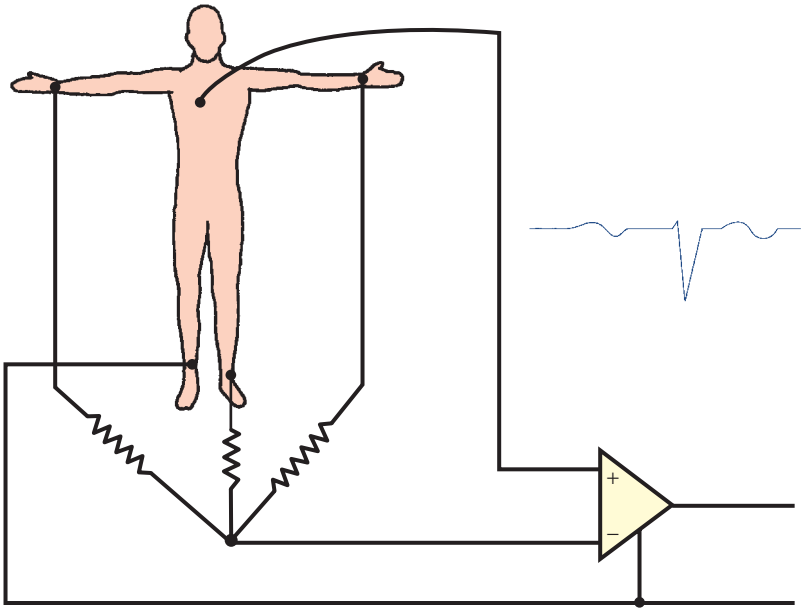


FIGURE 10-3 The method of electrocardiogram recording of the precordial leads is illustrated, along with an example of lead VI. The wavelike lines indicate resistors in the connections between the recording electrodes on the three limb leads that produce the negative poles for each of the V leads. *(Modified from Netter FH:* The Ciba collection of medical illustrations, vol 5. *In Yonkman FF, editor:* Heart, *Summit, NJ, 1978, Ciba-Geigy, p 51.)*

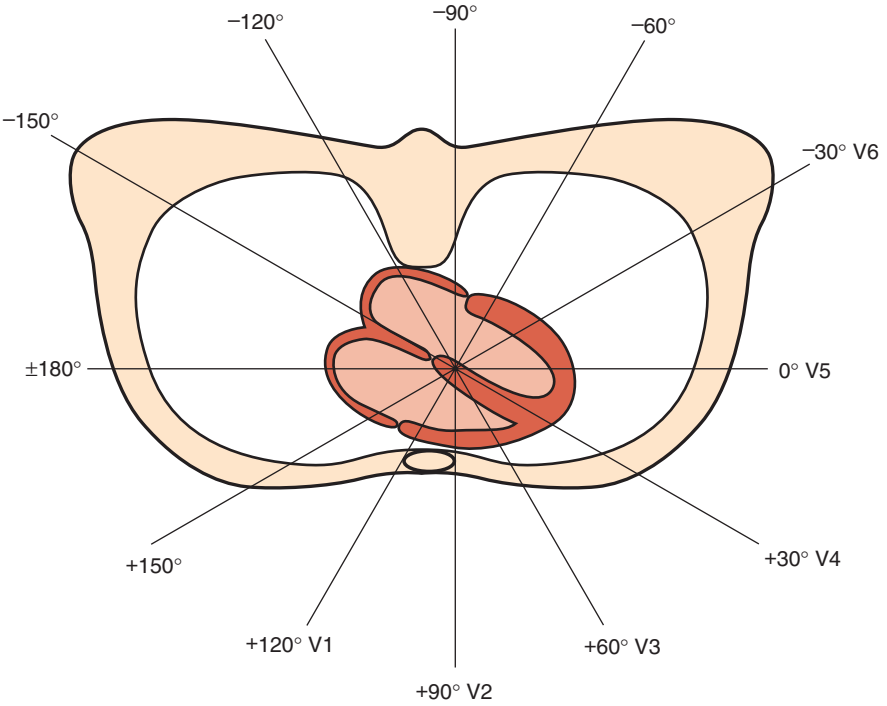


FIGURE 10-4 The orientation of the six precordial leads is indicated by lines from each of their recording sites through the approximate center of cardiac electrical activity. Extension of these lines through the chest indicates the opposite positions, which can be considered the locations of the negative poles of the six precordial leads.

is a direct extension of the line from the positive electrode to the center of cardiac electrical activity provided by the central terminal. The six leads are labeled V1 through V6 because the central terminal connected to all three of the limb electrodes provides their negative poles (Figure 10-3). Lead V1, with its positive pole on the right anterior precordium and its negative pole on the left posterior thorax, provides the view of cardiac electrical activity that best distinguishes left versus right cardiac activity (Figure 10-4). The sites of the exploring electrode are determined by bony landmarks on the anterior and left lateral aspects of the thorax, and the angles between the six transverse plane leads are approximately 30 degrees, the same as the angles between the six frontal plane leads.

The views of the cardiac electrical activity from the positive poles of these 12 standard ECG leads are presented in the typical displays provided by electrocardiographic recorders. However, the additional 12 views from the negative poles could also be presented to provide a "24-view ECG."

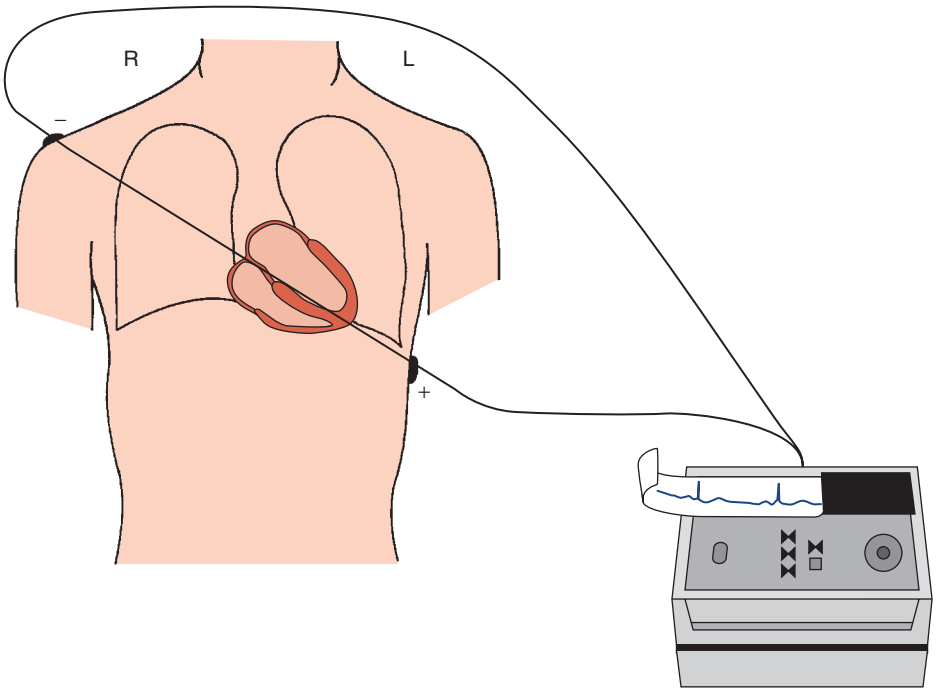


FIGURE 10-5 The schematic frontal-plane view of the heart in the thorax with electrodes, where the long axis intersects with the body surface. The positive electrode on the left lower thoracic wall and the negative electrode on the right shoulder are aligned from the cardiac base to apex parallel to the inter-atrial and interventricular septa and are attached to a single-channel electrocardiogram recorder. The ventricular repolarization wave is positively oriented. *L*, Left; *R*, right.

Basic Principles

Anatomic Orientation of the Heart Within the Body

The position of the heart within the body determines the "view" of the cardiac electrical activity that can be observed from any ECG recording electrode site on the body surface. The atria are located in the top or base of the heart, and the ventricles taper toward the bottom or apex. However, the right and left sides of the heart are not directly aligned with the right and left sides of the body. The long axis of the heart, which extends from base to apex, is tilted to the left and anteriorly at its apical end (Figure 10-5). Also, the heart is rotated so that the right atrium and ventricle are more anterior than the left atrium and ventricle.[8,9] These anatomic relationships dictate that an ECG lead providing a right anterior to left posterior view (such as V1) provides better differentiation of right versus left cardiac activity than does a lead providing a right lateral to left lateral view (such as lead I) (Figure 10-6).

The Cardiac Cycle

The timing and synchronization of contraction of myocardial cells are controlled by cells of the pacemaking and conduction system. Impulses generated within these cells create a rhythmic repetition of events called *cardiac cycles*. Each cycle is composed of electrical and mechanical activation (systole) and recovery (diastole). Since the electrical events initiate the mechanical events, a brief delay occurs between the onsets of electrical and mechanical systole and of electrical and mechanical diastole.

The electrical recording from inside a single myocardial cell as it progresses through a cardiac cycle is illustrated in the top panel of Figure 10-7. During electrical diastole, the cell has a baseline negative electrical potential and is also in mechanical diastole with separation of its contractile proteins. An electrical impulse arriving at the cell allows positively charged ions to cross the cell membrane, causing its depolarization. This movement of ions initiates electrical systole, which is characterized by an action potential (see Figure 10-7, middle panel). This electrical event then initiates mechanical systole, in which the contractile proteins slide over each other, thereby shortening the cell. Electrical systole continues until the positively charged ions are pumped out, causing repolarization of the cell. The electrical potential returns to its negative resting level. This return of electrical diastole causes the contractile proteins to separate again. The cell is then capable of being reactivated if another electrical impulse arrives at its membrane.

The ECG recording is formed by the summation of electrical signals from all of the myocardial cells (see Figure 10-7, lower panel). When the cells are in their resting state, the ECG recording produces a flat baseline. The onset of depolarization of the cells produces a relatively high-frequency ECG waveform. Then, while depolarization persists, the ECG returns to the baseline. Repolarization of the myocardial cells is represented on the ECG by a lower frequency waveform in the opposite direction from that representing depolarization.

Cardiac Impulse Formation and Conduction

The electrical activation of a single cardiac cell or even a small group of cells does not produce enough current to be recorded on the body surface. Clinical electrocardiography is made possible by the activation of atrial and ventricular myocardial masses that are of sufficient magnitude for their electrical activity to be recorded on the body surface.

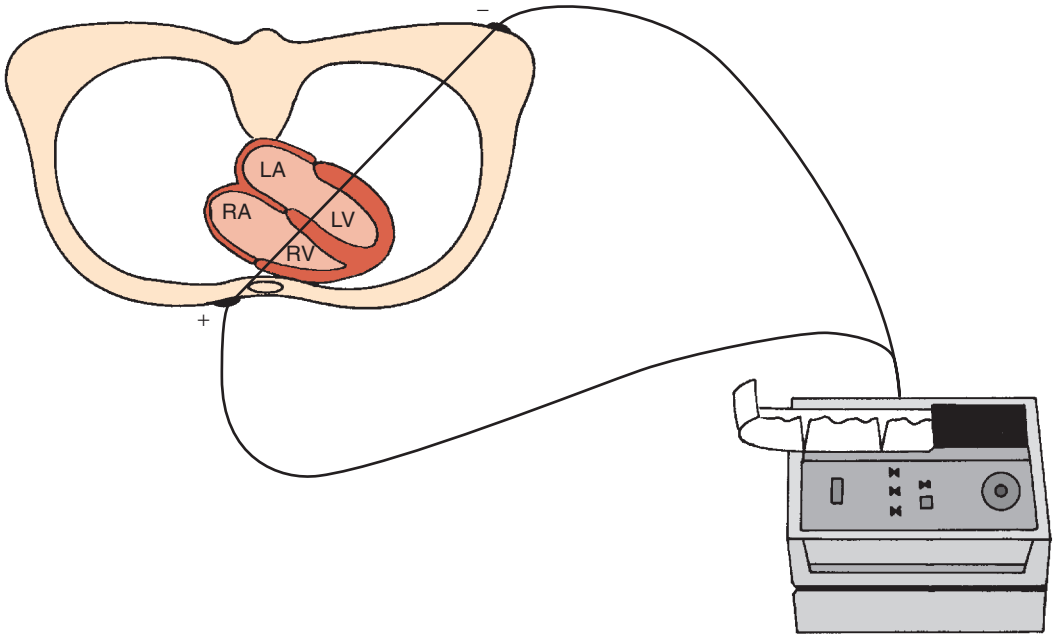


FIGURE 10-6 The schematic transverse-plane view of the heart in the thorax with electrodes, where the short axis intersects with the body surface. The positive electrode to the right of the sternum and the negative electrode on the back are aligned perpendicular to the inter-atrial and interventricular septa and are attached to a single-channel electrocardiogram recorder. The typically diphasic P and T waves and the predominately negative QRS complex recorded by electrodes at these positions are indicated on the electrocardiogram. *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.

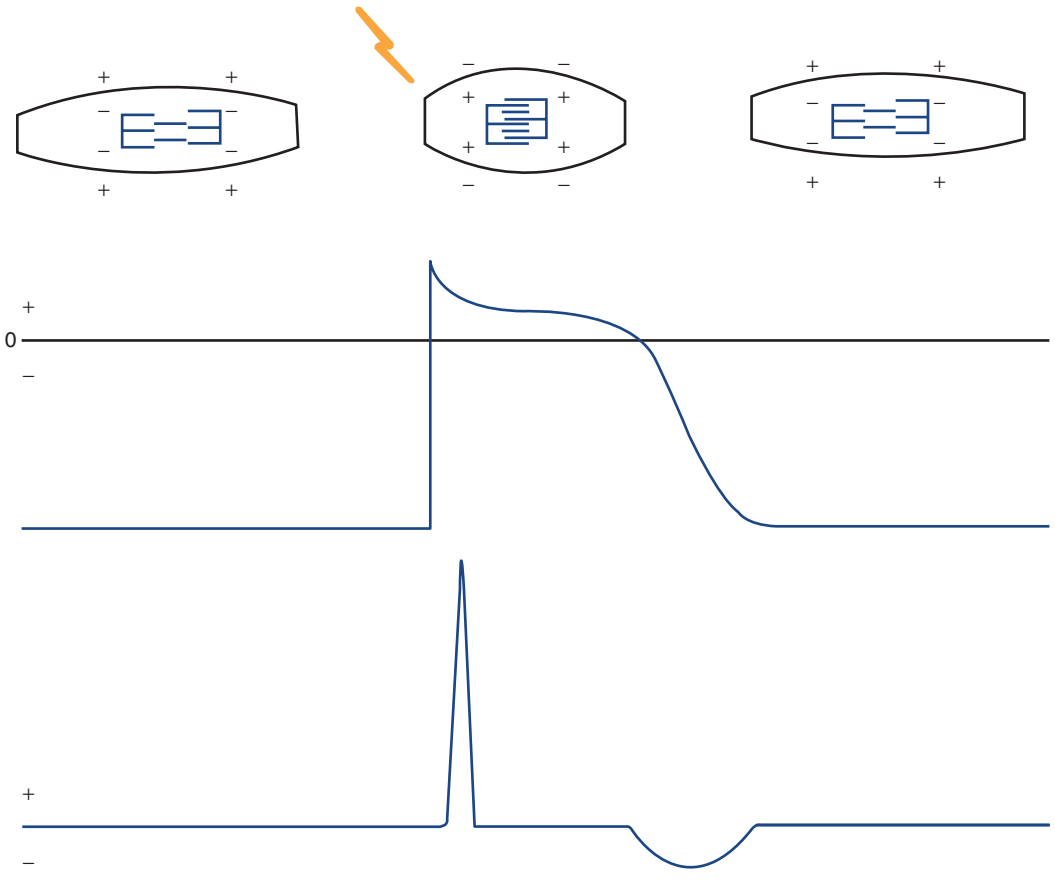


FIGURE 10-7 The schematic electrocardiogram recording beneath a cardiac cellular action potential. *(Modified from Thaler MS:* The Only EKG book you'll ever need, *Philadelphia, 1988, JB Lippincott, p 11.)*

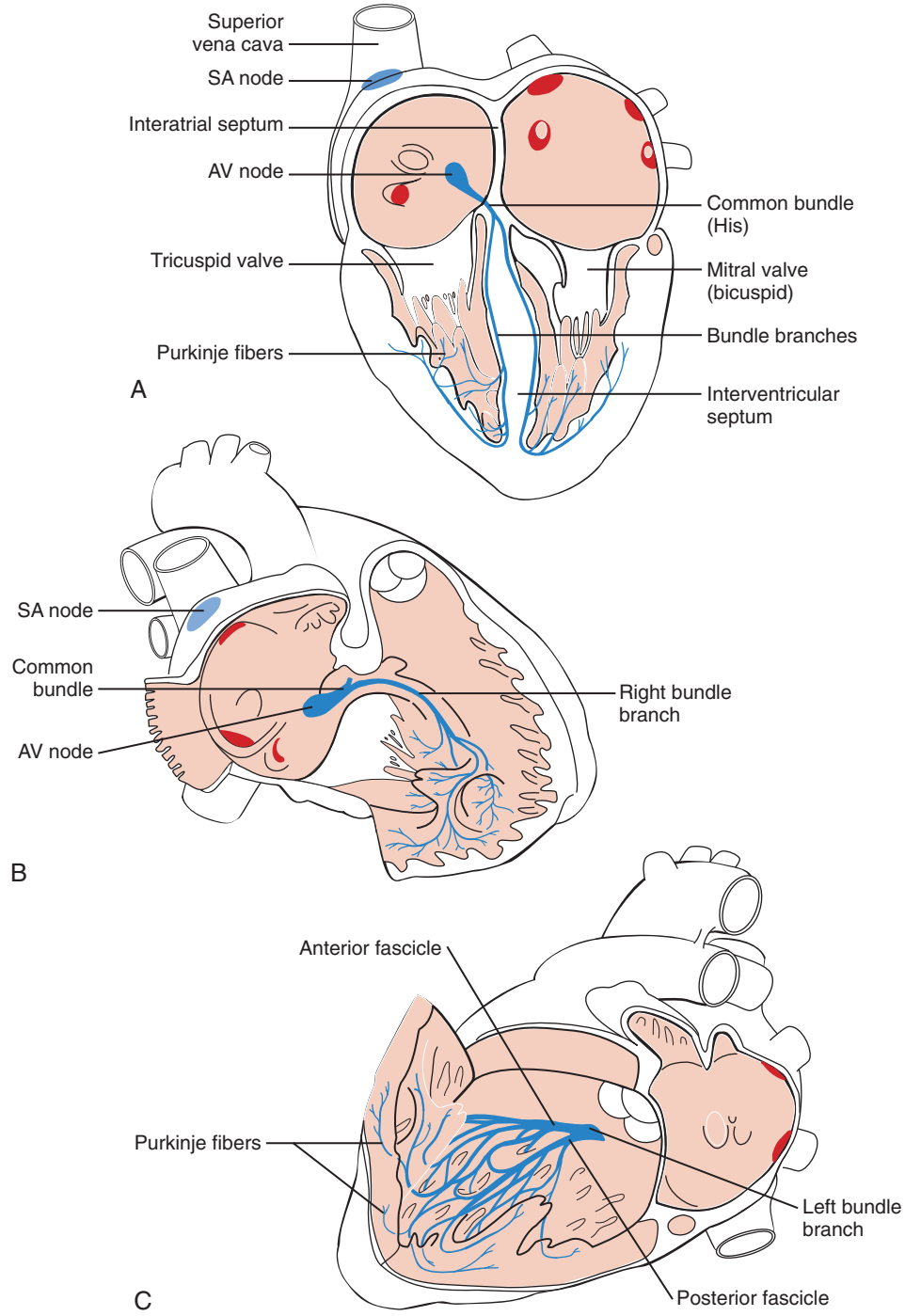


FIGURE 10-8 Three views of the anatomic relationships among the cardiac pumping chambers and the structures of the pacemaking and conduction system. **A,** From the anterior precordium. **B,** From the right anterior precordium looking onto the inter-atrial and interventricular septa through the right atrium and ventricle. **C,** From the left posterior thorax looking onto the septa through the left atrium and ventricle. *AV,* Atrioventricular; *SA,* sinoatrial. *(Modified from Netter FH:* The Ciba collection of medical illustrations, vol 5. *In Yonkman FF, editor:* Heart, *Summit, NJ, 1978, Ciba-Geigy, pp 13, 49.)*

Myocardial cells normally lack the ability for either spontaneous formation or rapid conduction of an electrical impulse. They are dependent for these functions on specialized (Purkinje) cells of the cardiac pacemaking and conduction system placed strategically through the heart (Figure 10-8). These cells are arranged in nodes, bundles, bundle branches, and branching networks of fascicles. They lack contractile capability but are able to achieve spontaneous electrical impulse formation (acting as pacemakers) and to alter the speed of electrical conduction. The intrinsic pacemaking rate is most rapid in the specialized cells in the sinus node and slowest in the specialized cells in the ventricles. The intrinsic pacing rate is altered by the balance between the sympathetic and parasympathetic components of the autonomic nervous system.[10-13]

The intraventricular conduction pathways include a common bundle (bundle of His), leading from the atrioventricular (AV) node to the summit of the interventricular septum, and its right and left bundle branches, proceeding along the septal surfaces to their respective ventricles (see Figure 10-8, *A*). The left bundle branch fans into fascicles that proceed along the left septal surface and toward the two papillary muscles of the mitral valve (see Figure 10-8, *B*). The right bundle branch remains compact until it reaches the right distal septal surface, where it branches into the distal interventricular septum and toward the lateral wall of the right ventricle (see Figure 10-8, *C*). These intraventricular conduction pathways are composed of fibers of Purkinje cells with specialized capabilities for both pacemaking and rapid conduction of electrical impulses. Fascicles composed of Purkinje fibers form networks that extend just beneath the surface of the right and left ventricular (LV) endocardium. The impulses then proceed slowly from the endocardium to the epicardium throughout the right and left ventricles.[14-16]

Electrocardiogram Waveforms

The initial electrical wave of a cardiac cycle represents activation of the atria and is called the *P wave* (Figure 10-9). Since the sinus node is located in the right atrium, the first part of the P wave represents the activation of this chamber. The middle section of the P wave represents completion of right atrial activation and initiation of left atrial activation. The final section of the P wave represents completion of left atrial activation. The AV node is activated during the inscription of the P wave. The wave representing electrical recovery of the atria is usually obscured by the larger QRS complex, representing the activation of the ventricles. From ECG lead II oriented from the cardiac base to the apex, the P wave is entirely positive, and the QRS complex is predominately positive. Minor portions at the beginning and end of the QRS complex may appear as downward or negative waves. The QRS complex may normally appear as one (monophasic), two (diphasic), or three (triphasic) individual waveforms. By convention, a negative wave at the onset of the QRS complex is called a *Q wave*. The first positive wave is called the *R wave*, regardless of whether or not it is preceded by a Q wave. A negative deflection following an R wave is called an *S wave*. When a second positive deflection occurs, it is termed *R′*. A monophasic negative QRS complex should be termed a *QS wave*.

The wave in the cardiac cycle that represents recovery of the ventricles is called the *T wave*. Since recovery of the ventricular cells (repolarization) causes a current counter to that of depolarization, one might expect the T wave to be inverted in relation to the QRS complex. However, epicardial cells repolarize earlier than endocardial cells, thereby causing the wave of repolarization to spread in the direction opposite that of depolarization. This results in a T wave deflected in a direction similar to that of the QRS complex (Figure 10-10). The T wave is sometimes followed

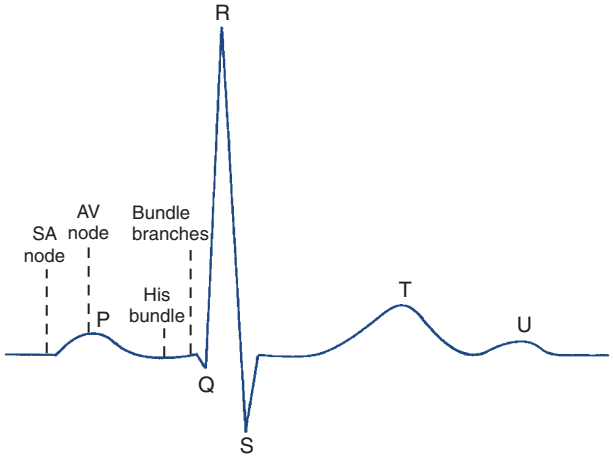


FIGURE 10-9 The visible waveforms represent activation of the atria (*P wave*), ventricles (*Q, R,* and *S waves*), and recovery of the ventricles (*T* and *U waves*). The timing of activation of the structures of the pacemaking and conduction system is also indicated. *AV,* Atrioventricular; *SA,* sinoatrial.

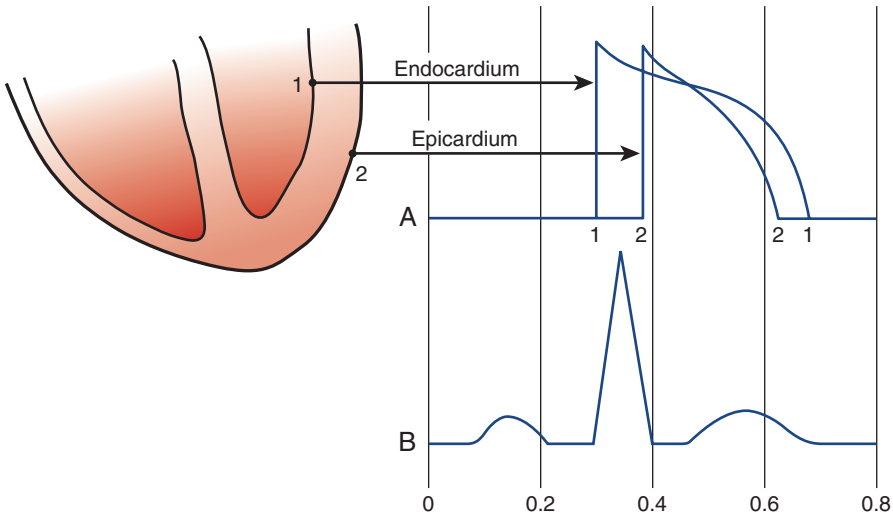


FIGURE 10-10 A, The frontal-plane view of the right and left ventricles, along with schematic recordings from left ventricular myocardial cells, on the endocardial *(1)* and epicardial *(2)* surfaces. **B,** The long-axis body surface electrocardiogram waveforms. The numbers below the recordings refer to the time (in seconds) required for these sequential electrical events.

by another small upright wave (the source of which is uncertain) called the *U wave*.

The time from the onset of the P wave to the onset of the QRS complex is called the *P-R interval*, regardless of whether the first wave in this complex is a Q wave or an R wave (Figure 10-11). This interval measures the time between the onsets of activation of the atrial myocardium and the ventricular myocardium. The designation *PR segment* refers to the time from the end of the P wave to the onset of the QRS complex. The *QRS interval* measures the time from the beginning to the end of ventricular activation. Since activation of the thicker left ventricle requires more time than that of the right ventricle, the terminal portion of the QRS complex represents only LV activation.

The term *ST segment* refers to the interval between the end of ventricular activation and the beginning of ventricular recovery. This term is used regardless of whether the final wave of the QRS complex is an R wave or an S wave. The junction of the QRS complex and ST segment is called the *J-point*. The interval from the onset of ventricular activation to the end of ventricular recovery is called the *Q-T interval*. This term is used regardless of whether the QRS complex begins with a Q wave or an R wave.

At low heart rates in a healthy person, the PR, ST, and TP segments are at the same horizontal level and form the *isoelectric line*. This line is considered as the baseline for measuring the amplitudes of the various waveforms. The TP segment disappears at higher heart rates when the T wave merges with the following P wave.[17-19]

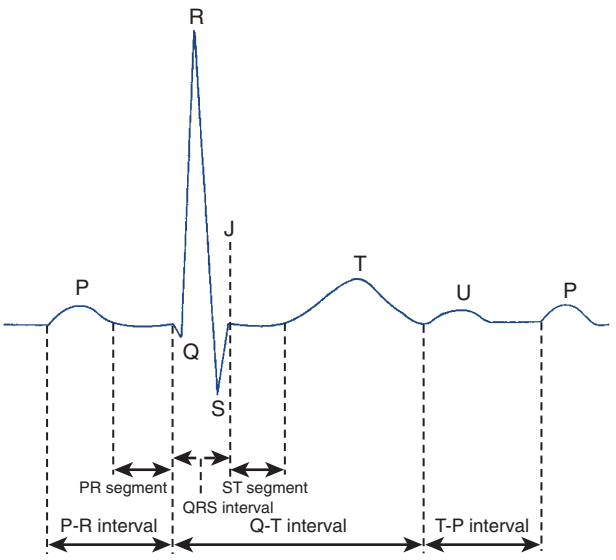


FIGURE 10-11 The magnified recording from the cardiac long-axis viewpoint is presented, with the principal electrocardiogram segments (*PR* and *ST*) and intervals (*P-R, QRS, Q-T,* and *T-P*) indicated.

Determining Left Versus Right Cardiac Electrical Activity

It is often important to determine if an abnormality originates from the left or the right atrium or ventricle of the heart. The optimal site for recording left versus right cardiac electrical activity is located where the extension of the short axis of the heart (perpendicular to the inter-atrial and interventricular septa) intersects with the precordial body surface (lead V1) (Figure 10-12).

The initial part of the P wave representing right atrial activation appears positive in lead V1 because of the progression of electrical activity from the inter-atrial septum toward the right atrial lateral wall. The terminal part of the P wave representing left atrial activation appears negative because of progression from the inter-atrial septum toward the left atrial lateral wall. This activation sequence produces a diphasic P wave (Figure 10-13).

The initial part of the QRS complex represents the progression of activation in the interventricular septum. This movement is predominately from left to right, producing a positive (R wave) deflection at this left-sided versus right-sided recording site. The mid-portion of the QRS complex represents the progression of electrical activation through the right ventricular (RV) myocardium and the LV myocardium. Since the posteriorly positioned left ventricle is much thicker, its activation predominates that of the anteriorly placed right ventricle, resulting in a deeply negative deflection (S wave). The final portion of the QRS complex represents the completion of activation of the left ventricle. This posteriorly directed excitation is represented by the completion of the S wave.

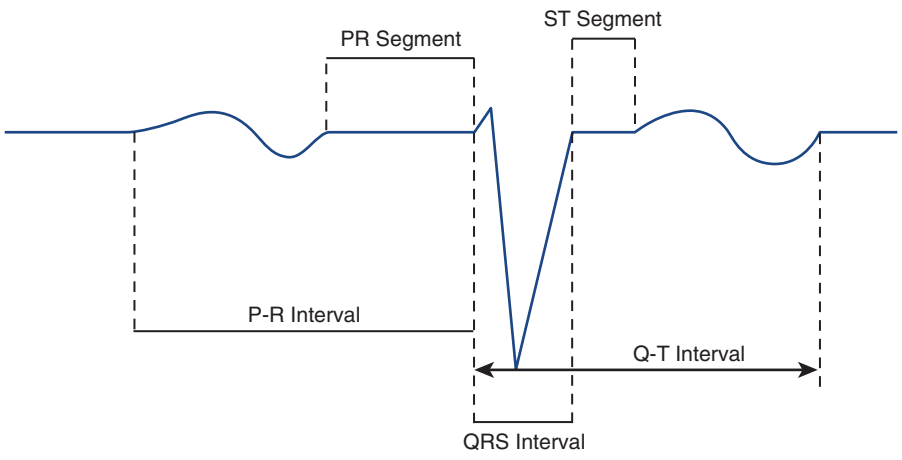


FIGURE 10-12 Magnified view of recording from the cardiac short-axis viewpoint with the principal electrocardiogram segments and time intervals indicated for the long-axis view. Lead V1 is shown.

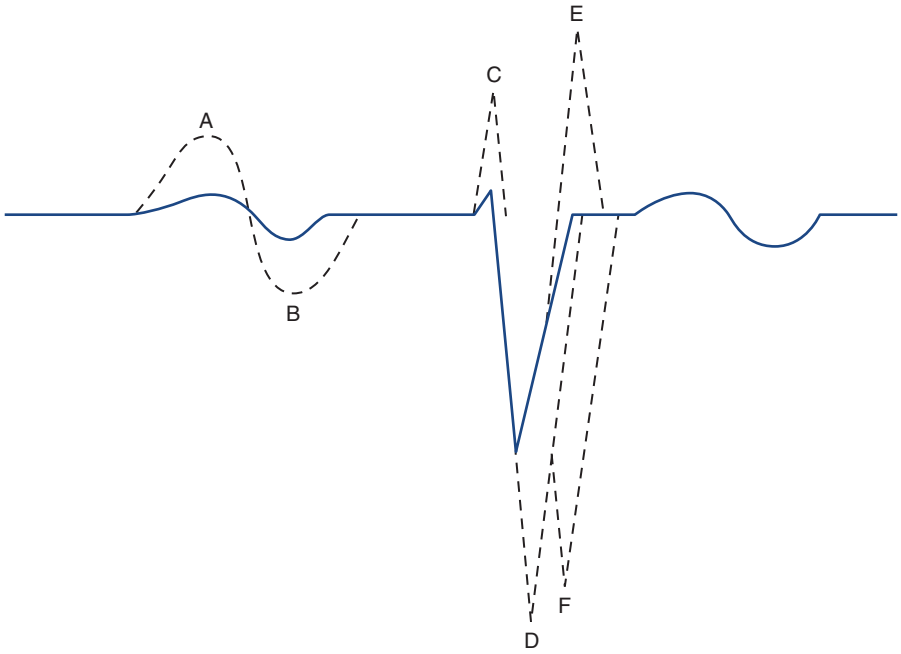


FIGURE 10-13 The electrocardiogram waveforms are reproduced with the alterations, indicated by *dashed lines,* that would typically result from enlargements of the right (*A*) and left (*B*) atrial chambers and the right (*C*) and left (*D*) ventricular chambers and from right-sided (*E*) and left-sided (*F*) intraventricular conduction delays.

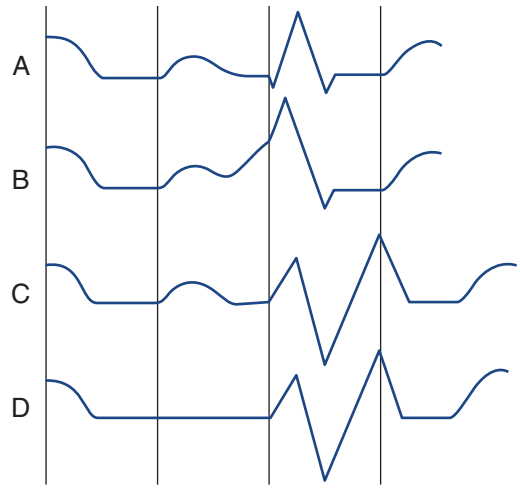


FIGURE 10-14 The normal P-to-QRS relationship and appearances (*A*) are contrasted with various conditions that produce obvious abnormalities (*B* through *D*). Each example begins and ends during a T wave.

The left versus right recording site is the key ECG view for identifying enlargement of one of the four cardiac chambers and localizing the site of a delay in ventricular activation (Figures 10-13 and 10-14). Right atrial enlargement produces an abnormally prominent initial part of the P wave, and left atrial enlargement produces an abnormally prominent terminal part of the P wave. Right ventricular (RV) enlargement produces an abnormally prominent R wave, whereas LV enlargement produces an abnormally prominent S wave. A delay in the right bundle branch causes RV activation to occur after LV activation is completed, producing an R′ deflection. A delay in the left bundle branch markedly postpones LV activation, resulting in an abnormally prominently S wave (see Figure 10-13).

Interpretation of the Normal Electrocardiogram

In interpreting every ECG, nine features should be examined systematically:

1. Rate and regularity
2. Rhythm
3. P-wave morphology
4. P-R interval
5. QRS complex morphology
6. ST-segment morphology
7. T-wave morphology
8. U-wave morphology
9. Q-T interval

Rate, regularity, and rhythm (1 and 2 above) are considered elsewhere in this text, and P-wave morphology (3 above) was discussed earlier.

P-R Interval

The P-R interval measures the time required for the impulse to travel from the atrial myocardium adjacent to the sinus node to the ventricular myocardium adjacent to the fibers of the Purkinje network. This normally lasts 0.10 to 0.22 seconds. A major portion of the P-R interval is caused by the slow conduction through the AV node, and this is controlled by the sympathetic-parasympathetic balance of the autonomic nervous system. Therefore, the P-R interval varies with the heart rate, being shorter at faster rates when the sympathetic component predominates, and vice versa. The P-R interval tends to increase with age.[20]

An abnormal P-wave direction is often accompanied by an abnormally short P-R interval, since the site of impulse formation has moved from the sinus node to a position closer to the AV node (Figure 10-15). However, a short P-R interval in the presence of a normal P-wave axis suggests either an abnormally rapid conduction pathway within the AV node or the presence of an abnormal bundle of cardiac muscle (bundle of Kent) connecting atria and ventricles and bypassing the AV node. This earlier-than-normal activation of the ventricular myocardium (ventricular preexcitation) creates the potential for electrical reactivation or re-entry into the atria to produce a tachyarrhythmia (the Wolff-Parkinson-White [WPW] syndrome).

A longer than normal P-R interval in the presence of a normal P-wave axis indicates delay in impulse transmission at some point along the pathway between the atrial myocardium and the ventricular myocardium (Figure 10-15). When a prolonged P-R interval is accompanied by an abnormal P-wave direction, the possibility that the P wave is actually associated with the preceding rather than the following QRS complex should be considered. When such retrograde activation from ventricles to atria occurs, the P-R interval is usually even longer than the preceding QRS to P (R-P) interval. When the P-R interval cannot be determined because of the absence of any visible P wave, an obvious abnormality of the cardiac rhythm is present.

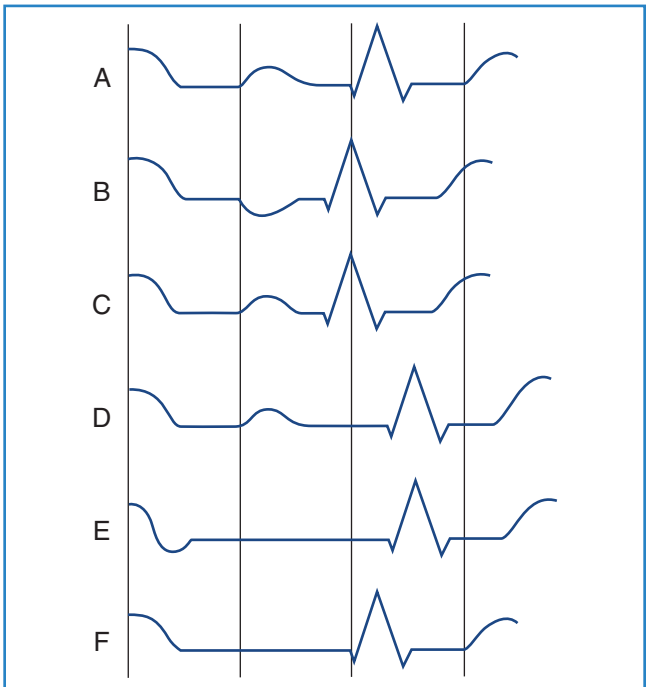


FIGURE 10-15 The normal P-to-QRS relationship (*A*) is contrasted with various abnormal relationships (*B* through *F*). Each example begins with the completion of a T wave and ends with the initiation of the T wave of the following cardiac cycle. The vertical time lines are at 0.2-second intervals. The P-R interval in (*A*) is therefore 0.2 seconds, which is near the upper limit of normal.

QRS Complex

The QRS complex is composed of higher-frequency signals than are the P and T waves, which causes its contour to be peaked rather than rounded. Positive and negative components of P and T waves are simply termed *positive* and *negative deflections*, whereas those of the QRS complex are assigned specific labels such as Q waves.

Q Waves

In some leads—V1, V2, and V3—the presence of a Q wave should be considered abnormal, and in all other leads (except III and aVR), a "normal" Q wave would be very small. The "upper limit of normal" for such Q waves in each lead is indicated in Table 10-1.[21] The absence of small Q waves in leads V5 and V6 should be considered abnormal. A Q wave of any size is normal in III and aVR because of their rightward orientations. Q waves may be enlarged by conditions such as local loss of myocardium (infarction), hypertrophy or dilation of the ventricular myocardium, or abnormalities of ventricular conduction.

R Waves

Since the precordial leads provide a panoramic view of the cardiac electrical activity progressing from the thinner right ventricle across the thicker left ventricle, the positive R wave normally increases in amplitude and duration from V1 to V4 or V5 (Figure 10-16). Reversal of this sequence with larger R waves in V1 and V2 can be produced by RV enlargement, and accentuation of the normal sequence with larger R waves in V5 and V6 can be produced by LV enlargement. Loss of normal R-wave progression from V1 to V5 may indicate loss of myocardium in the LV wall caused by myocardial infarction (MI).

Table 10-1 Wave Duration Limits

LIMB LEADS		PRECORDIAL LEADS	
LEAD	**UPPER LIMIT**	**LEAD**	**UPPER LIMIT**
I	<0.03 sec	V1	Any Q
II	<0.03 sec	V2	Any Q
III	None	V3	Any Q
aVR	None	V4	<0.02 sec
aVL	<0.03 sec	V5	<0.03 sec
aVF	<0.03 sec	V6	<0.03 sec

Modified from Wagner GS, Freye CJ, Palmeri ST, et al: Evaluation of a QRS scoring system for estimating myocardial infarct size. I. Specificity and observer agreement, *Circulation* 65:345, 1982.

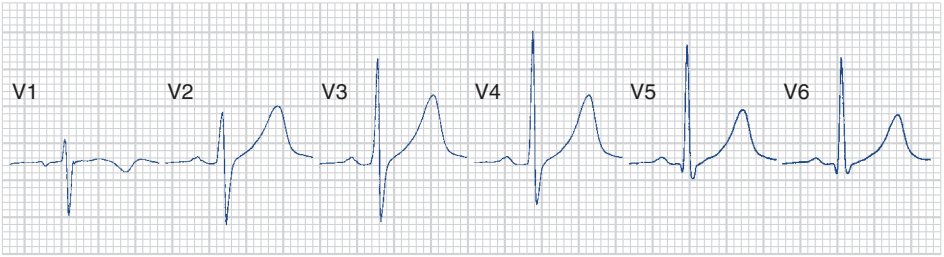


FIGURE 10-16 The typical panoramic display of the six precordial leads of the electrocardiogram, illustrating the normal progression and regression of R-wave and S-wave amplitudes.

S Waves

The S wave also has a normal sequence of progression in the precordial leads. It should be large in V1, larger in V2, and then progressively smaller from V3 through V6 (see Figure 10-16). As with the R wave, alteration of this sequence could be produced either by enlargement of one of the ventricles or by myocardial infarction.

The duration of the QRS complex is termed the *QRS interval*, normally ranging from 0.07 to 0.10 seconds. The interval tends to be slightly longer in males than in females and is measured from the beginning of the first appearing Q or R wave to the end of the last appearing R, S, or R′ wave. Multi-lead comparison is useful, since either the beginning or end of the QRS complex may be isoelectric in any single lead, causing underestimation of QRS duration. The onset of the QRS complex is usually quite apparent in all the leads, but its offset at the junction with the ST segment is often indistinct, particularly in the precordial leads. The QRS interval has no lower limit that indicates abnormality. QRS prolongation may be caused by LV enlargement, an abnormality in impulse conduction, or a ventricular site of origin of the QRS complex.

QRS Axis Determination

With the typical ECG display, a three-step method is used for determining the frontal plane QRS direction (termed *axis*):

Step 1. Identify the transitional lead, as defined by positive and negative components of the QRS complex of approximately equal amplitudes.

Step 2. Identify the lead that is oriented perpendicular to the transitional lead by using the hexaxial reference system (Figure 10-17).

Step 3. Consider the predominant direction of the QRS complex in the lead identified in step 2. If the direction is positive, the axis is equal to the positive pole of that lead. If the direction is negative, the axis is equal to the negative pole of that lead.

The frontal plane axis is normally directed leftward and either slightly superiorly or inferiorly: between −30 degrees and +90 degrees (see Figure 10-17). Therefore, the QRS complex is normally predominately positive in both leads I (with its positive pole at 0 degrees) and II (with its positive pole at +60 degrees). If the QRS is positive in lead I but negative in II, the axis is deviated leftward between −30 and −120 degrees. However, if the QRS is negative in I but positive in II, the axis is deviated rightward between +90 and +180 degrees. The axis is rarely directed entirely opposite the normal with predominately negative QRS orientation in both leads I and II.

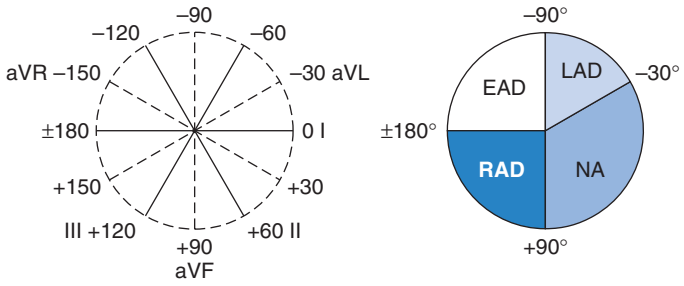
The frontal plane axis is typically rounded to the nearest multiple of 15 degrees. If it is directly aligned with one of the limb leads, the axis is designated as −30 degrees, 0 degrees, +30 degrees, +60 degrees, and so on. If it is located midway between two of the limb leads, it is designated as −15 degrees, +15 degrees, +45 degrees, +75 degrees, and so on. Examples of patients with various frontal plane QRS axes are presented in Figure 10-17.

The normal frontal plane QRS axis is rightward in the neonate, moves to a vertical position during childhood, and then moves to a more horizontal position during adulthood. In normal adults, the electrical axis is almost parallel to the anatomic base to the apex axis of the heart, in the direction of lead II. However, the axis is more vertical in thin individuals and more horizontal in heavy individuals. A QRS axis more positive than +90 degrees in an adult should be designated *right-axis deviation* (RAD) (see Figure 10-17, *B*), and an axis more negative than −30 degrees at any age should be designated *left-axis deviation* (LAD) (see Figure 10-17, *C*). RV hypertrophy may produce RAD and LV hypertrophy LAD. An axis between −90 and +180 degrees should be considered *extreme axis deviation* (EAD) without designating it as either rightward or leftward (see Figure 10-17, *E*).

ST-Segment Morphology

The ST segment represents the period when the ventricular myocardium remains in an activated or depolarized state. At its junction with the QRS (J-point), it typically forms a nearly 90-degree angle and then proceeds horizontally until it curves gently into the T wave. The length of the ST segment is influenced by factors that alter the duration of ventricular activation. Points along the ST segment are designated with reference to the number of milliseconds beyond the J point, such as "J + 20," "J + 40," and "J + 60."

The first section of the ST segment is normally located at the same horizontal level as the baseline formed by the PR segment and the TP segment, which fills in the space between electrical cardiac cycles. Slight up-sloping, down-sloping, or horizontal depression of the ST segment may occur as a normal variant. Another normal variant appears with early repolarization in the epicardial areas within the ventricles.[22] This causes displacement of the ST segment in the direction of the following T wave. Occasionally, as much as a 4-mm ST elevation may occur in leads V1 to V3 in normal young males.[23] The appearance of the



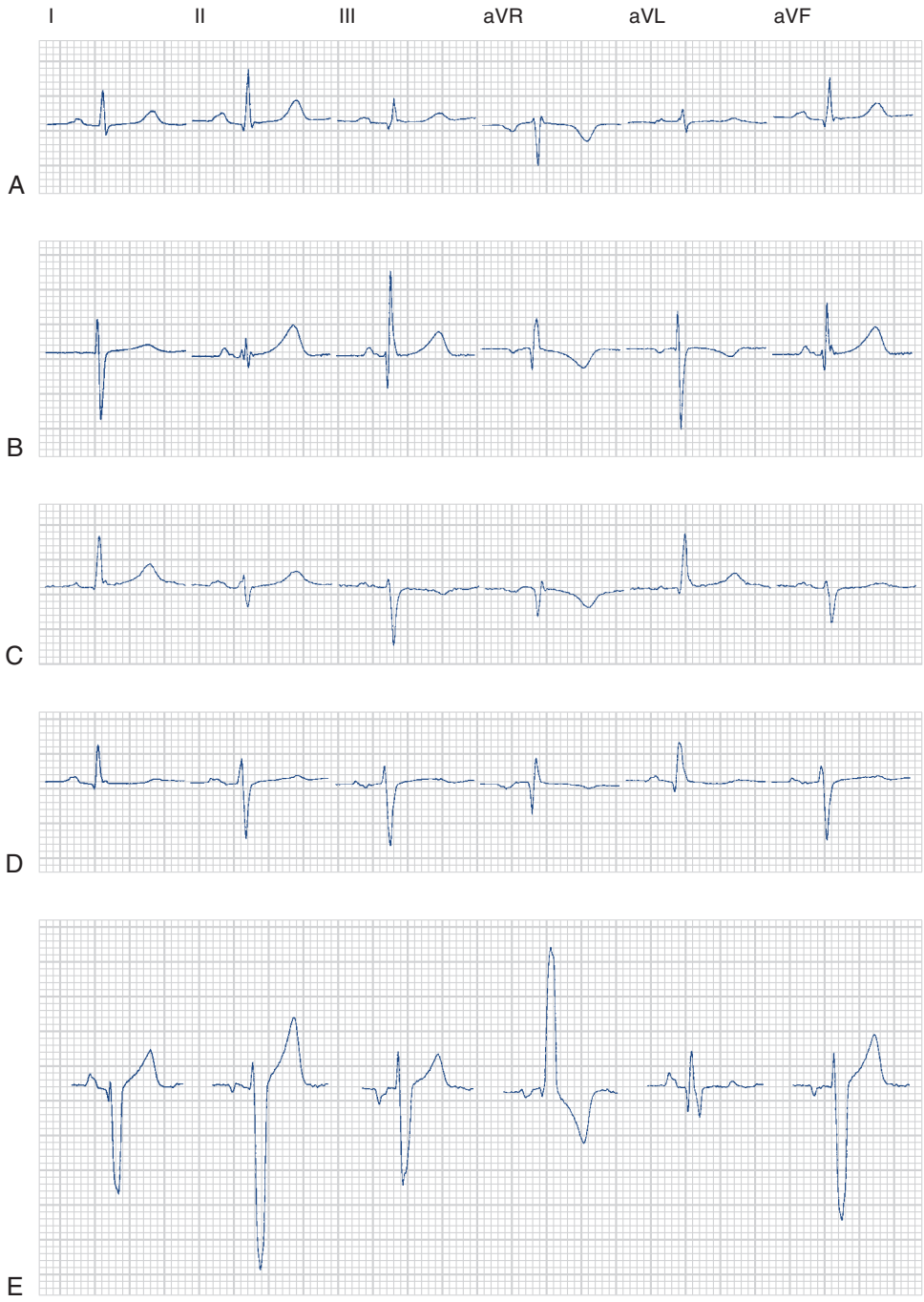


FIGURE 10-17 *Top left,* The frontal-plane hexaxial reference system. *Top right,*The sectors indicating the various designations of the frontal plane QRS axis in the adults: normal axis (*NA*), right-axis deviation (*RAD*), left-axis deviation (*LAD*), and extreme axis deviation (*EAD*). *Bottom,* Examples of various frontal plane QRS axes: **A,** +60 degrees; **B,** +150 degrees; **C,** –30 degrees; **D,** –60 degrees; **E,** –120 degrees.

ST segment may also be altered during exercise or with an altered sequence of activation of the ventricular myocardium.

T-Wave Morphology

The smooth, rounded shape of the T wave resembles the shape of the P wave. However, variation of monophasic versus diphasic appearance in the various leads is normal. The initial deflection of the T wave is typically longer than the terminal deflection, producing a slightly asymmetrical shape. Slight "peaking" of the T wave may occur as a normal variant, and notching of the T waves is common in children. The duration of the T wave itself is not usually measured but is, instead, included in the Q-T interval, as discussed later. The amplitude of the T wave, like that of the QRS complex, has wide normal limits. It tends to diminish with age and is larger in males than in females. T-wave amplitude tends to vary with QRS amplitude and should always be greater than that of any U wave that is present. T waves do not normally exceed 5 mm in any limb lead or 10 mm in any precordial lead. The T-wave amplitude tends to be lower in the leads providing the extreme views of both frontal and transverse planes: T waves do not normally exceed 3 mm in leads aVL and III, or 5 mm in leads V1 and V6.[24]

The direction of the T wave should be evaluated in relation to that of the QRS complex (Figure 10-18). The rationale for similar directions of these waveforms that represent the opposite myocardial events of activation and recovery has been presented earlier in the chapter (see "Basic Principles"). The method presented earlier for determining the direction of the QRS complex in the frontal plane should be applied for determining the direction of the T wave. The term QRS-T angle is used to indicate the number of degrees between the QRS complex and T-wave axes in the frontal plane.[25] A similar method can be applied in the transverse plane.

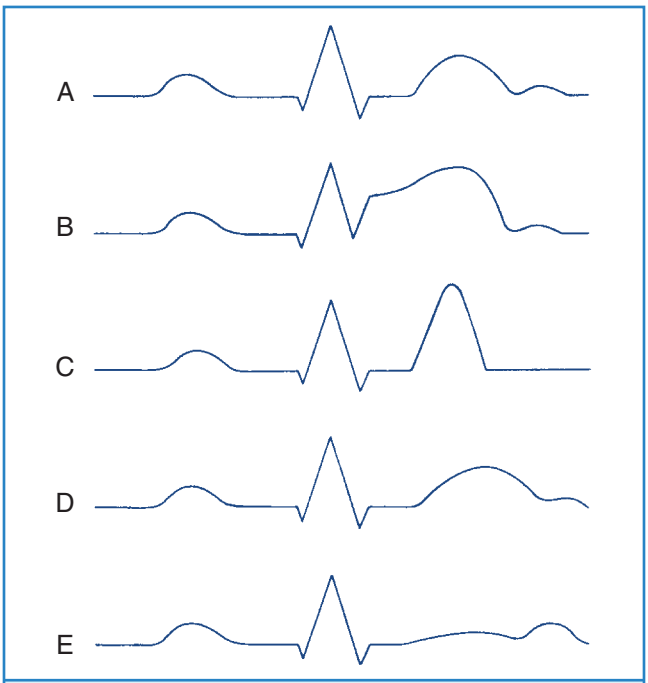


FIGURE 10-18 The normal QRS-to-T relationship (*A*) is contrasted with various abnormalities that may be associated with cardiac arrhythmias (*B* through *E*). Each example begins with the completion of a TP segment and ends with the initiation of the following TP segment.

U-Wave Morphology

The U wave is normally either absent, or present as a small, rounded wave following the T wave. It normally proceeds in the same direction as the T wave but with approximately 10% of the amplitude of the T wave. It is usually most prominent in leads V2 or V3.

Q-T Interval

The Q-T interval measures the duration of activation and recovery of the ventricular myocardium. It varies inversely with the heart rate. To ensure that recovery from one cardiac cycle is complete before the next cycle begins, the duration of recovery must decrease as the rate of activation increases. Therefore, the "normality" of the Q-T interval can be determined only by correcting for the heart rate. The corrected Q-T interval (QTc interval) rather than the measured Q-T interval is included in the ECG analysis. Bazett developed a formula for performing this correction, which has since been modified by Hodges and coworkers and MacFarlane and Veitch Lawrie.[20-22]

$$QTc = Q\text{-}T + 1.75\,(\text{Ventricular rate} - 60)$$

The normal value of the QTc is approximately 0.41 seconds with upper limits of 0.44 seconds in adult males and 0.46 seconds in adult females; children by age 15 usually have upper limits of 0.45 seconds. The QTc is slightly longer in females than in males and increases slightly with age. The accommodations of the duration of electrical recovery to the rate of electrical activation do not occur immediately but requires several cardiac cycles. Thus, an accurate QTc can be calculated only after a series of regular, equal cardiac cycles.

The diagnostic value of the Q-T interval is seriously limited by the difficulty of identifying the completion of ventricular recovery.

1. Commonly, a variation occurs in the Q-T interval among the leads. This occurs when the terminal portion of the T wave is isoelectric in some of the leads.[23] The longest Q-T interval measured in multiple leads should, therefore, be considered the true Q-T interval.

2. The U wave may merge with the T wave, creating a T-U junction, which is not on the baseline. In this instance, the onset of the U wave should be considered the approximate end of the Q-T interval.

3. At faster heart rates, the P wave may merge with the T wave, creating a T-P junction, which is not on the baseline. In this instance, the onset of the P wave should be considered the approximate end of the Q-T interval.

Marked elevation of the ST segment, increase or decrease in T-wave amplitude, prolongation of the QTc, or increase in U-wave amplitude may be an indication of underlying cardiac conditions that may produce serious cardiac rhythm abnormalities (Figure 10-19).

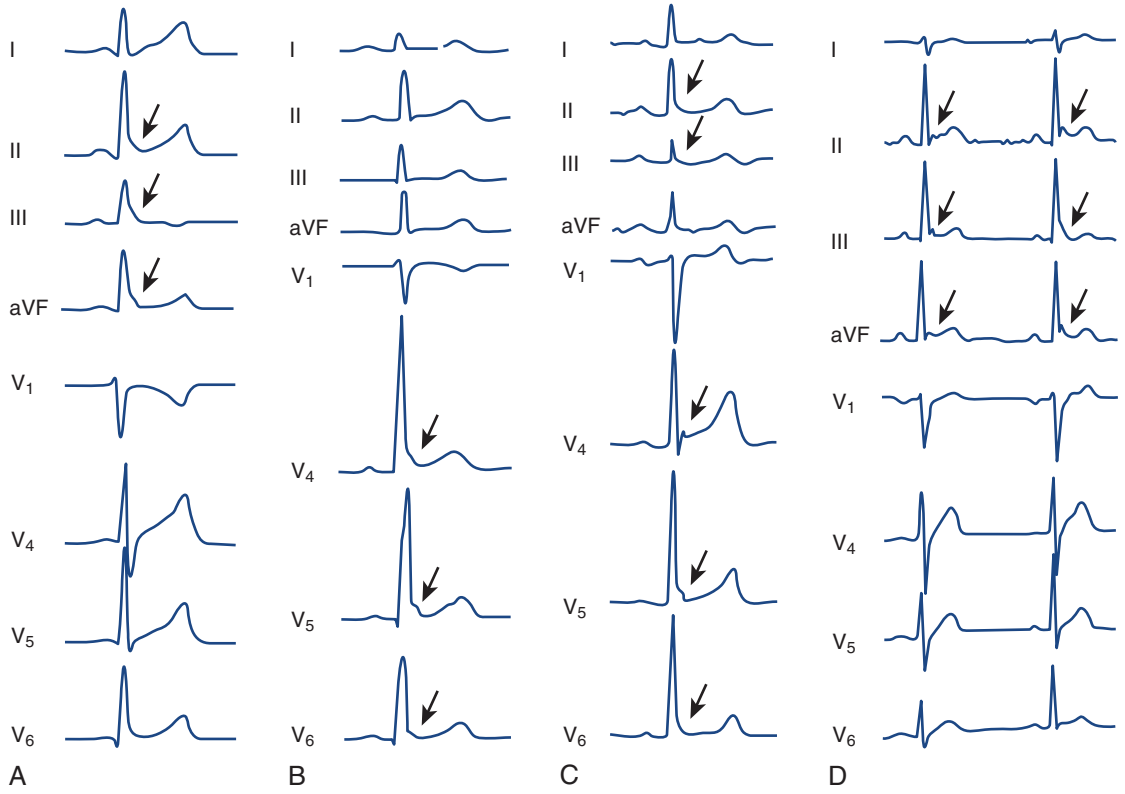


FIGURE 10-19 Electrocardiograms from four patients with early repolarization. In each panel, early repolarization is evident in the varying patterns of QRS slurring or notching in inferolateral leads (*arrows*). *D* shows a beat-to-beat fluctuation in this pattern.

Chamber Enlargement

Right Ventricular Dilation

The right ventricle dilates either during compensation for a volume overload or after its hypertrophy eventually fails to compensate for a pressure overload. This dilation causes stretching of the right bundle branch, which courses from the base to the apex on the endocardial surface of the right side of the interventricular septum (see Figure 10-8). Conduction of impulses within these right bundle Purkinje fibers is slowed so much that electrical activation arrives at the RV myocardium only after it has already been activated by spread of impulses from the left ventricle. This phenomenon, referred to as *right bundle branch block* (RBBB), is discussed later (see "Intraventricular Conduction Abnormalities"). This RV conduction abnormality may appear suddenly during the early or compensatory phase of a volume overload or during the advanced or failing phase of a pressure overload.

Right Ventricular Hypertrophy

RV hypertrophy occurs as compensation for pressure overload. In the neonate, the right ventricle is more hypertrophied compared with the left because of the greater resistance in the pulmonary circulation than in the systemic circulation during fetal development. Right-sided resistance is greatly increased when the placenta is removed.[26] From this time onward, ECG evidence of RV predominance is gradually lost as the left ventricle becomes hypertrophied in relation to the right. Therefore, hypertrophy, like dilation, may be a compensatory condition rather than a pathologic condition.[27] A pressure overload of the right ventricle may recur in later years because of increased resistance to the flow of blood through the pulmonary valve, the pulmonary circulation, or the left side of the heart.

The normal QRS complex in the adult is predominately negative in lead V1 with a small R wave followed by a prominent S wave. When the right ventricle hypertrophies in response to a pressure overload, this negative predominance may be lost. In milder forms, a late positive R wave appears. With moderate hypertrophy, the initial QRS forces move anteriorly (increased lead V1 R wave), and the terminal QRS forces move rightward (increased lead I S wave). With marked hypertrophy, the QRS complex may even become predominately positive (Figure 10-20). This severe pressure overload causes sustained delayed repolarization of the RV myocardium, producing negativity of the ST segment and the T wave, which has been termed *RV strain*.

Left Ventricular Dilation

The left ventricle dilates for the same reasons as described above for the right ventricle. However, the dilation does not stretch the left bundle enough to cause complete *left bundle branch block* (LBBB). This is most likely caused by anatomical differences between the the right and left bundles. The right bundle continues as a single bundle along its septal surface, but the left bundle divides almost immediately into multiple fascicles. LV dilation may produce only a partial or incomplete LBBB.

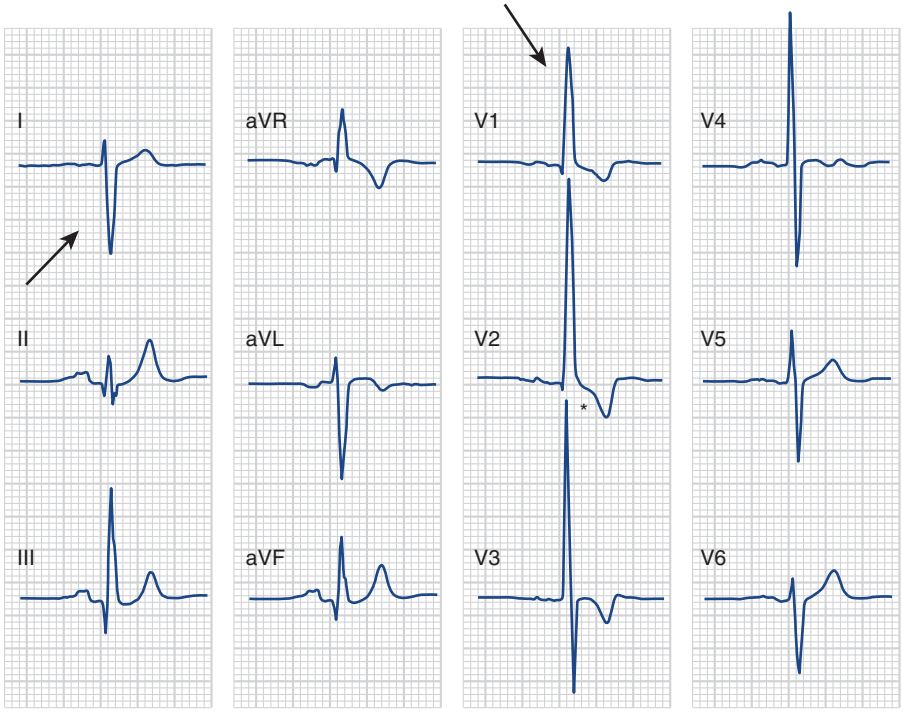


FIGURE 10-20 An 18-year-old man with congenital heart disease and pulmonary hypertension. *Arrows* indicate the changes of right ventricular hypertrophy in the QRS waveforms, and an *asterisk* indicates the ST- and T-wave changes of right ventricular strain.

Dilation enlarges the surface area of the left ventricle and moves the myocardium closer to the precordial electrodes, which increases the amplitudes of leftward and posteriorly directed QRS waveforms.[28] The S-wave amplitude is increased in leads V2 and V3, and the R-wave amplitude is increased in leads V5 and V6.

Left Ventricular Hypertrophy

As discussed earlier, the left ventricle normally becomes hypertrophied relative to the right ventricle following the neonatal period. Abnormal hypertrophy, which occurs in response to a pressure overload, produces exaggeration of the normal pattern of LV predominance on the ECG. Like dilation, hypertrophy enlarges the surface area of the left ventricle, which increases the voltages of leftward and posteriorly directed QRS waveforms, thereby causing similar shifts in the frontal plane axis and transverse plane transitional zone.

A longer time is required for the spread of electrical activation from the endocardial surface to the epicardial surface, prolonging both the time-to-peak R wave (intrinsicoid deflection) and the overall QRS duration. These conduction delays, induced by hypertrophy, may mimic incomplete or even complete LBBB (see "Intraventricular Conduction Abnormalities" below) (Figure 10-21).

Pressure overload leads to sustained delayed repolarization of the left ventricle, which produces negativity of both the ST segment and the T wave in leads with leftward or posterior orientation. This is referred to as *LV strain*.[29] The epicardial cells no longer repolarize early, causing the spread of recovery to proceed from the endocardium to the epicardium. This leads to deflection of the T wave in the opposite direction of the QRS complex. The mechanism that produces the strain is uncertain, but several factors are believed to contribute. The development of strain correlates well with increasing LV mass as determined by echocardiography.[30] Myocardial ischemia and slowing of intraventricular conduction are factors that may also contribute to strain.

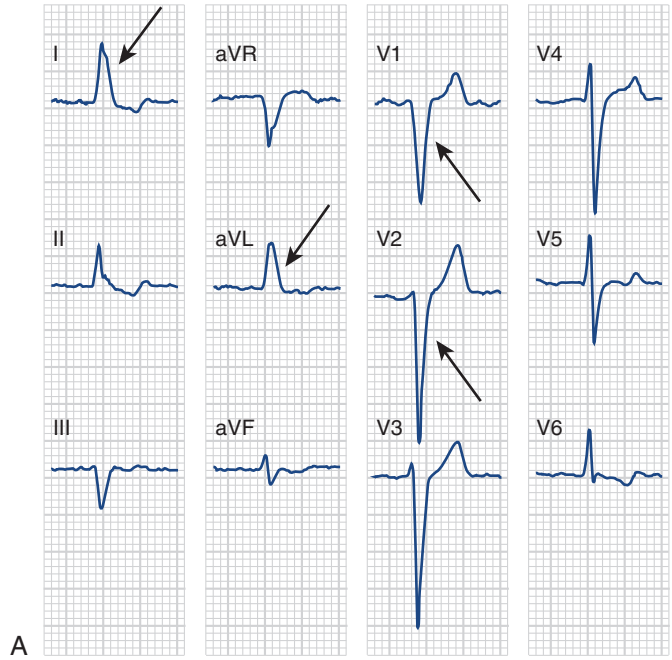
Intraventricular Conduction Abnormalities

Bundle Branch and Fascicular Block

Since the activation of the ventricular Purkinje system (see Figure 10-8) is not represented on the surface ECG, abnormalities of its conduction must be detected indirectly by their effects on myocardial activation and recovery. The most specific changes occur within the QRS complex. A conduction disturbance within the right bundle branch, left bundle branch, or left bundle fascicles or between the Purkinje fibers and the adjacent myocardium may alter the QRS complex and T wave. A conduction disturbance in the common or His bundle has a similar effect on activation of both ventricles and, therefore, does not alter the appearance of the QRS complex or T wave.

Unifascicular Blocks

This term is used when ECG evidence of blockage of only one of the fascicles is present. Isolated RBBB or left anterior fascicular block (LAFB) commonly occurs, whereas left posterior fascicular block (LPFB) is rare. Rosenbaum et al identified only 30 patients with LPFB compared with 900 patients with LAFB.[31]



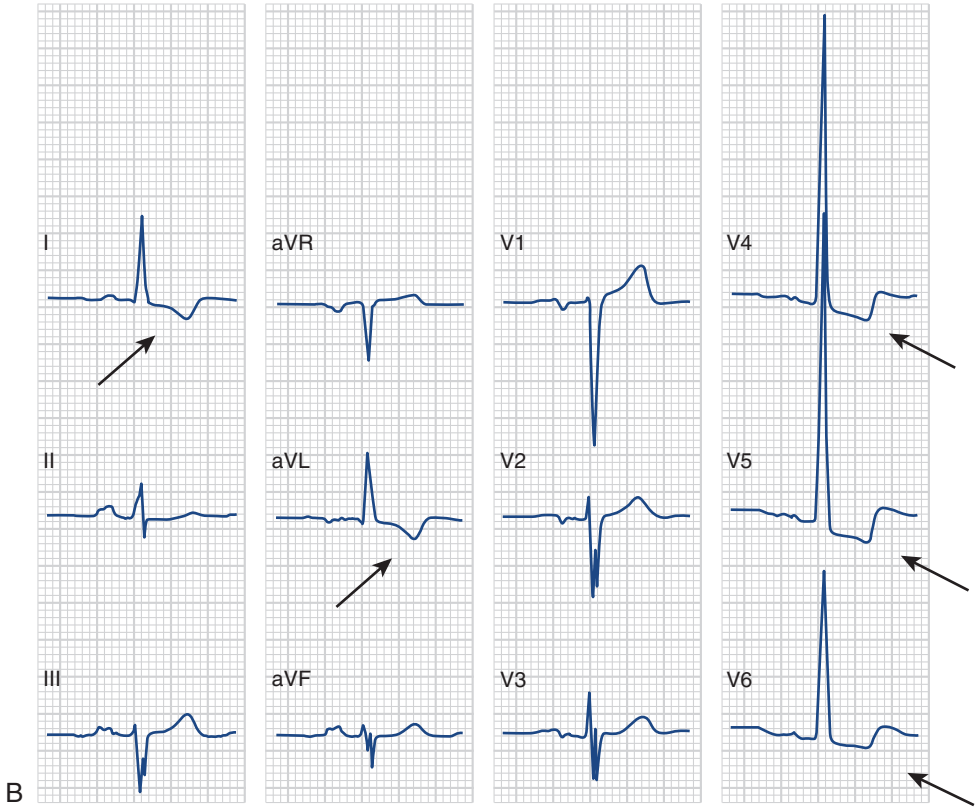


FIGURE 10-21 Twelve-lead electrocardiograms from a 75-year-old woman with symptoms of heart failure caused by longstanding hypertension (**A**) and a 70-year-old man with severe aortic valve stenosis just before surgical replacement (**B**). *Arrows* indicate intraventricular conduction delay (**A**) and ST-segment depression and T-wave inversion (**B**).

Right Bundle Branch Block

Since the right ventricle contributes minimally to the normal QRS complex, RBBB produces little distortion during the time required for LV activation. Figure 10-13, illustrates the minimal distortion of the early portion and marked distortion of the late portion of the QRS complex that typically occur with RBBB. The minimal contribution of the normal RV myocardium is completely subtracted from the early portion of the QRS complex and added later when the right ventricle is activated via the spread of impulses from the left ventricle. This produces a late prominent positive wave in lead V1 termed *R′* because it follows the earlier positive R wave produced by normal left to right spread of activation through the interventricular septum (Figure 10-22).

Left Antero-superior Fascicular Block

If the LA fascicles of the left bundle branch are blocked, the initial activation of the LV free wall occurs via the LP fascicles (Figure 10-23). Activation spreading from the endocardium to the epicardium in this region is directed inferiorly and rightward. Since the block in the LA fascicles has removed the competition from activation directed superiorly and leftward, Q waves appear in leads with their positive electrode on the left arm (leads I and aVL). Following this initial period, the activation wave spreads over the remainder of the LV free wall in a superior and leftward direction. This produces prominent R waves in leads I and aVL and prominent S waves in leads II, III, and aVF, causing a leftward shift of the QRS axis to at least –45 degrees. The overall QRS duration is prolonged to 0.10 to 0.20 seconds.[32]

LAFB is, by far, the most commonly occurring conduction abnormality involving the left bundle branch. Its presence was detected in 1.5% of a population of 8000 men 45 to 69 years of age.[33]

Left Postero-inferior Fascicular Block

If the LP fascicles of the LBB are blocked, the situation is reversed (see Figure 10-23). However, this rarely occurs as an isolated abnormality. The initial LV free wall activation occurs via the LA fascicles. Activation spreading from the endocardium to the epicardium in this region is directed superiorly and leftward. Since the block in the LP fascicles has removed the competition provided by activation directed inferiorly and rightward, Q waves appear in leads with their positive electrode on the left leg (leads II, III, and aVF). Following this initial period, the activation wave spreads over the remainder of the LV free wall in an inferior and rightward direction. This produces prominent R waves in leads II, III, and aVF and prominent S waves in leads I and aVL, causing a rightward shift of the QRS axis to at least +90 degrees.[33] The QRS duration is slightly prolonged as in LAFB. The diagnosis of LPFB requires absence of evidence of RV hypertrophy (RVH) because the much more common RVH itself can produce the same ECG pattern as LPFB.

Bifascicular Blocks

The term *bifascicular block* is used when involvement of two of the major Purkinje fascicles is evident on the ECG. Such evidence may appear at different times or may coexist on the same ECG. This term is sometimes applied to complete LBBB but is more

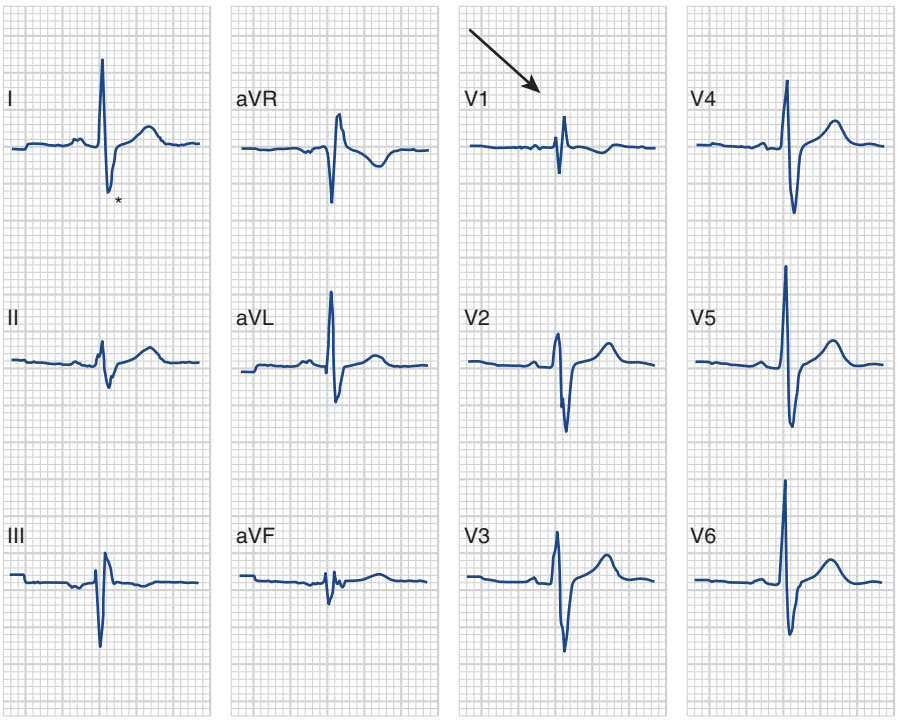


FIGURE 10-22 Twelve-lead electrocardiograms from a 17-year-old girl with an ostium secundum atrial septal defect. The *arrow* indicates the prominent terminal R′ wave in V1, and the *asterisk* indicates the right- and left-axis shifts, respectively.

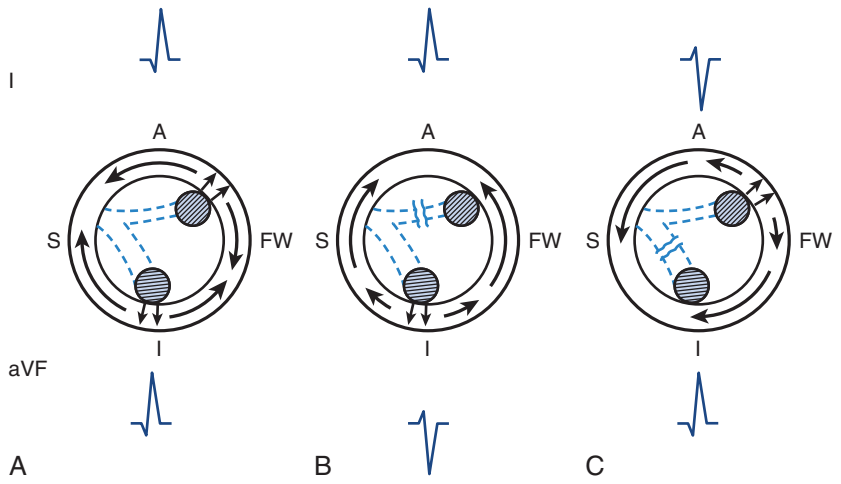


FIGURE 10-23 Schematic left ventricle viewed from its apex upward toward its base. The interventricular septum (*S*), left ventricular free wall (*FW*), and anterior (*A*) and inferior (*I*) regions of the left ventricle are indicated. The typical appearances of the QRS complexes in leads 1 (*top*) and aVF (*bottom*) are presented for normal (**A**), left anterior fascicular block (**B**), and left posterior fascicular block left ventricular activation (**C**). *Dashed lines* represent the fascicles; the two *wavy lines* crossing a fascicle indicate the sites of block. *Hatched circles* represent the papillary muscles; *outer rings* represent the endocardial and epicardial surface of the left ventricular myocardium. *Arrows* within the outer rings indicate the directions of the wavefronts of activation as they spread from the unblocked fascicles through the myocardium.

commonly applied to the combination of RBBB with either LAFB or LPFB. The term *bilateral bundle branch block* is also appropriate when RBBB and either LAFB or LPFB are present.[34] When bifascicular block is present, the QRS duration is prolonged to at least 0.12 seconds.

Left Bundle Branch Block

Figure 10-24 illustrates the marked distortion of the entire QRS complex produced by LBBB. Complete LBBB may be caused by disease either in the main LBB (predivisional) or in all of its fascicles (postdivisional). When the impulse cannot progress along the left bundle branch, it must first enter the right ventricle and then travel through the interventricular septum to the left ventricle.

Normally, the interventricular septum is activated from left to right, producing an initial R wave in the right precordial leads and a Q wave in leads I, aVL, and the left precordial leads. When complete LBBB is present, the septum is activated from right to left. This produces initial Q waves in the right precordial leads and eliminates the normal Q waves in the leftward-oriented leads.[35] The activation of the left ventricle then proceeds sequentially from the interventricular septum to the adjacent anterosuperior and inferior walls to the posterolateral free wall. This sequence of ventricular activation in complete LBBB tends to produce monophasic QRS complexes: QS in lead V1 and R in leads I, aVL, and V6.

Right Bundle Branch Block with Left Antero-superior Fascicular Block

Just as LAFB appears as a unifascicular block much more commonly compared with LPFB, it more commonly accompanies RBBB as a bifascicular block. The diagnosis is made by observing the late prominent R or R′ wave in precordial lead V1 of RBBB and the initial R waves and the prominent S waves in limb leads II, III, and aVF of LAFB. The QRS duration should be at least 0.12 seconds, and the frontal plane axis should be between −45 and −120 degrees (Figure 10-25).[33]

Right Bundle Branch Block with Left Postero-inferior Fascicular Block

This type of bifascicular block rarely occurs. Even when the ECG changes are entirely typical, the diagnosis should be made only in the absence of clinical evidence of RVH. The diagnosis of RBBB with LPFB should be considered when typical changes are observed in precordial lead V1 of RBBB and in the initial R waves and prominent S waves in limb leads I and aVL of LPFB. The QRS duration should be at least 0.12 seconds and the frontal plane axis at least +90 degrees (Figure 10-26).[36,37]

Acute and Chronic Ischemic Heart Disease

General Electrophysiological Principles

The process of electrical recovery of myocardial cells is more susceptible to ischemia than is that of electrical activation. Since ischemia caused by an increase in myocardial demand is not as profound as that caused by a complete cessation of coronary blood flow, it is manifested on the ECG only by changes in the waveforms representing the recovery process—the ST segments and T waves. The more profound ischemia that occurs with acute coronary occlusion produces a different array of changes in the ST segments and T waves and may even alter the QRS complexes. When the ischemia is maximally severe, because of the absence of protection by either collateral blood flow from other arteries or "metabolic ischemic preconditioning," electrical conduction through the myocardium may be slowed, causing QRS

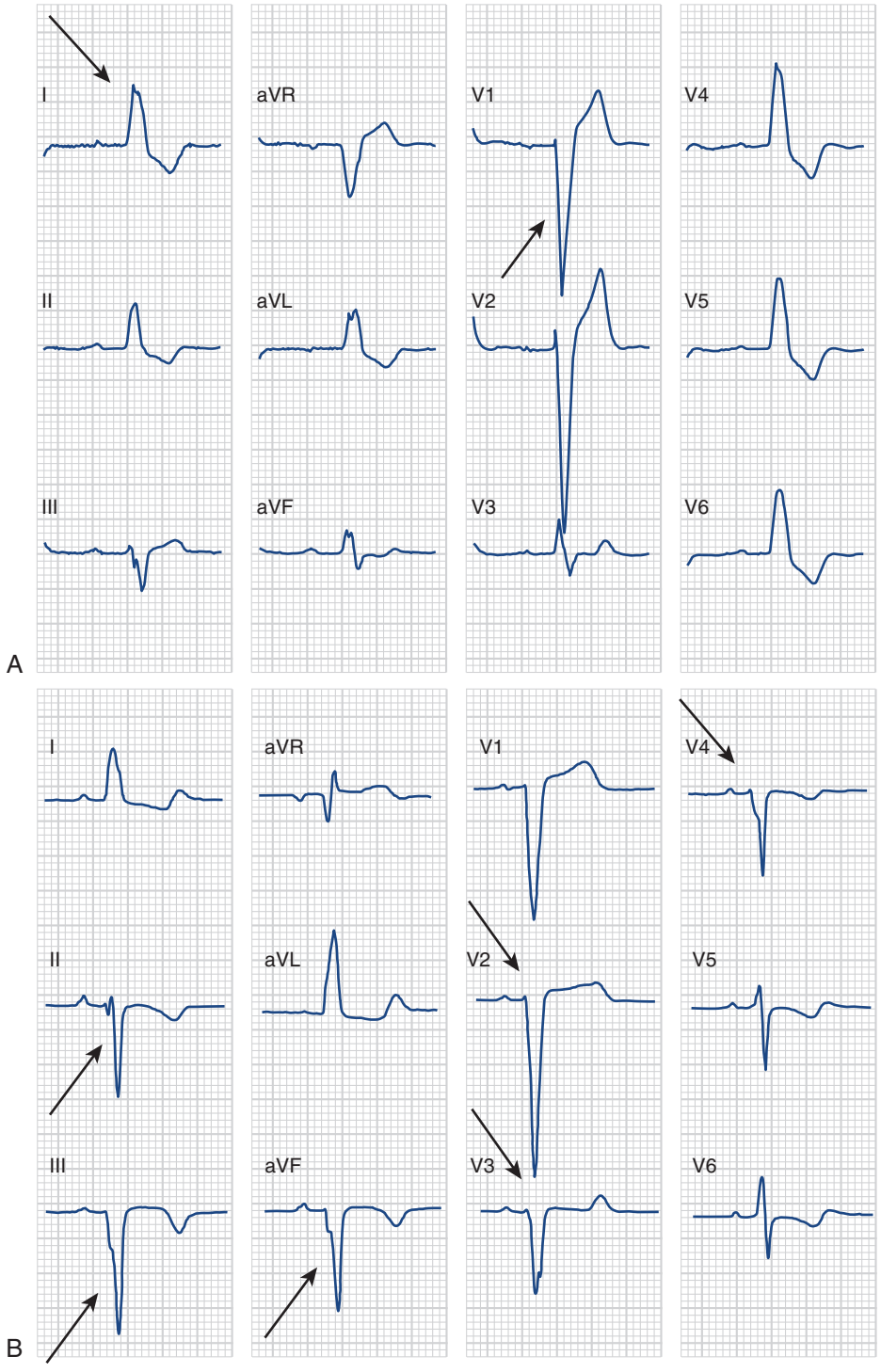


FIGURE 10-24 Twelve-lead electrocardiograms from an 82-year-old woman with no medical problems (**A**), a 71-year-old man with chronic heart failure (**B**), and a 74-year-old man with a long history of hypertension (**C**). *Arrows* in **A** and **C** indicate the typical characteristics of left bundle branch block in leads I and V1, and *arrows* in **B** indicate the deep S waves in leads II, III, and aVF and decreased R waves in leads V2 to V4.

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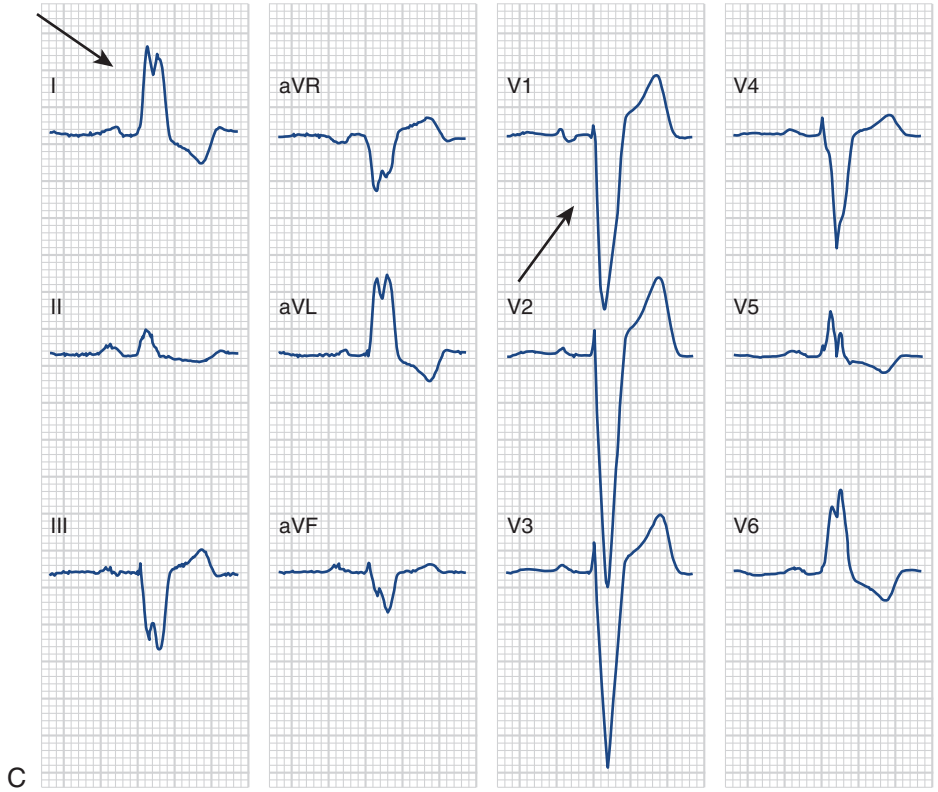

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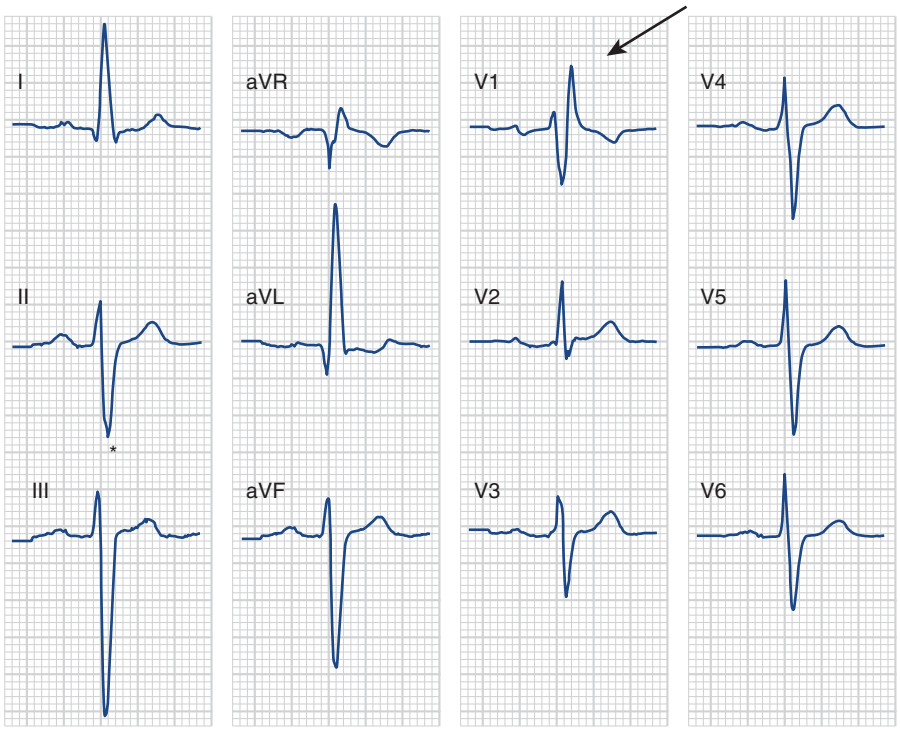


FIGURE 10-25 An 82-year-old man with fibrosis of both the right bundle branch and the anterior fascicle of the left bundle branch. The *arrow* indicates the prominent terminal R′ wave in V1, and the *asterisk* indicates the right- and left-axis shifts, respectively.

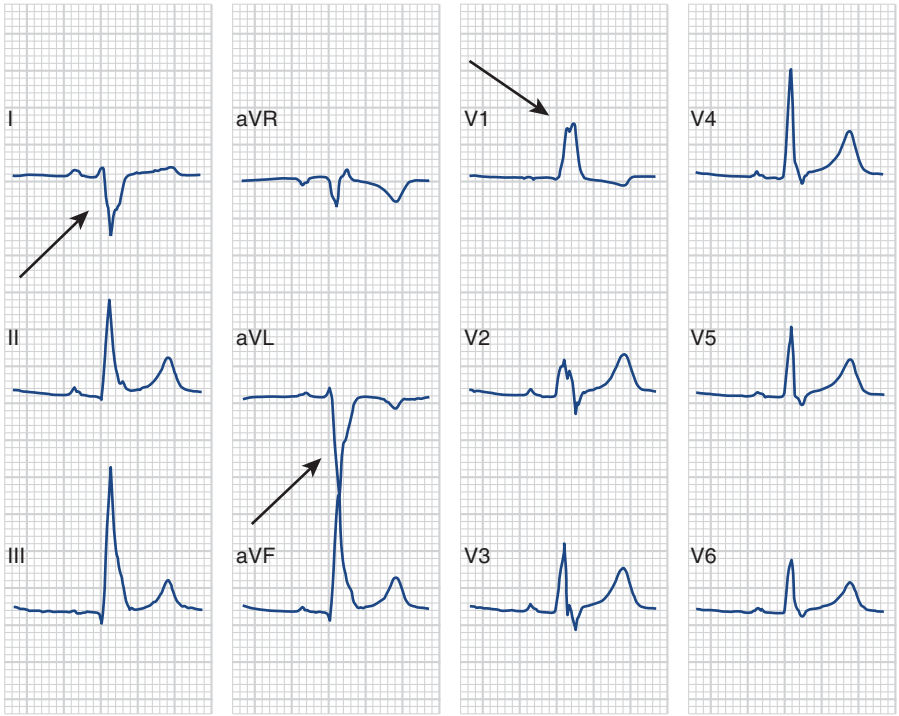


FIGURE 10-26 Twelve-lead electrocardiograms from an 82-year-old woman with no complaints and no other evidence of heart disease. *Arrows* indicate the prominent S waves in I and aVL and RR′ complex in V1.

prolongation, with distortion primarily in the terminal portion. When blood flow is not rapidly restored, the more permanent changes in the QRS waveforms of MI sequentially evolve.[38,39]

The ECG changes caused by a potentially reversible increase in myocardial metabolic demand or decrease in coronary blood flow are typically termed *ischemia* when the direction of the T wave is altered and *injury* when the level of the ST segment is deviated from those of the TP and PR segments of the baseline. However, the term *ischemia* is used more generally in this chapter in reference to the condition of a pathologic imbalance between supply and demand.

The thicker-walled left ventricle is much more susceptible to ischemia than is the right ventricle, and the endocardial linings of both are supplied by the cavitary blood. The subendocardial layer of LV cells is that most likely to become ischemic because it is located "at the end of the supply line" (Figure 10-27). Ischemia occurs when, in the presence of underlying coronary atherosclerosis, either an increase in myocardial demand or a decrease in coronary blood flow occurs.[40,41]

The typical ECG manifestation of ischemia caused by an increase in myocardial demand is deviation of the ST segment away from the entire involved left ventricle. Because of the location of the involved layer of the myocardium and the characteristic deviation of the ST segment of the ECG baseline, the term used is *subendocardial ischemia* (SEI).

The typical ECG manifestation of ischemia caused by acute occlusion of myocardial blood flow is deviation of the ST segment toward the specifically involved area. Because of the involvement of all layers of the myocardium (including the epicardium), the term that most accurately describes the ECG changes is *epicardial injury* (EI). Note that the term *injury* replaces the term *ischemia* because the changes are produced by a "current of injury" that flows between the normal and involved portions of the myocardium. The process of infarction deviates the QRS complex away from the involved area.[42] Unless poor myocardial remodeling results in wall thinning or even aneurysmal dilation, the ST segment soon returns to a position isoelectric with the remainder of the ECG baseline.

Myocardial Ischemia

Normally, the directions of the QRS complex and T wave are similar rather than opposite because of prolonged maintenance of the activated condition in the endocardial layer of myocardium. The ischemic subendocardial cells are unable to maintain prolonged activation, thereby causing the T wave on the ECG to become "inverted" in relation to the QRS complexes (Figure 10-28). Rapid inversion of the T wave typically occurs during successful reperfusion of autely ischemic myocardium. However, the T wave tends to return to its normal direction during the phase of recovery from the acute event. Normally, an angle of less than 45 degrees is present between the directions of the QRS complexes and the T waves in the frontal plane, and an angle of less than 60 degrees is present in the transverse plane. When the angles exceed these limits, in the absence of other abnormal conditions such as ventricular hypertrophy or bundle branch block, the presence of myocardial ischemia should be considered. The location of the ECG leads demonstrating these inverted T waves may be indicative of the specific location of the ischemic area within the LV myocardium. The lead groups that typically localize

the ischemia in the distributions of the three major coronary arteries are indicated in Figure 10-29.

T-wave changes are not as specific as are the ST-segment changes discussed in the following section for establishing the diagnosis of myocardial ischemia caused by increased demand. Inversion from the direction of the QRS commonly occurs as a normal variant or with other cardiac or noncardiac conditions. T-wave inversion is also not a sensitive sign of LV ischemia. The typical ST-segment changes of SEI occurs in the absence of T-wave inversion during periods of increased metabolic demand (Figure 10-30).[43]

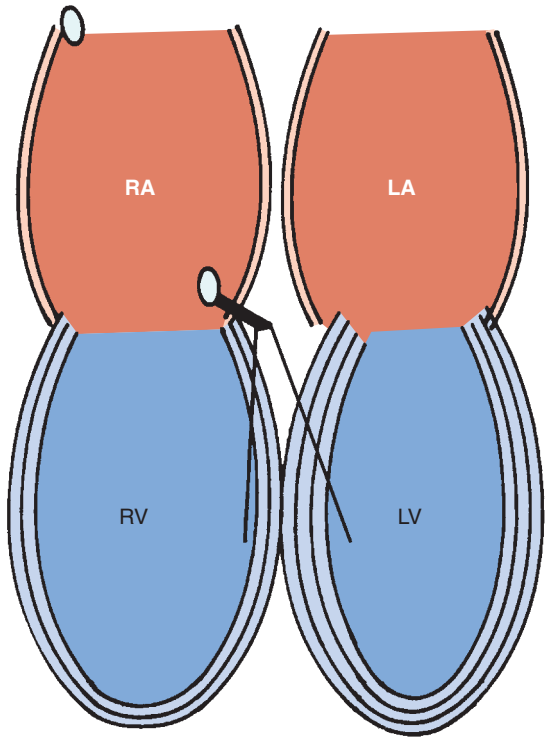


FIGURE 10-27 Schematic comparison of the relative thicknesses of the myocardium in the four cardiac chambers. The *ovals* indicate the locations of the sinoatrial and atrioventricular nodes; the His bundle (*thick short line*) and right and left bundle branches (*thin longer lines*) descend from the AV node into the interventricular septum. *LA*, Left atrium; *LV*, left ventricle; *RA*, right atrium; *RV*, right ventricle. *(Modified from Wagner GS, Waugh RA, Ramo BW:* Cardiac arrhythmias, *New York, 1983, Churchill Livingstone, p 2.)*

Like ST-segment depression, T-wave inversion usually resolves when the increased LV workload is removed. Unlike ST-segment depression, however, T-wave inversion may remain present for a prolonged period following the acute phase of MI. This chronic T-wave inversion should not be considered evidence of persistent ischemia. It represents an alteration in electrical recovery secondary to the infarction-induced changes in electrical activation in the same manner that T-wave inversion is an expected secondary occurrence with LBBB.

Subendocardial Injury

Normally, the ST segment is located at the same level as the remainder of the ECG baseline: isoelectric with the PR and TP segments. Observation of the changes in the appearance of the ST segment of a patient with a positive exercise stress test provides the pattern of the ECG changes known as SEI.[44]

When partial obstruction of a coronary artery prevents blood flow from increasing sufficiently during a time of increased metabolic demand, a "current of injury" is produced by the electrophysiological imbalance between the involved subendocardial layer and the noninvolved mid- and epicardial layers of the LV myocardium.[45,46] The ST-segment changes typically disappear when the myocardial demands are returned to baseline by reducing the metabolic demand, indicating that the myocardial cells have been only reversibly "ischemic." Such changes may occur during psychologically induced as well as physiologically induced episodes of increased myocardial metabolic demand.

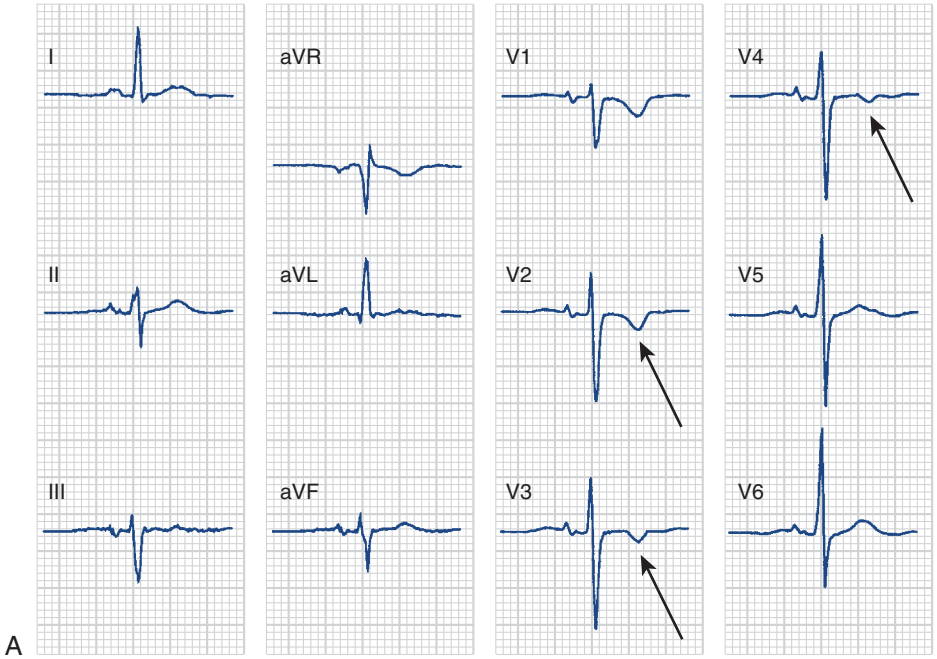
A combination of two diagnostic criteria has been typically required for the diagnosis of SEI:

1. At least 0.10-mV depression at the J-point of the ST segment
2. Either a horizontal or downward sloping of the ST segment toward the T wave

Lesser deviation of the ST segments could be caused by SEI or could be a variation of normal. Even the "diagnostic" ST-segment changes could be caused by an extreme variation of normal. When these ECG changes appear, they should be considered in the context of other manifestations of ischemia such as precordial pain, decreased blood pressure, or cardiac arrhythmias.[45,47]

ST–J-point deviation followed by an up-sloping ST segment may also be abnormal. A 0.1- to 0.2-mV depression of the J-point followed by an up-sloping ST segment that remains 0.1 mV depressed for 0.08 seconds, or a 0.2-mV depression of the J-point followed by an up-sloping ST segment that remains 0.2 mV depressed for 0.08 seconds may also be considered diagnostic of SEI.[48,49]

FIGURE 10-28 Schematic single ventricular cycles from an electrocardiogram lead oriented to the cardiac long axis are shown for normal (**A**), ischemic (**B**), and injury (**C**) conditions.



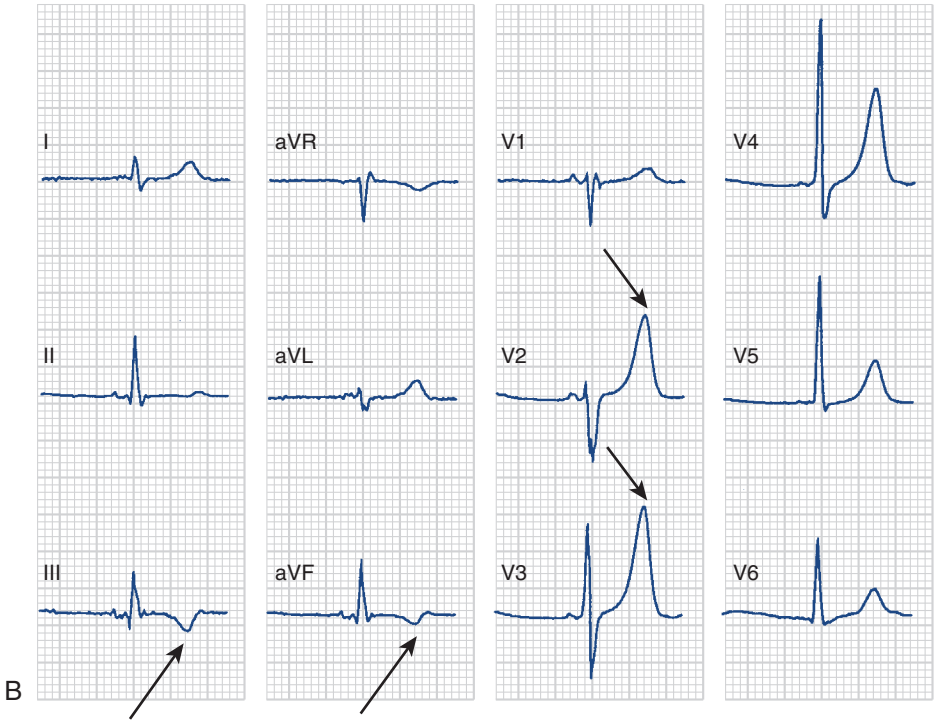


FIGURE 10-29 Twelve-lead electrocardiograms from a 63-year-old woman presenting to the emergency department with 2 hours of substernal chest pain (**A**), a 78-year-old man with an occluded right coronary artery vein graft 3 days after coronary bypass surgery (**B**), and an 83-year-old man with a previous anterior infarct and recurrent resting chest pain after abdominal surgery (**C**). Coronary angiography revealed high-grade stenosis of the proximal left circumflex artery. *Arrows* in **A**, **B**, and **C** indicate abnormally directed T waves.

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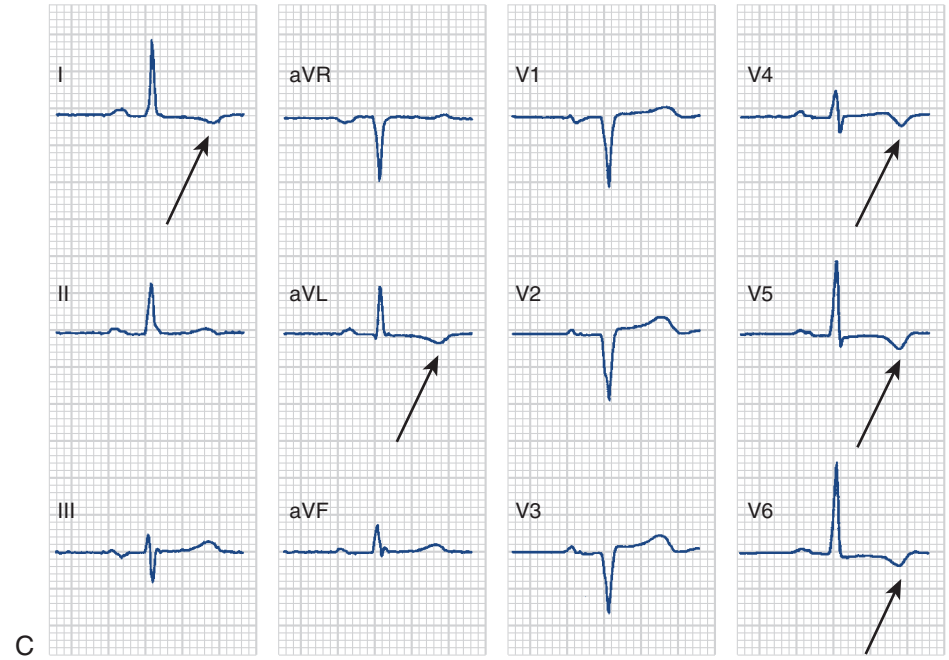

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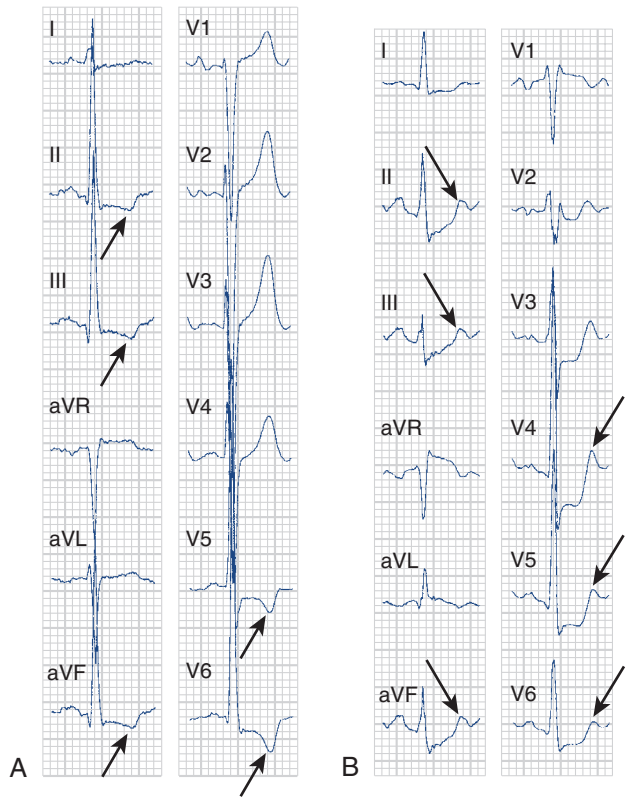


FIGURE 10-30 Resting and exercise 12-lead electrocardiograms from a 47-year-old man (**A**) and a 72-year-old man with sustained chest pain during exercise stress testing (**B**). *Arrows* indicate negative T waves in **A** and positive T waves in **B** after the diagnostically depressed ST segments.

The positive poles of most of the standard limb and precordial ECG leads are directed toward the left ventricle. In deviating away from the left ventricle, the ST-segment changes of SEI appear negative or depressed in groups of either leftward (I, aVL, or V4 to V6) or inferiorly (II, III, aVF) oriented leads. The location of the ECG leads with the ST segment depression is not indicative of the location of the ischemic area of the LV subendocardium.

The appearance of the ST segments with LV SEI is similar to that occurring with severe LV hypertrophy, referred to as *strain*. The ST-segment depression of LV strain appears chronically as one of the manifestations of LV hypertrophy. Also, marked SEI may occur acutely with sub-total occlusion of the main left coronary artery. This is typically accompanied by signs of LV failure because complete occlusion of this major LV blood supply usually causes sudden death.

The maximal ST-segment depression of SEI is almost never seen in leads V1 to V3. (When the maximal ST-segment depression is located in these leads, the cause is either RV strain or posterior EI.) The ST-segment depression of LV SEI usually resolves immediately following removal of the excessive cardiovascular stress. When the ST-segment depression occurs in the absence of an increased LV workload, the presence of subendocardial infarction should be considered. However, infarction is confirmed only if there is accompanying abnormal elevation of serum biochemical markers.[50]

Epicardial Injury

Just as ST-segment changes are reliable indicators of ischemia caused by increased myocardial demand, they are also reliable indicators of ischemia caused by insufficient coronary blood flow. Observation of the position of the ST segments (relative to the PR and TP segments) in a patient experiencing acute precordial pain provides clinical evidence regarding the presence or absence

of severe myocardial ischemia or developing infarction. However, many normal variations occur in the appearance of ST segments (Figure 10-31).[51-53]

It may be difficult to differentiate abnormal ST-segment changes of EI from variations of normal when the ST-segment deviation is minimal. The presence of one of the following criteria is typically required for diagnosis of EI:

1. Elevation of the origin of the ST segment at its junction (J-point) with the QRS of:
   - **a.** Greater than 0.10 mV in two or more limb leads or precordial leads V4 to V6
   - **b.** Greater than 0.20 mV in two or more precordial leads V1 to V3
2. Depression of the origin of the ST segment at the J-point of greater than 0.10 mV in two or more of precordial leads V1 to V3

The greater threshold is required for ST elevation in leads V1 to V3 because there is often a normal slight ST elevation present.

The deviated ST segments typically either are horizontal or slope toward the direction of the T waves. The sloping produces greater deviation of the ST segment as it moves farther from the J-point toward the T wave. Various positions along the ST segment are sometimes selected for measurement of ST-segment deviation, either for establishing the diagnosis of EI or for estimating its extent. The "J," "J + 0.02 seconds," and "J + 0.06 seconds" points of the ST segment have all been considered.

Because the ST-segment changes of EI deviate toward the involved area of the myocardium, they appear positive or elevated in the ECG leads with their positive poles pointing toward the lateral, inferior, or anterior aspects of the left ventricle. The ST segments appear negative or depressed in the ECG leads with their positive poles pointing away from the posterior aspect of the left ventricle.

Often, both ST-segment elevation and depression appear on different leads of a standard 12-lead ECG. Usually, the direction of the greater deviation should be considered primary and the direction of the lesser deviation considered secondary or reciprocal. However, there are exceptions to this rule. When EI involves both the inferior and the posterior aspects of the left ventricle, the ST depression in leads V1 to V3 may equal or exceed the elevation in II, III, and aVF (Figure 10-32).

EI most commonly occurs in the distal aspect of the area of the LV myocardium supplied by one of the three major coronary arteries (Figure 10-33).[54] The relationships among the coronary artery, LV quadrant, sectors of the quadrant, and diagnostic ECG leads are indicated in Table 10-2.

In about 90% of individuals, the posterior descending artery originates from the right coronary artery (RCA), and the left circumflex (LCx) artery supplies only part of a single LV quadrant. This has been termed *right coronary dominance*. In the other 10% with left coronary dominance, the posterior descending artery originates from the LCx artery, and the RCA supplies only the right ventricle.

EI may also involve the thinner-walled RV myocardium when its blood supply via the RCA becomes insufficient. RV EI is represented on the standard ECG as ST segment elevation in leads V1 and V2, with greater elevation in lead V1 than in V2 and with even greater elevation in the more rightward additional leads V3R and V4R (Figure 10-34).

The entire ST-segment elevation disappears abruptly when EI persists for only the 1 to 2 minutes that are required for

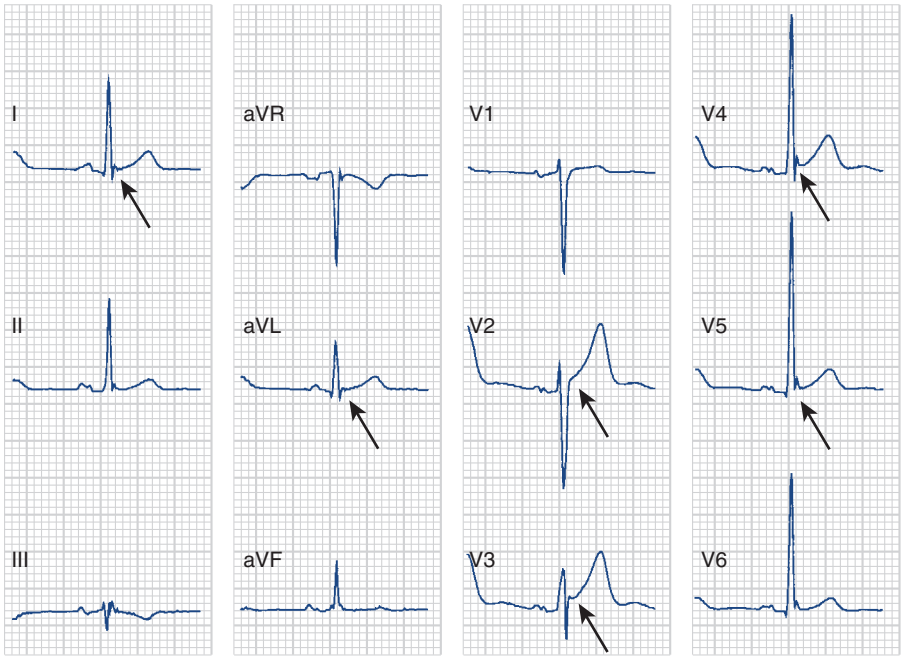


FIGURE 10-31 Twelve-lead electrocardiogram from a 34-year-old man with a strong family history of heart disease presenting for the fourth time within 1 year to an emergency department with severe chest pain. *Arrows* indicate ST-segment elevation in many leads.

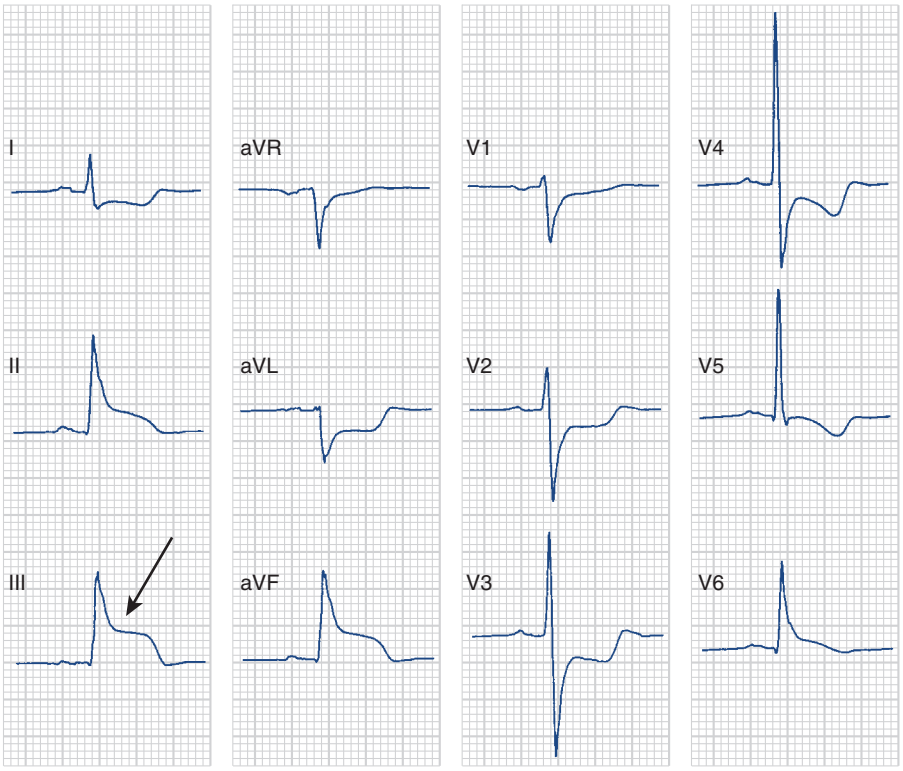


FIGURE 10-32 Twelve-lead electrocardiograms illustrating acute epicardial injury after 1 minute of balloon occlusion in the mid–right coronary artery of a 47-year-old man with symptoms of unstable angina. *Arrow* indicates the maximal ST-segment deviation directed toward the involved regions.

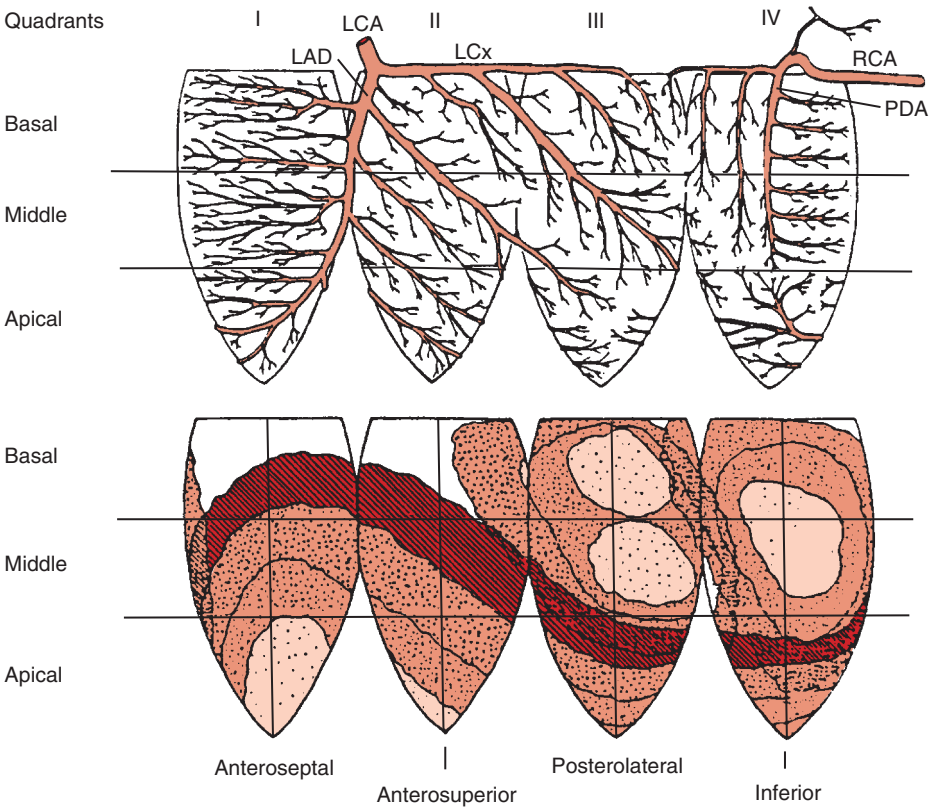


FIGURE 10-33 The 12 sectors of the left ventricular myocardium defined by the four quadrants and the three levels. The distributions of the coronary arteries (left coronary artery [*LCA*], left anterior descending [*LAD*] artery, left circumflex [*LCx*] artery, right coronary artery [*RCA*], and posterior descending [*PDA*] artery) are related to the distributions of insufficient blood supply resulting from occlusions of the respective arteries (*bottom*). The four grades of shading from light to dark indicate the size of the involved region as small, medium, large, and very large, respectively. *(From Califf RM, Mark DB, Wagner GS:* Acute coronary care in the thrombolytic era*, Chicago, 1988, Year Book, pp 20–21.)*

Table 10-2 Injury Terminology Relationships

CORONARY ARTERY	LEFT VENTRICULAR QUADRANT	SECTORS	DIAGNOSTIC LEADS	COMMON TERMS
LAD	Anteroseptal	All	V1-V3 (elevation)	Anterior
	Anterosuperior	All	I, aVL (elevation)	Lateral
	Inferior	Apical	V4-V6 (elevation)	Lateral
	Posterolateral	Apical	V4-V6 (elevation)	Lateral
Posterior descending artery	Inferior	Basal, middle	II, III, aVF (elevation)	Inferior
LCx artery	Posterolateral	Basal, middle	V1-V3 (depression)	Posterior

LAD, Left anterior descending artery; *LCx*, left circumflex artery.

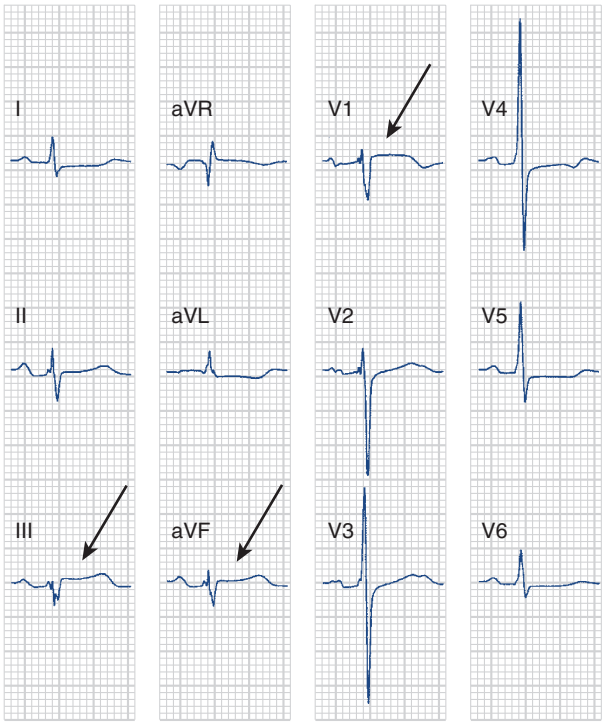


FIGURE 10-34 A 12-lead electrocardiogram after 1 minute of balloon occlusion in the proximal right coronary artery in a 65-year-old woman presenting with acute precordial pain of sudden onset. *Arrows* indicate the inferior epicardial injury appearing as ST-segment elevation in leads III and aVF and right ventricular epicardial injury appearing as ST-segment elevation in lead V1.

Table 10-3 T-Wave Amplitude Limits (mV)

LEAD	MALES AGED 40–49 YEARS	FEMALES AGED 40–49 YEARS	MALES AGED 50+ YEARS	FEMALES AGED 50+ YEARS
aVL	0.30	0.30	0.30	0.30
I	0.55	0.45	0.45	0.45
aVR	0.55	0.45	0.45	0.45
II	0.65	0.55	0.55	0.45
aVF	0.50	0.40	0.45	0.35
III	0.35	0.30	0.35	0.30
V1	0.65	0.20	0.50	0.35
V2	1.45	0.85	1.40	0.70
V3	1.35	0.85	1.35	0.85
V4	1.15	0.85	1.10	0.75
V5	0.90	0.70	0.95	0.70
V6	0.65	0.55	0.65	0.50

Presentation of upper limit T-wave amplitudes (in mV rounded to the nearest 0.05) in each lead by gender and age for normal subjects from Glasgow, Scotland. The leads are arranged in the panoramic sequence.
Modified from Macfarlane PW, Lawrie TDV: *Comprehensive electrocardiology*, vol 3, New York, 1989, Pergamon Press, pp 1446–1457.

percutaneous transluminal coronary angioplasty (PTCA). However, EI produced by coronary thrombosis typically persists throughout the minutes to hours required for clinical administration of some form of reperfusion and then resolves only following restoration of flow. The disappearance of EI may reveal the already developed QRS changes of infarction that have previously been obscured by the injury current. In some patients, multiple episodes of ST-segment elevation and resolution have been documented by continuous monitoring following the initiation of intravenous thrombolytic therapy. In the absence of successful thrombolytic therapy, eventually, the ST-segment elevation gradually resolves as the area with EI becomes infarcted.[55,56]

Sometimes the ST-segment deviation of EI is accompanied by a marked increase in T-wave amplitude produced by local hyperkalemia. These primary T-wave elevations have been termed *hyperacute T waves* and persist for only a brief period after the acute coronary thrombosis (Figure 10-35).[57] Hyperacute T waves may, therefore, be useful in timing the duration of the EI when a patient presents with acute precordial pain.

Definition of the amplitude of the T wave required to identify hyperacute changes during EI requires reference to the upper limits of T-wave amplitudes in the various ECG leads of normal subjects. Table 10-3 presents the upper limits of T-wave amplitudes in each of the 12 standard leads in both females and males in the older than 40 years age group in the Glasgow, Scotland, normal database.[58] A rough estimate of the normal upper limits of T-wave amplitude would be (1) at least 0.5 mV in the limb leads and (2) at least 1.00 mV in the precordial leads.

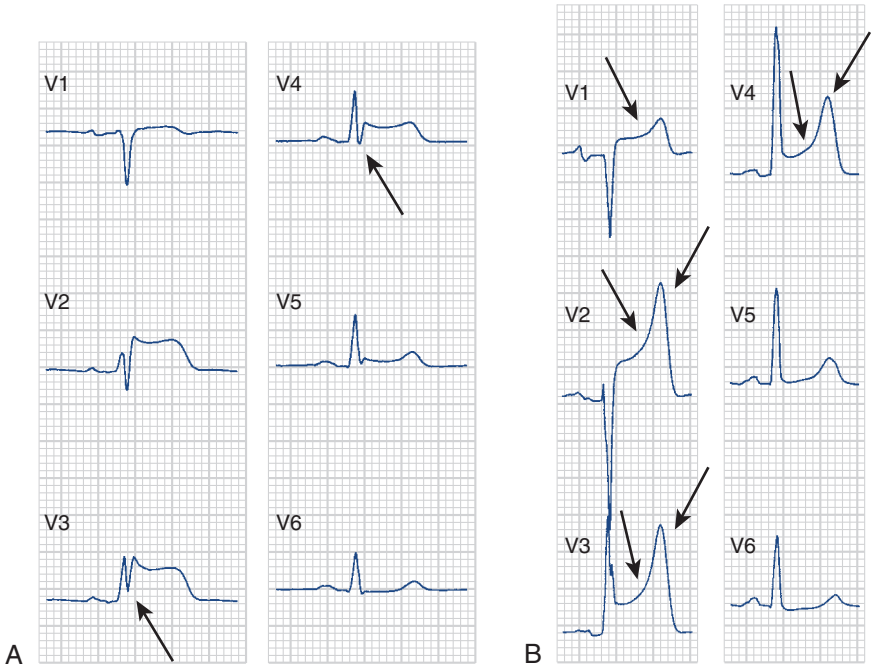


FIGURE 10-35 The six precordial leads of the electrocardiogram after 1 minute of balloon occlusion of the left anterior descending coronary artery in a 74-year-old woman with a 5-year history of exertional angina (**A**) and a 51-year-old man with an initial episode of precordial pain (**B**). *Arrows* indicate ST-segment elevation and hyperacute T waves in **A** and disappearance of the S wave from below the TP-PR segment baseline in **B**.

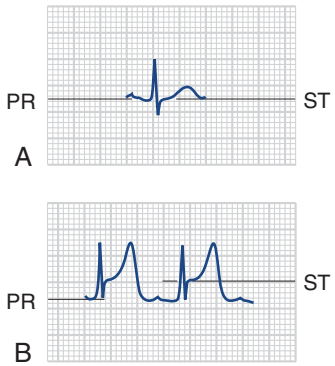


FIGURE 10-36 **A**, An electrocardiogram recording made before balloon inflation in which the PR and ST baselines are at the same level and a 0.03-mV S wave is present. **B**, During balloon occlusion, the ST segment is elevated by 0.03 mV by the epicardial injury current; the S wave also deviates upward so that it just reaches the PR segment baseline.

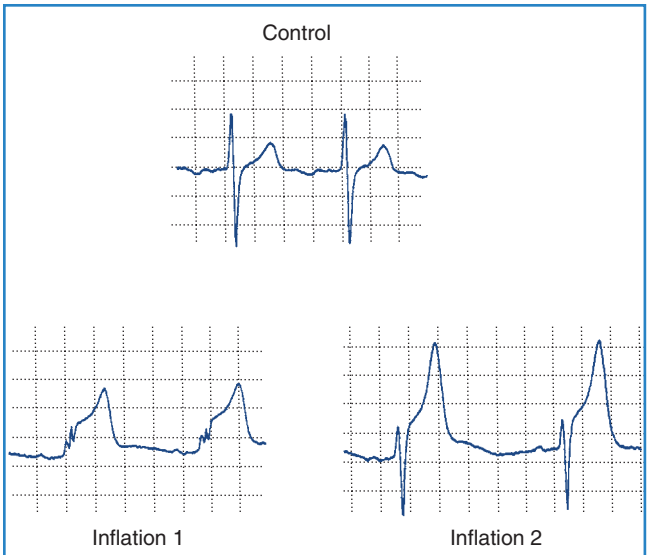


FIGURE 10-37 Recordings of two cardiac cycles in lead V2 from baseline (control) and after 2 minutes each of two different periods of balloon occlusion of the left anterior descending coronary artery. *(From Wagner NB, Sevilla DC, Drucoff MW, et al: Transient alterations of the QRS complex and the ST segment during percutaneous transluminal balloon angioplasty of the left anterior descending coronary artery,* Am J Cardiol *62:1038–1042, 1988.)*

EI begins during the QRS complex. This may result in secondary deviation of the QRS waveforms in the same direction as that of the ST segments. This distortion affects the amplitudes but not the durations of the QRS waveforms and in their later more than their earlier waveforms.[59]

The deviation of the ST segments confounds the capability of measuring the amplitudes of the QRS waveforms. As illustrated in Figure 10-36, the PR-segment baseline remains as the reference for the initial QRS waveform, but the terminal waveform maintains its relationship with the ST-segment baseline.

Primary changes may also occur in the QRS complexes immediately following the onset of EI as seen in Figure 10-37 during PTCA. The deviation of the QRS waveforms toward the area of the EI is considered primary because its increase in amplitude is greater than that of the ST segment, and its duration is also prolonged. The most likely cause of the primary QRS deviation is ischemia-induced delay in subendocardial electrical activation. The mid- and epicardial layers of the area with EI are activated late, thereby producing an unopposed positive QRS waveform. The QRS would deviate in the negative direction in leads V1 to V3 with EI in the posterolateral left ventricle.[60]

Myocardial Infarction

When insufficient coronary blood flow persists after the myocardial glycogen reserves have been depleted, the cells become irreversibly ischemic, and the process of necrosis or MI begins.[61,62] The QRS complex is the most useful aspect of the ECG for the evaluation of the presence, location, and extent of MI. As indicated previously, the QRS waveforms deviate toward the area of potentially reversible EI, secondarily because of the current of injury and primarily because of myocardial activation delay. The process of infarction begins in the most severely ischemic subendocardial layer. QRS deviation toward the ischemic area is replaced by QRS deviation away from the infarcted area.[63] Since no electrical activation of the infarcted myocardium occurs, the summation of activation spread is away from the involved area.

The rapid appearance of the abnormalities of the QRS complex produced by an anterior infarction during continuous ischemia monitoring is illustrated in Figure 10-38. Myocardial reperfusion is accompanied by rapid resolution of the EI and a shift of the QRS waveforms away from the anterior LV wall. Though it may appear that the therapy has caused the infarction, it is much more likely that the infarction had already occurred before the initiation of the therapy, but its detection on the ECG was probably obscured by the secondary QRS changes of the EI.

As previously mentioned, EI involving the thin RV free wall may be manifested on the ECG by ST-segment deviation, but RV infarction is not manifested by significant alteration of the QRS complex. RV free wall activation is insignificant in comparison with activation of the thicker interventricular septum and LV free wall.

MI evolves from EI in the distal aspects of the areas of LV myocardium supplied by one of the three major coronary arteries (see Figure 10-33 and Table 10-2).[64] The basal and middle sectors of the posterolateral quadrant of the left ventricle are located away from the positive poles of all 12 of the standard ECG leads. Therefore, posterior infarction is indicated by a positive rather than negative deviation of the QRS complex. Additional leads on the posterolateral thorax would be required to record the ST-segment elevation caused by EI and the negative QRS deviation caused by MI in this area.[65]

The initial portion of the QRS complex deviates most prominently away from the area of infarction and is represented on the ECG by prolonged Q-wave duration. The initial QRS waveform may normally be negative (a <30-ms Q wave) in all leads except V1 to V3. The presence of any Q wave is considered abnormal in only these 3 of the 12 standard leads. Table 10-1 indicates the upper limits of normal of the Q-wave duration in the various ECG leads.[66] Instead of amplitude, duration of the Q wave should be used in the definition of abnormality because the amplitudes of the individual QRS waveforms vary with the overall QRS amplitude. Q-wave amplitudes may be considered abnormal only in relation to R-wave amplitudes (discussed later).

Many cardiac conditions other than MI are capable of producing abnormal initial QRS waveforms. Ventricular hypertrophy, intraventricular conduction abnormalities, and ventricular preexcitation commonly cause prolongation of Q-wave duration. The term *Q wave* as used here also refers to the Q-wave equivalent of abnormal R waves in leads V1 and V2. Therefore, the following steps should be considered in the evaluation of Q waves regarding the presence of MI:

1. Are abnormal Q waves present in any lead?
2. Are criteria present for other cardiac conditions that are capable of producing abnormal Q waves?
3. Does the extent of Q-wave abnormality exceed that which could have been produced by that other cardiac condition?

In the absence of abnormal Q waves, the deviation of the QRS complex away from the area of the MI may be represented by diminished R waves. Table 10-4 indicates the leads in which R waves of less than a certain amplitude or duration may be indicative of MI.[67]

An infarct produced by insufficient blood flow via the LAD might be limited to the anteroseptal quadrant (see Figure 10-34). It might also extend into the anterosuperior quadrant or into the apical sectors of other quadrants commonly referred to as *anterior, anterolateral,* or *anteroapical infarction,* respectively.

When the RCA is dominant, its sudden complete obstruction typically produces an inferior infarction in the basal and middle sectors of the inferior quadrant. Also, with this anatomy, the typical distribution of the LCx artery is limited to the LV free wall between the distributions of the anterior and posterior descending arteries. Sudden complete occlusion produces only a posterior

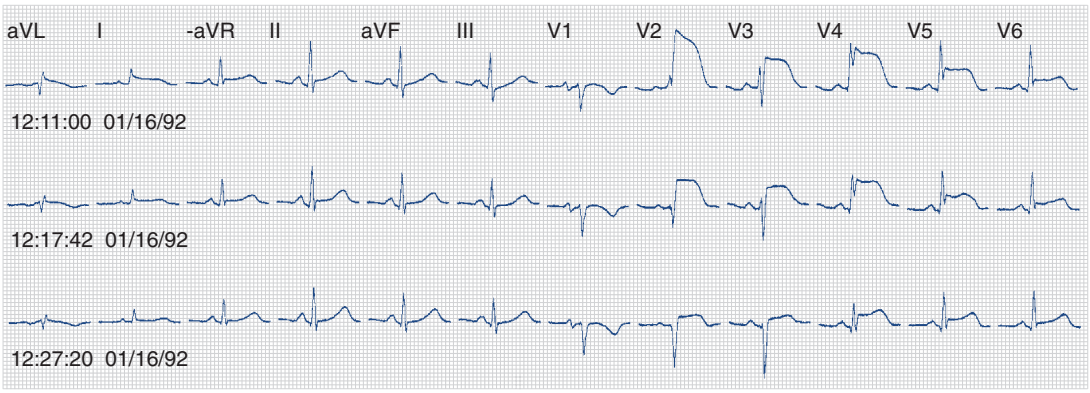


FIGURE 10-38 Continuous electrocardiogram monitoring during the first 27 minutes of intravenous thrombolytic therapy (begun at 12:00:00) in a 69-year-old man with acute thrombotic occlusion of the left anterior descending coronary artery. The 12 standard leads of the electrocardiogram are presented in the panoramic format after 11, 17, and 27 minutes of therapy.

infarction, as illustrated by QRS deviation away from that region in Figure 10-39.

When the left coronary artery is dominant, a sudden complete obstruction of the RCA can only produce infarction in the right ventricle, which would not likely produce changes in the QRS complex. The LCx artery then supplies the middle and basal sectors of both the posterolateral and inferior quadrants, and its obstruction can produce an inferoposterior infarction. This same combination of LV locations can be involved when RCA dominance is present and one of its branches extends into the typical LCx distribution. The ECG, therefore, indicates the region infarcted but not whether the RCA or LCx artery is the "culprit artery."

Table 10-4 R Wave Lower Limits

LIMB LEADS		PRECORDIAL LEADS	
LEAD	**CRITERIA FOR ABNORMAL**	**LEAD**	**CRITERIA FOR ABNORMAL**
I	R amp ≤ 0.20 mV	V1	None
II	None	V2	R dur ≤0.01 second or amp ≤0.10 mV
III	None	V3	R dur ≤0.02 second or amp ≤0.20 mV
aVR	None	V4	R amp ≤0.70 mV or ≤ Q amp
aVL	R amp ≤ Q amp	V5	R amp ≤0.70 mV or ≤2 × Q amp
aVF	R amp ≤ 2 × Q amp	V6	R amp ≤0.60 mV or ≤3 × Q amp

amp, Amplitude; *dur,* duration.

Variations occur among individuals with regard to the areas of LV myocardium supplied by the three major coronary arteries. These variations may occur either congenitally or because atherosclerotic obstruction in one artery results in collateral blood supply from another artery. For example, the posterior descending artery may extend its supply to include the apical sector of the inferior quadrant. In this instance, its sudden complete obstruction could result in QRS deviation away from leads V4 to V6 in addition to leads II, III, and aVF, causing an inferoapical infarction. Similarly, the LCx artery could supply the apical sector of the posterolateral quadrant, causing a posteroapical infarction. A marginal branch of the LCx artery may supply a portion of the anterosuperior quadrant and be responsible for a posterolateral infarction.

The posterior aspect of the apex may be involved when either a dominant RCA or the LCx artery is acutely obstructed, and inferior, posterior, and apical locations are apparent on the ECG (Figure 10-40).

Estimating Infarct Size

An individual patient may have single infarcts varying in size in the distributions of any of the three major coronary arteries or may have multiple infarcts. Selvester and coworkers developed a method for estimating the total percentage of the left ventricle infarcted using a weighted scoring system.[68] Computerized simulation of the sequence of electrical activation of the normal human left ventricle formed the basis for the 31-point scoring system, each point accounting for 3% of the left ventricle.[69] The Selvester QRS scoring system includes 50 criteria from 10 of the 12 standard leads with weights ranging from 1 to 3 points per criteria (Figure 10-41). Criteria have been established for both anterior and posterior infarct locations in precordial leads V1 and V2. In addition to the Q-wave and decreased R-wave criteria typically

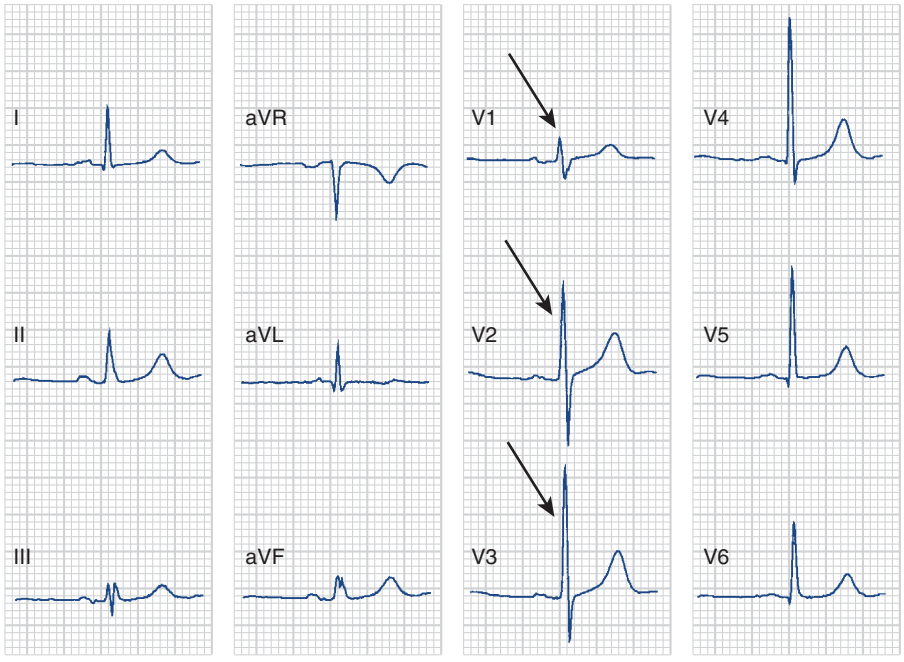


FIGURE 10-39 A 12-lead electrocardiogram from a 70-year-old man 1 year after an acute posterior wall myocardial infarction. Coronary angiography showed complete occlusion of a nondominant left circumflex coronary artery (the right coronary artery supplied the posterior descending artery). *Arrows* indicate the increased R waves in leads V1 to V3.

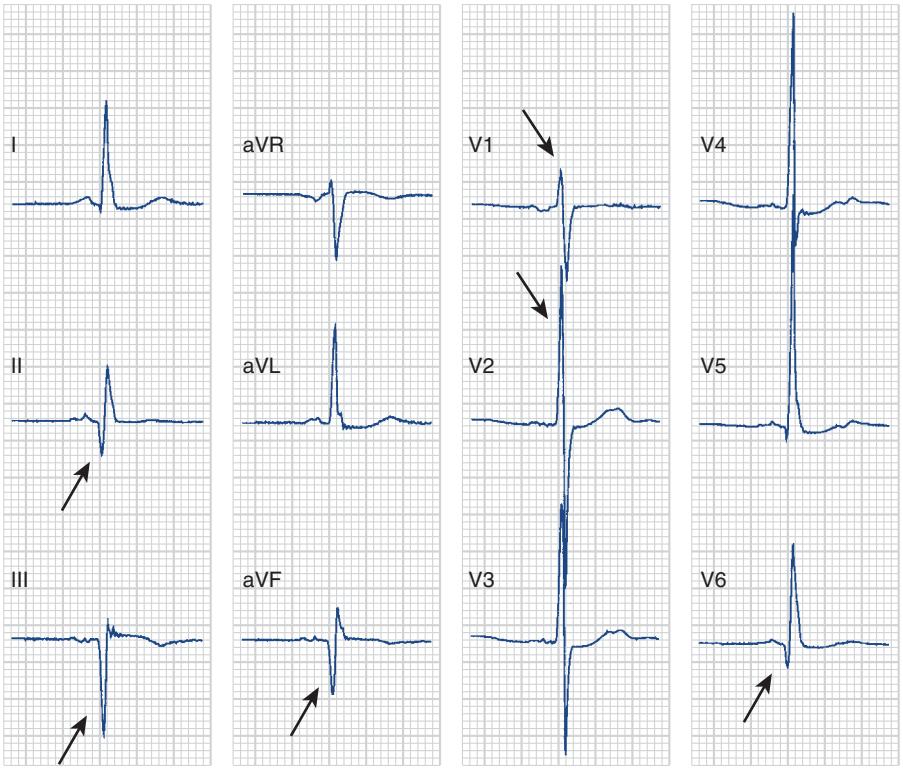


FIGURE 10-40 Serial 12-lead electrocardiograms from a previous routine examination. *Arrows* indicate abnormal initial QRS forces due to myocardial infarction.

Complete 50-Criteria, 31-Point QRS Scoring System

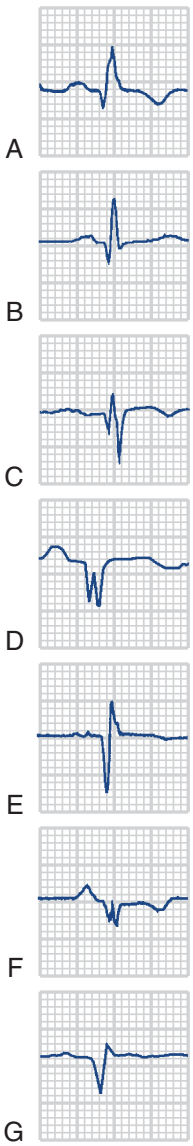
Lead	Maximum Lead Points	Criteria	Points
I	(2)	Q ≥ 30 ms	(1)
		R/Q ≤ 1	(1)
		R ≤ 0.2 mV	(1)
II	(2)	Q ≥ 40 ms	(2)
		Q ≥ 30 ms	(1)
aVL	(2)	Q ≥ 30 ms	(1)
		R/Q ≤ 1	(1)
aVF	(5)	Q ≥ 50 ms	(3)
		Q ≥ 40 ms	(2)
		Q ≥ 30 ms	(1)
		R/Q ≤ 1	(2)
		R/Q ≤ 2	(1)

V_1			
Anterior	(1)	Any Q	(1)
Posterior	(4)	R/S ≥ 1	(1)
		R ≥ 50 ms	(2)
		R ≥ 1.0 ms	(2)
		R ≥ 40 ms	(1)
		R ≥ 0.6 mV	(1)
		Q and S ≤ 0.3 mV	(1)

V_2			
Anterior	(1)	Any Q	(1)
		R ≤ 10 ms	(1)
		R ≤ 0.1 mV	(1)
		R ≤ RV_1 mV	(1)
Posterior	(4)	R/S ≥ 1.5	(1)
		R ≥ 60 ms	(2)
		R ≥ 2.0 mV	(2)
		R ≥ 50 ms	(1)
		R ≥ 1.5 mV	(1)
		Q and S ≤ 0.4 mV	(1)

V_3	(1)	Any Q	(1)
		R ≤ 20 ms	(1)
		R ≤ 0.2 mV	(1)
V_4	(3)	Q ≥ 20 ms	(1)
		R/S ≤ 0.5	(2)
		R/Q ≤ 0.5	(2)
		R/S ≤ 1	(1)
		R/Q ≤ 1	(1)
		R ≤ 0.7 mV	(1)
V_5	(3)	Q ≥ 30 ms	(1)
		R/S ≤ 1	(2)
		R/Q ≤ 1	(2)
		R/S ≤ 2	(1)
		R/Q ≤ 2	(1)
		R ≤ 0.7 mV	(1)
V_6	(3)	Q ≥ 30 ms	(1)
		R/S ≤ 1	(2)
		R/Q ≤ 1	(2)
		R/S ≤ 3	(1)
		R/Q ≤ 3	(1)
		R ≤ 0.6 mV	(1)

FIGURE 10-41 The maximal number of points that can be awarded for each lead is shown in parentheses following each lead name (or left ventricular region within a lead for leads V1 and V2). The number of points awarded for each criterion is indicated in parentheses after each criterion name. The QRS criteria from 10 of the 12 standard electrocardiogram leads are indicated. Only one criterion can be selected from each group of criteria within a bracket. All criteria involving R/Q or R/S ratios consider the relative amplitudes of these waves. *(Modified from Selvester RH, Wagner GS, Hindman NB: The Selvester QRS scoring system for estimating myocardial infarct size. The development and application of the system,* Arch Intern Med *145:1877–1881, 1985. Copyright 1985 American Medical Association.)*



	LEAD aVF	Q DURATION	R/Q RATIO	TOTAL POINTS
A		0.03 sec (1)		1
B		0.03 sec (1)	≤2:1 (1)	2
C		0.03 sec (1)	≤1:1 (2)	3
D		0.03 sec (1)	≤1:1 (2)	3
E		0.04 sec (2)	≤1:1 (2)	4
F		0.04 sec (2)	≤1:1 (2)	4
G		≥0.05 sec (3)	≤1:1 (2)	5

FIGURE 10-42 *A* through *G*, Variations in the appearance of the QRS complex in lead aVF representing the changes of inferior infarction. The numbers of QRS points awarded for the Q-wave duration and the R/Q amplitude ratio criteria met in the various electrocardiograms given as examples are indicated in parentheses. The total number of QRS points awarded for lead aVF are indicated for each example in the final column. *(Modified from Wagner GS, Freye CJ, Palmeri ST, et al: Evaluation of a QRS scoring system for estimating myocardial infarct size. I. Specificity and observer agreement,* Circulation *65:342–347, 1982.)*

used for the diagnosis and localization of infarcts, this system for size estimation also contains criteria relating to the S wave.[67]

In the Selvester scoring system, a very important consideration is the Q-wave duration. This measurement is easy when the QRS complex has discrete Q, R, and S waves.[67] Figure 10-42 presents sequentially smaller positive deflections located between the initial abnormal negative deflection (Q wave) and the terminal normal negative deflection (S wave). The true Q-wave duration should be measured along the ECG baseline from the onset of the initial negative reflection to either the onset of the positive deflection or to the point directly above the peak of the notch in the negative deflection. Satisfaction of only a single Selvester scoring criterion may represent either a normal variant or an extremely small infarct. This system may be confounded by two infarcts located in opposite sectors of the left ventricle. The opposing effects on the summation of the electrical forces may cancel each other, producing falsely negative ECG changes. For example, the coexistence of both anterior and posterior infarcts creates the potential for underestimation of the total percentage of the left ventricle infarcted.

The ST-segment changes that are prominent during EI typically disappear when the ischemic myocardium either infarcts or regains sufficient blood supply. Their time course of resolution is accelerated by reperfusion via the culprit artery. When re-elevation of the ST segments is observed, further EI or a disturbance in the pericardium is suggested. EI is typically limited to a particular area of the left ventricle. When the ST-segment elevation occurs in leads representing multiple LV areas, acute bleeding into the pericardium should be considered.[70] This may be the first indication that the infarct has caused a myocardial rupture with leakage of blood into the pericardial sac. If this process remains undetected, cardiac arrest may result from pericardial tamponade, in which myocardial relaxation is restricted by the blood in the enclosed pericardial space.

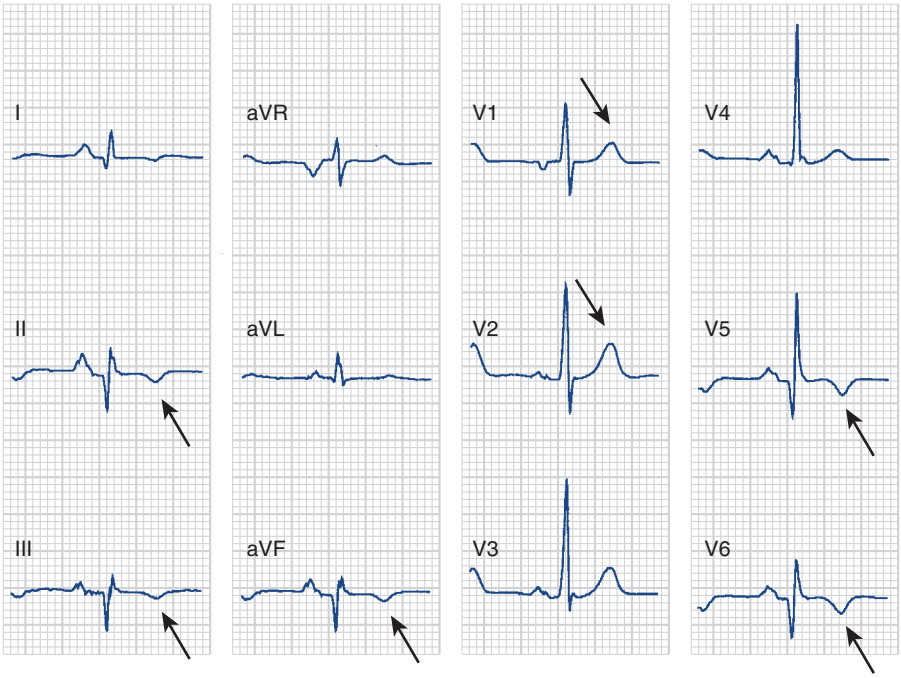


FIGURE 10-43 A 12-lead electrocardiogram from a 53-year-old man 5 days after an inferoposterior-lateral infarction. *Arrows* indicate negative T waves in leads with abnormal Q waves but positive T waves in leads with abnormal R waves.

In some patients, the ST-segment elevation does not completely resolve during the acute phase of the MI. This more commonly occurs with anterior infarcts than with those in other locations. This lack of ST-segment resolution has been associated with the thinning of the LV wall caused by infarct expansion.[71,72] The extreme manifestation of infarct expansion is the formation of a ventricular aneurysm. The incidence of such extreme infarct expansion is reduced by successful thrombolytic therapy.

The movement of the T waves toward the area of the EI, like that of the ST segments, resolves as the ischemic myocardium either recovers or infarcts. Unlike the ST segments, however, the T waves do not typically return to their normal positions as the process of infarction evolves. The T waves move past the isoelectric position until they are directed away from the area of infarction.[73] They assume an appearance identical to that of "ischemic T waves," even though no ongoing myocardial ischemia is present. Typically, the terminal portion of the T wave is the first to become inverted, followed by the middle and initial portions.

Similarly, when the posterolateral quadrant of the LV is involved, the T waves eventually become markedly positive. Figure 10-43 illustrates the tall positive T waves in leads V1 and V2 that accompany the negative T waves in other leads during the chronic phase of an inferoposterior-apical infarction.

Future Roles of the Electrocardiogram

Much of the practical information provided by the careful quantitative interpretation of the standard 12-lead ECG was unknown 5 years ago. As this diagnostic method enters its second century, many areas for future elucidation still remain. Some examples are:

- How can ECG indicators of timing of the acute infarction process add to historical timing to predict myocardial salvageability?
- How well do the changes in the various waveforms reflect the size of the acutely ischemically threatened area?
- Can infarct sizing methods be improved to more accurately quantify multiple infarcts?

As large multicenter clinical trials provide ECG data and non-ECG standards for definitions of criteria, these and many other new clinical diagnostic and prognostic methods will emerge in the second century of electrocardiography.

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CHAPTER 11

Principles of Electropharmacology

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Long before actual medicines were available for arrhythmias, much had been written about the theoretical mechanisms of arrhythmias.[1,2] Today, these studies still provide a rational argument for why a certain drug with certain properties should be an effective antiarrhythmic agent. For example, as discussed in Chapter 2, re-entrant excitation involves a circulating excitatory wavefront along a certain path and has a certain conduction velocity (CV) and refractoriness (effective refractory period [ERP]); thus we have the concept that wavelength (λ) = CV × ERP. Depending on path length and the value of λ, the re-entrant circuit will have an excitable gap. Any change in λ would be expected to determine the inducibility and stability of re-entrant excitation. On the basis of this concept, antiarrhythmic drugs are known to affect properties of cardiac excitability (class I and IV drugs) and refractoriness (class III drugs). Class II drugs remain specific for blocking β-adrenergic receptors. Thus what has emerged is a classification of drugs that depends on a drug's effect on certain ionic channels or receptors of the cardiac cell sarcolemma (Vaughan Williams classification).[3] However, as a result of the Cardiac Arrhythmia Suppression Trial (CAST), which was designed to suppress premature ventricular depolarizations, some of these drugs lost favor, particularly for treatment of ventricular arrhythmias.

For arrhythmias caused by abnormal impulse generation, drug effects were determined by using multicellular cardiac preparations that exhibited a certain cellular electrical phenotype, abnormal automaticity, or triggered activity. Most tissues used in these drug screens were from normal hearts, and their effectiveness may or may not extend to tissues of diseased hearts.

Thus most drugs currently used interrupt the direct mediators of electrogenesis, cardiac ion channels, by affecting the channel pore, the channel's gating mechanism, or both. In 2001, the members of the Sicilian Gambit, while not disposing of the Vaughan Williams drug classification, emphasized the important and emerging role of new drug targets for pharmacological therapy and/or prevention (Figure 11-1).[4] These suggestions were based on the concept that most hearts that need antiarrhythmic drugs are "remodeled," which means that drugs are not working at all or not working well because the fundamental nature of the ion channel "pore" or channel gating mechanism has been altered by an underlying disease. A clear example here is the effect of flecainide in patients following myocardial infarction (CAST) and its effect on a re-entrant circuit and the remodeled sodium channels of cells surviving in the infarcted heart.[5,6]

Since then, an explosion in knowledge has occurred regarding the fundamental cell biology and biophysics of cardiac ion channels, the mediators activated, the molecular and cellular bases of remodeling of the cardiac cell in acquired heart diseases, the bases of gene-based cardiac arrhythmias, and, last but surely not the least, a wider appreciation of abnormalities of intracellular calcium (Ca^{2+}) in arrhythmogenesis. With this new knowledge, new targets for drugs and drug development are being identified.

Biology and Biophysics of Cardiac Ion Channels

From numerous detailed single-cell, voltage-clamp studies, it has become obvious that a very specific heterogeneity in ionic current properties exists, depending on whether the ion channel target is in a ventricular cell (either epicardial or endocardial), a Purkinje cell, or an atrial cell. This has led to the rational development of drugs that target atrial-specific ion channels. For example, since I_{Kur}, the ultra-rapid delayed rectifier potassium (K^+) current (encoded by the *Kv1.5* gene), is thought to occur only in atrial cells, I_{Kur} blockers have been used to convert atrial fibrillation (AF). Unlike I_{Kr} blockers, I_{Kur} blockers should delay atrial repolarization (a class III effect) without affecting ventricular repolarization. At this time, these agents remain investigational; on further study, many have been found to have a multiple-ion channel–blocking effect. An additional concern is that even *complete* I_{Kur} blockade would not lead to sufficient prolongation of atrial repolarization to terminate re-entrant excitation.

Newer antiarrhythmic class III agents have been developed for their marked reverse-use dependence (e.g., nifekalant), for selective I_{Ks} blockade (e.g., HMR1556), and for blockade of I_{to}, a major repolarizing K^+ current that is found in both atrial and ventricular cells (e.g., tedisamil). In addition, several amiodarone derivatives have been developed to produce agents with a similar ion channel–blockade profile as that of amiodarone but with fewer side effects. An example is dronedarone, an amiodarone derivative with no iodine. Like amiodarone, dronedarone blocks multiple K^+ currents to prolong ventricular action potential duration (APD).

A drug that blocks inward plateau currents would be considered an anti–class III drug in that it should shorten APD. An antianginal drug, ranolazine, is being investigated for its antiarrhythmic properties, since it strongly inhibits the late I_{Na} current with little or no effect on peak I_{Na}.[7] Thus ranolazine would shorten APD rather than reduce excitability in cardiac tissues. More interestingly, this drug, by blocking sodium (Na^+) influx into the cardiac cell, would be expected to reduce intracellular Na^+ and therefore would indirectly affect intracellular Ca^{2+} and all its sequelae (see below).

One form of re-entrant excitation is anisotropic re-entry, which was first considered in atrial samples.[8] In this type of re-entry, conduction in the longitudinal direction is faster than that in the transverse direction. Spach and his colleagues

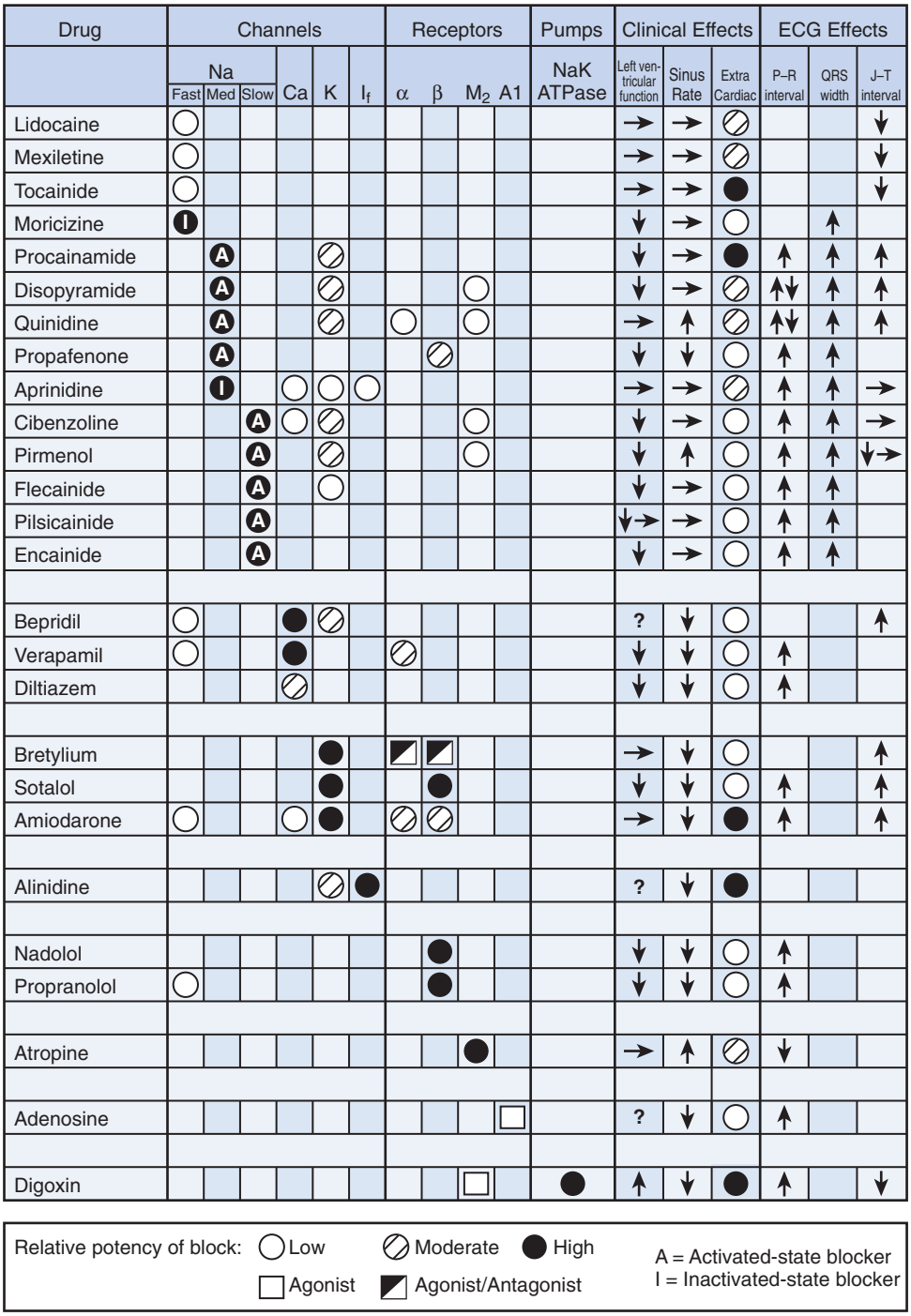

FIGURE 11-1 Drug targets for pharmacological therapy and intervention. *(From New approaches to antiarrhythmic therapy, part I: Emerging therapeutic applications of the cell biology of cardiac arrhythmias,* Circulation *104:2865–2873, 2001.)*

suggested that a component of conduction slowing in the transverse direction in these cardiac tissues was caused by a change in gap junctional conductance. Thus slowing of conduction was brought about by the uncoupling of cells at the level of the gap junctional proteins, for example, connexins 43 and 40 (Cx43 and Cx40). While experiments have clearly shown that gap junctional uncouplers (e.g., heptanol) are, in fact, arrhythmogenic, a preferential effect appears to occur on transverse conduction velocities in various animal models. Thus a corollary would be that in re-entrant circuits in highly remodeled substrates such as those affected by cell uncoupling caused by ischemia, one would expect drugs that *enhance* gap junctional conductance to be antiarrhythmic. Rotigaptide is now under study as a gap junctional coupler. In experimental arrhythmia models, this drug improves conduction and abolishes lines of block that perpetuate circuits and therefore has been deemed antiarrhythmic. This experimental

drug is thought to affect coupling by preventing dephosphorylation of Cx43, a ventricular gap junctional protein, or by maintaining phosphorylation of the protein.

Factors Contributing to Cardiac Remodeling

Altered Mediators of Electrogenesis

Cardiac remodeling is an all-encompassing term that can refer to both structural and functional changes in cardiac cells in response to a disease. It is an adaptive response of the heart that, when over-compensated, can be maladaptive.[4]

The cardiac cellular action potential changes differ in several types of disease, from chronic reduction in excitability (post-MI hearts), to APD prolongation in heart failure, to APD shortening in chronic AF. As such, the cellular ionic channel changes in different acquired diseases are varied, from a loss in Na^+ current function in cells of the epicardial border zone after MI to the enhancement of the constitutively active I_{KAch} in atrial cells in AF. In some cases, drugs have been developed to specifically target the remodeled channels of the diseased cell. The best example is the development of tertiapin-Q–type drugs that block I_{KAch} to prolong atrial APDs shortened by muscarinic activation of I_{KAch}. Tertiapin-Q is a highly selective blocker of Kir3, the ion channel subunit that underlies I_{KAch}. It can significantly prolong the duration of the AF-remodeled atrial AP, where I_{Kach} activity is upregulated.[9]

Upstream Components of Remodeling

The process of the remodeling of the substrate is very complicated, so it is no wonder that several nonconventional antiarrhythmics (so called because their targets are *not* mediators of electrogenesis) have shown considerable promise as ameliorators of remodeling. The goal of using such agents is not to inhibit the mediators of electrogenesis per se but, rather, to protect the myocardium from both structural and functional remodeling caused by the acquired disease. Mediators of remodeling now include wall stress, neurohumoral activation (autonomic nervous system [ANS], renin-angiotensin-aldosterone system [RAAS], and endothelin system), cytokines, reactive oxygen species, ischemia, and, of course, intracellular Ca^{2+} (see below). These mediators can act alone or together to affect the myocardium. Here the goals of pharmacologic therapy are to (1) reduce the effects of these agents, (2) reduce their actions to remodel ion channel proteins, and (3) reduce their effects on the myocardial structure (e.g., fibrosis). In this way, an arrhythmia, if initiated, would be self-limiting because of the more "normal" nonremodeled substrate. These drugs then affect the mediators that are upstream from the sarcolemmal ion channel protein.

Local neurohumoral activation can be in the form of enhanced angiotensin (A-II) production, marked sympathetic activation, aldosterone production, or all of these. Obviously, excessive sympathetic activation via α-adrenergic and β-adrenergic receptors causes subsequent activation of multiple intracellular phosphorylation paths, which can affect ion channel function (e.g., marked increase in pacemaker function) acutely. However, chronically, such stimulation can alter levels of transcription factors (e.g., cyclic adenosine monophosphate [cAMP] response element-binding [CREB]). Class II drugs are an obvious choice of therapy in this situation, and agents with both α-blockade and β-blockade (e.g., carvedilol) can reduce overall neurohumoral activation and thus prevent remodeling of ion channel proteins.

A-II activation and subsequent activation of angiotensin 1 (AT1) receptors occur in response to myocardial stretch, which is known to affect long-term ion channel function (e.g., I_{to} [Kv4.3] and Cx43). As a result, intracellular pathways through Gq pathways are augmented, deoxyribonucleic acid (DNA) synthesis is modulated, and cellular hypertrophy and fibrosis are enhanced. Ion channel proteins are both upregulated or downregulated and an arrhythmogenic substrate can be formed. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) obviously would protect the myocardium from such changes and may, in some cases, be antiarrhythmic. Some suggest that these agents may even reverse the ongoing remodeling process.

Activation of the RAAS system can also lead to an upregulation of aldosterone, and augmented aldosterone has been implicated in the enhanced formation of cardiac collagen and fibrosis. In some hearts, enhanced myocardial fibrosis can add to marked ion channel remodeling to produce the arrhythmic substrate. Blockers of aldosterone such as eplerenone would prevent fibrosis and thus reduce the likelihood of an arrhythmia.

Calmodulin kinase II (CaMKII) is a mediator of several processes in the heart, including excitation-contraction (EC) coupling, automaticity, gene transcription, and cellular hypertrophy. This kinase is upregulated in many acquired forms of cardiac disease and contributes to marked remodeling of the heart. Two potential mechanisms exist for CaMKII activation. In one, CaMKII activation results from elevation of the RAAS system, since pro-oxidant conditions of A-II superoxide formation increase NADPH (nicotinamide adenine dinucleotide phosphate) oxidase leading to CaMKII activation. β-Adrenergic stimulation—via its effect to augment Ca^{2+} influx—promotes Ca^{2+} or CaM binding within the CaMKII domain, thus activating the enzyme. Thus inhibitors of CaMKII would be expected to ameliorate remodeling and be antiarrhythmic.

3-Hydroxy-3 methylglutaryl coenzyme A reductase inhibitors (statins) are widely used for their cholesterol-lowering effect, but recent data suggest that they can exert antiarrhythmic effects because of cholesterol-independent effects. Statins have been shown to increase endothelial nitric oxide (NO) production by stimulating and upregulating endothelial nitric oxide synthase (eNOS) by prolonging eNOS messenger ribonucleic acid (mRNA) half-life. Thus increased NO availability induces cardioprotection, particularly in the left atrium (LA). Statins also inhibit Rac1 (Ras-related C3 botulinum toxin substrate 1), which then leads to an inhibition of NADPH oxidase activity, an important component of the oxidative stress response involved in some types of ion channel remodeling. The anti-inflammatory effects of statins have also been well established, as statins reduce the number of inflammatory cells and inhibit adhesion molecules. Thus an accumulation of these effects would prevent the occurrence of a remodeled ion channel if cytokine activation is the cause of the maladaptive change.

Gene-Based Arrhythmias

Major advances have occurred in our understanding of the genetic basis of several forms of inherited arrhythmia syndromes. With these advancements has come the development of gene-specific therapies that depend on the genes involved in the syndrome.

Cardiac sodium channel (SCN5a) mutations are involved in at least four genetic disorders: long QT syndrome type 3 (LQT3), some forms of Brugada syndrome (BrS), progressive conduction disease (CCD), and sick sinus syndrome. The last three disorders are considered to be caused by loss of function of the Na^+ channel. For LQT3 patients (a gain of function from the destabilization of Na^+ channel inactivation leading to an enhanced late I_{Na}), a rational approach to therapy has been to use long-acting Na^+ channel–blocking drugs (e.g., class I, mexiletine) to reduce Na^+ influx during the plateau. This would reduce the pathologically prolonged APD and long QT. Disease-associated genes here include *SCN5a* (the α-subunit of the cardiac Na^+ channel), *CAV3* (caveolin 3 protein), and *SCN4B* (a major accessory β-subunit essential for the proper functioning of the cardiac Na^+ channel).

For loss of function of the Na^+ channel, no specific Na^+ channel agonists would be useful in restoring excitability to the mutant channel cardiac cells. While trafficking defective mutants have been identified in Na^+ channels and are associated with BrS, they can be "rescued" using mexilitene. However, Na^+ channel–rescuing agents are not practical, since, at this time, most candidates also have Na^+ channel–blocking effects. Some have suggested that by blocking K currents (e.g., I_{to}), the altered plateau of action potentials in BrS can be overcome, restoring normal electrical function and preventing the initiation of arrhythmia in BrS patients. To this end, quinidine (class I) and tedisamil, a new agent, have been tested. Interestingly, isoproterenol has also been reported to be antiarrhythmic (see www.BrugadaDrugs.org).

Calcium channel mutations are involved in at least two genetic disorders, Timothy syndrome/LQT (a gain of function caused by the enhanced late I_{CaL}), and some forms of BrS combined with short QT syndrome (SQT; loss in function, APD shortening). Gene products involved here are *CACNA1C* (Timothy syndrome/LQT), and *CACNA1C*, and *CACANB2* (in SQT/BrS). Rational therapy would be Ca^{2+} channel blockers (class IV) for patients with Timothy syndrome/LQT and Ca^{2+}channel activators for patients with short QT/BrS.

Multiple K^+ channel mutations underlie both LQT (LQT1, LQT2, LQT5, and LQT6) and SQT syndromes (SQTS1, SQTS2, and SQTS3). LQTS variants that are linked to K^+ channel mutations are dominant-negative or trafficking defects. Despite differing biophysical mechanisms, these mutants all result in a loss in K^+ channel function at the cell membrane. Genes associated with these variants are *KCNQ1*, *KCNH2*, *KCNE1*, *KCNE2*, and *KCNJ2*. Thus loss of K^+ repolarizing currents leads to pathologic APD prolongation, which, under the appropriate sympathetic stimulation, can lead to early after-depolarizations (EADs) and torsades de pointes (TdP). On the one hand, β-blockers (class II) are useful in some forms of LQT (e.g., LQT1) since they ameliorate the effects of the sympathetic-induced triggers. On the other hand, for the second most common form of LQT, LQT2, β-blocker therapy is not always useful. Here the goal of therapy should be to counter the loss of function in I_{Kr} and thus correct the potentially malignant long APD. In this case, some have proposed that by increasing plasma K^+ concentrations (K^+ supplementation), one would enhance I_{Kr} conductance and, in so doing, counter the mutant channel loss in function. Recent experimentation has also suggested that a class of drugs could rescue mutant I_{kr} channels to restore APD values. More commonly, K^+ channel activators such as nicorandil have been proposed as an appropriate therapy.

Characterized by AF, ventricular fibrillation (VF), or both, SQT syndrome reflects the opposite of long QT syndrome in that it results from K^+ channel mutations leading to a gain in function. Three forms of this syndrome have been described. SQTS1 (gain in function of KCNH2[I_{Kr}]), SQTS2 (gain in function of KCNQ1[I_{Ks}]) and SQTS3 (gain in function of KCNJ2 [Kir2.1, major protein of I_{K1}]). Specific K^+ channel blockers would be useful to normalize the patient's QT intervals to protect from the initiation of lethal ventricular arrhythmias. Probably, hydroquinidine (class I), which blocks multiple K^+ currents, would be the most successful.

Loss in function of connexin proteins (GJAS, Cx40) and the I_f protein (HCN4) have both been linked to AF and sinus node dysfunction, respectively. At this time, no agents are used to activate the function of these channels for antiarrhythmic control.

Intracellular Calcium and Targets

Under normal conditions (see Chapter 2), during systole, Ca^{2+} is released from the sarcoplasmic reticulum (SR) through a channel known as the *ryanodine receptor* (RyR). The important property of RyR protein is its open probability that is increased by the elevation of cytoplasmic Ca^{2+} concentration $[Ca^{2+}]_i$. Thus Ca^{2+} entry into the cell via the L-type Ca^{2+} current produces a small increase of Ca^{2+}, which leads to an opening of the RyR and the release of a much greater amount of Ca^{2+} from the SR. This process is known as *calcium-induced calcium release* (CICR).

When a cell is "overloaded" with calcium, Ca^{2+} leaks out of the SR and waves of CICR propagate along the cell. It appears that Ca^{2+} waves occur when the SR Ca^{2+} content is elevated above a threshold value.[10,11] Some of the Ca^{2+} in the wave is pumped out of the cell by the electrogenic Na^+-Ca^{2+} exchange (NCX). The resulting current depolarizes the membrane and can initiate an action potential (Figure 11-2).

Drugs that decrease Na^+-K^+ pump to increase Ca^{2+} to produce a positive inotropic effect are available. However, as is known, digitalis-type compounds also increase Ca^{2+} to such an extent as to cause triggered arrhythmias, presumably by causing spontaneous SR Ca^{2+} release, which then initiates a Ca^{2+} wave. A desirable antiarrhythmic agent would be one that modulates Ca^{2+} so that Ca^{2+} does not increase Ca^{2+}-dependent currents to cause depolarization and action potentials of cells. If the spontaneous Ca^{2+} releases are targeted, then the initiators of Ca^{2+} waves, delayed after-depolarizations (DADs), and thus triggering beats could be reduced.

The arrhythmias mentioned above result when SR Ca^{2+} content is increased above the threshold level at which waves are produced. Recent work has suggested that a decrease of threshold may also produce waves. One example relates to arrhythmias seen in heart failure, where the involvement of DADs in some ventricular arrhythmias has been shown.[12,13] However, studies on heart failure have found that the SR Ca^{2+} content is actually decreased, which suggests that the threshold for Ca^{2+} release may be lower such that Ca^{2+} waves occur at a lower SR Ca^{2+} content. This may be a consequence of the increased leakiness of the RyR during diastole such that Ca^{2+} efflux is increased at a given SR Ca^{2+} content. The exact molecular mechanisms responsible for this are still being debated, but it may be associated with the increased phosphorylation of the RyR caused by protein kinase A or CaMKII.[14-16]

An example of the occurrence of DADs in the absence of increased SR Ca^{2+} content is provided by catecholaminergic polymorphic ventricular tachycardia (CPVT). This arrhythmia is seen in patients during exercise or other stress. The similarity of the

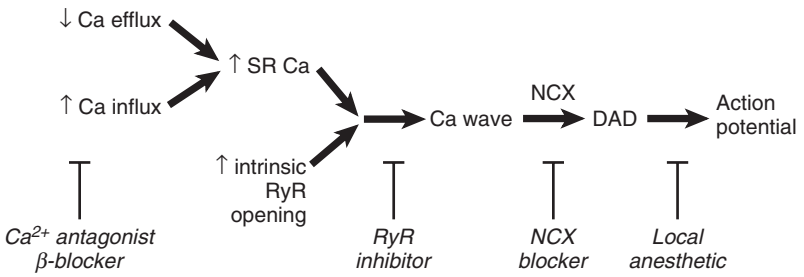

FIGURE 11-2 Schematic diagram of the genesis of delayed after-depolarizations (DADs) and possible therapeutic strategies. The upper part of the diagram shows the factors leading to a triggered action potential. Ca^{2+} waves can be produced either by an increase of sarcoplasmic reticulum (*SR*) Ca^{2+} content or an increase in the opening of the ryanodine receptor (*RyR*). The increased SR content can be produced by either increased Ca^{2+} influx or decreased Ca^{2+} efflux across the cell membrane. The Ca^{2+} wave activates the Na^+-Ca^{2+} exchange (NCX) and the resulting inward current will produce a DAD, which, if above threshold, will result in an action potential. The sites of action of various therapeutic maneuvers are shown below. Ca^{2+} antagonists will decrease Ca^{2+} entry into the cell. β-blockers will decrease phosphorylation of the L-type Ca^{2+} channel, thereby decreasing Ca^{2+} entry, and will decrease phosphorylation of phospholamban, thereby decreasing SR Ca activity and SR Ca^{2+} content. Drugs that decrease RyR opening will increase the threshold SR Ca^{2+} content required to produce a wave. Blockers of NCX will decrease the depolarizing current produced by a wave. Finally, local anesthetics will decrease the probability that a given DAD will activate an action potential.

abnormalities in the electrocardiogram (ECG) to those observed in digitalis toxicity led to the suggestion of similarities in the underlying mechanisms. Genetic studies have shown that many patients with CPVT have a mutation in RyR or the intrasarcoplasmic protein calsequestrin. The current hypothesis is that the mutated protein causes an increased leak of Ca^{2+} from the SR. Thus Ca^{2+} waves and DADs occur at a lower SR Ca^{2+} content than in controls.[17]

Potential Therapies for Delayed After-Depolarization–Related Arrhythmias

In principle, as indicated in Figure 11-2, arrhythmias can be treated in several ways: (1) by preventing DAD, (2) by preventing DAD from producing an action potential, or (3) by both. The latter can potentially be achieved by Na^+ channel blockers. A better solution, however, would be to remove the underlying DAD directly. Again, several potential approaches to this are possible. In the case of arrhythmias resulting from Ca^{2+} overload, it may be possible to remove the underlying "overload." Local anesthetics reduce intracellular Na^+ concentration as a consequence of decreasing Na^+ entry; therefore, via NCX, this will decrease the Ca^{2+} load. β-Blockers (class II) are the mainstay of therapy for patients with CPVT, but even with this therapy, the recurrence rate is about 30%. β-Blockers decrease the cellular Ca^{2+} load by decreasing phosphorylation of the L-type Ca^{2+} channel and phospholamban, the latter leading to a decrease of SERCA2 activity and thus SR Ca^{2+} content. It would also be possible to modulate Ca^{2+} by affecting the membrane transports or channels involved in Ca^{2+} homeostasis. L-type Ca^{2+} channel pore blockers obviously decrease Ca^{2+} influx and, in so doing, would be expected to eventually reduce the SR load and $[Ca^{2+}]_i$ and diminish force. Thus, Ca^{2+} channel pore blockers will affect Ca^{2+} but at the expense of force generation. Alternatively, one might target the molecular mechanism involved in the inactivation of the Ca^{2+} channel proteins or the Ca^{2+}-dependent processes known to affect the Ca^{2+} channel function (e.g., CaMKII) or the small proteins (e.g., Gem) that are known to affect Ca^{2+} channel subunit assembly.

An alternative approach would be to stop the Ca^{2+} wave from developing. One caution is required here. Although the Ca^{2+} efflux during the wave is proarrhythmogenic, it does have the useful effect of removing Ca^{2+} from the cell. Abolishing the wave may result in an increase of diastolic $[Ca^{2+}]_i$ and thus impair relaxation. Many drugs target the RyR. The local anesthetic tetracaine decreases RyR opening and thereby increases the SR threshold. In experimental studies, tetracaine was shown to abolish Ca^{2+} waves.[18] Tetracaine is not used clinically for this purpose, since at concentrations at which it affects the RyR, it also blocks sarcolemmal Na^+ channels. Very recent work has shown that flecainide suppresses CPVT arrhythmias both in humans and in a murine model.[19] This appears to be caused by a combination of a direct effect to decrease RyR opening that decreases the occurrence of Ca^{2+} waves and an effect to inhibit Na^+ channels.

Another compound is JTV519 (K201), which has been shown to decrease arrhythmias in animal models. JTV519 (K201) and its sister drug S107 appear to affect SR Ca^{2+} leak.[20-22] This drug is a 1,4 benzothiazepine and thus can also decrease the L-type Ca^{2+} current. However, in isolated SR vesicle systems, it has been shown to reduce Ca^{2+} leak by restoring the normal FKBP12.6 stabilization of the RyR complex and improving defective gating.[20,23,24]

If the calsequestrin gene defect that occurs in some patients causes an increased free $[Ca^{2+}]_{SR}$, the effect will be that the probability of opening of the RyR increases, which is positive inotropic and potentially arrhythmogenic. Restoration of the protein and its proper level by gene therapy would ameliorate this arrhythmogenic defect, but this being a useful alternative is still a distant possibility. Using a compound that would cause the existing calsequestrin to have a higher affinity for Ca^{2+} would be antiarrhythmic but may have possible negative inotropic effects.

Would modulation of the Na/Ca exchanger activity be antiarrhythmic? NCX serves to maintain Ca^{2+} homeostasis and in several acquired diseases appears to be "upregulated." Therefore reducing Na/Ca forward mode function would be expected to reduce the size of the current enhanced for any given change in Ca^{2+}. Therefore there would be a decrease in the depolarization produced by the Ca^{2+} waves of the triggering beats. However the consequences of nonselective inhibitors of this transporter are

complex. KB-R7943 is a well-characterized inhibitor but its specificity is open to question. A newer agent, SN-6, holds promise for reducing cell injury in the presence of ischemia but there are no data on its antiarrhythmic effects. There are also other agents such as SEA0400 that inhibit the exchanger.[25] A recent study using the XIP peptide in normal and failing cells in fact shows a positive inotropic effect of the peptide.[26] Indirect effects of such XIP effects would be expected to reduce Ca^{2+}-dependent activation of I_{ti} and XIP-induced SR Ca^{2+} release would shorten the APD prolonged by aberrant Ca^{2+}. Finally, at least in principle, it is clearly possible to partially inhibit NCX and thereby decrease the depolarizing current generated by a Ca^{2+} wave. The problem with this approach, however, is that it will increase $[Ca^{2+}]_i$ and lead to other undesirable consequences.

Would modulation of SR Ca^{2+} adenosine triphosphatase (ATPase; SERCA2) function be antiarrhythmic? Overexpression of SERCA would increase Ca^{2+} uptake into the SR at the expense of Ca^{2+} efflux via the Na^+-Ca^{2+} exchanger. Therefore, decreased Na^+-Ca^{2+} exchanger current would be evident immediately. In this way, on the one hand, cytosolic Ca^{2+} would (should) decrease and the SR fill, increasing the amplitude of the stimulated Ca^{2+} transient. On the other hand, the increase of SR Ca^{2+} content might make Ca^{2+} waves more likely. Gene transfer techniques to treat arrhythmias are still far from being used in practice, but some studies have offered proof-of-principle results. SERCA overexpression via gene transfer techniques has been shown to do just this, but no reports of an antiarrhythmic effect exist, although it decreases aftercontractions and also accelerates APDs.[27,28] In a more recent report, SERCA2a overexpression previous to ligation of the left anterior descending coronary artery greatly reduced episodes of ventricular tachycardia plus VF.[29] This effect was aligned with a decrease in Ca^{2+}. Pharmacologic enhancement of SERCA pump activity is possible; however, it is not known if these agents are antiarrhythmic.

Stimulation of SERCA pump activity could be *arrhythmic* if it occurred in the presence of an RyR channel mutation that leads to spontaneous Ca^{2+} release. Such releases in the setting of enhanced SR filling would increase the likelihood of triggering a Ca^{2+} wave and thus a DAD. A combination of an agent that would stimulate the pump and one that would prevent spontaneous Ca^{2+} release should therefore be effective.

Future Directions

With sophisticated molecular techniques, certain arrhythmias may come to be identified as being dependent on intracellular Ca^{2+} for either their initiation or perpetuation. Further, the aberrant Ca^{2+}-binding protein(s) will be identified, and using molecular approaches, the amino acid basis of the Ca^{2+}-binding site will be identified. With this knowledge, new drugs that would correct the Ca^{2+}-binding problem in a highly specific way and thus ameliorate the problem will certainly be developed.

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CHAPTER 12

Principles of Clinical Pharmacology

Jacques Turgeon and Paul Dorian

Most antiarrhythmic drugs are administered in a relatively fixed dose, without taking into account the many sources of variability in the effect produced by a given dose. Although the extent of this variability is difficult to quantify in individual patients and the relationship between drug dose and clinical outcome in individual patients may be impossible to predict, knowledge of pharmacokinetic and pharmacodynamic principles can be very useful for the clinician to enhance the efficacy and decrease the toxicity of antiarrhythmic drugs.

It cannot be overemphasized that standard dose recommendations for antiarrhythmic drugs apply to the hypothetical "average patient" and that marked inter-individual variability in drug concentration for a particular dose can occur. In addition, the relationship between drug dose and drug concentration is not linear over the entire dosage range usually employed, and thus a given dose increment may result in differential relative increases in drug effect at the lower end versus the upper end of the dosage range. Given the marked variability and unpredictability of drug effects, the clinician needs to be alert to the possibility of a greater than or less than expected effect for a "standard" dose of a given drug; a useful general approach is to identify, a priori, some target clinical effects before drug administration and to carefully observe patients for toxicity during the initial phases of drug treatment. If the desired effect (e.g., a given amount of refractoriness or cardiac repolarization [QT] prolongation, heart rate slowing, blood pressure reduction) is not achieved and toxicity is absent, doses may be increased until some predefined effect threshold is encountered or the maximum recommended dose of the drug is administered. Although some patients could potentially receive additional benefit from using larger than recommended doses of a given drug, increasing doses in this situation is not recommended, given the paucity of data from clinical trials regarding the safety of such an approach.

Basic Concepts in Pharmacokinetics

Pharmacokinetics is the science that describes the relationship between the dose of a drug administered and the concentrations observed in biologic fluids. Two parameters are of major importance to understand pharmacokinetics: clearance (CL) and volume of distribution (Vd). These parameters are independent but constitute major determinants of drug disposition; in other words, they will not influence each other, but both of them will dictate the time that a drug resides within the organism: the elimination half life ($t_{1/2}$). From this concept, the following equation is derived:

$$CL = \frac{Vd \times 0.693}{t_{1/2}} \quad (1)$$

Thus, the greater the clearance, the shorter is the elimination half-life. The larger the volume of distribution, the longer is the elimination half-life.

"Clearance" reflects the ability of an organ or of the entire body to get rid of ("clear") the drug in an irreversible manner. This ability to clear the drug will dictate the mean plasma concentrations observed after a given dose:

$$CL = \frac{\text{Dose}}{\text{Average concentration}} \quad (2)$$

Thus conditions that increase the clearance of a drug (such as enzyme induction) will tend to decrease the mean plasma concentrations; the elimination half-life will also become shorter. Conversely, conditions that decrease the clearance of a drug (such as enzyme inhibition) will increase the mean plasma concentrations of the drug; its elimination half-life will become longer. Finally, the total body clearance of a drug reflects the ability of each organ to clear this drug.

$$CL = CL_{kidneys} + CL_{liver} + CL_{intestine} + CL_{skin} \ldots \quad (3)$$

$$CL = CL_{renal} + CL_{metabolic} \quad (4)$$

When the metabolic or renal clearance of a drug is decreased, the total clearance becomes smaller, the plasma concentrations rise, and the elimination half-life becomes longer. For example, dofetilide and sotalol are cleared primarily by renal excretion. Patients with chronic or acute renal dysfunction will have higher serum concentrations and longer half-life than those with normal renal function. Doses need to be adjusted for renal dysfunction or if renal function changes during therapy. A higher incidence of drug-induced proarrhythmia in older adults receiving these drugs may, in part, be a consequence of failure to adjust doses on the basis of the expected decline in renal function with age, which is not directly reflected in increases in serum creatinine concentration.

The volume of distribution reflects the apparent volume of liquid in which the drug is dissolved (distributed) in the organism. The larger the volume of distribution, the lower are the observed plasma concentrations and the less available the drug for being eliminated by specific organs (the elimination half-life is then longer). For example, the distribution of antiarrhythmic drugs into body tissues will yield, for some drugs such as amiodarone, a very large volume of distribution that results in extremely long

half-lives. Conversely, digoxin is distributed in lean body tissues, and the volume of distribution is lower in patients with renal failure, which compounds the effects of decreased renal excretion of digoxin and increasing the likelihood of digoxin toxicity in these patients.

Absorption of drugs can vary with timing of dose in relation to a meal. For example, concentrations of dronedarone (a currently investigational antiarrhythmic drug) are twofold to threefold higher when taken with a meal compared with peak concentrations when taken on an empty stomach.[1]

Intersubject Variability in Drug Action

Even though it is obvious that each human being has physiological characteristics that are unique, we are always disconcerted when unexpected effects are observed in a particular patient following administration of a drug. These effects are labeled as unexpected on the basis of "usual" responses observed in the "normal" population. The so-called expected response (which, in fact, reflects the average response) is often derived from selected patients enrolled in clinical trials during drug development under well-controlled conditions. This may not always represent the real-world situation. In everyday practice, patients are treated in settings where concomitant diseases and varying physiological and pathologic conditions are encountered and multiple drugs are administered.

Several factors can modulate the response obtained following the administration of a particular drug to a particular patient at a particular time. This statement argues against the "one size fits all" concept and clearly defines the need for individualized drug therapy. To fully integrate the basic principles underlying clinical pharmacology, the prescriber needs to understand the principles of pharmacokinetics, pharmacodynamics, and drug efficacy. Figure 12-1 depicts the three major principles that define the relationship between drug dose and clinical outcome.

As discussed earlier, pharmacokinetics describes the relationship between the dose administered and the observed concentrations of a drug or its metabolites in selected biologic fluids. Concentrations of active or toxic substances at their effector or toxic sites are often of the greatest interest. Pharmacodynamics describes the relationship between the concentration of an active substance at its effector site and the physiological effects observed. Currently, most drugs are aimed at either direct or indirect modulation of a protein function. For most of them, there is a range of concentrations for which changes in protein function are linearly related to drug concentration. Finally, drug efficacy links the physiological effects observed following the administration of a drug to clinical outcome. Several major clinical trials in recent years, such as the Cardiac Arrhythmia Suppression Trial, have demonstrated that achievement of expected pharmacodynamic response is not necessarily related to a desirable clinical outcome (i.e., drug effectiveness).[2,3]

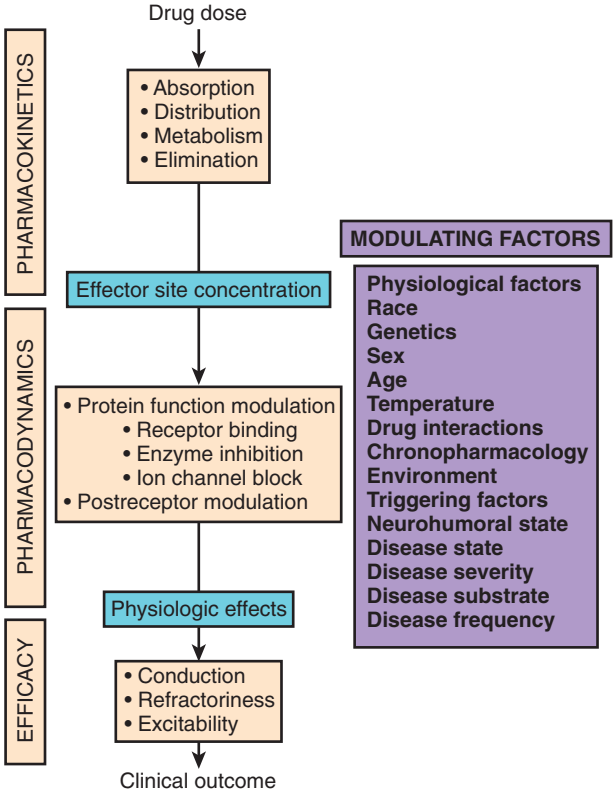

FIGURE 12-1 Principles of clinical pharmacology: factors that affect the relationship between drug dose and clinical outcome for antiarrhythmic drugs. Note that this illustration does not take into account extracardiac (e.g., autonomic) effects of drugs, which further complicate the relationship between the physiological state and the drug effect.

Drugs with a Narrow Therapeutic Index: Antiarrhythmic Agents

The notion that monitoring plasma drug concentrations could provide a method for adjusting doses to reduce inter-individual variability in response arose during the development of new antimalarial drugs during World War II. Shortly thereafter, this notion was applied to quinidine therapeutics.[4] This concept was derived from the well-recognized relationships between "normal" plasma ion concentrations or hormonal levels and a "normal" physiological state. Using such a framework, it was observed in initial trials that plasma concentrations of quinidine below 3 μg/mL were rarely associated with an antiarrhythmic response, whereas concentrations above 8 μg/mL were frequently associated with QRS widening, cinchonism, and hypotension.[5] Thus, a tentative therapeutic range of 3 to 8 μg/mL was defined.

Using the same approach, relatively well-defined therapeutic ranges were also established for lidocaine (4 to 8 μg/mL), mexiletine (500 to 1000 ng/mL), and procainamide (4 to 8 μg/mL) for patients presenting with ventricular arrhythmias.[6-9] However, as drug assays developed further and experience accumulated, it became evident that the therapeutic concentration window was very wide with these antiarrhythmic agents and that wide intersubject variability existed. Therapeutic ranges, such as the one for quinidine (2 to 5 μg/mL), had to be redefined because of impurities and metabolites interfering with early fluorometric methods.[10] Also, the overlap between effective and toxic concentrations (narrow therapeutic/toxic window) in different patients was significant, and it became almost impossible to predict, for a specific patient, plasma levels associated with efficacy or toxicity.

Subsequently, another important source of intersubject variability was identified in patients treated with the potent class Ic

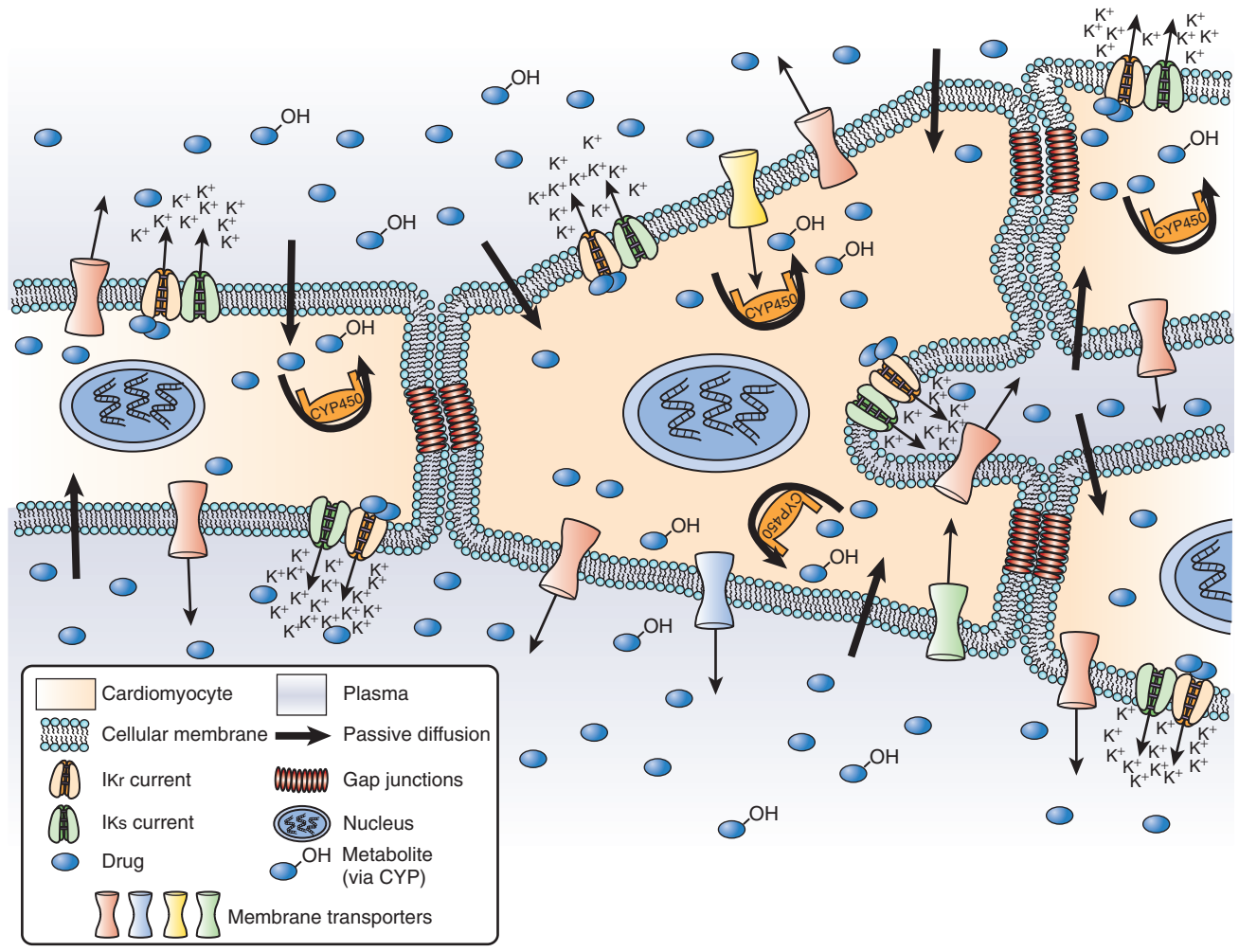

FIGURE 12-2 Illustrations of numerous factors that must be considered in the understanding of a drug's action on cardiac potassium channels. The drug must be transported inside the myocyte while facing influx and efflux transporters. Once inside, the drug may be metabolized by locally expressed CYP450 and other enzymatic systems. Competition for binding to IKr may occur as well as potentiation through combined binding to IKr and IKs.

antiarrhythmic agent encainide.[11] In a small clinical study, 10 of 11 patients with ventricular arrhythmias responded to the drug (encainide) with arrhythmia suppression and QRS widening, and the eleventh had no response. In the 10 responders, peak plasma encainide ranged from 3 to 200 ng/mL. In the single nonresponder, peak plasma encainide was the highest (300 ng/mL). Further studies demonstrated the importance of active metabolites (O-demethyl encainide [ODE] and 3 methoxy-O-demethyl encainide [MODE]) in accounting for encainide action, but a simple therapeutic range—based solely on the plasma concentrations of the parent compound or in combination with the metabolites—could not be defined.[12]

Propafenone is another class Ic antiarrhythmic agent that shows wide intersubject variability in its response and in the formation of active metabolites.[13] In addition, the drug exhibits varying electrophysiological (sodium, calcium, and potassium channel block) and pharmacologic (β-blocking) effects depending on the route of administration, the metabolism status, and the plasma concentrations of its enantiomers.[13,14] Several investigators have tried to derive combined therapeutic ranges for the metabolites—the enantiomers—and for the combinations of the parent drug plus metabolites, without success.

The situation with antiarrhythmic agents is not unique and is observed with other drugs that have a narrow therapeutic index. For example, doses and plasma concentrations of warfarin that were required to maintain the international normalized ratio (INR) within acceptable limits (2 to 3) vary widely among individuals.[15-17] There is no rationale to use the plasma concentrations of each warfarin enantiomer, rather than INR values, to adjust warfarin doses.

The notion that the plasma concentrations of a drug should be maintained within a range to guarantee drug response and prevent toxicity is appealing. The problem is that this range most likely needs to be defined for each individual. Several factors must then be considered in addition to the plasma concentrations of the parent compound. A better understanding of the clinical pharmacology of drugs with cardiac electrophysiological effects, including antiarrhythmic and non-antiarrhythmic agents, will be useful for optimal prescribing.

Pharmacogenetics

As discussed earlier, at the same dose, not every individual will have the same plasma concentrations (pharmacokinetics). As well, at the same plasma concentration of a drug, not every individual will exhibit the same physiological response (pharmacodynamics). And with the same physiological response, not every individual will have the same clinical outcome (drug efficacy). Part of this variability can be explained by genetic factors: Pharmacogenetics is the study of inter-individual variability in drug response caused by genetic factors.

Genetically Determined Pharmacokinetic Factors

Genetically determined abnormalities in the ability to biotransform drugs range from apparently benign conditions such as Gilbert's syndrome (a deficiency in glucuronyl transferase activity) to the rare but potentially fatal syndrome of pseudo-cholinesterase deficiency. This most widely studied polymorphic drug oxidation trait is a deficiency in the cytochrome P450 isozyme (CYP2D6) responsible, among others, for the biotransformation of the antihypertensive drug debrisoquine to its inactive 4-hydroxy metabolite.[18,19] Following the oral administration of a single 10-mg dose of debrisoquine, a metabolic ratio (debrisoquine/4-hydroxydebrisoquine), established from an 8-hour urinary excretion profile, can discriminate between two distinct phenotypes.[20] Individuals with a ratio greater than 12.6 are defined as poor metabolizers (PMs), whereas a value less than this antimode reflects the ability to extensively metabolize (EM) the probe drug. Family studies indicated that the deficient trait is inherited as an autosomal recessive character.[18] Regardless of geographic location, about 5% to 10% of whites are PMs. At the other end of the spectrum, 2% to 5% are known as ultra-rapid metabolizers (UM), since they exhibit very high expression levels and activity of CYP2D6.

The *CYP2D6* gene is located on the long arm of chromosome 22 (q11.2-qter).[21] Deletion or transition mutations in the gene lead to splicing errors during messenger ribonucleic acid (mRNA) processing and result in unstable proteins.[22,23] Therefore, the CYP2D6 protein is functionally absent in PMs. Deoxyribonucleic acid (DNA) assays based on allele-specific amplification with the polymerase chain reaction (PCR) allow identification of approximately 95% of all PMs.[23-25]

CYP2D6 activity can also be inhibited by drugs, including quinidine, some tricyclic antidepressants, and some selective serotonin reuptake inhibitors (SSRIs; fluoxetine and paroxetine).[26]

CYP2D6 can metabolize substances via various C-oxidations, including aromatic, alicyclic, and aliphatic hydroxylation; N- and S-oxidation; as well as O-dealkylation. For example, the metabolism of several classes of cardiovascular drugs such as β-blockers and class I antiarrhythmic drugs, as well as the metabolism of neuroleptics and antidepressants, co-segregates with the debrisoquine 4-hydroxylase polymorphism.[27] The clinical consequences of genetically determined polymorphic drug metabolism depend on the pharmacologic activity or toxicity of the parent compound compared with that of the metabolites formed by CYP2D6. Clinically important variations can be encountered in the following four situations:

1. Pharmacologic effects are mediated by the parent compound alone.
2. A metabolite is more active than the parent compound.
3. The parent compound and the metabolite have different pharmacologic effects.
4. Toxicity resides within the metabolite.

The following examples for the four situations listed above are provided only for illustrative purposes, since some drugs are no longer or rarely used. The principles underlying these examples are, nevertheless, important to consider while prescribing antiarrhythmic agents.

Pharmacologic Effects Are Mediated by the Parent Compound Alone

Mexiletine is a class Ib antiarrhythmic agent that undergoes stereoselective disposition because of an extensive metabolism; less than 10% of an administered oral dose is recovered unchanged in urine.[28,29] The major metabolites formed by carbon and nitrogen oxidation are hydroxymethylmexiletine, p-hydroxymexiletine, m-hydroxymexiletine, and N-hydroxymexiletine.[28-31] Antiarrhythmic activity resides solely in mexiletine, and all metabolites are inactive. The formation of hydroxymethylmexiletine, p-hydroxymexiletine, and m-hydroxymexiletine is genetically determined and co-segregates with polymorphic debrisoquine 4-hydroxylase (CYP2D6) activity.[32] Hence, subjects with the EM phenotype form large amounts of these metabolites. Conversely, clearance of mexiletine is twofold smaller and elimination half-life is longer in subjects with the PM phenotype. Consequently, at the same dose, mean plasma concentrations of mexiletine are higher, and drug accumulation is expected to occur in PM patients during chronic therapy.[32] This may lead to side effects such as ataxia and muscle weakness because of the increased block of sodium channels in peripheral nerves.

Combined administration of low-dose quinidine, which is a selective and potent inhibitor of CYP2D6, inhibits mexiletine metabolism through its three CYP2D6 major oxidative pathways and alters mexiletine disposition to such an extent that the pharmacokinetic parameters of the drug are no longer different between EMs and PMs.[32] Mexiletine and quinidine have been used in combination to improve antiarrhythmic efficacy and to decrease the incidence of gastrointestinal side effects.[33] Because of decreased clearance and increased elimination half-life during quinidine coadministration, EM patients undergoing combined therapy should exhibit higher trough concentrations and lesser peak-to-trough fluctuations in mexiletine plasma concentrations. Drug accumulation and long-term side effects remain a risk if dosage adjustments are not made.

Some β-blockers are metabolized by CYP2D6 (metoprolol and timolol, for example). As for mexiletine, the parent compound itself is responsible for drug action. Hence, PMs of CYP2D6 exhibit an increased ratio of peak plasma concentrations–dose compared with EMs or UMs and are very sensitive to the drugs. Conversely, UMs are resistant to β-blocking effects, and this necessitates administration of higher doses of the drugs; caution should be exercised in patients receiving high doses of β-blockers under conditions of drug-drug interactions with CYP2D6. Indeed, combined use of high-affinity CYP2D6 substrates (fluoxetine, paroxetine) or inhibitors (quinidine, terbinafine) with β-blockers in EMs or UMs is associated with increased β-blocking effects because of inhibition of CYP2D6-mediated metabolism.

Bradycardia and Raynaud syndrome are not uncommon in PMs, EMs, or UMs under these conditions.

Specific genotypes are associated with metabolic bioinactivation and, hence, the dose requirement or efficacy of certain drugs. For example, a specific genetic profile (activity of CYP2C9) is associated with higher or lower than average doses required to maintain the INR in the desired range for patients receiving warfarin therapy, and dose prediction based on a pharmacogenetic algorithm is superior to empiric dosing in rapidly achieving the desired target INR.[34]

A Metabolite Is More Active than the Parent Compound

Initial clinical trials with encainide reported a series of observations that led to important conclusions about the potential role of active metabolites in mediating drug effects. In the study of encainide effects as related to metabolite concentrations, among the 11 subjects, ODE and MODE were found in the urine of the 10 responders with respect to clinical effects but were not detected in the single nonresponder.[11] Electrophysiological studies demonstrated that ODE is approximately 10-fold more potent a sodium channel blocker than the parent drug, whereas MODE is approximately threefold more potent; the metabolites had refractoriness-prolonging properties, whereas the parent drug had only minor effects.[12,35-37]

Drug metabolism studies clearly demonstrated that CYP2D6 is involved in the sequential metabolism of encainide into ODE and into MODE.[12] Patients unable to form ODE or MODE are therefore PMs with low CYP2D6 activity. In normal volunteers with the EM phenotype, pretreatment with low-dose quinidine decreased encainide systemic clearance fivefold and decreased the partial metabolic clearance of encainide to ODE + MODE 13-fold.[38] These data are compatible with the finding of inhibition of encainide biotransformation by quinidine (inhibition of CYP2D6). Coadministration of quinidine to volunteers having EM properties blunted encainide-induced QRS prolongation.[38]

Clopidogrel, useful when combined with acetylsalicylic acid (ASA) in stroke prevention in patients with atrial fibrillation who are not eligible for warfarin therapy, is metabolized from a prodrug to active drug by cytochrome P450 2C19. Patients with loss of function-variant alleles in the gene encoding this enzyme have apparent failure of clopidogrel efficacy (as demonstrated in studies in patients with vascular disease).[26,39]

The Parent Compound and the Metabolite Have Different Pharmacologic Effects

Systematic evaluation of the dose-response and concentration-response relationships for propafenone demonstrated substantial inter-individual variability in the extent of QRS prolongation and in minimal effective plasma concentrations required for arrhythmia suppression. Follow-up studies have shown that propafenone biotransformation to 5-hydroxy propafenone is catalyzed by CYP2D6 and that 5-hydroxy propafenone exerts sodium channel blocking action in vitro similar to those of the parent drug; however, a second metabolite, N-desalkyl propafenone, is somewhat less potent.[40-42] Administration of low-dose quinidine for a short period to a group of patients receiving chronic propafenone therapy resulted in a 2.5-fold increase in plasma propafenone with a commensurate decrease in 5-hydroxy propafenone concentrations.[43]

Although propafenone and 5-hydroxy propafenone are roughly equipotent as sodium channel blockers, the parent drug is substantially more potent as a β-blocker.[14] High concentrations of propafenone that can be observed in PMs can produce clinically detectable β-blockade similar to approximately 20 mg of propranolol every 8 hours. Propafenone metabolism is known to be saturable in EMs; that is, doubling the daily dosage from 450 to 900 mg/day results in a disproportionate sixfold increase in mean plasma propafenone concentrations.[44] Thus β-blocking effects are expected in patients with the PM phenotype or in EMs receiving high dosages of the drug.[44]

Combined administration of propafenone and quinidine was also tested over a 1-year period in patients with atrial fibrillation in the Combined Administration of Quinidine and Propafenone for Atrial Fibrillation (CAQ-PAF) study.[45] The objective of the study was to demonstrate that combined administration of propafenone and quinidine would be superior to propafenone alone to prevent the recurrence of atrial fibrillation. The rationale was that increased plasma propafenone concentrations caused by combined quinidine administration would be associated with additional electrophysiological (sodium, potassium, and calcium channel blocks) and pharmacologic (β-blocking) effects that are mediated mostly by propafenone itself compared with the effects that can be observed from propafenone and its 5-hydroxy metabolite. The results demonstrated that chronic administration of quinidine was able to inhibit CYP2D6 and propafenone metabolism over a 1-year period. Recurrence of atrial fibrillation was very low in genetically determined PMs (1 of 11) and in patients with propafenone plasma levels greater than 1500 ng/mL but very high in patients with propafenone plasma concentrations lower than 1000 ng/mL. This example illustrates that combined drug administration to alter patient phenotype can be associated with improved efficacy of a drug.

Venlafaxine is another example of a drug and its metabolite having different pharmacologic effects between EMs and PMs. Venlafaxine is a new-generation drug considered a first-line agent for the treatment of depressive disorders. It strongly inhibits presynaptic reuptake of noradrenaline and serotonin and weakly inhibits the presynaptic reuptake of noradrenaline and serotonin. It also weakly inhibits dopamine reuptake.[46] Following oral administration, venlafaxine undergoes extensive first-pass metabolism.[47,48] It is metabolized to several metabolites, including O-desmethyl venlafaxine, a pharmacologically active metabolite that inhibits noradrenaline and serotonin reuptake with potencies similar to those of venlafaxine.[49] The disposition of venlafaxine is genetically determined and co-segregates with CYP2D6 activity in humans.[50] Subjects with the PM phenotype have fourfold to eightfold higher plasma concentrations of venlafaxine and a 20-fold lower capability to form the O-desmethyl metabolite. Since the O-desmethyl metabolite and venlafaxine have a similar potency for serotonin reuptake, no difference in antidepressant activity is expected between EMs and PMs of CYP2D6. However, case studies suggested that higher plasma concentrations of venlafaxine caused by low CYP2D6 activity could increase the risk of cardiovascular toxicity, since venlafaxine (and possibly not the metabolite) is a potent blocker of the cardiac sodium channel.[51] Venlafaxine has weak affinity for CYP2D6 and low propensity for causing drug interaction. However, several other CYP2D6 substrates such as the first-generation H_1 antagonist diphenhydramine, can inhibit the metabolism of venlafaxine, increase the plasma concentrations of the parent compound up to fourfold,

and potentially predispose patients to increased risk of cardiac toxicity.[52]

Toxicity Resides Within the Metabolite

A major form of toxicity-limiting chronic procainamide therapy is the drug-induced lupus syndrome.[53] The exact mechanism whereby procainamide is capable of initiating this autoimmune syndrome is unclear. In preliminary metabolic studies, incubation of procainamide with mouse hepatic microsomes produced a reactive metabolite.[54] Comparison with microsomal incubations of compounds modified at the site of the aromatic amine (N-acetyl procainamide [NAPA], p-hydroxyprocainamide, or desaminoprocainamide) led to the conclusion that oxidation of the primary aromatic amine of procainamide is involved in the production of such a reactive metabolite.[53,55] The formation of N-hydroxyprocainamide was confirmed in both rat and human hepatic microsomes, and characterization of the reaction showed that it was mediated by cytochrome P450.[56,57] Moreover, in vitro studies with genetically engineered microsomes expressing high levels of CYP2D6 exhibited the highest activity for the formation of N-hydroxyprocainamide.[58] In vitro results were corroborated by clinical observations that the formation of nitroprocainamide, the potentially stable end product of N-hydroxyprocainamide, was absent in PMs of CYP2D6 but present in subjects with high CYP2D6 activity.[50] Finally, formation of N-hydroxy procainamide was prevented in EMs during the combined administration of quinidine, a potent CYP2D6 inhibitor.[50] These results indicate that CYP2D6 becomes the key enzyme in the formation of the toxic metabolite. Subjects with functionally deficient CYP2D6 activity (PMs) may therefore be at lower risk of procainamide-induced lupus erythematosus.

Genetically Determined Pharmacodynamic Factors

Over the past decade, great advances in the field of molecular biology have made it possible to elucidate the genetic causes of the inherited forms of the long QT syndrome (LQTS).[59-61] These exciting discoveries have important implications for the understanding and therapy of this condition and have led to a better understanding of cardiac repolarization and arrhythmias in general. However, the prevalence of inherited LQTS is low. It is increasingly recognized that the concomitant use of older and recently introduced agents whether from new therapeutic classes or from those once believed to be safe (such that they were made available over the counter) put patients at increased risk for cardiac toxicity. Indeed, the list of drugs associated with the acquired form of LQTS is still growing. Genetic markers associated with an increased risk of drug-induced LQTS have also been identified.[63] That is, mutations in genes encoding for specific ion channel proteins predispose patients, who are otherwise apparently "normal," to excessive responses to drugs causing prolongation of cardiac repolarization and increased risk of torsades de pointes. In 1998, Priori et al demonstrated for the first time that a recessive variant of the Romano-Ward LQTS is present in the population.[64] A homozygous missense mutation in the pore region of KvLQT1 was found in a 9-year-old boy with normal hearing, a prolonged Q-T interval, and syncopal episodes during exercise. However, the parents of the proband were heterozygous for the mutation and had a normal Q-T interval. In 1997, Donger et al identified a missense mutation in the C-terminal domain of KvLQT1 that was not associated with significant prolongation of the Q-T interval but the administration of QT-prolonging drugs predisposed patients to torsades de pointes.[65] These recent observations suggested that mutations in cardiac potassium channel genes (and possibly other genes encoding for proteins involved in cardiac repolarization) may predispose patients with normal Q-T intervals to the acquired LQTS during treatment with drugs modulating cardiac repolarization.

Drug Interactions

Clinicians and regulatory agencies have recently been concerned about the risk of prolongation of cardiac repolarization caused by drugs other than antiarrhythmic drugs. This concern is justified, since electrocardiogram (ECG) monitoring is not routinely employed in therapy with several of these agents. Such undesirable drug actions were first reported, as proarrhythmic events following the administration of the H1 antagonist terfenadine.[66,67] The underlying mechanism of Q-T interval prolongation and torsades de pointes during terfenadine therapy was shown to be related to I_{Kr} block.[68,69] Block of I_{Kr} was also demonstrated for several other agents, such as astemizole, cisapride, pimozide, thioridazine, droperidol, domperidone, macrolide antibiotics (erythromycin, clarithromycin), imidazole anti-fungals, and sildenafil, which have all been associated with proarrhythmic events and deaths in some patients.[70-78]

Proarrhythmia with these drugs is almost always observed during combined drug administration. Therefore, some authors have concluded that concomitant treatment with I_{Kr} blockers may predispose patients to proarrhythmia. However, this hypothesis has not been proven. Competitive antagonism at the receptor level would predict that combined use of I_{Kr} blockers should lead to a decrease in drug effects rather than synergistic activity. Indeed, combined use of dofetilide and NAPA, or NAPA and diphenhydramine, is associated with a decrease in action potential prolongation when the drugs are used together compared with when the drugs are used alone. Similarly, concomitant administration of dofetilide and erythromycin was associated with a decrease in overall action potential prolongation compared with dofetilide alone.[79] Thus, proarrhythmia observed during the concomitant administration of I_{Kr} blockers in patients cannot be related solely to their electrophysiological properties on I_{Kr}.

Proarrhythmia with combined use of I_{Kr} blockers is usually observed under conditions of decreased metabolic capacity. For example, the induction of torsades de pointes during concomitant therapy with terfenadine and erythromycin or ketoconazole has been explained mainly on the basis of a specific cytochrome P450 enzyme inhibition.[80,81] Terfenadine is known to be metabolized by CYP3A4.[82] Erythromycin and imidazole (oral anti-fungals) are known inhibitors of CYP3A4; in subjects receiving the combination of terfenadine and erythromycin, erythromycin causes a decrease in the formation of the inactive acid metabolite as well as accumulation of terfenadine, which may lead to prolongation of cardiac repolarization (QT) and torsades de pointes. A similar mechanism can be described for other agents. Thus, combined administration of CYP3A4 substrates leads to the accumulation of one of these drugs; if the drug exhibits potent I_{Kr} blocking properties, proarrhythmia (torsades de pointes) caused by prolonged repolarization may be observed.

A third factor may also play a major role in drug-induced LQTS. P-glycoprotein (P-gp) is a versatile transporter that is able to pump a wide variety of xenobiotics outside a cell.[83] P-gp is

located primarily in the villous columnar epithelial cells of the small intestine and in hepatocytes, but it can also be found in cardiac myocytes.[84] CYP3As and P-gp can function together by preventing cellular entry of lipophilic toxic compounds or by decreasing intracellular concentration of drugs. P-gp and CYP3As share tremendous substrate or inhibitor specificity, or both, so that the substrates or inhibitors of CYP3A4 can also simultaneously inhibit P-gp. Under conditions of combined treatment with I_{Kr}–CYP3A4–P-gp substrates, not only plasma concentrations but also intracellular cardiac concentrations of I_{Kr} blockers can be increased. Some frequently used drugs can also inhibit P-gp, including amiodarone, verapamil, and itraconazole. These drugs can lead to digoxin toxicity by reducing digoxin excretion.

Finally, as with CYP3A4, significant inter-individual variation exists in the expression of P-gp, and genetic polymorphisms have been described for both *CYP3As* and *MDR1* (P-gp).[85,86] The authors of this chapter have found that 29% of Canadians of French origin possess two mutated alleles (exon 26) of *MDR1*, which have recently been associated with altered drug concentrations.[86] Thus, some patients may be at increased of proarrhythmia caused by mutations in these genes as well as mutations in genes associated with LQTS.

Summary

Individualized therapy is slowly emerging as a favored approach to improve efficacy and limit toxicity. This approach will be even more important in the near future as treatments derived from biotechnologies are increasingly used. In fact, these treatments may be aimed at correction of a specific gene defect (specific mutation or gene deletion) in a specific patient, and fully individualized therapy will therefore be necessary. Obtaining optimal response to conventional drug treatment may also be achieved by individualized drug therapy. This is partly explained by genetic factors or concomitant drug interactions that modulate responses to drugs between patients and within patients with time.

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CHAPTER 13

Fundamentals of Cardiac Stimulation

Rahul Mehra and Paul Belk

In the past few decades, the scientific basis and the technology of electrical stimulation of the heart has advanced significantly and spurred on the development of implantable pacemakers and defibrillators, providing clinical benefit to millions of patients. Concurrently, scientists, armed with sophisticated experimental tools and computational power, have been challenged to understand the fundamental mechanisms of electrical stimulation. Understanding the mechanism may lead to innovative applications and also increase the efficiency of electrical stimulation, thereby decreasing the size of the implantable devices and increasing their longevity.

The fundamental concepts of electrical stimulation can be divided into three aspects: (1) intracellular stimulation, (2) extracellular stimulation, and (3) the relationship between the two. Intracellular stimulation occurs when one of the electrodes is *inside* the cell, which helps clinicians understand the fundamental transmembrane changes required to excite cardiac cells. Extracellular stimulation occurs when electrodes are located *outside* the cardiac cell. It is important to understand how the extracellular stimulus sets up the necessary conditions for intracellular stimulation. Recent experimental and modeling data have provided unique insights into this complex relationship.

Intracellular Stimulation

Most of the clinically relevant aspects of cardiac stimulation are direct consequences of intracellular properties. Recordings of the electrical responses of single cardiac cells can be obtained with a fine electrical probe inside the cell and by measuring the voltage on that probe relative to the region outside the cell membrane. This probe can be used to manipulate the voltage across the membrane and record the response. The nature of electrical response in single cardiac cells has been characterized by using this technique.

A "resting" cardiac cell maintains a voltage across its membrane, which is called *transmembrane potential*. This transmembrane voltage (V_m) is normally between 70 and 90 millivolts (mV), with the inside of the cell being negative compared with the outside (extracellular) space. When a cardiac cell is electrically "triggered," it initiates an action potential. The action potential begins with a very rapid increase in V_m by nearly 100 mV (depolarization). The membrane voltage remains at a slightly positive value for around 200 ms. This is called the *plateau phase* because the voltage is relatively flat. At the end of the plateau, the cell begins a repolarization phase, returning to the resting voltage in a few tens of milliseconds. The total duration of the action potential can vary significantly, depending on the frequency of cell stimulation, with higher frequencies leading to shorter action potentials. The fundamental characteristic of an action potential is that once it is begun, that is, once it is triggered, it proceeds autonomously.

How is an action potential triggered in a single cell? The cell membrane has a variety of voltage-sensitive ion channels, that is, proteins that allow the passage of a particular species of ion but only at a critical transmembrane voltage (V_t). The action potential is initiated when V_m is reduced to the V_t, at which the sodium (Na^+) channels are activated, resulting in a large migration of Na^+ ions into the cell. This is followed by a reversible sequence of changes in the permeability to various other ions, which gives rise to an action potential.

The important parameter, therefore, is the minimum stimulation current required to bring the transmembrane voltage to this critical value (V_t). This minimum current is dependent on two properties of the membrane: capacitance and resistance. If the membrane only had resistance and no capacitance, an increase in stimulus current would change the transmembrane potential as per Ohm's law (Voltage = Current × Resistance). When enough current (called *rheobase current*) is injected for the transmembrane potential to reach the critical value, an action potential would be initiated. In such a situation, excitation of the cell would depend only on the current and not on the duration of the stimulation pulse.

The situation gets slightly more complex because of membrane capacitance. Membrane capacitance does not allow the voltage to change instantaneously across the membrane when the stimulus is applied. Charge must be deposited on the membrane to cause a change in V_m. Building this charge takes time, since charge is the product of the stimulation current and its duration. If an applied stimulation pulse fails to excite the cell, it is because the membrane did not reach V_t, so it is necessary to increase the stimulation current, stimulation duration, or both. The relationship between the strength of the stimulus and its duration necessary to initiate excitation is referred to as the *strength/duration curve*. Irrespective of the duration, the stimulus current must always be greater than the rheobase, since that is the minimum current required to reach V_t across membrane resistance. At shorter durations, more stimulus current is required. Figure 13-1, *A*, shows the effect of different stimulation currents on the potential V_m of a single cell. Initially, as the current is applied, membrane voltage rises because of membrane capacitance. In the lower trace, V_m reaches a maximum value that is below V_t; then, once the current is discontinued, it goes back to the resting membrane potential (MP). In the upper trace, however, the stimulus

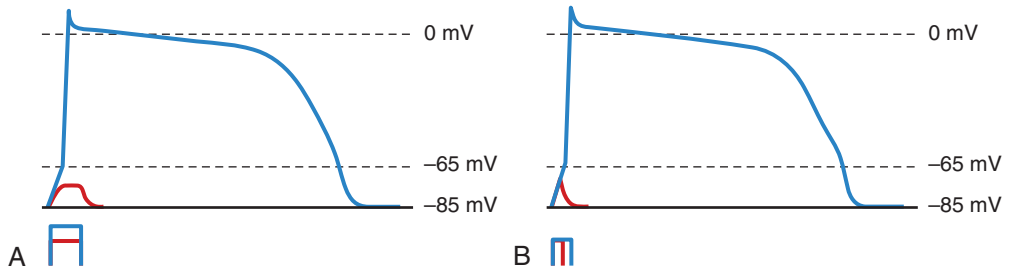

FIGURE 13-1 A, Schematic representation of the effect of increasing amplitude of a constant current stimulus on the transmembrane potential of a cardiac cell. With the smaller amplitude stimulus (*red*), the membrane potential changes from –85 to about –75 mV and recovers to –85 mV after the stimulus is turned off. With the larger stimulus (*blue*), the cell transmembrane potential reaches the critical threshold value of –65 mV, and an action potential is initiated. **B,** The effect of increasing duration of a constant current stimulus on the transmembrane potential of a cardiac cell. With the smaller duration stimulus (*red*), the membrane potential changes from –85 to about –70 mV and recovers to –85 mV after the stimulus is turned off. When the duration is increased further (*blue*), the cell transmembrane potential reaches the critical threshold value of –65 mV, and an action potential is initiated.

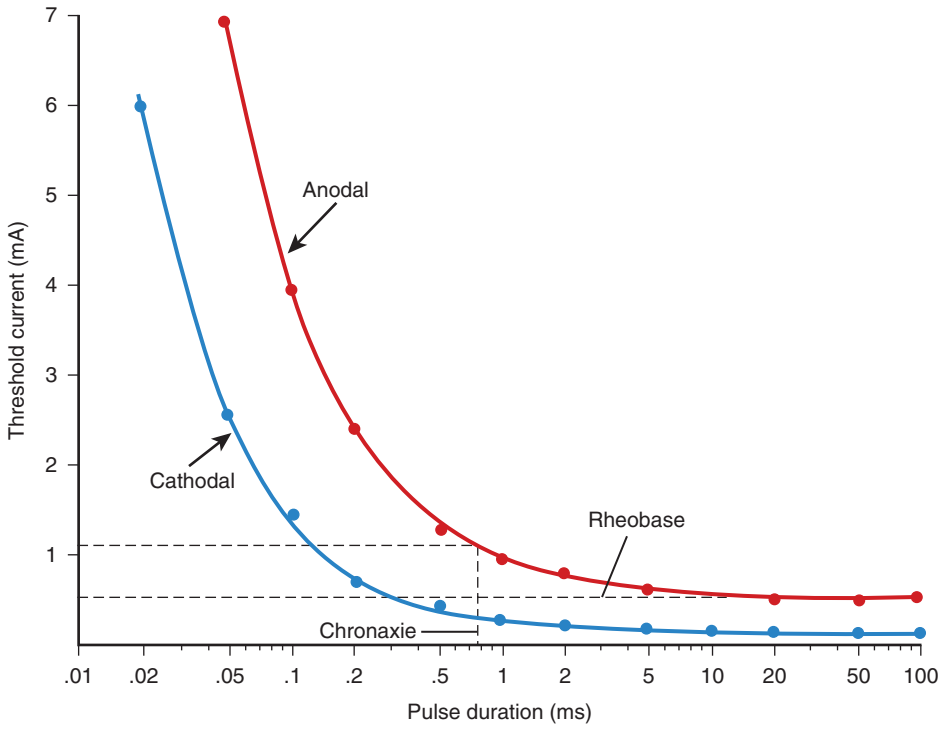

FIGURE 13-2 Strength/duration curve measured with cathodal and anodal stimuli in a canine ventricle. The pulse durations are plotted on a logarithmic scale. Note that the threshold becomes stable at pulse durations >10 ms; this threshold is called the *rheobase*. *Chronaxie* is the stimulus duration required to excite tissue at twice the rheobase. *(From Mehra R:* Myocardial vulnerability to arrhythmias with cathodal, anodal and bipolar stimulation *[PhD dissertation #75-21384; University Microfilms], Ann Arbor, MI, 1975, University of Michigan.)*

current is sufficient to increase membrane voltage above V_t (65 mV in this case), which activates the Na^+ channels and initiates the action potential. At a constant stimulus amplitude (see Figure 13-1, *B*), when the stimulus is turned off very quickly after a very short duration, the threshold V_t is not reached because of membrane capacitance, and the cell does not elicit an action potential. When the duration is increased, V_m continues to increase until it reaches the threshold potential V_t, eliciting an action potential. It is this property of cell capacitance that gives rise to a relationship between duration of the stimulus and the amplitude required to elicit excitation (strength-duration curve, as in Figure 13-2). Also, this type of excitation occurs after the stimulus is turned "on" and before it is turned "off" and is referred to as *make excitation*.

It is important to note that the threshold voltage V_t at which excitation occurs is not constant but depends on the extent of cellular repolarization from the previous action potential at the time the stimulus is applied. This is because the Na^+ channels must reset to their resting state, and this only happens after repolarization is complete. For coupling intervals closer to the

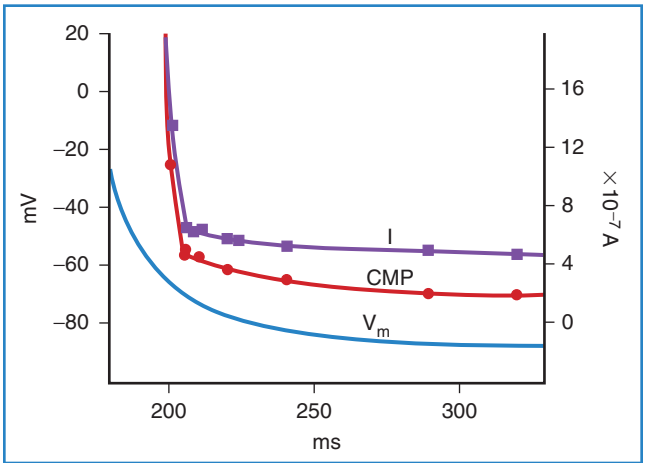

FIGURE 13-3 Critical membrane potential (*CMP*), depolarizing current threshold *(I)*, and transmembrane potential *(V_m)* as a function of delay from the onset of an action potential. The ordinate is the potential in millivolts or current threshold and the abscissa is in milliseconds. The CMP is almost constant at intervals longer than 200 ms, and I represents the intracellular strength/interval curve with a depolarizing stimulus. *(From Hoshi TM: Excitability cycle of cardiac muscle examined by intracellular stimulation,* Jap J Physiol *12:433, 1962.)*

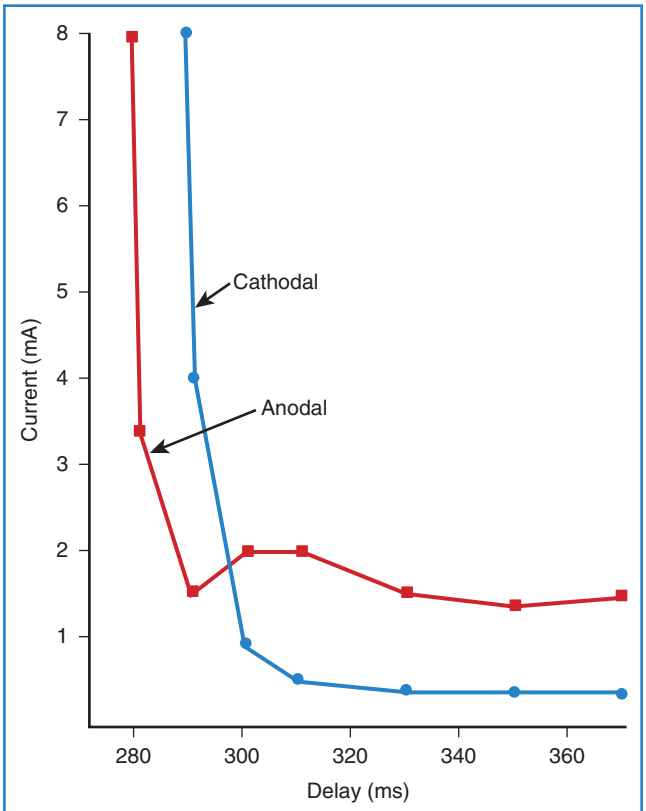

FIGURE 13-4 Typical unipolar cathodal and anodal strength/interval curves obtained in a patient with an acute unipolar electrode (11 mm^2 in area). The ordinate represents the excitation current threshold in milliamperes, and the abscissa represents the delay of the stimulus from the stimulus pacing the ventricle at 90 beats/min. Note that anodal refractory periods are shorter than cathodal refractory periods for most stimulus currents. *(From Mehra R, Furman S: Comparison of cathodal, anodal and bipolar strength-interval curves with temporary and permanent electrodes,* Br Heart J *41:468–476, 1979.)*

repolarization phase (earlier in the cardiac cycle), the threshold voltage V_t increases, thereby increasing the stimulus (either current or duration) needed to initiate excitation. With a depolarizing stimulus (one that reduces V_m), the threshold for excitation is lowest in diastole and increases as the stimulus approaches systole. The threshold voltage V_t (termed *critical membrane potential* [CMP]; Figure 13-3) and the transmembrane current required to excite cells with intracellular stimulation at various intervals in the cardiac cycle were measured by Hoshi et al in canine Purkinje fibers.[1] Figure 13-3 shows that the CMP was between 60 and 65 mV and relatively constant throughout the diastolic phase and the terminal phase of repolarization of the MP. In the rapid phase of repolarization, the CMP increased sharply and so did the current threshold. This results in a hyperbolic curve that describes the relationship between the current threshold for excitation and the time delay from the onset of the action potential of a depolarizing stimulus. This curve is referred to as the *intracellular strength/interval curve* and has a shape very similar to the strength/interval curve with an extracellular electrode that results in tissue excitation caused by depolarization (Figure 13-4).

The second type of excitation occurs when the cardiac cell is hyperpolarized (made more negative than the resting potential) to a critical value after the stimulus is turned off. This is called *break excitation*. It was initially observed in nerve fibers and associated with the termination of a hyperpolarizing pulse.[2] Using optical mapping techniques, Wikswo et al[3] were also able to demonstrate that the break excitation occurred in cardiac tissue after the end of the stimulus from the region that was hyperpolarized. During the hyperpolarized state, the tissue is inexcitable because its Na^+ channels are inactivated, and excitation is observed only after the hyperpolarizing stimulus is turned off. There is no consensus on the mechanism responsible for break excitation. Two concepts have been proposed: (1) In the mechanism proposed by Roth et al, break excitation from the hyperpolarized region occurs only when adjacent depolarized areas are present and does not occur in tissue that is uniformly hyperpolarized.[4] At the end of the stimulus, current diffuses from the depolarized areas to the hyperpolarized areas to initiate excitation. This hypothesis suggests that break excitation is a result of the syncytial properties of the tissue and not a property of the cell membrane alone. (2) Computer simulation conducted by other investigators indicated that break excitation in the hyperpolarized tissue may be possible by itself without the diffusion of current from adjacent tissue.[5] This controversy has not yet been resolved.

Extracellular Stimulation

To understand extracellular stimulation, it is useful to envision a train of excitation processes, of which intracellular stimulation is the final event. These processes are (1) generation of the stimulus in the pulse generator, (2) transfer of current from the generator to the electrode pair and into the extracellular space, and (3) transfer of current from the extracellular space to the cardiac cell membranes resulting in cellular excitation.

The first two processes will be discussed in this section. The characteristics of the electrical stimulus and the terminology used for extracellular electrodes will be reviewed first. Then we will

discuss the stimulus variables that affect extracellular stimulation such as its duration, polarity, and the timing in the cardiac cycle and electrode variables such as the size of electrode and the electrode tissue interface.

Electrical Stimulus

In individual cardiac cells, a minimum threshold current is required to cause excitation. Decades of experimental observations with extracellular electrodes demonstrate the same behavior in cardiac tissue. Stimulus strength may be measured as a voltage or current amplitude. The current threshold is a more physiological measurement of excitation, since it is independent of the resistance of the electrode or the tissue. If the resistance is high, the voltage threshold will increase, as it is equal to the current threshold times the resistance of the tissue. The current density (current per unit area) is an even more accurate determinant of the basic requirement for excitation. It is postulated that in order to elicit excitation, a certain minimum number of cells (a "critical mass") must be excited. Since the heart is a syncytium, that is, an aggregate of interconnected cardiac cells, once this critical volume of cells is excited, the conduction propagates to the rest of the heart. Therefore, a minimum amount of current per unit area must exist in order to excite this aggregate of cardiac cells. This is called *current density threshold*. The current density required for cardiac excitation is typically between 2 and 2.5 mA/cm^2 at the electrode-tissue interface.[6,7]

External cardiac stimulators are typically designed to provide an output pulse that maintains its voltage or current throughout the duration of the pulse and are referred to as *constant voltage* or *constant current stimuli*. Because of the polarization characteristics of the electrode-tissue interface (to be discussed later), resistance increases during the pulse and an increasing voltage is required to maintain the constant current stimulus. This results in a significant increase from V_o at the beginning of the stimulus to V_t at the end of the stimulus. Figure 13-5, *A*, illustrates a typical constant current stimulus, where the output current is approximately constant in amplitude from the onset to the offset of the stimulus. Physiological stimulators used in laboratories typically provide constant voltage or constant current stimuli, but these designs draw significant power. To reduce power drain and ensure safe operation in implantable pacemakers, the most efficient circuits use a capacitor. This can continuously draw current from a battery throughout the cardiac cycle and deliver a short stimulus (typically <2 ms) on demand. The result is that the stimulus from most implantable pacemakers has an exponentially decaying

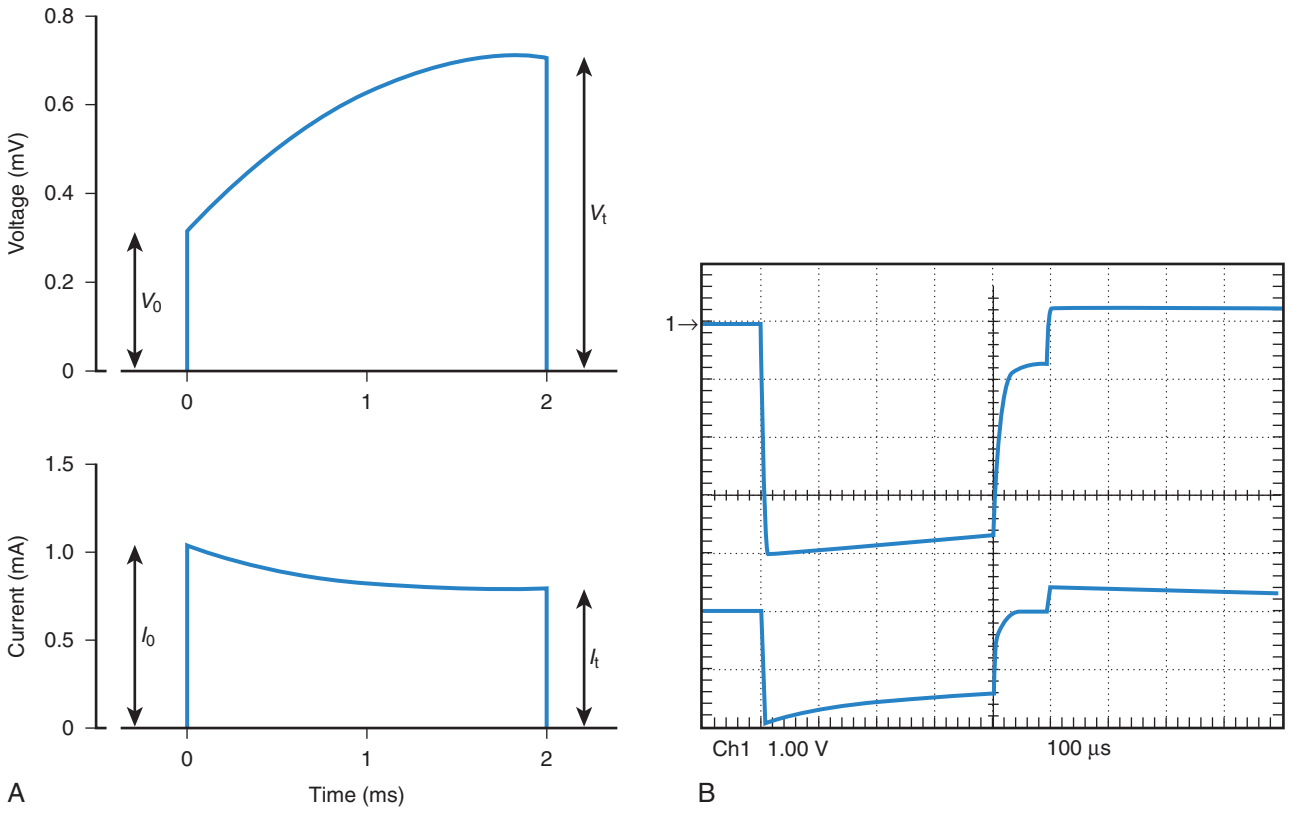

FIGURE 13-5 A, Voltage waveform measured at the electrode during a constant current stimulus. The current amplitude is almost constant at 1.0 mA through the stimulus duration of 2 ms. Significantly increasing stimulus voltage from 0.3 V at the beginning of the stimulus to 0.7 V at its end is required to maintain this constant current through the tissue. This is because of the increasing polarization resistance during the pulse. **B,** Voltage (*top*) and current (*bottom*) waveform of a 4-V, 0.4-ms stimulus measured at the output of a typical pacemaker. The voltage is decaying exponentially during the pulse and is followed by a "recharge" of an opposite polarity. The current waveform decays at a greater rate because of increasing resistance from the beginning of the stimulus to the end. After the end of the 0.4-ms stimulus, the current returns to zero and is followed by a recharge stimulus of a small magnitude but longer duration. (***A,*** *From Furman S, Parker B, Escher DJW, et al: Endocardial threshold of cardiac response as a function of electrode surface area,* J Surg Res *8:161–166, 1968.)*

voltage profile, that is, a slight decrease occurs in voltage output from the beginning of the stimulus to the end of the stimulus (see Figure 13-5, *B*). The exponentially decaying voltage output results from a capacitor at the output of the pacemaker. The current waveform that is generated has an even higher rate of decay because of electrode polarization, which results in increasingly higher resistance during the pulse.

Electrode Terminology

Electrical stimulation must always be applied through electrode pairs so that current injected at one electrode returns to the stimulator through the other electrode. Figure 13-6 shows the commonly used electrode configurations. When one of the electrodes is located *inside* the heart and another is located *away from* the heart (e.g., on the skin surface or subcutaneously), this configuration is described as *unipolar*. The electrode in contact with (or closest to) the heart is called the *stimulating electrode*, and the electrode away from the heart is called the *indifferent electrode*. The indifferent electrode is usually quite large compared with the stimulating electrode to lower the resistance of the stimulation configuration. When the stimulating electrode is negative with respect to the indifferent electrode, the stimulation is called *cathodal*. When the stimulating electrode is positive, the stimulation is referred to as *anodal*.

In most implanted systems, both electrodes are within the same chamber of the heart, usually separated by approximately 1 cm. This configuration is described as *bipolar*. In practice, the distal of the two electrodes, that is, "the tip," is more likely to be in contact with tissue than is the more proximal electrode (see Figure 13-6).

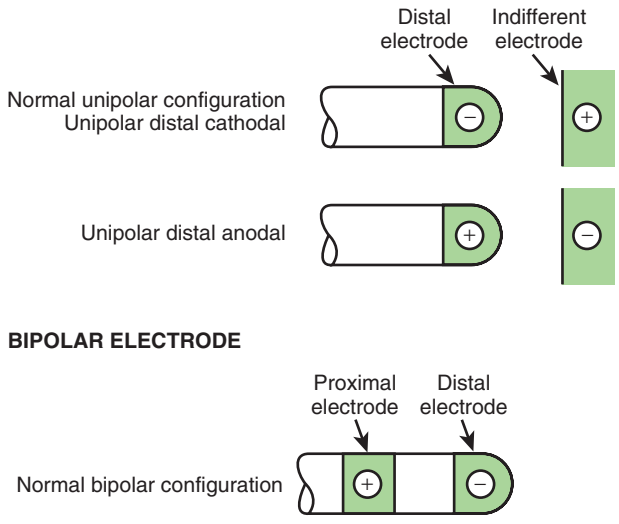

FIGURE 13-6 Unipolar and bipolar electrode configurations. The normal unipolar pacing configuration is one in which the tip of the electrode is negative (distal cathodal) with an indifferent positive electrode. The unipolar distal anodal configuration reverses the polarities and is not used because of higher anodal thresholds. The normal bipolar configuration uses the tip (distal) electrode as the cathode and the ring (proximal) electrode as the anode. *(From Mehra R, Furman S: Comparison of cathodal, anodal and bipolar strength-interval curves with temporary and permanent electrodes,* Br Heart J *41:468–476, 1979.)*

Effect of Stimulus Duration (Strength/Duration Curve)

Experimental studies on extracellular stimulation indicate that it is much easier to excite tissue when the stimulus duration is long rather than short. This behavior is also observed during intracellular stimulation; its mechanism was discussed previously. The strength/duration curve is the relationship between the strength of the stimulus required to elicit excitation and the duration of the stimulus. With increasing duration, the thresholds always decrease. Figure 13-2 shows the cathodal and anodal strength duration curves measured in a canine ventricle. Both curves approach a minimum threshold at long pulse durations, although the anodal threshold is observed to be higher than the cathodal threshold. At very long durations, the current threshold reaches the minimum value, the *rheobase,* which is approximately 0.2 mA for the cathodal and 0.5 mA for an anodal stimulus (see Figure 13-2). As with single-cell stimulation, the rheobase is the minimum stimulus strength required for excitation. For stimulation intensity of twice the rheobase, the pulse duration required for excitation is called *chronaxie*. Chronaxie represents the "knee" of the strength/duration curve because the current threshold increases very rapidly for pulse durations shorter than chronaxie and decreases relatively slowly for pulse durations longer than chronaxie. In Figure 13-2, the chronaxie for anodal stimulation is about 0.75 ms.

For an implantable device, consistent pacing must be maintained at minimum stimulus energy to maximize the longevity of the device. Optimization of electrode design and pulse duration can help minimize the dissipation of energy per pulse. The dissipated energy increases with the duration of the pulse, the resistance of the electrode, and the square of the stimulation current, Unlike the current strength/duration curves, the energy strength/duration curve typically has a U shape, which indicates a pulse duration at which the energy dissipated per pulse would be minimum (Figure 13-7). Pacing at this unique pulse duration can maximize device longevity. This duration is not always the same and will depend on the electrode material and its design.

Effect of Stimulus Timing (Strength/Interval Curve)

The stimulus threshold required at various intervals within the cardiac cycle is represented by the strength/interval curve. The threshold is lower during diastole and increases as the stimulus coupling is shortened and systole is approached. This indicates that it is more difficult to re-excite the cardiac tissue soon after it has been excited.[8-10] As discussed previously, this behavior is caused by inactivation of Na^+ channels early in the cardiac cycle. At a very short coupling interval, the tissue cannot be re-excited even with a large stimulus. Figure 13-4 shows a set of strength/interval curves that were determined in a patient with a constant current stimulus when the ventricle was paced at 90 beats/min. With a cathodal stimulus, the threshold is relatively low (0.4 mA) at intervals greater than 310 ms, that is, after the end of the T wave of the paced beat. The tissue cannot be re-excited any earlier than 288 ms even with an 8-mA stimulus, and this is its relative refractory period. The relative refractory period is a fundamental property of excitable tissue, and it determines the maximum rate at which it can be stimulated. When the polarity of the electrode is reversed to anodal, the shape of the strength/interval curve

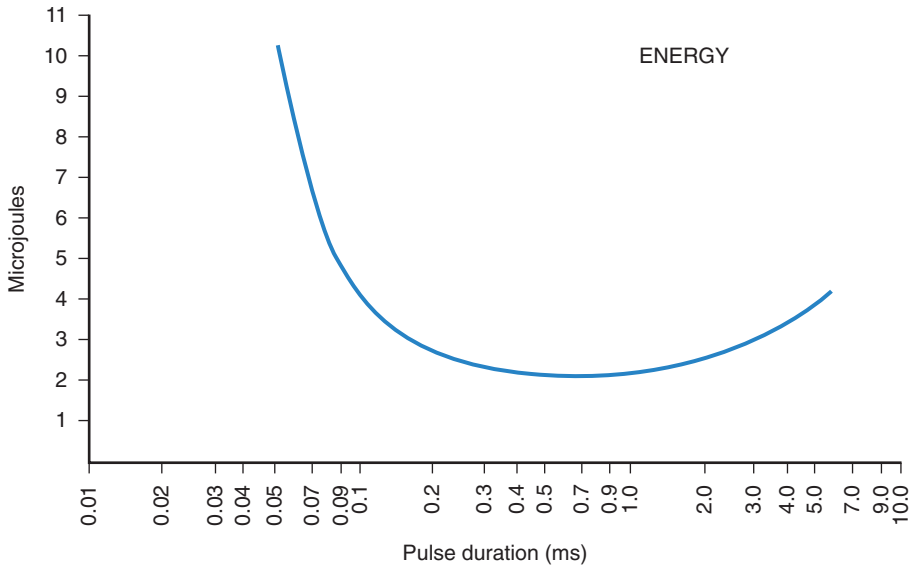

FIGURE 13-7 Energy (in microjoules) required to pace the ventricle at various pulse durations with a chronic endocardial lead in a canine ventricle. In this case, the minimum energy is consumed at durations ranging from 0.25 to 1.0 ms. Energy consumption increases at shorter and longer durations. *(From Furman S, Hurzler P, Mehra R: Cardiac pacing and pacemakers IV: Threshold of cardiac stimulation,* Am Heart J *94:115–124, 1977.)*

changes significantly. The anodal threshold is higher during diastole, but the relative refractory period is shorter. This implies that an anodal stimulus can initiate excitation earlier on the T wave than a cathodal stimulus. In Figure 13-4, with an 8-mA stimulus, the anodal refractory period is about 10 ms shorter than with a cathodal stimulus. Another key characteristic of the anodal strength/interval curve is that as the coupling interval of the stimulus is decreased, the threshold first increases, then decreases, and is followed again by a significant increase in threshold at the shortest coupling. This reduction in threshold at the short coupling interval of the stimulus is referred to as the *anodal dip*.

To understand the factors responsible for the shape of the anodal strength-interval curve, it is important to re-address the issue of "make" and "break" excitation. Break excitation was first demonstrated by Dekker et al[11] in cardiac tissue. He measured the excitation thresholds during the make excitation (following the stimulus onset and before its termination) and the break excitation (following the end of the stimulus) of the pulses. He observed that these thresholds varied with the polarity of the stimulus as well as the timing of the stimulus within the cardiac cycle. The make and break thresholds were measured when anodal and cathodal stimuli were delivered through the epicardial electrodes of the canine ventricle. Figure 13-8 illustrates the make and break thresholds with long-duration stimuli. To measure the make excitation threshold, the stimulus was initiated at various intervals within the cardiac cycle. For break threshold measurements, the stimulus was initiated in the absolute refractory period and ended at different intervals within the cardiac cycle. Excitation was observed after the termination of the stimulus. The thresholds for break excitation had the characteristic anodal dip with higher thresholds during diastole and the make excitation thresholds had the characteristic hyperbolic shape. This suggests that during diastole, make excitation thresholds are lower and that the break thresholds are lower during the relative refractory period. Break excitation has also been observed experimentally with short-duration stimuli.[3,12,13] Sidorov et al[13] used optical mapping

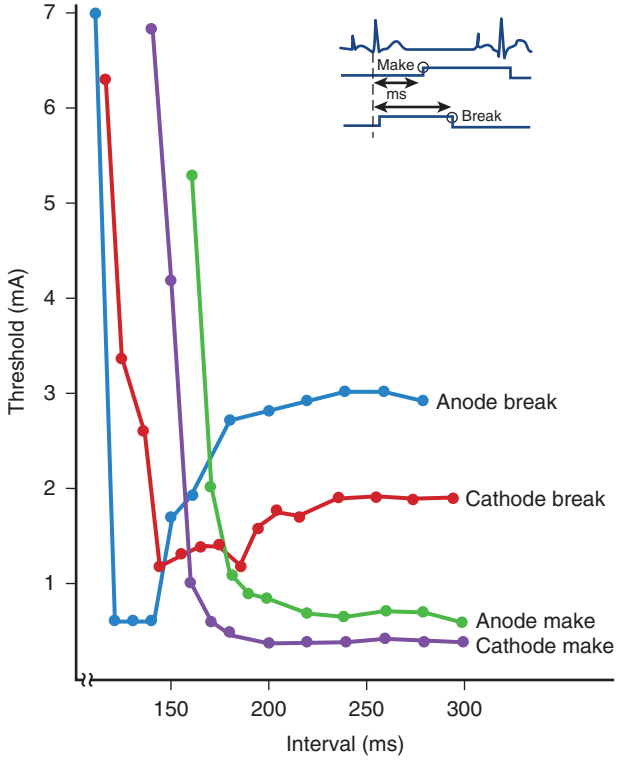

FIGURE 13-8 Typical ventricular thresholds plotted as a function of the interval in milliseconds after the preceding normally conducted QRS complex for each of the modes of stimulation—anode make, anode break, cathode make, and cathode break for a long-duration stimulus. Make excitation occurs after the stimulus onset and before its offset, whereas break excitation occurs after the stimulus has been terminated. *(From Dekker E: Direct current make and break thresholds for pacemaker electrodes on the canine ventricle,* Circ Res *27:811, 1970.)*

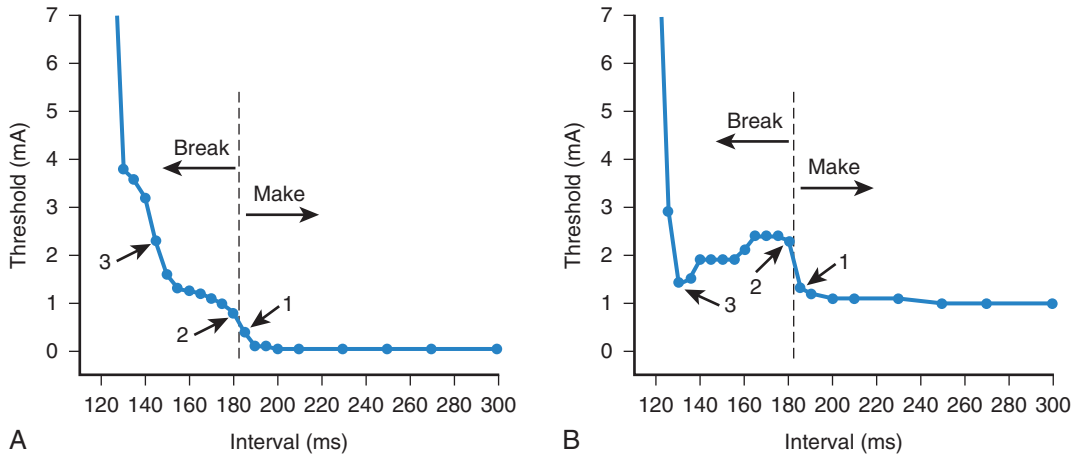

FIGURE 13-9 Unipolar cathodal (**A**) and anodal (**B**) strength/interval curves composed of make and break excitation. The vertical dashed line corresponds to the transition from make stimulation to break stimulation mechanism. The points of the curve corresponding to the shortest interval for make stimulation and the longest interval for break stimulation are depicted by the numbers 1 and 2, respectively. The stimulus duration was 20 ms. *(From Sidorov VY, Woods MC, Baudenbacher P, Baudenbacher F: Examination of stimulation mechanism and strength-interval curve in cardiac tissue,* Am J Physiol Heart Circ Physiol *289:H2602–H2615, 2005.)*

techniques to show that the transition of the stimulation mechanism from the make threshold to the break threshold always coincided with the final descending portion of both the anodal and the cathodal strength/interval curves (Figure 13-9).

A very unusual property of anodal stimulation in the relative refractory period is the "no-response" phenomenon.[14-16] Typically, the term *threshold* implies that any stimulus that is of greater magnitude would result in excitation of the tissue. Within the relative refractory period, when the current strength of an anodal stimulus is increased above threshold, excitation is initiated. Paradoxically, when the stimulus amplitude is increased further, the stimulus becomes ineffective and is no longer able to excite. For example, in the strength/interval curve of Figure 13-10, an anodal stimulus at 130-ms delay can initiate excitation only when its magnitude is between 1.0 and 1.7 mA. When the stimulus is increased further, excitation does not occur. This is called the *no-response zone*. At a much larger stimulus, excitation may again be re-established. The time interval in the relative refractory period during which this no-response phenomenon occurs is usually very short. Although this phenomenon has been observed in canine hearts, it has not been reported in the clinical literature.

With endocardial electrodes, the tip electrode will typically contact the myocardium and is made the cathode because of its lower threshold for excitation. The proximal electrode (the anode) may not always contact cardiac tissue. If it does, it could elicit an excitation, depending on the stimulus output and the anodal threshold. The bipolar excitation threshold at any time in the cardiac cycle is equal to the lower of the cathodal and anodal thresholds determined at the two electrode sites.[6] Therefore the bipolar strength/interval curve follows the lower of the cathodal and anodal curves, as illustrated in Figure 13-11. This indicates that with a bipolar stimulus, excitation would arise from both electrode sites if the stimulus output were above the anodal and cathodal thresholds and selectively from one electrode if the stimulus output is in between the cathodal and anodal thresholds. For example, in Figure 13-11, *A*, a 2-mA stimulus at 380-ms

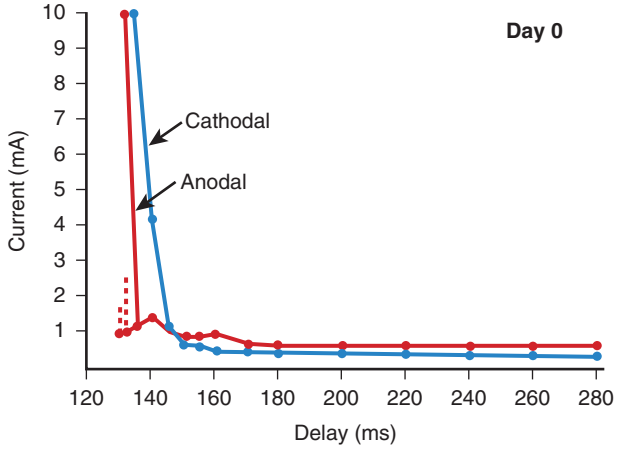

FIGURE 13-10 Unipolar cathodal and anodal strength/interval curves obtained in a canine ventricle immediately following endocardial electrode insertion. In the anodal strength/interval curves, the dotted lines represent the range of stimulus currents, which were effective in initiating excitation. For example, at a 130-ms delay, only a stimulus between 1.0 and 1.7 mA caused excitation. Larger stimuli were ineffective. This is referred to as the *no-response phenomenon* and has been observed only with anodal stimuli and at short coupling intervals. *(From Mehra R, McMullen M, Furman S: Time dependence of unipolar cathodal and anodal strength interval curves,* PACE *3:526–530, 1980.)*

coupling would excite only the tissue at the cathode, whereas a 7-mA stimulus would result in excitation from the cathode as well as from the anode.

Effect of Electrode Size

Since a minimum current density is required for stimulation, the threshold of excitation is dependent on electrode size. Studies

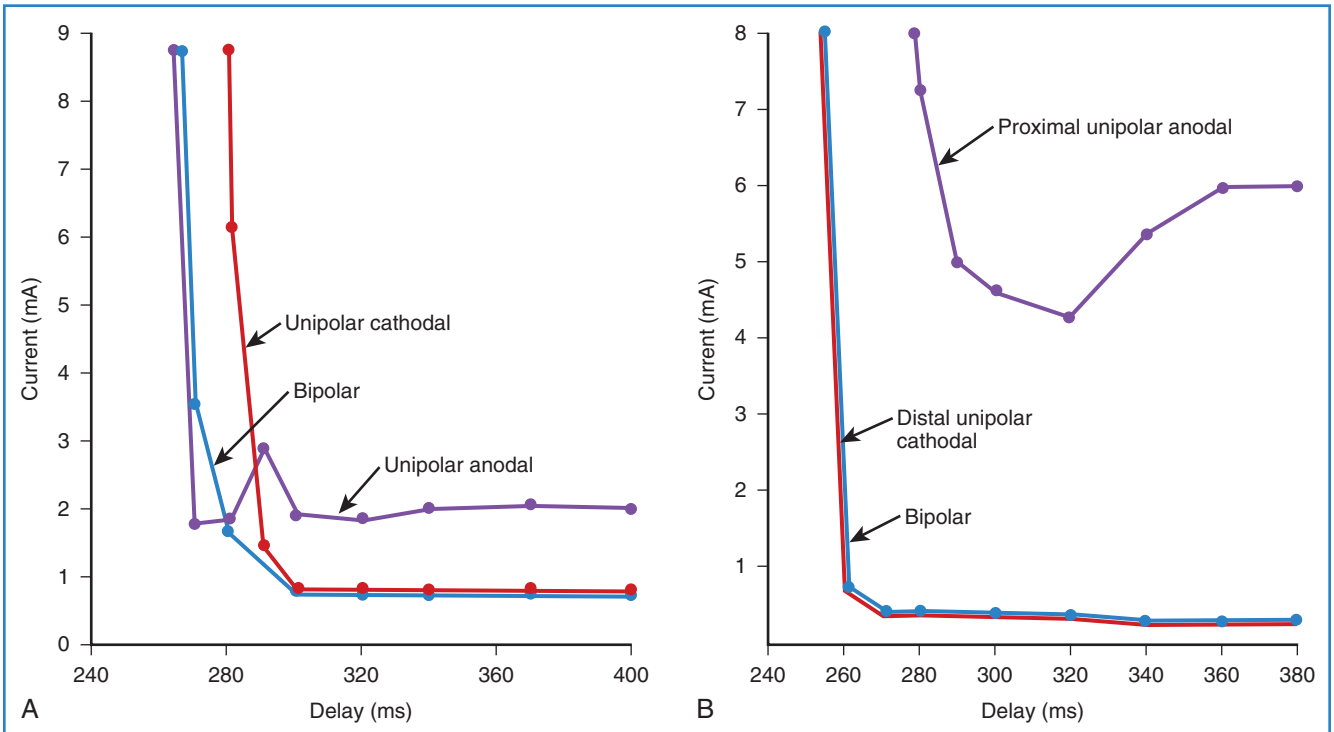

FIGURE 13-11 A, Relationship among distal unipolar cathodal, proximal unipolar anodal, and bipolar strength/interval curves in a patient with a temporary lead. For the proximal unipolar anodal thresholds, the ring is the anode and the indifferent electrode is the cathode. For the distal unipolar cathodal threshold, the lead tip is the cathode. The bipolar threshold at any delay is equal to the lower of the cathodal and anodal thresholds. **B,** In this patient, the proximal unipolar anodal thresholds are relatively high; therefore the distal unipolar cathodal and bipolar strength/interval curves are the same. *(From Mehra R, Furman S: Comparison of cathodal, anodal and bipolar strength-interval curves with temporary and permanent electrodes,* Br Heart J *41:468–476, 1979)*

have demonstrated that during diastole, the current threshold for cardiac pacing is directly proportional to the electrode surface area ranging from about 10 to 50 mm^2 (Figure 13-12). As indicated in Figure 13-12, smaller electrodes require less current for excitation. At the same time, the resistance of a smaller electrode is higher, since the resistance of a spherical electrode is inversely proportional to its radius. This gives rise to the question: Would the energy required for excitation increase or decrease with smaller size electrodes? The current required to stimulate tissue increases as does the area of the electrode (the square of the electrode radius), while the resistance is inversely proportional to the radius. Therefore, smaller electrodes require less energy for stimulation, as they save more energy in reduced current density than they lose in increased resistance. For this reason, the surface area of commercial implantable electrodes has become smaller over the years. Making the electrodes extremely small has some disadvantages. Extremely small electrodes are susceptible to being dislocated easily, and they also tend to show a greater increase in chronic thresholds caused by the formation of the fibrotic capsule.

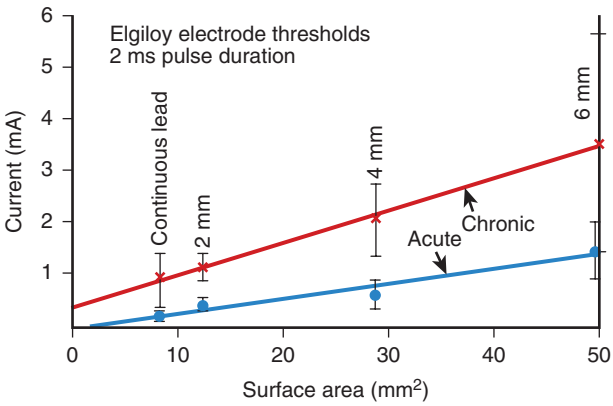

FIGURE 13-12 Acute and chronic current thresholds of four electrodes with increasing surface area. Each of the thresholds is measured with a 2-ms duration pulse. *Continuous lead*, *2 mm*, *4 mm*, and *6 mm* denote electrodes of increasing surface area. Note that both the acute and chronic thresholds increase with increasing area but that the slope of the lines is different. *(From Furman S, Hurzler P, Parker P: Clinical thresholds of endocardial cardiac stimulation: A long term study,* J Surg Res *19:149–155, 1975.)*

Tissue Fibrosis

It has been observed that because of the trauma caused by the electrode, tissue damage and edema occur acutely, and this tissue becomes fibrotic over time (Figure 13-13).[17,18] The fibrotic capsule increases the separation between the electrode and the excitable

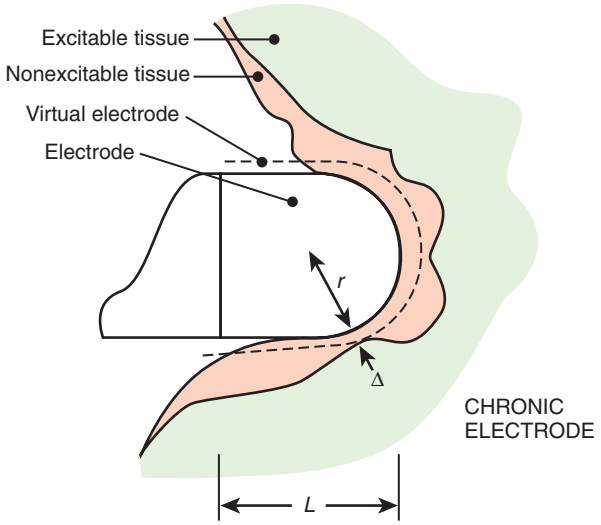

FIGURE 13-13 Schematic diagram of a chronically implanted electrode. An irregularly shaped fibrous capsule of nonexcitable tissue forms around the electrode, which increases the separation between the electrode and the excitable tissue. The *dotted line* indicates that the radius of the electrode has increase from *r* to a virtual electrode of radius $r + \Delta$. This is responsible for the chronic increase in pacing thresholds. *(From Furman S, Hurzler P, Parker P: Clinical thresholds of endocardial cardiac stimulation: A long term study,* J Surg Res *19: 149–155, 1975.)*

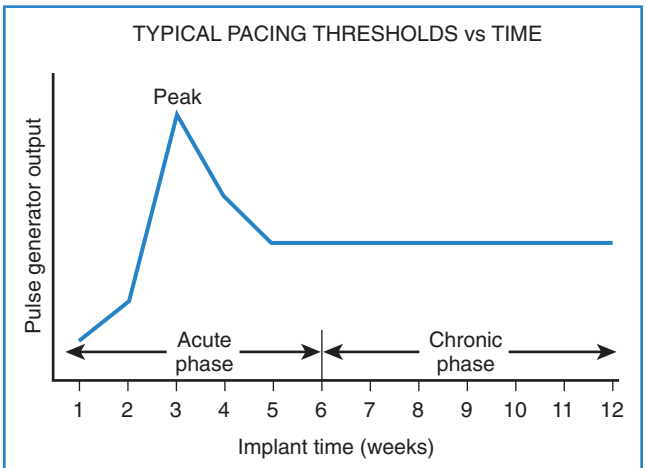

FIGURE 13-14 Typical change in pacing threshold as a function of implant time with a nonsteroid pacing electrode. Between 2 and 3 weeks, the threshold increases significantly but stabilizes to a lower value later.

tissue and therefore decreases the current density (current per unit area) at the excitable tissue. As the electrode matures from acute to chronic, the radius of the virtual electrode increases from r to r + Δ, as illustrated in Figure 13-13. Therefore, a greater stimulus current is needed to reach the threshold current density in the excitable tissue. This increases the pacing thresholds after electrode implantation, as shown in Figure 13-14. A significant increase occurs in thresholds in the 4- to 8-week period; with increasing time, the size of this edematous capsule shrinks and is replaced by a fibrotic layer. This causes the excitation threshold to decrease again and stabilize chronically.

One of the major advances in electrode technology has been the development of electrodes that elute small quantities of the corticosteroid dexamethasone sodium phosphate.[19] These steroid electrodes are characterized by a minimal change in threshold from implantation to a follow-up period of several years. The acute rise in stimulation threshold that occurs because of the formation of inflammation and edema adjacent to the pacing electrode is reduced dramatically. Although it has been hypothesized that the steroid reduces the size of the fibrotic layer and thus minimizes the rise in threshold, the exact mechanism by which steroid leads improve pacing efficiency is not well understood.

Electrode Polarization

For pacing efficiency to be high, minimal energy should be lost at the electrode-tissue interface, and all the energy of the stimulus should be dissipated in cardiac tissue. Unfortunately, energy is lost with most electrodes because of the electrochemical reactions at the electrode-tissue interface, which is referred to as *polarization*.[20,21] In the electrode, the flow of current is caused by the movement of electrons, whereas in the tissue, it is caused by the movement of ions. The chemical reactions that occur at the electrode-tissue interface to convert electronic flow to ionic flow are complex and vary with the metal and electrode geometry being used. If the electrode was nonpolarizable, the voltage and current waveforms would be identical, and no energy would be wasted at the interface. Figure 13-5, *A*, illustrates a typical voltage waveform with a polarizable electrode when a constant current stimulus is applied. Initially, the voltage is low but increases because of increasing impedance as a result of polarization. The electrochemical reactions at the anode and the cathode are different. New materials that tend to reduce polarization have been developed. Among these are the porous and platinized electrodes, which have voltage or current characteristics that approach those of nonpolarizable electrodes.

Goals of Cardiac Stimulation in Implantable Devices

The pacing thresholds in a physiological situation are dynamic and change with alterations in metabolic activity, pH, lead maturity, and so on. If one were to set the magnitude of the pacemaker output at the pacing threshold measured at the time of implantation, pacing capture could be lost frequently. The two methods of resolving this issue are (1) pacing with a higher stimulus, that is, incorporating a "safety factor," and (2) developing systems that automatically measure the threshold and adjust the stimulus output accordingly. The appropriate safety factor setting would be based on the type of lead and the expected changes in the threshold. Clearly, the higher the safety factor, the higher is the pacing output, which results in greater battery drain and shorter device longevity. The systems that automatically adjust the output on the basis of the pacing threshold require the ability to assess capture from the same lead as the one from which pacing is being conducted. This requires the use of special low-polarization leads or unique algorithms.

Relationship Between Intracellular Stimulation and Extracellular Stimulation

The section above discussed the observation that in order to elicit excitation, V_m must be altered. The question then arises: How does an extracellular stimulus change V_m? A fully quantitative answer to this question remains elusive even now, but virtually all qualitative features of the relationship between extracellular stimulation and intracellular stimulation can now be explained. Two breakthroughs from the previous decade account for this understanding: (1) high-resolution optical mapping studies, and (2) bi-domain computer models.

Optical mapping of cardiac tissue was made possible by the incorporation of voltage-sensitive fluorescent dyes into cardiac membranes. These dyes, under external illumination, emit light at a wavelength that is proportional to the transmembrane voltage. It is therefore possible to produce two-dimensional transmembrane voltage maps of the region of cardiac tissue with high spatial resolution. Such apparatus can be configured to view millisecond-by-millisecond evolution of transmembrane voltages. Thus, one can create a "movie" of transmembrane changes as excitation is initiated and as it spreads. Several investigators have used this optical mapping technique to measure V_m around an extracellular unipolar electrode.[3,12,22] Their key observation was that adjacent areas of hyperpolarization and depolarization are present, and this pattern has been referred to as the *dog bone shape* (Figure 13-15). For example, with cathodal stimulation (Figure 13-15, *A*), it was observed that the tissue directly underneath the electrode is depolarized and that it has a dog-bone shape with the long axis of the dog bone perpendicular to the axis of the fibers. In this axis, the tissue is only depolarized, and its amplitude decreases with increasing distance. However, in the axis parallel to the fibers, the tissue directly underneath the electrode is depolarized, but it changes polarity and is hyperpolarized about a millimeter away from the electrode, as illustrated by the blue image in Figure 13-15, *A*. If the polarity of the extracellular stimulus is reversed to an anodal stimulus, the shape of the dog bone remains quite similar with reversal of the hyperpolarized and depolarized regions (Figure 13-15, *B*).

As strange as these observations appeared, computer simulations of cardiac tissue using the bi-domain model had already predicted them. In the bi-domain model, intracellular and extracellular spaces are considered to be two distinct domains and are separated by a high resistance. It is assumed that the intracellular space of each cell is coupled with its neighbors' through low-resistance intracellular channels. Intracellular and extracellular spaces are also assumed to be anisotropic, that is, their electrical conductivity is different when it is measured parallel versus perpendicular to the orientation of the cells. Early theoretical work with bi-domain models assumed that anisotropic conductivity ratios for intracellular and extracellular spaces were equal. If equal anisotropic ratios are assumed for intracellular and extracellular spaces and an extracellular stimulus is applied from a point source, the shape of the V_m contours is ellipsoid, with the V_m decreasing with increasing distance.[3] Therefore, all of the tissue would be either depolarized or hyperpolarized, but not both. This is incompatible with experimental observations, which demonstrated adjacent areas of depolarization and hyperpolarization during extracellular stimulation (see Figure 13-15). Recent simulations with the bi-domain model have assumed that intracellular and extracellular spaces are both anisotropic, but not to the same extent. The anisotropic conductivity ratio in the extracellular space is typically about 2:1, whereas it is 10:1 in the intracellular space. This property of cardiac tissue seems to be responsible for many of its interesting electrical features. With simulation of unequal anisotropic properties, adjacent areas of depolarization and hyperpolarization appear in a dog bone shape, very similar to experimental observations.[3,23] Adjacent areas of depolarization and hyperpolarization are produced because the rate of change of the intracellular and extracellular potentials is nonuniform. The size and shape of the depolarized and hyperpolarized regions change with anisotropy ratios. This is demonstrated in the two-dimensional schematic presented in Figure 13-16. The dog bone shape represents the depolarized region, and the shaded area represents the hyperpolarized region. Depolarization occurs underneath the cathodic electrode, where the current enters a syncytium of cells, and hyperpolarization occurs where the current exits the cells. If the polarity of the stimulus were anodal, the dog bone region would be hyperpolarized, and depolarization

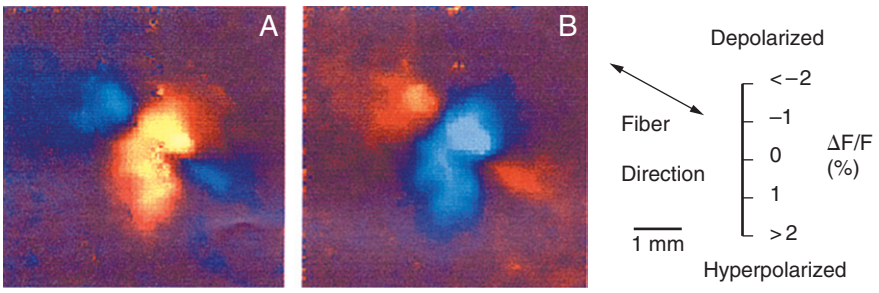

FIGURE 13-15 False-color images of the transmembrane potential associated with injection of current into refractory cardiac tissue. **A,** The image for a 10-mA, 2-ms cathodal stimulus applied at a point electrode. Note the dog bone–shaped depolarized region (*orange*) and a pair of adjacent hyperpolarized regions (*blue*). The fiber orientation is from lower right to upper left. The *bar* shows the fractional change in fluorescence. **B,** The complementary image for a 10-mA, 2-ms anodal stimulus at the same location of the heart. Note that the dog bone is now hyperpolarized region (*blue*), whereas the adjacent areas are depolarized (*orange*). *(From Wikswo JP, Lin SF, Abbas RA: Virtual electrodes in cardiac tissue: A common mechanism for anodal and cathodal stimulation,* Biophys J *69:2195–2210, 1995.)*

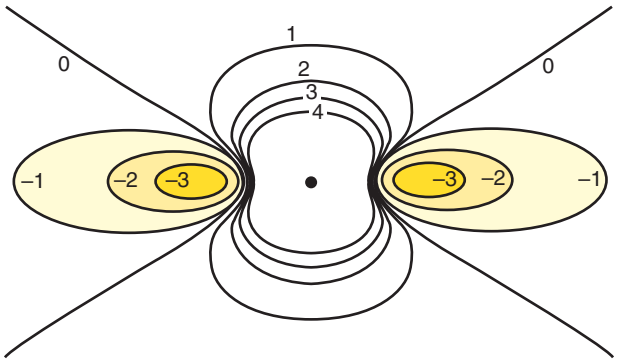

FIGURE 13-16 Transmembrane potentials induced by an extracellular unipolar electrode in a two-dimensional tissue based on the bi-domain model with unequal anisotropic ratios in intracellular and extracellular spaces. The central dot denotes an electrode through which the cathodal stimulus is delivered. The fibers are arranged horizontally, and the hyperpolarized regions of the tissue are shaded. The units of transmembrane potential are arbitrary. *(From Roth BJ: The pinwheel experiment revisited,* J Theor Biol *190:389–393, 1998.)*

would be observed in the adjacent region. These voltage nonuniformities can be further accentuated by electrical uncoupling of cells by ischemia, presence of fibrotic tissue, blood vessels, fiber curvature, and so on. All these variables can play a pivotal role in altering V_m potentials during extracellular stimulation.

Apart from the shape of depolarized and hyperpolarized regions, optical mapping studies and the bi-domain model indicate where excitation is initiated with extracellular stimulation. Depending on which threshold is lower, make excitation can occur from the depolarized area or break excitation from the hyperpolarized area. For example, during cathodal stimulation, the region directly underneath the electrode is depolarized, and if it reaches the critical threshold, the excitation wavefront would be initiated. This is illustrated in the optical maps presented in Figure 13-17 and the schematic in Figure 13-18. During a cathodal stimulus of 10 mA, excitation is typically initiated from the depolarized dog-bone region (see Figures 13-17, *A*, and 13-18, *A*) following the make of the stimulus. If the stimulus were anodal, make excitation could occur in the depolarized region a few millimeters from the electrode, provided the make threshold is lower than the break threshold in the hyperpolarized region. In Figure

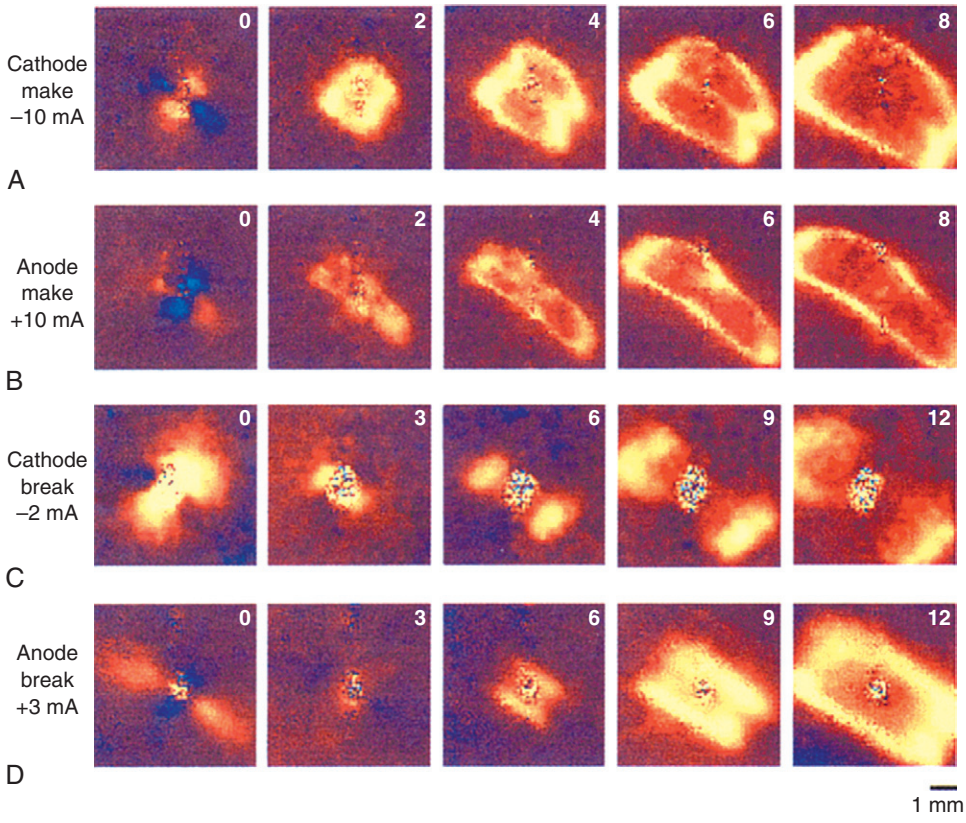

FIGURE 13-17 False-color images of the transmembrane potential associated with injection of current into fully repolarized excitable cardiac tissue. The number inside each frame is time in milliseconds. *Upper two rows:* **A,** Make excitation. Cathodal make excitation with 1-ms, 10-mA stimulus. **B,** 1-ms, 10-mA anodal make stimulation in the same heart. *Lower two rows:* **C,** Break stimulation; 180-ms, 2-mA cathodal break stimulation. **D,** Anodal break stimulation with a 3-mA, 150-ms long-duration stimulus. The direction of the epicardial fibers is from lower right to upper left. Color scale is the same as in Figure 13-15. *(From Wikswo J P, Lin SF, Abbas RA: Virtual electrodes in cardiac tissue: A common mechanism for anodal and cathodal stimulation,* Biophys J *69: 2195–2210, 1995.)*

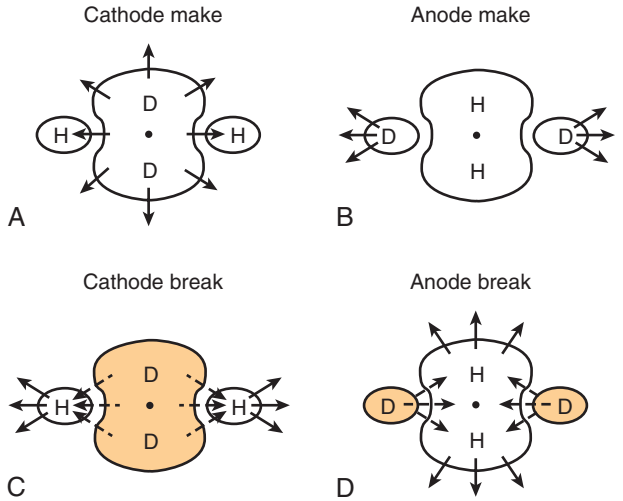

FIGURE 13-18 A schematic representation of the four mechanisms of stimulation based on the results of the bi-domain model: **A,** Cathode make. **B,** Anode make. **C,** Cathode break. **D,** Anode break. Myocardial fibers are oriented horizontally, and the electrode site is indicated as a dot in the center. *D* indicates depolarized tissue, and *H* indicates hyperpolarized tissue. *Solid arrows* show the initial direction of wavefront propagation; *dotted arrows* indicate diffusion of depolarization into the adjacent hyperpolarized tissue after the end of the stimulus. *Shading* denotes the tissue that is rendered inexcitable by a prolonged depolarization. *(From Roth BJ: Strength-interval curves for cardiac tissue predicted using the bidomain model,* J Cardiovasc Electrophysiol *7:722, 1996.)*

13-17, *B*, the make threshold is lower, and excitation occurs from the two yellow regions.

As discussed previously, excitation can also be initiated from the hyperpolarized region after the stimulus is turned off (*break stimulation*). Break excitation occurs from the hyperpolarized region. For example, during a cathodal pulse, the tissue under the electrode is depolarized, and the distal tissue is hyperpolarized (see Figures 13-17, *C*, and 13-18, *C*). If the stimulus amplitude is not enough to elicit make excitation from the depolarized regions, then after the end of the pulse, break excitation could begin from the hyperpolarized region, as shown in Figure 13-17, *C*. This will propagate rapidly along the fiber axis. In a similar manner, if the anodal make excitation does not occur from the depolarized region, break excitation will occur from the hyperpolarized regions, as illustrated in Figures 13-17, *D*, and 13-18, *D*.

The bi-domain model has been able to simulate the shape of the cathodal and anodal strength-interval curves, the presence of the anodal dip, the no-response phenomenon, and the ratio of anodal and cathodal thresholds with large surface area electrodes.[24-26] The model predicts that with short-duration stimuli, the shape of the cathodal strength/interval curve is primarily determined by the make excitation of the depolarized tissue. However, with an anodal stimulus at long coupling intervals, stimulation occurs because of make excitation distal to the electrode, as it has the lowest threshold. At short coupling intervals, the break threshold in the hyperpolarized regions becomes lower and gives rise to the dip in the anodal strength-interval curve. These observations are very similar to the experimental observations illustrated in Figures 13-8 and 13-9. At any coupling interval within the cardiac cycle, the lower of the make or break thresholds determines the excitation threshold. For example, with an anodal stimulus, excitation would be caused by make excitation at long coupling and break excitation at shorter coupling.

In experimental clinical studies, the ratio of anodal and cathodal thresholds was observed to be 2.8 with acute electrodes and 1.5 with chronic electrodes.[27] This has also been observed using the bi-domain model, which indicates that if the distance between the electrode and the excitable tissue is increased because of a perfusion bath or fibrotic tissue, the ratio of the excitation thresholds decreases.[28] The amplitude of depolarization potential change induced by a cathodal stimulus is reduced dramatically close to the electrode, whereas with an anodal stimulus, the change in the depolarization potential farther away from the electrode is reduced much less. The ratio of maximum depolarization to maximum hyperpolarization also decreases with increasing electrode tissue separation, thus reducing the ratio of anodal and cathodal excitation thresholds.

Future of Cardiac Excitation

Current understanding of cardiac stimulation has increased dramatically in the past decade with the availability of optical mapping techniques and computational efficiencies. The focus of this chapter has been primarily on the fundamental aspects of electrical stimulation related to *near-field* stimulation, that is, stimulation close to the electrode, rather than *far-field* stimulation, which plays an important role in cardiac defibrillation. Significant strides have been made in the understanding of the mechanisms of far-field stimulation. Several other areas of cardiac stimulation, such as its statistical nature and the effect of stimulation waveforms, were not discussed here. The fundamental understanding of these areas continues to be enhanced by mapping and simulation techniques.

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All references cited in this chapter are available online at expertconsult.com.

CHAPTER 14

Fundamental Concepts in Defibrillation

Nipon Chattipakorn and Raymond E. Ideker

Sudden cardiac death (SCD) is a major health problem in developed countries.[1] Most deaths are believed to be caused by ventricular fibrillation (VF).[2] Currently, electrical defibrillation is the only effective means for terminating this fatal arrhythmia. The mortality rate from SCD has decreased in the past decade, partly because of the improved understanding of the nature of this fatality as well as the development of defibrillation devices. Recent advances in external defibrillators have led to the introduction of public-access defibrillators, which promises to significantly reduce the mortality rate of SCD. Recent advances in implantable defibrillators, such as the use of a biphasic waveform, have led to smaller intravenous devices that have been shown to significantly benefit certain groups of patients.[2-4] Despite these wide applications of transthoracic and intracardiac defibrillators, a great need for better means of defibrillation still exists. With better understanding of the fundamental mechanisms of defibrillation, it may be possible to devise strategies to improve defibrillation efficacy. This chapter presents some factors that are believed to be important and, perhaps, crucial in determining the outcome of a defibrillation shock.

Shock Creates Nonuniform Potential Gradient Distribution in the Heart

The success of defibrillation is dependent on the strength of the shock and is thought to be achieved by shock changing the transmembrane potential of the myocardial fibers. This change in the transmembrane potential is caused by current flow between the extracellular and intracellular spaces that is generated by the electrical shock. When the shock is delivered, different amounts of current flow through different parts of the heart. The distribution of this current flow is directly related to the potential gradient, the change in shock potential over space, and the spatial derivative of the potential gradient generated by the shock across the heart.[5-7] For shocks delivered from intracardiac electrodes, the distribution of the potential gradient is markedly nonuniform in that the high potential gradients are located near the electrodes that deliver the shock and the low potential gradients exist some distance away from the electrodes.[8] Other factors such as myocardial fiber curvature and orientation, myocardial connective tissue barriers, blood vessels, and scar tissue also have been shown to directly influence the transmembrane potential.[9-12]

When a shock is delivered to the heart, the pattern of potential voltages and potential gradient distributions created by the shock depends on the configuration of the shocking electrodes. In the case of a 1-V shock delivered from the electrodes on the right atrium (anode) and on the left ventricular (LV) apex (cathode), the largest negative potentials are created by the shock at the apex. The voltage drop is also marked at the ventricular apex, the region where the defibrillation electrode is located (Figure 14-1, *A*).[13] Figure 14-1, *B*, shows the potential gradients calculated from this potential distribution. For this configuration of the shocking electrodes, the potential gradient distribution is markedly uneven in that the potential gradient is much larger and changes faster (as indicated by narrow spacing between isogradient lines) in the apical portion than in the basal portion of the ventricles. For a 1.5-V shock delivered from electrodes at the lateral base of the right (anode) and left (cathode) ventricles (Figure 14-2), the voltage drop is marked at the regions close to the shocking electrodes (see Figure 14-2, *A*). The strongest potential gradient regions are in the basal portion of the ventricles near the electrodes, and the weakest gradient regions are near the apex, far from the shocking electrodes (see Figure 14-2, *B*).[13] Thus, regardless of the shocking electrode configuration, the distribution of the potential gradient created by shocks has a similar pattern. The high potential gradient region with rapidly changing gradients is near the defibrillation electrodes, and the low potential gradient regions frequently occur far from the shocking electrodes.[8,13]

Physiological Responses of the Myocardium to Stimuli

When an electrical stimulus is delivered to a myocardial fiber, several responses can be observed, depending on the stimulation strength, that is, the potential gradient created by a stimulus, and the phase of the action potential of the fiber at the time of stimulation.[14] If the stimulus is strong (above threshold) and is delivered to a cell that is in its resting state or is relatively refractory, a new action potential will be generated (Figure 14-3, *A*).[15] If the stimulus is weak (below the threshold) and is delivered to the cell at its resting state or refractory state, no response will be observed. However, if the stimulus is very strong (much above the threshold) and is delivered to a cell even at its highly refractory state, a graded response can occur (see Figure 14-3, *B*). The size of the graded response increases with the increase of the stimulus magnitude, the coupling interval, or both.[16] This graded response prolongs the action potential duration as well as the refractory period of the cardiac cell.[17,18] This type of cardiac response has been proposed to be a possible defibrillation mechanism, which is known as the *refractory period extension (RPE) hypothesis*.[19,20] This hypothesis states that successful shocks must be sufficiently strong to prolong the refractory period of cardiac tissue across the heart so that ectopic activation occurring after the shock, if any, will be prevented from propagation that could lead to re-entry and VF. However, because of the uneven

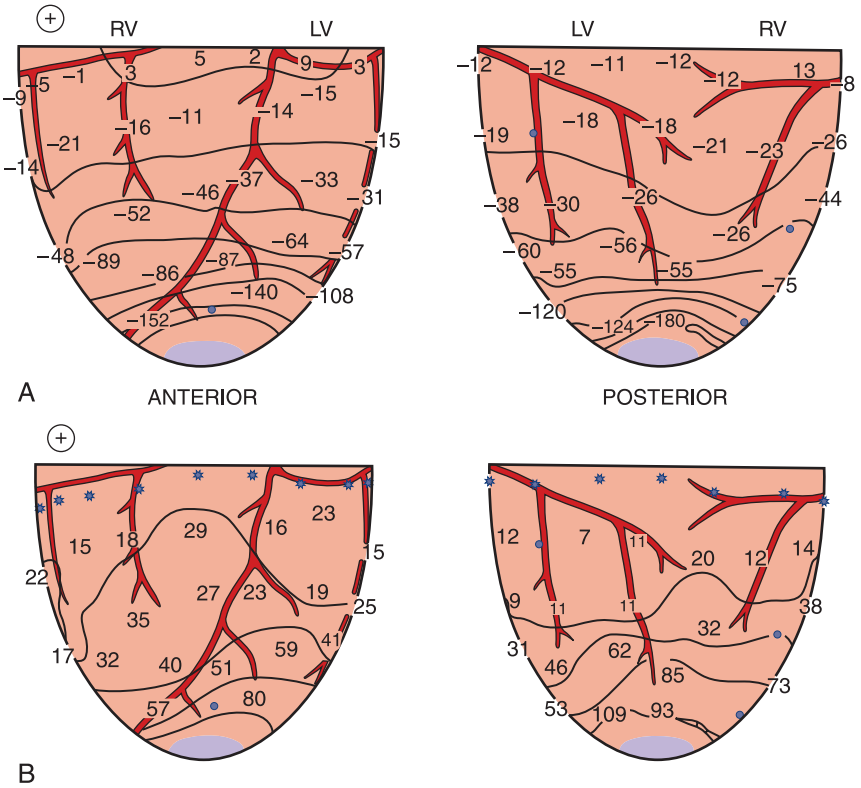

FIGURE 14-1 The epicardial maps of potential and potential gradient distribution created by a 1-V shock delivered from electrodes (*shaded circles*) at the apex (cathode [–]) and right atrium (anode [+]). The maps are displayed as two complementary projections of the anterior (*right map*) and posterior ventricles (*left map*). Numbers represent the potential (**A,** millivolt) and potential gradient (**B,** millivolt per centimeter) at their sites. *Solid circles* indicate inadequate recording sites. *Asterisks* indicate electrode sites near the ventricular border for which the gradient could not be calculated. The isopotential lines are 25 mV per shock volt (25 mV/V) apart; the isogradient lines are 25 mV/cm/V apart. **A,** The isopotential lines were close together at the apex where the shocking electrode was located and gradually became farther toward the base, indicating an uneven distribution of the potentials across the ventricles. **B,** The isogradient map calculated from **A.** An uneven gradient distribution caused by the shock is shown with the high-gradient area close to the apex where the shocking electrode was located and the low gradient area at the base far from the electrode. *(From Chen PS, Wolf PD, Claydon FJ, et al: The potential gradient field created by epicardial defibrillation electrodes in dogs,* Circulation *74:626–636, 1986.)*

distribution of potential gradients, to prevent these ectopic activations, potential gradients generated by the shock are stronger than needed in most regions of the heart to achieve the minimum required potential gradient for refractory period extension where the shock field is weakest.

Myocardial Responses to the Shock Delivered During Ventricular Fibrillation

During early VF, many wandering activation fronts are present at all times on the heart.[21] At different times during the same or different VF episodes, activation sequences are not constant and can differ markedly.[22,23] When shocks of the same or different strengths are delivered during VF, myocardial responses to each shock can be different from one shock to the next, depending on the state of the ventricles when the shock is given. Since these responses are thought to be crucial in determining defibrillation success, shocks of the same strength delivered to a fibrillating heart can sometimes succeed and other times fail to defibrillate. As a result, no definite threshold in shock strength demarcates successful defibrillation from failed defibrillation. The relationship between shock strength and defibrillation success can, therefore, be characterized as probabilistic. Other factors that may contribute to the probabilistic nature of defibrillation success include changes in autonomic tone and changes in heart volume during VF.[24,25] Although defibrillation success is probabilistic, as shock strength becomes stronger, the chance of defibrillation success becomes greater (Figure 14-4) for both transthoracic and intracardiac defibrillation.[26,27]

Regions of Immediate Postshock Activation

Defibrillation studies have demonstrated that the relationship between regions where activation appears on the heart soon after the shock and the extracellular potential gradient distribution created by the shock are well correlated. It has been proposed that for defibrillation to be achieved, it is necessary to raise the potential gradient throughout all, or almost all, of the ventricular myocardium to a certain minimum level.[28] This statement is supported by the findings that following weak shocks that fail to defibrillate, the immediate postshock activations arise at multiple sites throughout the ventricles.[29] With stronger shock strength, the numbers of sites of immediate postshock activation are decreased and are no longer found in the high potential gradient regions. Figure 14-5 demonstrates the sites of postshock activation recorded from the same animal as shown in Figures 14-1 and

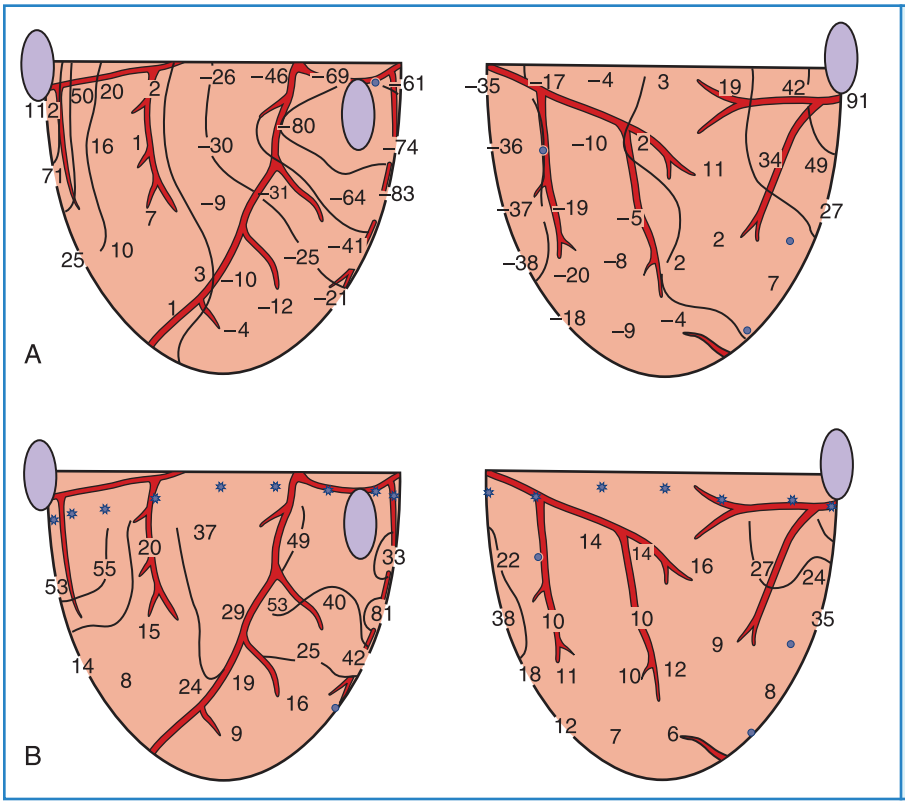

FIGURE 14-2 The epicardial maps of potential and potential gradient distribution created by a 1.5-V shock delivered from electrodes (*shaded circles*) at the right (anode [+]) and left (cathode [–]) ventricular bases. **A,** The isopotential lines were close together near the two shocking electrodes. **B,** The isogradient map calculated from **A.** Regions of high potential gradient were near the two defibrillation electrodes. *(From Chen PS, Wolf PD, Claydon FJ, et al: The potential gradient field created by epicardial defibrillation electrodes in dogs,* Circulation *74:626–636, 1986.)*

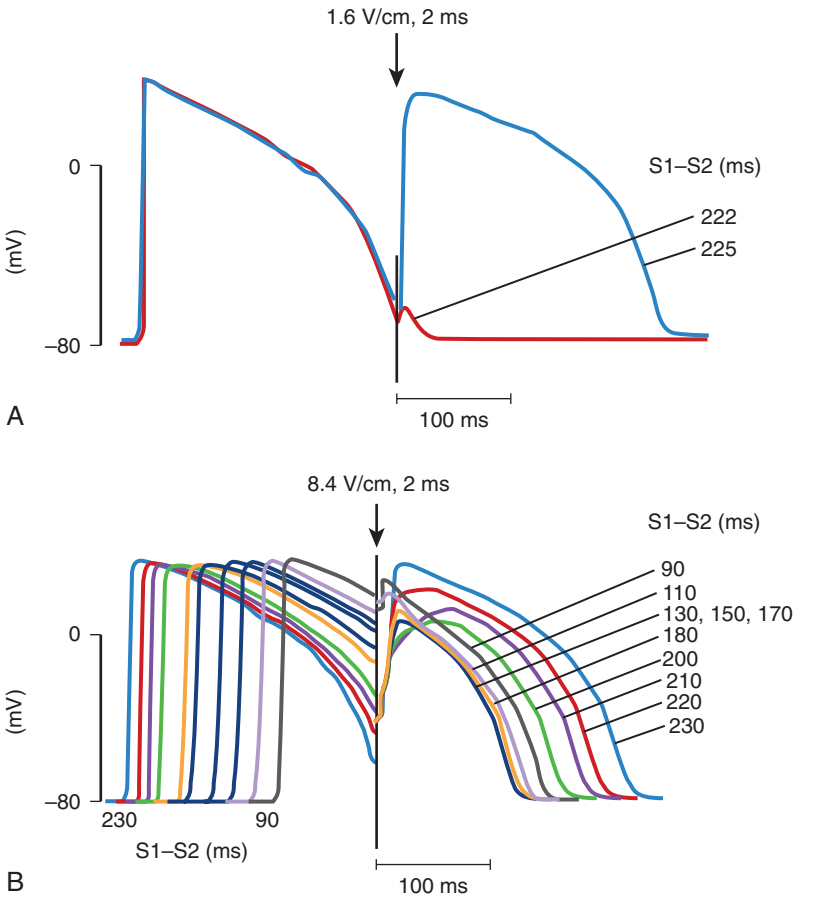

FIGURE 14-3 A, All-or-none cellular responses to an S2 shock field stimulus (1.6 V/cm at the cell) taken from single-cell recordings. There was almost no cellular response when S2 was delivered at an S1-S2 interval of 222 ms. However, a new action potential was generated when an S2 shock was delivered only 3 ms later than the first one that had no response. **B,** Recordings illustrating a range of action potential prolongation caused by an S2 field stimulus (8.4 V/cm at the cell). The recordings are taken from the same cell and are aligned with the S2 time. The coupling intervals of S1-S2 are indicated at the bottom of the recordings before S2 is given. The S1-S2 intervals for each of the responses after S2 are indicated to the right of the recordings. The degree of action potential prolongation increased as the S1-S2 interval increased. *(From Knisley SB, Smith WM, Ideker RE: Effect of field stimulation on cellular repolarization in rabbit myocardium. Implications for reentry induction,* Circ Res *70:707–715, 1992.)*

14-2. In the study, shocks were delivered from two different electrode configurations; the site of the earliest recorded postshock activation was at the base of the ventricles for a shock given from the right atrial and ventricular apical electrodes (see Figure 14-5, *A*) and was at the apex of the ventricles for the shock given from the right and left ventricular basal electrodes (see Figure 14-5, *B*). Both regions correspond to the weak potential gradient area created by shocks delivered from each shocking electrode configuration (see Figures 14-1, *B*, and 14-2, *B*). These results suggest that the potential gradient field created by the shock is important in determining the immediate response of the myocardium to defibrillation shocks. Since the potential gradient field created by the shock is markedly uneven, a strong shock is normally required to create a potential gradient that reaches the optimal level at the region where the gradient field is weakest in the ventricles. However, this strong shock can be detrimental, since it can create excessively high gradient near the shocking electrodes and may damage the myocardium.[30,31] Several studies have shown that this detrimental effect can lead to postshock conduction block and arrhythmias.[32]

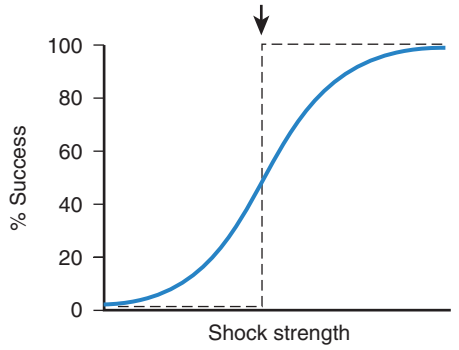

FIGURE 14-4 The probability of defibrillation success curve. The defibrillation threshold is not a discrete value (*dashed line*). The relationship between shock strengths and defibrillation success is characterized as a sigmoidal-shaped dose–response curve (*solid line*). High-strength shocks have a greater chance of defibrillation success than do low-strength shocks. *(Modified from Davy JM, Fain ES, Dorian P, Winkle RA: The relationship between successful defibrillation and delivered energy in open-chest dogs: Reappraisal of the "defibrillation threshold" concept,* Am Heart J *113:77–84, 1987.)*

Why Do Shocks Fail to Defibrillate?

Following the near-threshold shocks that fail to defibrillate, the earliest recorded postshock activation that propagates throughout all, or almost all, of the myocardium always arises in the low potential gradient regions. After several such organized cycles in rapid succession, activation becomes more disorganized, allowing fibrillation to resume. Currently, two possible mechanisms are thought to explain the origin of these early postshock activation cycles in the low potential gradient regions. The first one is known as the *critical mass hypothesis*. According to this hypothesis, the gradient field created by the shock is too weak to halt the fibrillatory wavefronts present in those regions, allowing the fibrillation to continue propagation after the shock.[33-35] The second hypothesis is known as the *upper limit of vulnerability hypothesis for defibrillation*. This hypothesis suggests that a shock of near-threshold strength is already strong enough to terminate all fibrillatory wavefronts, including those in the low gradient regions. However, this shock fails to defibrillate because it creates new activation fronts in these regions.[29,36,37] These activations then spread out, eventually causing block and disorganized activations

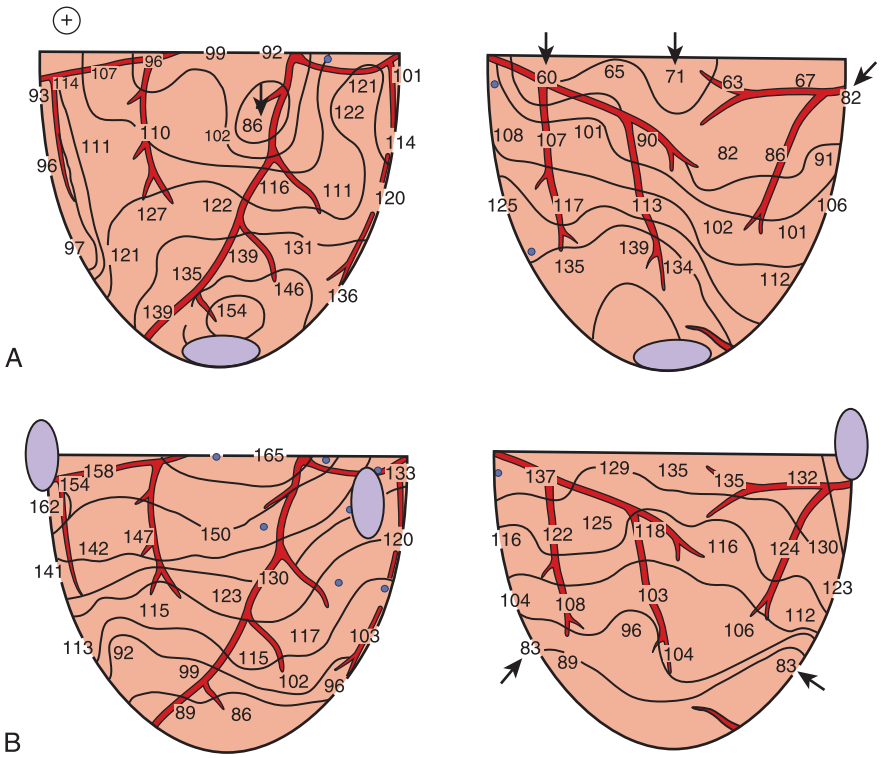

FIGURE 14-5 Isochronal maps of the first postshock activation. The *thin solid lines* are isochrones spaced 10 ms apart. *Numbers* represent activation times at each recording electrode in milliseconds relative to the shock onset. **A,** A 4.9-J failed defibrillation shock given via electrodes placed at the right atrium and the apex during ventricular fibrillation. The sites of earliest postshock activation were located at the base of the ventricles (*arrows*), the weak potential gradient region created by the shock delivered from this electrode configuration, as indicated by the gradient map shown in Figure 14-1, *B*. **B,** A 23.2-J failed defibrillation shock given via electrodes placed at the right and left ventricular bases during ventricular fibrillation. The sites of the earliest activation were located at the posterior and apical aspects of the ventricles (*arrows*), the weak potential gradient region for this configuration of the shocking electrodes, as indicated by the gradient map shown in Figure 14-2, *B*. *(From Chen PS, Wolf PD, Claydon FJ, et al: The potential gradient field created by epicardial defibrillation electrodes in dogs,* Circulation *74:626–636, 1986.)*

across the ventricles, degenerating back into VF. These two hypotheses continue to be debated.[38-40] Whatever the mechanism is, these two hypotheses agree that since the direct effect of the shock at each myocardial region depends on both the strength of the shock (i.e., the potential gradient) and the phase of the cardiac cycle at the time the shock is delivered, the shock potential gradient or its derivative must be sufficiently high to stop fibrillatory fronts on the ventricles or not create new activations that allow fibrillation to resume, or both.[29,36,37]

The Critical Point Hypothesis: Classic Interpretation

Previous cardiac mapping studies demonstrated that following failed defibrillation with shocks near the defibrillation threshold (DFT) in strength, the pattern of activation after the shock was different from the VF activation pattern immediately prior to the shock.[29,36] These findings suggest that the postshock activation was not the unaltered activation continuing from VF activation prior to the shock in that region. Rather, the shock terminated all VF activation fronts but failed to defibrillate because it generated a new activation in the weak gradient region that degenerated into VF. The critical point hypothesis has been proposed to explain how a shock generates a new activation in this weak gradient area that leads to fibrillation. The concept of this hypothesis is based on the relationships among the distribution of potential gradients created by the shock, the state of the myocardium at the time of the shock, and the myocardial response to the shock. This hypothesis was proposed theoretically by Winfree and later was demonstrated experimentally by Frazier et al.[41,42] During the shock, different responses of cardiac tissue to an electrical stimulation can be observed. As a result, depending on the state of the cardiac tissue at the time of the shock, some regions of the myocardium can be directly activated by the shock field to undergo a new action potential, and other regions can undergo RPE caused by a graded response of the action potential.[15,17,43,44] Thus, an activation front arises after the shock that terminates at a critical point on the boundary between these two types of regions. This blindly ending activation front propagates to form a functional re-entrant circuit.

Frazier et al tested this hypothesis by delivering a shock to the canine heart during paced rhythm (Figure 14-6).[42] A row of epicardial stimulating wires on the right of the recording region is

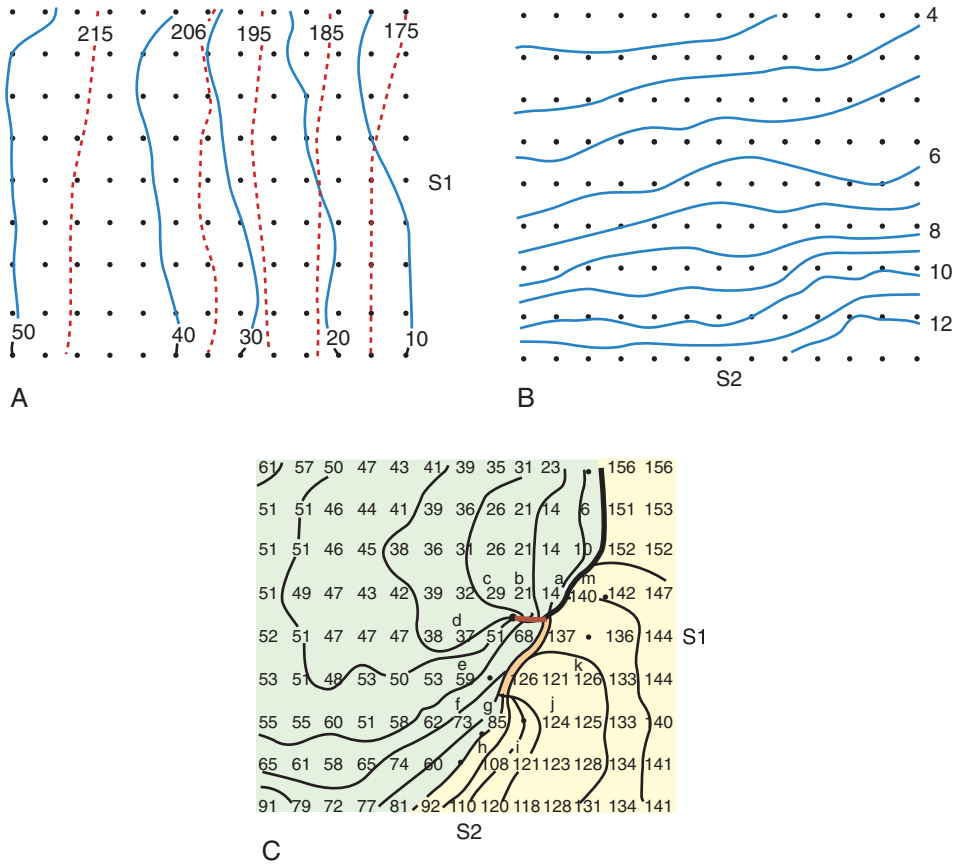

FIGURE 14-6 Re-entrant circuit formation by a shock. **A,** Activation times during the last S1 beat (*solid lines*) and recovery times to a local 2-mA stimulus (*dashed lines*) in milliseconds. **B,** Distribution of potential gradient created by the S2 stimulus in volts per centimeter. **C,** The initial activation pattern immediately after the S2 is delivered. *Numbers* give activation times at each recording electrode in milliseconds timed from the S2 stimulus. The *solid lines* portray isochronal lines spaced at 10-ms intervals. The *yellow area* indicates portions of the mapped region thought to be directly activated by the S2 stimulus field. A frame line (*heavy solid line*) represents the origin of the activation front propagating away from the directly activated region and also indicates the transition between the map for this activation cycle and the map for the next cycle (not shown). The *brown line* indicates a zone of functional conduction block at the center of the re-entrant circuit. *(From Frazier DW, Wolf PD, Wharton JM, et al: Stimulus-induced critical point. Mechanism for electrical initiation of re-entry in normal canine myocardium,* J Clin Invest *83:1039–1052, 1989.)*

used to deliver S1 pacing. Figure 14-6, *A*, shows activation times and recovery times distributed across the mapped region during the last S1 pacing beat. Solid lines represent the spread of the activation front away from the S1 electrodes, and dashed lines represent the recovery times estimated from the refractory period to a local 2-mA stimulus. The S2 shock is delivered through a long narrow electrode placed near the bottom of the mapped region that is perpendicular to the activation front arising from the S1 pacing stimulus. The potential gradients created by a large premature S2 shock (Figure 14-6, *B*) demonstrate that the highest potential gradient is located in the region close to the S2 electrode and weakens with distance away from the S2 electrode. S2 shocks are delivered to scan the vulnerable period following the last S1.

Figure 14-6, *C*, demonstrates the initial activation pattern when a re-entrant circuit is formed after the S2 shock is delivered at an S1–S2 coupling interval when a dispersion of refractoriness is present across the mapped region. Following the strong S2 stimulation, an activation front first appears a few centimeters away from the S2 electrode with one end terminating blindly at a point in the center of the mapped region where the S2 potential gradient is approximately 6 V/cm and where the tissue is just passing out of its absolute refractory period.[42] This point is called the *critical point for re-entry*. This activation front then propagates away from the S1 electrode, pivots around the critical point, later spreads through the lower left quadrant, and forms a re-entrant circuit as it enters the right lower quadrant that continues for over 10 cycles before degenerating into VF.

The formation of the re-entrant circuit is proposed to be caused by different cardiac tissue responses to the S2 shock field in different cardiac regions at the time the shock is delivered. According to the cardiac tissue responses to the S2 shock, the mapped region can be divided into four zones that roughly form quadrants (centered at the critical point). The myocardium in the hatched region (top and bottom right quadrants) recovers sufficiently at the time of the shock so that it is directly activated. The myocardium in the top left quadrant is not directly activated because it is more refractory than the tissue in the hatched region. Since the shock potential gradient is weaker than the critical value needed to cause a graded response in the top quadrant, the myocardial refractoriness in this quadrant is not extended. However, the potential gradient created by the shock in the bottom quadrant is stronger than the critical value. Therefore, the refractoriness of the cardiac tissue in the bottom left quadrant close to the S1 pacing electrode is prolonged by a graded response, since the myocardium in this region is less refractory than that of the myocardium far from the S1 pacing electrode. The majority of the myocardium in the bottom left quadrant is too refractory to be affected by the shock, although it is exposed to a strong potential gradient. As a result, the activation front forming in the directly activated region (yellow area) can propagate only from the top right quadrant to the top left quadrant. Directly excited activation in the bottom right quadrant cannot propagate to the left, since it is blocked by the myocardium in a prolonged refractory state. By the time the activation front from the top left quadrant enters the bottom left quadrant, the cardiac tissue in the bottom left quadrant has already recovered, allowing this activation to propagate through it and to re-enter the directly activated tissue in the lower right quadrant which has, by this time, also recovered excitability. As a result, a counterclockwise re-entrant circuit is formed around the critical point.

The Critical Point Hypothesis: New Interpretation

Recent optical mapping studies have shown that when an electrical stimulus is applied to the myocardium, different polarities of transmembrane potential changes are observed near the stimulating electrode.[6,10,45-47] During a defibrillation shock, it has been proposed that depolarized and hyperpolarized regions caused by the shock are interspersed throughout the heart.[10,48,49] By using an optical mapping technique to investigate the mechanism of failed defibrillation, Efimov and colleagues recently demonstrated a different type of re-entrant circuit formation than that by the classic critical point.[48] Their results showed that the formation of a critical point where a re-entrant circuit is observed depends on the magnitude and distribution of depolarization and hyperpolarization of the transmembrane potential created by the shock. A critical point is formed on the boundary between depolarized and hyperpolarized regions when the magnitude and rate of change of transmembrane polarization across this boundary are sufficiently large. In the region where the tissue is hyperpolarized by the shock, this hyperpolarization can "de-excite" tissue that was depolarized just before the shock, thus restoring the excitability of the myocardium in that region.[6,48] According to these results, the potential gradient and refractoriness are not critical for re-entrant circuit formation. Figure 14-7 illustrates re-entrant circuit formation based on the classic and the new forms of the critical point hypothesis.

Figure 14-7, *A*, illustrates the classic type of critical point formation as demonstrated by Frazier and colleagues.[42] The S1 pacing electrode is located on the left, and the S2 shocking electrode is at the bottom of the mapped region. When the shock is delivered, the myocardium that is directly activated (DA) by the S2 shock is located near the S1 pacing electrode. Myocardium that has RPE is in the region near the S2 electrode. As a result, the activation arising in the DA region can propagate only unidirectionally in a clockwise manner around the critical point.

An idealized diagram illustrating the new type of critical point formation is shown in Figure14-7, *B*. When a shock is delivered, it creates regions of depolarization adjacent to regions of hyperpolarization.[10,46,47] The magnitude of depolarization caused by the shock in the DA region is high at the top (large positive numbers) and gradually decreases toward the bottom (small positive numbers). Adjacent to the depolarized region is a region of hyperpolarization. The magnitude of hyperpolarization caused by the shock is also high (large negative numbers) and gradually decreases from the top toward the bottom (small negative numbers). The pattern of transmembrane potential distribution produced by the shock creates a large gradient between the depolarized and hyperpolarized regions, as indicated by the closely spaced isolines at the top center of the panel. The large gradient between the two adjacent transmembrane polarities allows an activation front to propagate from the depolarized region into the hyperpolarized region (arrow at the top). No propagation is present in the bottom half of the panel because the gradient in transmembrane potentials is too small. As a result, a critical point is formed at the intersection of the frame and block lines (indicated by hatched [black] and solid lines [red], respectively) where one end of the propagating activation front terminates. Thus, activation arising in the DA region propagates unidirectionally from the top toward

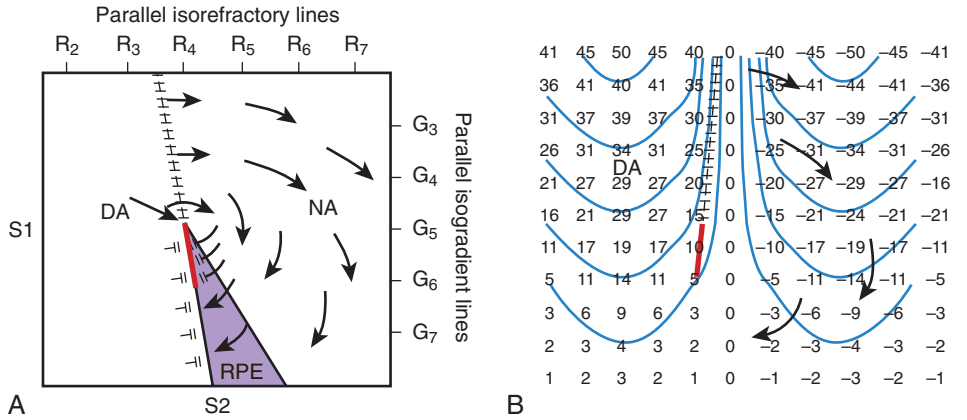

FIGURE 14-7 Two types of hypothesized critical points. **A,** Idealized diagram corresponding to the experiment shown in Figure 14-6 is shown with a critical point formed at the intersection of a critical shock potential gradient of G_5 and a critical tissue refractoriness of R_4. S1 pacing is performed from the left to cause a dispersion of refractoriness at the time of the S2 shock, with R_2 representing less refractoriness and R_7 more refractoriness. The S2 shock is given during the vulnerable period from the bottom of the region with large-gradient G_7 at the bottom and small-gradient G_3 at the top. The region labeled *DA* (directly activated) is sufficiently recovered so that it is directly activated by the gradient field. The area in the *purple region,* although more refractory, is exposed to a higher gradient and undergoes refractory period extension (*RPE*) so that activation in the DA tissue cannot propagate through this region. The region *NA* is too refractory to be affected even with a large gradient. Thus, propagation conducts unidirectionally from the *DA region* to the *NA region* at the top, encircling the critical point, re-entering the DA region to create a re-entrant circuit. **B,** An idealized diagram is shown of a critical point caused by adjacent regions of depolarized and hyperpolarized transmembrane potential changes. Numbers represent transmembrane changes with isolines spaced every 10 mV beginning at –45 mV. DA occurs to the left of the frame line where depolarized transmembrane potential changes are above the threshold. Where the gradient in transmembrane potential is high, as indicated by the closely spaced isolines at the top center of the panel, conduction can occur into the hyperpolarized region. Below, where the gradient in transmembrane potential is smaller, propagation cannot occur. A critical point is formed at the intersection of the frame (*hatched*) and block (*red*) lines where one end of the propagating activation front terminates in both panels. *(From Chattipakorn N, Ideker RE: Mechanism of defibrillation. In Aliot E, Clementy J, Prystowsky EN, editors:* Fighting sudden cardiac death: A worldwide challenge, *New York, 2000, Futura.)*

bottom (arrows) and re-enters the DA region later, forming a clockwise re-entrant circuit.

Although these two interpretations suggest different mechanisms of critical point formation, they both indicate that defibrillation fails because of re-entrant activation caused by the shock, which later degenerates into VF. Most cardiac mapping studies using a large-animal model have shown that a re-entrant activation pattern is rarely observed after a shock that fails to defibrillate and that is near the defibrillation threshold in strength. [29,35,50-53] Epicardial focal activation patterns are commonly observed in these studies. Transmural or Purkinje-myocardial re-entry has been proposed to be the possible mechanism giving rise to the activation fronts with the epicardial focal activation pattern that is observed in these studies; this pattern is caused by epicardial breakthrough instead of having a true focal origin.[29,35,51-53] To test this hypothesis, three-dimensional mapping is needed. Currently, only a few three-dimensional studies have been performed to investigate the defibrillation mechanism. Chen and colleagues performed a transmural cardiac mapping study and demonstrated that only a few episodes of fibrillation after a failed defibrillation shock are initiated by a re-entrant circuit.[50] Many appear to arise from a focus. Consistent with this finding, a recent three-dimensional cardiac mapping study demonstrated that the earliest postshock activation after near–defibrillation threshold shocks arise in a focal pattern.[54] These findings suggest that the current interpretations of critical point formation may only partially explain the mechanisms of defibrillation and that the relationship between the shock delivered to a fibrillating heart and cardiac responses to the shock is complex.

Table 14-1 Threshold

	MA	V/cm
Diastolic pacing	0.5	1
Ventricular fibrillation	20	6
Defibrillation	10,000	6

From Ideker RE, Zhou X, Knisley SB: Correlation among fibrillation, defibrillation, and cardiac pacing, Pacing Clin Electrophysiol *18:512–525, 1995.*

Upper Limit of Vulnerability and Defibrillation Mechanism

VF can be induced when an electrical stimulus within a certain range of strengths is delivered to the myocardium during the vulnerable period of the cardiac cycle in normal sinus or paced rhythm.[55] The lowest stimulation strength that can induce VF is known as the *VF threshold* (Figure 14-8). As the stimulation strength is increased, VF can still be induced until the stimulus strength reaches a value above which VF can no longer be induced again. This strong stimulation strength that no longer induces VF, no matter when this stimulus is delivered during the vulnerable period of repolarization, is known as the *upper limit of vulnerability* (ULV) (see Figure 14-8).[56] Table 14-1 shows the estimated threshold of the stimulus current and the voltage gradient required for different myocardial responses.[28]

The existence of the ULV has been linked to the mechanism of defibrillation.[36,37] Since fibrillation is thought to be maintained

by re-entry, activation fronts should be continuously present. If so, repolarization should also occur continuously. When a shock is delivered to defibrillate the heart, it is probable that some portions of the myocardium are in the vulnerable period while they are exposed to the shock. The defibrillation shock, therefore, can induce VF in this region if the shock gradient in this region is stronger than the VF threshold but weaker than the ULV, which results in failed defibrillation. However, if the shock is sufficiently strong that it surpasses the ULV across the whole heart, VF will not be induced, resulting in successful defibrillation. Therefore, according to this concept, to successfully defibrillate, the shock must be strong enough that it will not induce new activation(s) that can lead to refibrillation after the shock. Indeed, it has been shown that the ULV and the defibrillation threshold are well correlated (Figure 14-9), suggesting that the existence of the ULV is a possible explanation for defibrillation mechanism.[29,36,56-59] This hypothesis is known as the *ULV hypothesis for defibrillation*, which states that a successful shock must terminate all VF activation fronts and, at the same time, not generate new postshock activation that can reinitiate fibrillation.[60,61]

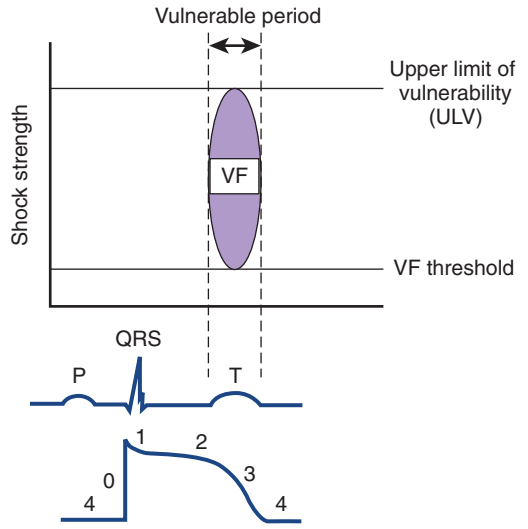

FIGURE 14-8 Diagram illustrating the relationship among the shock strength, the vulnerable period, and ventricular fibrillation *(VF)*. Shocks of a strength at or above the VF threshold induce VF *(oval)* when delivered at an appropriate time during the vulnerable period (corresponding to a portion of the T wave on the electrocardiogram or the repolarization phase of the action potential). Shocks stronger than the upper limit of vulnerability *(ULV)*, however, no longer induce VF when given at any time during the cardiac cycle. *(From Chattipakorn N, Ideker RE: Mechanism of defibrillation. In Aliot E, Clementy J, Prystowsky EN, editors:* Fighting sudden cardiac death: A worldwide challenge, *New York, 2000, Futura.)*

The critical point hypothesis has been proposed to explain the relationship between the defibrillation threshold and the ULV (Figure 14-10).[28] When a shock is delivered, the potential gradients created by the shock are high in the region closest to the electrode and progressively decrease with distance from the electrode. Since a certain critical potential gradient is required to form a critical point, a weak shock (i.e., at the VF threshold) can create the critical potential gradient only in the region closest to the shocking electrode (see Figure 14-10, line a), resulting in critical point formation near the S2 electrode. As the shock strength becomes stronger, the critical gradient will move further from the shocking electrode (see Figure 14-10, lines b to h). Thus, the formation of critical points and re-entrant circuits will move farther away from the shocking electrode. When the shock is strong enough that the potential gradients created by the shock are greater than the critical value throughout the ventricular myocardium (see Figure 14-10, line i), no critical point will be created in the ventricles, and no re-entrant circuit will be formed. This shock strength, therefore, reaches the level of the ULV when the shock is delivered during the vulnerable period of normal sinus or paced rhythm and will successfully defibrillate when the shock is delivered during VF. This concept recently has been tested and is supported experimentally by a study from Idriss and colleagues.[62]

Although re-entrant circuit formation around the critical point has been proposed to be responsible for defibrillation failure and VF induction during a T-wave shock, the re-entrant pattern is not

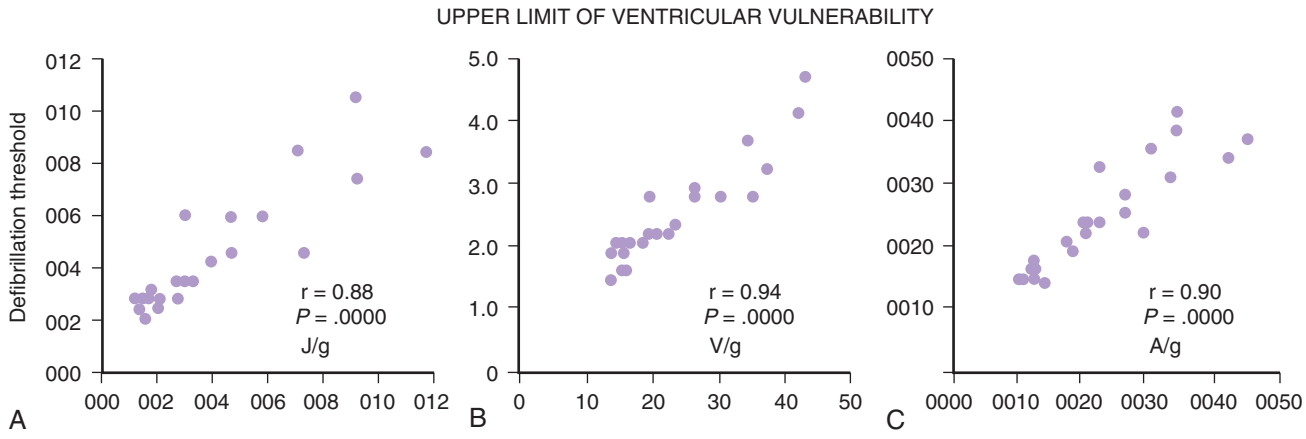

FIGURE 14-9 Correlation of the defibrillation threshold and the upper limit of vulnerability for electrodes on the right atrium (anode) and the left ventricular apex (cathode). Results are obtained from 22 dogs and expressed in units of energy (**A**), voltage (**B**), and current (**C**). All units are expressed per gram of heart weight. *(From Chen PS, Shibata N, Dixon EG, et al: Comparison of the defibrillation threshold and the upper limit of ventricular vulnerability,* Circulation *73:1022–1028, 1986.)*

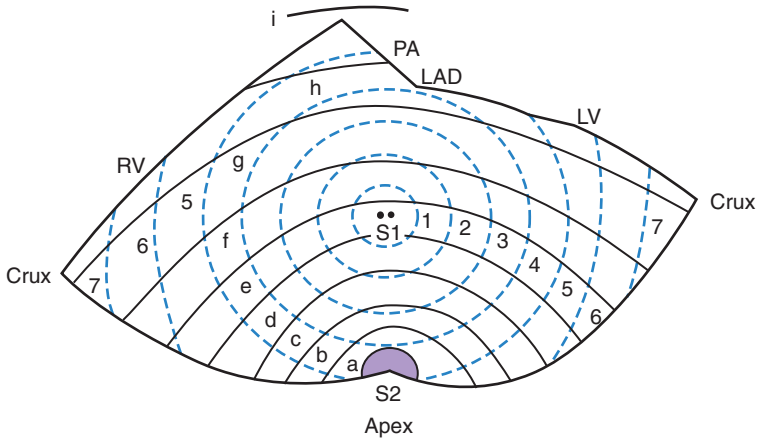

FIGURE 14-10 An illustration of a hypothesized critical point formation when a shock is given to the ventricles. The epicardial surface of the canine heart is depicted as if the ventricles were folded out after an imaginary cut was made from the crux to the apex. Isorecovery lines *(dashed lines 1 to 7)*, representing different degrees of refractoriness, are concentric about the pacing site labeled *S1*. Large premature stimuli are delivered from the apex of the heart through the electrode labeled *S2,* with the return electrode located elsewhere in the body away from the heart. Isogradient lines *(solid lines a to i)*, representing different levels of extracellular potential gradient, are concentric about the S2 electrode, with the smallest values in the ventricles occurring in the small region at the top of the ventricles representing the pulmonary outflow tract. *RV*, Right ventricle; *LV*, left ventricle; *PA*, pulmonary artery; *LAD*, left anterior descending coronary artery. *(From Ideker RE, Tang ASL, Frazier DW: Ventricular defibrillation. In Epstein AE, Saumont R, editors:* Cardiac pacing and electrophysiology, *Orland, FL, 1991, Saunders.)*

frequently observed in most studies.[35,51-53,63] These results suggest that the critical point hypotheses may only partially explain the mechanisms of defibrillation and VF induction. For example, recent VF induction and defibrillation studies in porcine models, using near-threshold strength shocks, demonstrated that rapid repetitive postshock activations arising focally from the weak potential gradient region are responsible for VF re-induction in failed defibrillation.[53,63,64] No epicardial re-entry was found in those studies. While intramural re-entry may be responsible, several studies have suggested that shock-induced automaticity or triggered activity may be responsible for these rapid repetitive activations arising after the shock.[65-68] These findings indicate that other mechanisms, that is, focal activity, may be responsible for defibrillation failure. It is important to note that most of the re-entrant activity has been reported in studies that applied weak shocks, that is, well below the defibrillation threshold, in a small heart model, for example, guinea pig or rabbit.[48,69,70] Focal activity, however, has been demonstrated in studies that applied strong shocks, that is, near the defibrillation threshold, to induce VF or to defibrillate canine and porcine hearts.[36,51,53,63]

Near-Threshold Shocks and Mechanism of Defibrillation

Why do some shocks succeed and others fail to terminate VF? The answer to this simple question remains surprisingly elusive. Although defibrillation has been extensively studied for many years, its mechanisms continue to be debated.[38-40] The inconsistent results obtained from these studies could be influenced by the differences in shock strengths and the species used in those studies. To minimize the effect of shock strength and species differences on shock outcome, recent studies have investigated the mechanisms of defibrillation using only the near-defibrillation threshold strength shocks; also, the studies have been performed in whole pig hearts, and this large animal model has been used because it has physiological and anatomic similarities to the human heart.[51-53,71]

Following near-threshold defibrillation shocks that successfully defibrillated 50% of the time (DFT_{50}), Chattipakorn and colleagues demonstrated that the patterns of the first postshock activation cycle are indistinguishable between successful and failed shocks.[53] However, in this study, starting at cycle 2, activation cycles arose on the epicardium progressively faster and the time to traverse the ventricles was progressively slower in failed shocks than in successful shocks (Figures 14-11, *A* and *B*). These first few postshock activations always arose focally at the LV apex, the region where the shock potential gradient field was weak for the shocking electrode configuration (right ventricular [RV] apex–superior vena cava [SVC]) used in this study (Figure 14-12).[8] These findings suggested that it is the number and rapidity of the postshock activation cycles, not the immediate postshock activation, that determines the shock outcome. To test this hypothesis, a subsequent study in which one to five pacing stimuli were delivered at the LV apex following a shock above the defibrillation threshold.[72] The shock itself always successfully defibrillated, and the five pacing stimuli mimicked the rapid successive postshock cycles observed in the DFT_{50} shock study. To re-initiate VF, three rapid successive postshock pacing stimuli were always required; one or two pacing stimuli never re-initiated VF even at the shortest coupling intervals that captured. These findings were consistent with the DFT_{50} shock study and supported the hypothesis that the number and rapidity of postshock activations determine shock outcome.[53,72]

The ULV hypothesis states that failed defibrillation has a mechanism similar to that of VF induction caused by a shock delivered during the vulnerable period. A recent study was carried out to test this hypothesis by using shocks of the same strength near the ULV that induced VF 50% of the time (ULV_{50}) to compare the results with those when DFT_{50} shocks were given during fibrillation.[63] The study demonstrated that the patterns of the first postshock activation were indistinguishable from shocks that induced VF and shocks that did not (Figure 14-13). In VF induction episodes, the subsequent cycles arose progressively faster, and the

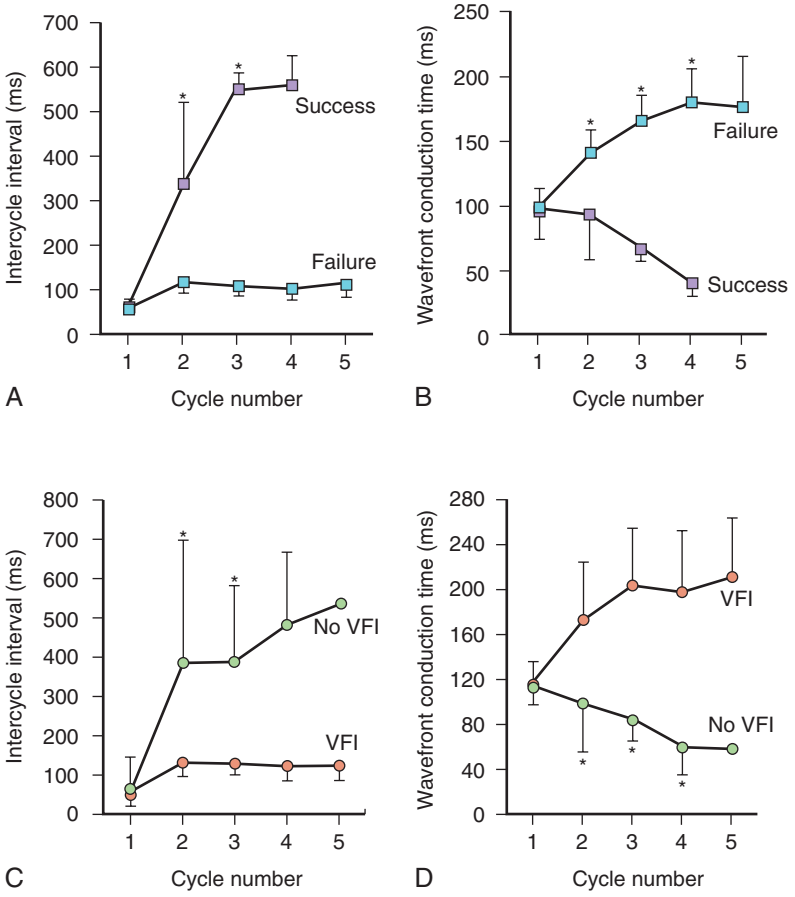

FIGURE 14-11 The intercycle interval (the interval between the onset of two successive postshock cycles) and the wavefront conduction time (the time the cycle needs to traverse the ventricles) of the first five postshock cycles following defibrillation shocks all of the same strength that successfully defibrillate 50% of the time, DFT_{50} (**A** and **B**) and shocks during the vulnerable period of paced rhythm that induced VF 50% of the time, ULV_{50} (**C** and **D**). *Asterisk* signifies a significant difference between the two outcomes for that cycle. *Success*, Successful defibrillation, *Failure*, failed defibrillation, *VFI*, successful VF induction by upper limit of vulnerability (ULV) shocks, *NoVFI*, failed VF induction by ULV shocks.

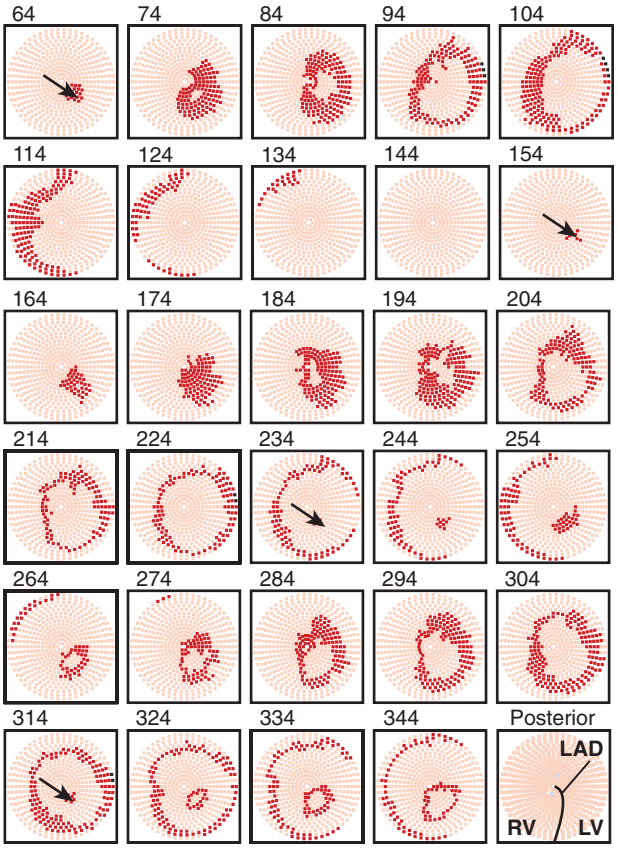

FIGURE 14-12 Example of postshock cycles following a failed DFT_{50} defibrillation shock. The orientation of the recording electrodes (*pink or red squares*) relative to the ventricles is shown in the bottom right map. Each panel shows in red the electrode sites at which dV/dt is ≤–0.5 V/s at any time during a 10-ms interval indicating activation. *Numbers* above the frames indicate the start of each interval in milliseconds relative to the shock onset. *Arrows* indicate the site of earliest recorded activation for each cycle. The first cycle appeared on the epicardium 64 ms after the shock at the anteroapical left ventricle (LV) and propagated toward the anterobasal LV. The second cycle (154 ms) arose on the epicardium in the same region as the first cycle and also propagated away in a focal pattern. The third (235 ms) and the fourth (315 ms) cycles arose before the activation front from the previous cycle disappeared. *(Reproduced with permission from Chattipakorn N, Fotuhi PC, Ideker RE. Prediction of defibrillation outcome by epicardial activation patterns following shocks near the defibrillation threshold,* J Cardiovasc Electrophysiol *11:1014–1021, 2000.)*

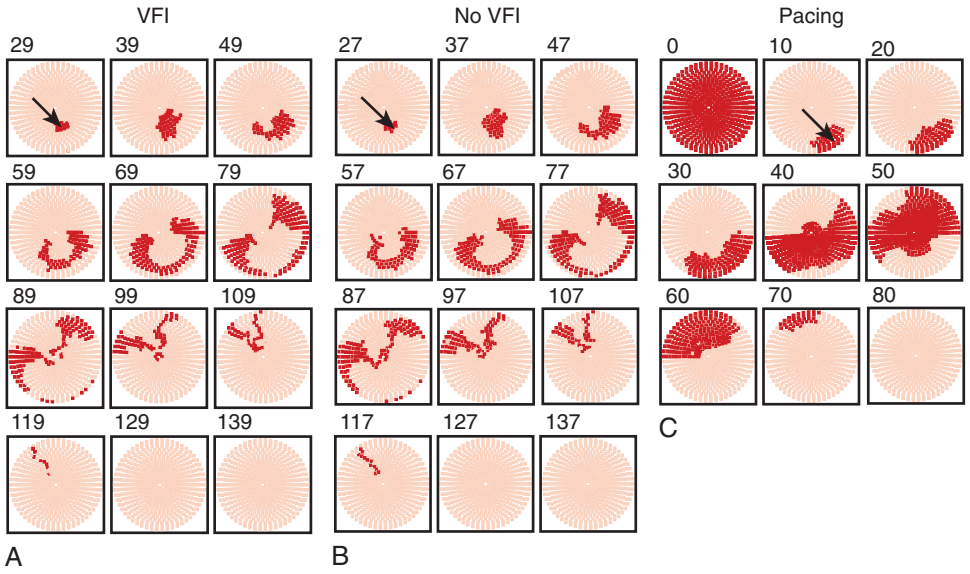

FIGURE 14-13 Examples of postshock cycle 1 following ULV_{50} shocks for VFI (**A**) and No VFI (**B**) and of a paced cycle (**C**) from the same animal. Map orientation is similar to Figure 14-12. *Arrows* indicate the early site for each cycle. **A,** Cycle 1 arose at anteroapical LV, propagated toward the anterobasal LV and blocked over RV apex. **B**, Cycle 1 arose in the same region as in **A** and propagated similarly. **C,** Activation initiated by pacing from anterobasal epicardial LV propagated without slowing across the apex, suggesting that no anatomic block was present at the apex. *ULV50*, Vulnerable period of paced rhythm that induced VF 50% of the time; *VFI*, ventricular fibrillation induction; *NoVFI*, failed ventricular fibrillation induction; *LV*, left ventricle; RV, right ventricle. *(Reproduced with permission from Chattipakorn N, Rogers JM, Ideker RE: Influence of postshock epicardial activation patterns on initiation of ventricular fibrillation by upper limit of vulnerability shocks,* Circulation *101:1329–1336, 2000.)*

time to traverse the ventricles was progressively longer than in the episodes in which shocks did not induce VF (see Figures 14-11, *C* and *D*). These results were similar to the findings obtained from the DFT_{50} shock study, supporting the ULV hypothesis for defibrillation.[53] To test whether the number and rapidity of postshock cycles determined the shock outcome for VF induction, as suggested by the defibrillation pacing study described above, in a similar study one to five pacing stimuli were delivered at the LV apex following a shock stronger than the ULV.[64] The shock itself never induced VF, and the five pacing stimuli mimicked the rapid successive postshock cycles observed in the near-threshold shock study. The results demonstrated that three rapid successive postshock pacing stimuli are always required to induce VF; one or two pacing stimuli never reinitiated VF even at the shortest coupling intervals that captured. These findings were all consistent with the defibrillation pacing study and confirmed that the number and rapidity of postshock activations determined shock outcome.[53,63,64]

Small Arrhythmogenic Region after Near-DFT Shocks

Results from the near-threshold studies for both defibrillation and VF induction were all consistent in that following the shock, the sites of earliest activation always arose at the LV apex, the low shock potential gradient region for the RV apex–SVC shocking electrode configuration.[8] Activations arose repeatedly faster but in an organized pattern from this region for at least five cycles before degenerating into VF, as observed in both defibrillation and VF induction studies.[51,53,63,64] It is not known what produces these postshock activations and why this postshock activity spontaneously stops after a few cycles leading to a successful defibrillation or failed VF induction in some cases, while it continues and generates VF leading to failed defibrillation or successful VF induction in others. However, these findings underscore the extreme importance of this small arrhythmogenic region after the shock. The similarity of the immediate postshock activation pattern between successful and failed shocks suggests that the global dispersion of refractoriness following the shock may not be the key determinant for the success or failure of defibrillation in normal hearts. Rather, the state of the small arrhythmogenic region from which the postshock cycles arise is the crucial determinant of shock outcome.

Several studies have strongly supported this hypothesis. Studies in which a tiny shock, 50 to 100 V, was given to a small electrode on the epicardium at the LV apex, the site of weakest potential gradient where the early postshock cycles arise, just before or after the standard defibrillation shock was given from electrodes at the RV apex and SVC have demonstrated that the total defibrillation threshold energy was decreased by 60% compared with the defibrillation threshold for shocks through the RV–SVC electrodes alone.[73-75] When the small electrode was placed elsewhere on the epicardium, it had little or no effect on the defibrillation threshold. A recent VF induction study showed that the same general phenomenon occurs after the initiation of VF by a stimulus slightly larger than the VF threshold.[76] Defibrillation shocks delivered from an electrode immediately adjacent to the electrode from which VF was initiated could significantly lower the defibrillation threshold for shocks delivered for the first three post-induction cycles compared with the defibrillation threshold for defibrillation shocks delivered after 10 seconds of VF when activations no longer arose solely from the area of original initiation (Figure 14-14). In one study, subendocardial

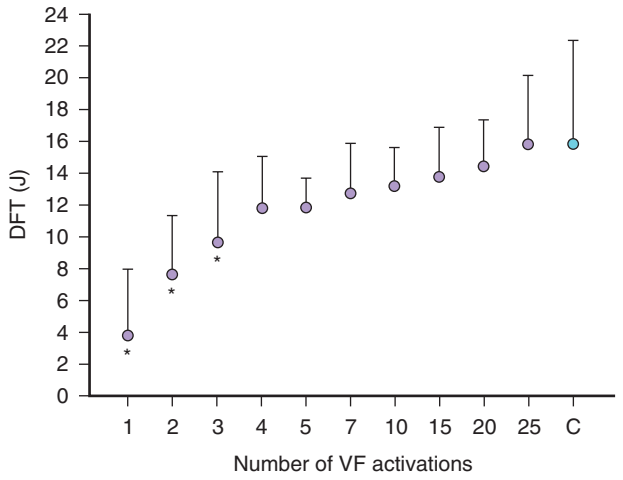

FIGURE 14-14 Increase in defibrillation threshold (*DFT*) with time demonstrating that shocks given from defibrillation electrodes located near the site of initiation of VF have a low DFT for the first few cycles following VF induction, implying that VF is maintained for the first few cycles by activation fronts arising in this localized region. VF was initiated from and defibrillation shocks were given from the RV in 7 pigs. Defibrillation shocks were timed to be given after 1 to 5 cycles and after 10 seconds of VF (*Control, C*). The mean ± standard deviation DFT rises sharply for shocks given after 1 to 4 VF cycles and then rises more gradually for shocks given after up to 25 VF activations. *Asterisks* signify that the DFT is significantly less at that number of VF cycles than for C. *VF*, Ventricular fibrillation; *RV*, right ventricle. *(From Strobel JS, KenKnight BH, Rollins DL, Smith WM, Ideker RE: The effects of ventricular fibrillation duration and site of initiation on the defibrillation threshold during early ventricular fibrillation,* J Am Coll Cardiol *32:521–527, 1998.)*

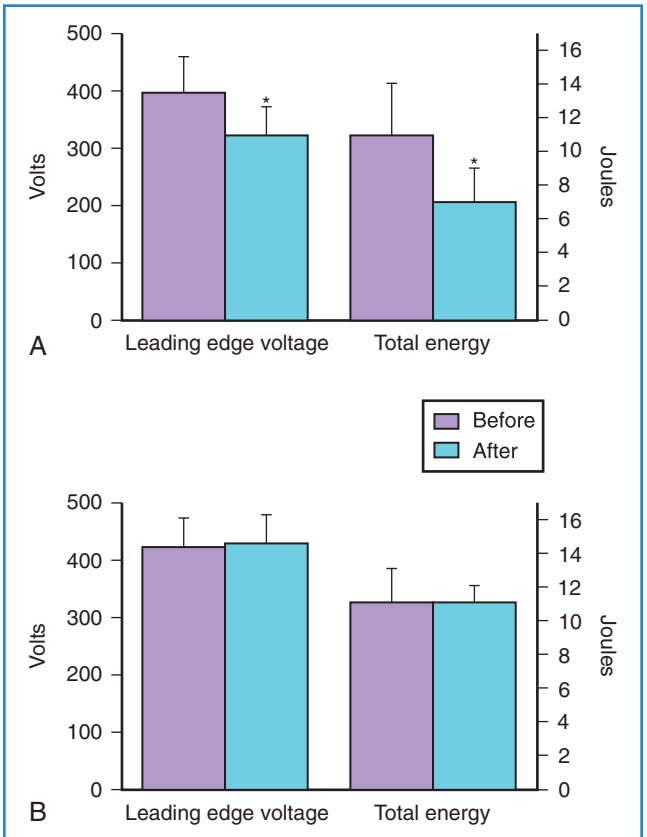

FIGURE 14-15 ULV shocks determined before and after ablation performed at the LV apex (**A**) and the LV base (**B**). Delivered voltage and energy at the ULV were significantly decreased after the LV apex ablation by 19% and 34%, respectively. However, no difference was observed in the ULV shocks required before and after the LV base ablation. *Asterisk* signifies that the ULV is significantly less after ablation than before ablation. *ULV,* Upper limit of vulnerability; *LV,* left ventricle. *(From Chattipakorn N, Fotuhi PC, Zheng X, Ideker RE: Left ventricular apex ablation decreases the upper limit of vulnerability,* Circulation *101:2458–2460, 2000.)*

radiofrequency ablation was performed at the site where the early postshock activation arose after VF induction by near-ULV shocks.[77] Ablation of this arrhythmogenic site resulted in a marked decrease in the ULV, whereas little or no effect on the ULV was found when ablation was done elsewhere (Figure 14-15). All of these studies underscore the crucial importance of this small region that gives rise to activations after the shock in determining defibrillation outcome.

Source of Postshock Activation After Near-DFT Shocks

The sources of the early postshock activations and the cellular mechanism responsible for the rise of these postshock activities have not been clearly elucidated. Although after-depolarizations and triggered activity have been proposed to be responsible for these postshock activations, triggered activity was not found to be the responsible mechanism in another study.[78,79] The Purkinje system has also been proposed as the possible source of these early repetitive postshock activations.[54,80] Recently, transmural and endocardial cardiac mapping in porcine models demonstrated that the Purkinje system is active during these early postshock activations, suggesting that it could be the source following near-DFT shocks.[81] Intracellular calcium ($[Ca]_i$) oscillations have been proposed as a possible mechanism for early postshock activation.[82] In an optical mapping study of Langendorff-perfused rabbit ventricles, a heterogeneous distribution of $[Ca]_i$ was demonstrated.[82] In that study, the first postshock activation was always in regions where low $[Ca]_i$ was surrounded by elevated $[Ca]_i$, that is, a $[Ca]_i$ sinkhole.[82] It has been proposed that $[Ca]_i$ sinkholes are formed by the heterogeneous distribution of calcium transients caused by the shock.[83]

Postshock Isoelectric Window: Is It Truly Electrically Silent?

Previous cardiac mapping studies have demonstrated that following defibrillation shocks, the postshock interval (the interval between the shock and the first postshock activation that propagated globally across the ventricles) is longer for successful defibrillation than for failed defibrillation.[29,36] This postshock interval was believed to be electrically silent and was known as the *isoelectric window*.[36] The isoelectric window is thought to exist because of the refractory period prolongation caused by the shock. Several studies showed that when compared with failed defibrillation shocks, successful defibrillation shocks cause a larger degree of RPE that occurs over a larger area.[19,84]

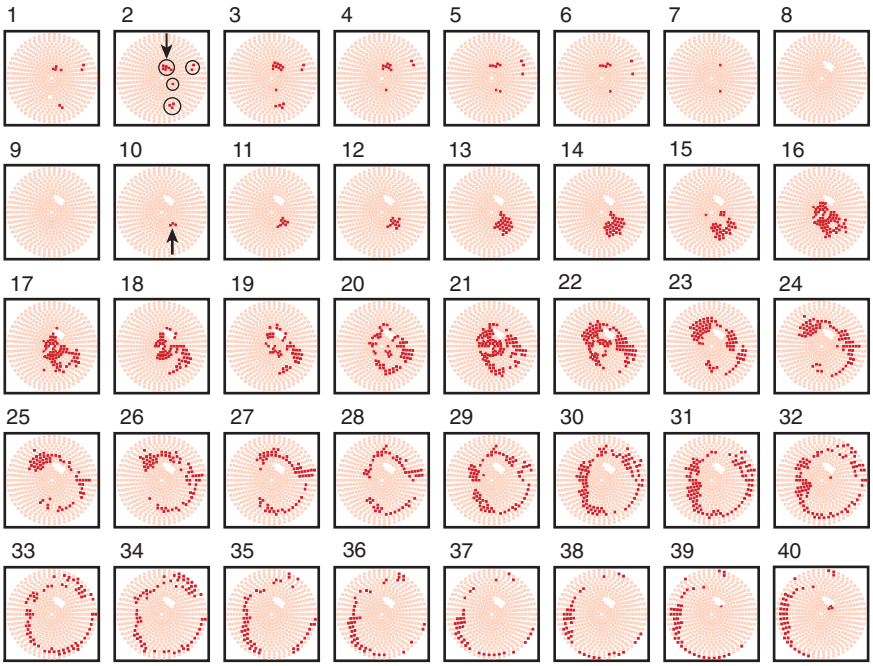

FIGURE 14-16 The presence of locally propagated activation (LPA) following a failed defibrillation shock. Each map represents a polar view of the ventricles. The interval between consecutive maps is 2 ms. Each *red dot* represents local activation at 1 of 504 epicardial electrodes. LPAs were detected 48 ms after the shock (*circles, frame 1*), propagated locally and disappeared; after this, a first globally propagated activation (GPA) was observed (*arrow, frame 10*). The GPA wavefront blocked without propagating through one LPA region (*circle with arrow, frame 2*). White dots from frames 8 through 40 indicate the LPA region in which this block occurred. *(From Chattipakorn N, KenKnight BH, Rogers JM, et al: Locally propagated activation immediately after internal defibrillation,* Circulation *97:1401–1410, 1998.)*

By using an optical mapping technique, Dillon demonstrated that during fibrillation, RPE caused by the shock can be observed at any time if the shock is delivered to the myocardium when the cardiac tissue just passes its upstroke of the fibrillatory action potential.[85] Dillon found that regardless of the electrical state of the myocardium immediately before the shock, all of the myocardium in the mapped region repolarizes and comes back to the resting state at the same time following successful defibrillation. Dillon assumed that failed defibrillation occurs by re-entry after the shock caused by the nonuniform dispersion of refractory period across the heart; he hypothesized that successful shocks require that the immediate postshock repolarization time be constant throughout the myocardium to decrease the dispersion of refractoriness. This is known as the *synchronization of repolarization hypothesis*. Since defibrillation success is dependent on shock strength, the concept of synchronization of repolarization has been extended to a new hypothesis for defibrillation known as the *progressive depolarization hypothesis*.[39] This hypothesis was proposed to unify the mechanism by which shocks terminate or induce fibrillation. As the shock strength progressively increases, the depolarized regions as well as the degree of RPE progressively increase across the heart, resulting in less dispersion of refractoriness caused by synchronization of repolarization time. Similar to the critical point hypothesis, the progressive depolarization hypothesis suggests that the immediate myocardial responses following the shock are crucial in determining defibrillation or the outcome of VF induction.

Electrical and optical cardiac mapping studies have demonstrated that the postshock interval is not totally electrically silent.[48,52,69] Most shocks were seen to be well below the defibrillation threshold in optical mapping studies, whereas only shocks near the defibrillation threshold were used in the electrical mapping study. This study reported that before the first postshock activation that propagates globally across the heart is observed, activations occur immediately after the shock but only propagate locally for a short distance and then disappear.[52] These locally propagated activations were observed in both successful defibrillation and failed defibrillation (Figure 14-16). Thus, the isoelectric window is not truly electrically silent. The existence of these immediate postshock locally propagated activations suggest that a uniform refractoriness distribution across the ventricles may not be necessary for successful defibrillation, since such refractoriness should have prevented this activation. Results from defibrillation and VF induction studies using shocks of similar strength near the threshold, so that variations in shock strength would not influence the results obtained, strongly support this idea.[35,51,52,63,64] These recent findings suggest that the progressive depolarization observed in previous studies is dependent on shock strength and may not have a direct cause-and-effect relationship on the outcome of defibrillation.

Harmful Effects of Strong Shocks

Although defibrillation success is dependent on shock strength, successful defibrillation is not always observed with a very strong shock. Figure 14-17 demonstrates the detrimental effect of a very high strength shock that is delivered to the heart, since the probability of success is decreased.[86] It has been shown that when a shock much stronger than the ULV is given to the heart, it can induce VF regardless of the state of the action potential of that cardiac tissue.[58,87] For defibrillation using an intracardiac electrode configuration, the region exposed to the high potential gradient is close to the shocking electrode. For shocks near the defibrillation threshold delivered from electrodes placed at the SVC and RV apex, Walker et al demonstrated that the immediate postshock activation often arises at the LV apex where the potential gradient is weak.[88] In this study, when the shock strength was increased to a few hundreds volts above the defibrillation threshold, the immediate postshock activation arose near the RV

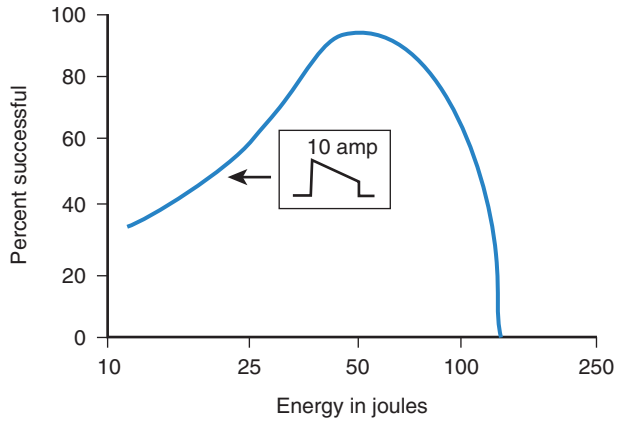

FIGURE 14-17 Relationship between the success rate of transthoracic ventricular defibrillation and the energy content of a trapezoidal shock in canine models. The energy of the 10-amp leading-edge shock is augmented by increasing the duration of the shock. *(From Schuder JC, Rea RF, Stoeckle H: Transthoracic ventricular defibrillation with triangular and trapezoidal waveform,* Circ Res *19:689–694, 1966.)*

electrode where the potential gradient was high, but VF was not induced. With a shock a few hundred volts higher, tachyarrhythmic-like activation arose from the high gradient region immediately following the shock. Jones and colleagues have shown that electroporation and myocardial damage were observed when an excessively high-strength shock (above ~50 V/cm) was given to the myocardium.[89] Furthermore, electroporation induced by the shock has been shown to depend on both the location and the dimension of the active region of the shocking electrode and that the infarcted myocardium is more vulnerable to electroporation than is the normal myocardium.[90,91] This could be responsible for the low probability of defibrillation success as well as the high chance of VF induction with very strong shocks.[19,89,92]

Ongoing Debate on Defibrillation Mechanisms

Although defibrillation has been extensively investigated over the past few decades and much has been discovered, defibrillation mechanisms continue to be debated. The immediate postshock myocardial responses to the shock as well as the immediate postshock activation pattern, that is, re-entry, have been proposed to be crucial in defibrillation success. However, recent studies suggested that the immediate postshock myocardial responses can have a focal origin and are not absolutely crucial in determining shock outcome.[52,63,93] Instead, for shocks near the defibrillation threshold, the number and rapidity of repetitive postshock activations arising from the small arrhythmogenic region located in the low potential gradient area appear to be the key determinants for defibrillation outcome.[63,64] These different findings suggest that the mechanism of defibrillation is complex. It is also possible that the mechanism of defibrillation changes as VF continues because the mechanism of VF maintenance after it has been present a few minutes has recently been reported to differ from that of early VF.[94,95] It is hoped that the development of high-resolution three-dimensional recording techniques that do not alter the electrophysiological properties of the myocardium will help resolve the inconsistencies of results from previous studies.

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CHAPTER 15

Principles of Catheter Ablation

Ann C. Garlitski, Munther K. Homoud, and N.A. Mark Estes III

Ablative therapy for cardiac arrhythmias is based on the rationale that for every arrhythmia, a critical anatomic region of abnormal pulse generation or propagation is required for the arrhythmia to be initiated and sustained. Selective destruction of that area of myocardial tissue results in elimination of the arrhythmia. This principle was first demonstrated in 1968 in successful surgical division of a bundle of Kent in a patient with Wolff-Parkinson-White (WPW) syndrome.[1] Since then, catheter-mediated ablative techniques have nearly completely replaced surgical procedures because of high clinical success rates and minimal morbidity associated with catheter techniques. Other chapters in this book deal with specific mapping and ablation techniques; this chapter deals specifically with the conceptual basis, biophysical principles, and pathologic lesions of catheter ablation.

Historical Background

The first catheter techniques of ablation used direct current with a conventional external defibrillator to deliver energy between the catheter placed adjacent to the cardiac structure targeted and an adhesive electrode with a large surface area applied to the skin. The first reported targeted use of catheter ablation for elimination of atrioventricular (AV) conduction in humans was in 1982, although accidental ablation had been reported by Vedel in 1979.[2,3] Although direct-current shock was effective for ablation, significant complications related to barotrauma occurred.[4] Catheter-based ablative techniques did not gain widespread acceptance until the advent of radiofrequency (RF) ablation. The first clinical application of RF current occurred when Harvey Cushing, working with W.T. Bovie, used high-frequency current for electrocoagulation.[5] Since then, multiple animal studies have evaluated the influence of electrode size, electrode-tissue contact pressure, pulse power, duration, impedance, and temperature.[6-8] In vivo observations were made in animal models with the use of RF energy in the ventricles, the atrium, the coronary sinus, and the tricuspid annulus.[9-16] These observations were critical to the successful application in humans reported in the early 1990s.[17,18]

Radiofrequency Ablation

Biophysical Aspects of Radiofrequency Ablation

RF energy spans a wide range of frequencies, exhibiting a varying combination of resistive and dielectric properties. The RF band of 300 to 30,000 kHz is used for coagulation, ablation, and cauterization of tissues in medicine. Frequencies lower than 100 kHz stimulate excitable muscular tissue as well as cardiac tissue, resulting in muscle contractions and pain. Frequencies greater than 1000 kHz are effective in generating tissue heating; however, as frequencies increase, the losses along the transmission line increase, and the mode of heating changes from resistive heating to dielectric heating.[19] Therefore, for ease of application, safety, and patient comfort, most standard RF generators produce signals in the range of 300 to 750 kHz.[20]

Application of RF current to the myocardium results in the generation of heat because of resistive losses in a di-electric medium (Figure 15-1). The magnitude of heating is proportional to the power density within tissue, which diminishes in proportion to the radius to the fourth power. Because of this property, only a small volume of myocardial tissue is heated directly by the RF energy (<2 mm in most cases), whereas the remaining tissue heating occurs via conduction.[8] Haines and Watson have developed a simplified thermodynamic model to study the dynamics of heat transfer within a uniform medium at steady state. In this model, tissue temperature falls in an inverse proportion to the distance from the heat source (Figure 15-2). It also predicts that when the temperature at the electrode-tissue interface is maintained at a constant by varying the power, the lesion size should be proportional to the temperature and to the electrode radius.[8] Clinical studies have demonstrated the association of higher electrode-tissue temperature and larger tip electrodes with larger RF lesion size and procedure efficacy.[17,21] However, the temperature of the subendocardial tissue can exceed 100° C and result in rapid steam expansion and crater formation, often accompanied by an audible popping sound.[7] These so-called *pop lesions* may be associated with coagulum formation on the RF ablation electrode and result in thrombogenicity, or these lesions may result in rupture, particularly of thin-walled structures such as atria.

In general, RF lesions are created by application in a unipolar fashion. Current passes between the tip of an ablating electrode in contact with the myocardium and a grounded reference patch electrode placed externally on the patient's skin.[22] Because RF current is an alternating current, the polarity of connections from the electrodes to the generator is unimportant. The surface area of the standard ablating electrode (approximately 12 mm^2) is significantly smaller than the surface area of the dispersive electrode (100 to 250 cm^2), and thus the power density and resultant tissue heating are highest at the electrode-tissue contact point, and no substantive heating occurs at the dispersive skin electrode.

The temperature rise at the electrode-tissue interface is rapid ($t_{1/2}$, 7 to 10 seconds). However, thermal conduction to deeper tissue layers occurs more slowly, resulting in a steep tissue

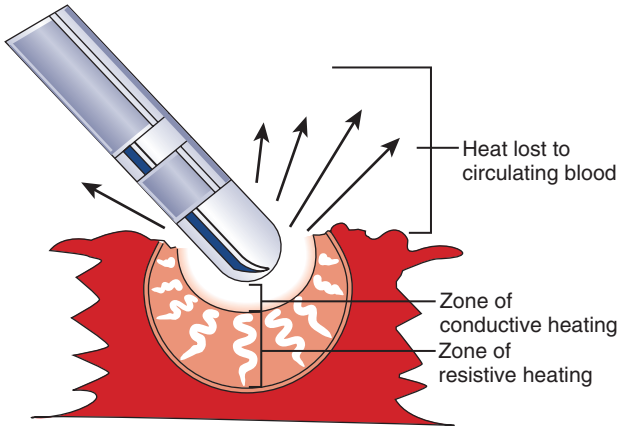

FIGURE 15-1 Tissue heating with radiofrequency energy. Superficial tissue close to the electrode-tissue interface is ablated via resistive heating, whereas the deeper myocardium is heated via conductive heating. Convective cooling occurs because of blood flow near the electrode-tissue interface and in the coronary circulation. *(Modified from Avitall B, Helms R:* Determinants of radiofrequency-induced lesion size, *ed 2, Armonk, NY, 2000, Futura.)*

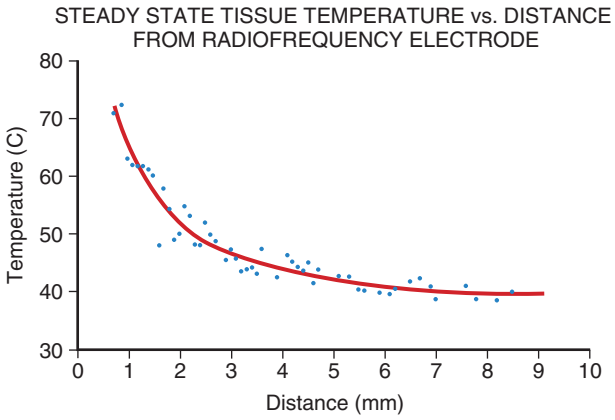

FIGURE 15-3 Radiofrequency energy was delivered to isolated perfused and superperfused canine right ventricular free wall. The tissue temperature (in degrees Celsius) was measured with a thermistor at a distance of 2.5 ± 0.2 mm from the radiofrequency electrode and after the 120 seconds of energy delivery. The electrode tip temperature was 80° C. *(Modified from Wang P, et al:* Physics and biology of catheter ablation, *Armonk, NY, 1998, Futura.)*

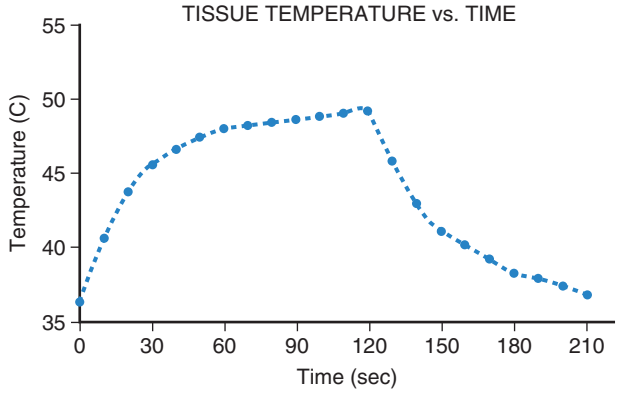

FIGURE 15-2 Radiofrequency energy was delivered to isolated perfused and superfused canine right ventricular free wall. The tissue temperature (in degrees Celsius) was measured with a thermistor. The steady-state temperature as a function of distance is shown. *(Modified from Wang P, et al:* Physics and biology of catheter ablation, *Armonk, NY, 1998, Futura.)*

gradient. Studies have shown that steady-state lesion size is not achieved until after 40 seconds of ablation and that intramyocardial temperature rises steeply until it reaches a plateau at 60 seconds, with the majority of heating occurring within the first 30 seconds (Figure 15-3).[23] However, because heating of the deeper layers is delayed, tissue temperature will continue to rise in the deeper layers despite the termination of energy delivery.[24] This thermal latency phenomenon may be responsible for the progression of the undesirable effects of ablation such as AV nodal block despite prompt cessation of energy delivery in clinical situations.

Clinically, the efficacy of RF ablation depends on precise target site mapping and adequate lesion formation.[21,25,26] A wide range of experimental and clinical observations support the notion that applied energy, power, and current are not precise indicators of the extent of lesion formation.[27] By contrast, actual electrode-tissue interface temperature remains the best predictor of actual lesion volume.[23] Typically, 55° C to 65° C is the target temperature for many temperature control catheters used clinically.[28,29] If the temperature is lower than 50° C, none or minimal tissue necrosis is expected. However, excessive heating leads to coagulum formation and limitation of lesion size.

A number of clinically available RF ablation systems use temperature monitoring during ablation to prevent the formation of coagulum and achieve adequate electrode–myocardial tissue temperature. They either use a thermocouple or a thermistor placed in the catheter tip.[30] A thermocouple is composed of two metals that are in contact with each other and generate a small current proportional to ambient temperature. Typically, thermocouples are placed within the catheter tip in contact with the distal electrode. A thermistor is essentially a semiconductor, which has an intrinsic resistance that changes in a predictable fashion with temperature. Small thermistors can be incorporated into a catheter tip and are thermally isolated from the shredding tissue with an insulating sleeve.[30] Currently, such catheters are used as part of a temperature monitoring, closed-loop feedback system, in which the RF generator automatically adjusts the power to maintain a user program temperature. Clinical use of temperature monitoring has resulted in a decreased incidence of coagulum formation during ablation.[25]

Numerous limitations may result in discrepancies between the recorded temperature and the true electrode–myocardial tissue temperature. The catheter electrode may not be in intimate contact with the myocardium at the site of the thermistor or thermocouple. This may underestimate the myocardial interface temperature, particularly at sites where the catheter electrode may be parallel, rather than perpendicular, to the endocardial surface, such as occurs with accessory pathway ablation via the trans-septal approach.[31] In addition, temperature monitoring becomes difficult as the electrode size increases or the electrode geometry changes. As the electrode size increases, the maximal temperature may be greatly underestimated by measuring just the

tip temperature by a single-point thermocouple. Also, in longer electrodes used for linear ablation, the temperature at the edges may exceed the temperature in the electrode body, a phenomenon called the *edge effect*.[32]

Pathologic Aspects of Radiofrequency Ablation

Cellular injury during RF ablation is primarily mediated via thermal mechanisms. In addition, some direct effects of electrical energy may occur on the myocyte, particularly the sarcolemmal membrane. Thermal injury seems to be the dominant cause of coagulation necrosis in the central zone of RF lesion, whereas at the border zone, thermal as well as electrical energy contributes to lesion formation.

Research using mammalian cell culture lines has shown that tissue survival during hyperthermia is a function of both temperature and time.[33] Higher temperatures lead to a more rapid and greater degree of cell death. In vitro studies have shown that irreversible myocardial cell death during conventional ablation likely occurs between 52° C and 55° C.[34] Typically, RF catheter ablation results in a high temperature (55° C to 60° C) for a relatively short time (30 to 60 seconds). In tissue immediately adjacent to the electrode, rapid tissue injury occurs, but in tissue heated by conductive heating, a relatively delayed myocardial injury occurs, with increasing distance from the RF electrode.[7] Clinical outcome during catheter ablation has been shown to correlate with maximum tissue temperature achieved, with a temperature of 62° C ± 15° C associated with *irreversible* electrophysiological effects and a temperature of 50° C ± 15° C associated with *reversible* electrophysiological effects.[21]

The hyperthermia induced by RF energy has immediate and profound effects on cellular electrophysiology, structure, and function. These include the cellular effects on plasma membrane, the cytoskeleton, the nucleus, and cellular metabolism. Exposure to high temperatures results in inhibition of membrane transport proteins and structural changes to ion channels and ion pumps.[35,37,38] Thermal effects on the cytoskeleton include disruption of stress elements, loss of plasma membrane support, and membrane blebbing.[39,40] Nuclear structure and function are lost.[41] With denaturation of metabolic proteins, cellular metabolism is inhibited.[42] The microvasculature is damaged, and microvascular blood flow is reduced.[43] At the level of the plasma membrane, transient nonspecific ion-permanent pores are formed in a plasma membrane.[44] These effects cause an initial reversible loss of conduction immediately after the initiation of RF energy, which is likely caused by an electrotonic-induced and heat-induced cellular depolarization. Irreversible loss of electrophysiological function occurs immediately after successful ablation; this is likely caused by thermal tissue injury, which results in focal coagulation necrosis. A secondary inflammatory response and ischemia occur as a consequence of microvascular damage, which may cause progression of tissue injury within the border zone.[43] Alternatively, in approximately 5% to 10% of cases, the RF-induced tissue injury resolves within the border zone, leading to late recovery of electrophysiology function and arrhythmia recurrence.

Determinants of Lesion Size

RF energy produces lesions that are homogeneous and well demarcated from surrounding tissue (Figure 15-4).

The lesion size in RF ablation is affected by several factors, including electrode configuration and size, power, duration, temperature, and myocardial tissue properties.[45] The shape of the electrode can affect the size of the RF lesion by affecting the current density. Although needle-shaped electrodes have yielded the largest lesion size, dome-shaped electrodes are in use clinically because of their practical design.[46] Electrode size has also been shown to be an important determinant of the lesion size in RF ablation. With increasing electrode size, the lesion size increases, as long as the electrode surface maintains contact with the endocardial surface and power is used to maintain the current density.[47] Increasing the electrode size at some point may decrease the lesion size when a significant proportion of the electrode is not in contact with the myocardium, and thus energy is dissipated into the blood pool. Studies have shown that lesion size is nearly doubled with 4-mm electrodes compared with 2 mm electrodes. Similarly, lesion size continues to increase as the tip electrode size is increased from 4 mm to 8 mm but decreases with larger electrode sizes.[48] In addition, significant char and coagulation formation is observed with electrode size greater than 8 mm.

With increasing duration of energy delivery, the lesion size increases but then reaches a plateau. In vitro studies have shown that in RF ablation, lesion size increases within the first 30

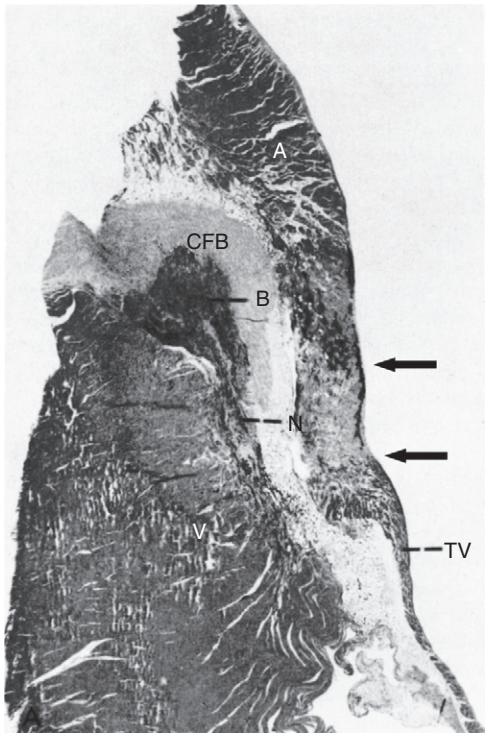

FIGURE 15-4 A low-power view of an ablated atrioventricular node (*N*). The end of the node and the beginning of the penetrating bundle (*B*) are replaced by hemorrhage, with the area of coagulation necrosis extending to the adjacent atrial and ventricular myocardium. The *arrows* demarcate the discrete area of necrosis that extended to the summit of the ventricular septum (*V*), especially on the right side (hematoxylin and eosin stain; ×16 magnification). *CFB*, Central fibrous body; *A*, atrial myocardium; *TV*, tricuspid valve. *(Modified from Huang S, Bharati S, Graham A, et al: Closed chest catheter desiccation of the atrioventricular junction using radiofrequency energy—a new method of catheter ablation,* J Am Coll Cardiol *9:349–358, 1987.)*

seconds, but the rate of increase significantly diminishes with extended power delivery.[34] Similarly, lesion size increases as the temperature increases. However, as discussed earlier, when the temperature becomes excessive, the incidence of coagulation formation increases, thus impairing the ability to increase lesion size further. The coupling of RF energy to the endocardial surface is enhanced by improved contact of the electrode with the myocardium.[23] Instability of the catheter electrode results in fluctuating temperatures because of convective loss of energy resulting in poor tissue heating. The efficiency of energy transfer between the RF catheter tip and the endocardium is also dependent on catheter-tissue orientation and the angle of the electrode contact. With perpendicular or oblique placement, lower temperatures are achieved compared with parallel electrode orientation.[49,50]

Cooled Radiofrequency Ablation

A technologic development that uses the fundamentals of RF-energy but improves its method of delivery is cooled RF ablation. Cooling of the ablation electrode tip has been shown to reduce both overheating of the electrode–tissue interface and impedance rise during RF delivery, which allows for greater power delivery. During cooled RF ablation, maximum temperature is achieved just below the endocardial surface, which translates into a deeper lesion.[51-53] Since the catheter irrigant cools the tip-tissue interface, the measured catheter tip temperature will have an even greater discrepancy with tissue temperature compared with standard RF delivery.[54] As a result, lower maximal electrode temperatures are imposed during RF delivery.[55]

The tip of the catheter can be cooled either by using a *closed-loop (internal) design*, in which saline is circulated through the catheter lumen and the ablation electrode, or by an *open (external) design*, in which saline is irrigated via small holes at the tip of the electrode (Figure 15-5). In the power-controlled mode, power settings range from 20 W to a maximum of 50 W with infusion rates more than 17 mL/min and 36 mL/min for external and internal irrigation, respectively. Saline flow rates and tissue contact pressure also affect the size of the lesion.[56] A balance between high flow rates exists, resulting in a larger lesion and potential waste of RF current caused by overcooling. Contact pressure has also been shown to affect lesion diameter and thrombus formation. A deeper lesion is achieved with high catheter pressure, particularly in a perpendicular position, as less heat is lost to the blood pool and more energy is transmitted to the tissue. As a result, in locations where high contact pressure is readily achieved, such as the coronary sinus, power output levels should be reduced to less than 30 W to avoid complications.[56] When a resistant site to ablation is encountered, increasing the duration of ablation, rather than applying higher power, may be a better choice for increasing lesion depth.[57] Although open-loop systems do not completely prevent the risk of impedance rise and popping, Yokoyama et al demonstrated, in an animal model, that an open-loop system, compared with a closed-loop system, results in lower incidences of thrombus formation as well as steam pops.[58,59]

Cooled RF ablation has been shown to be effective and safe in patients with a variety of arrhythmias, particularly atrial flutter (AFL), atrial fibrillation (AF), and ventricular tachycardia (VT).[60-62] In a canine model, Gerstenfeld et al performed pulmonary vein isolation and compared the histopathology of the lesions of an 8-mm tip standard RF catheter at 70 W, 20 seconds, 60° C and 50 W, 60 seconds, 50° C with a 3.5-mm irrigated tip ablation catheter at 35 W, 60 seconds, 45° C. The irrigated tip lesions resulted in less endocardial eschar formation, pulmonary vein (PV) stenosis, or damage to collateral structures.[63] In clinical trials, an open irrigated tip catheter has been shown to be more efficacious than a conventional 4-mm tip catheter with respect to AF recurrence.[64] Cooled RF ablation has also been extensively evaluated in single-center and multi-center studies of the ablation of VT.[62] Soejima et al revealed a superior efficacy of cooled tip (89%) versus standard RF energy (54%) ($P = .003$) in the termination of VT at isthmus sites where an isolated potential was present.[65] The largest trial, to date, of catheter ablation for recurrent monomorphic VT after myocardial infarction (MI) is the Thermocool VT trial.[66] Ablation abolished all inducible VTs in 49% of patients. The procedure mortality rate was 3%, with no strokes.

The ability of cooled RF energy to treat VT from an epicardial approach has also been demonstrated. In a canine model, it was shown that standard techniques of RF ablation are not sufficient

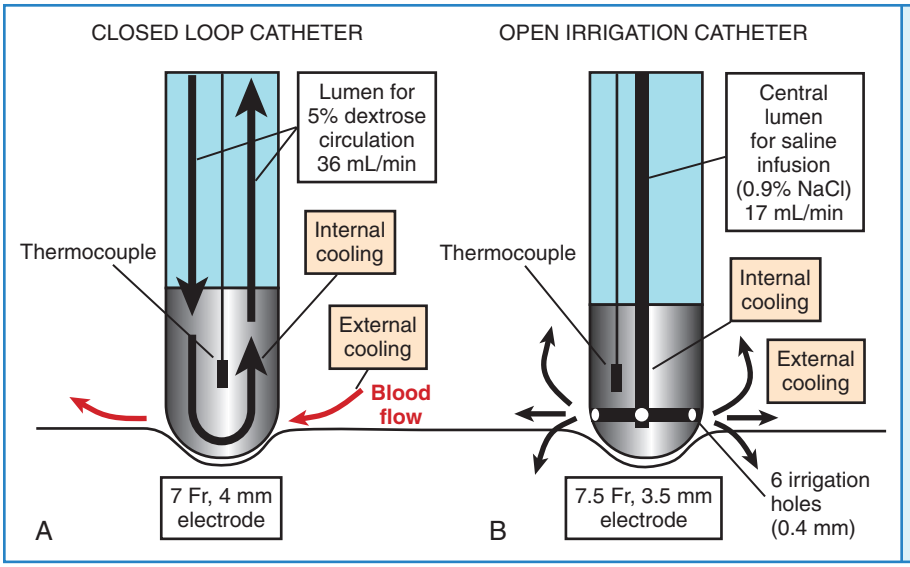

FIGURE 15-5 Schematic representation of the irrigated electrode catheters. **A,** Closed-loop irrigation catheter has a 7 Fr, 4-mm tip electrode with an internal thermocouple. **B,** Open-irrigation catheter has a 7.5 Fr, 3.5-mm tip electrode with an internal thermocouple and six irrigation holes located around the electrode, 1.0 mm from the tip. *(Modified from Yokoyama K, Nakagawa H, Wittkampf F, et al: Comparison of electrode cooling between internal and open irrigation in radiofrequency ablation lesion depth and incidence of thrombus and steam pop,* Circulation *113:11–19, 2006.)*

to create lesions in the pericardial space where convective cooling by blood is lacking. Fenelon et al demonstrated that an irrigated 4-mm tip catheter, compared with a standard RF 4-mm tip catheter, can deliver high power outputs, 43 W versus 16 W, and deeper lesions, 6.4 mm versus 3 mm, respectively.[67] Whether endocardial RF or epicardial RF energy is delivered, a caveat to the application of external irrigation is that for the administration of a potentially significant volume of fluid, peri-procedural precautions should be taken to manage the volume load.

Cryoablation

Cryoablation is unique in that it causes tissue injury by freezing and thawing rather than by hyperthermia. This mode of ablation results in minimal tissue destruction and preserves the basic underlying tissue architecture. A large body of clinical experience has been accumulated in the use of cryothermy in the surgical treatment of tachyarrhythmias, in which it has been proven to be safe and effective. Cryoablation has been used extensively intraoperatively for the creation of AV block or ablation of atrial tachycardia (AT) and VT.[68,69] In 1998, the first percutaneous catheter ablation using cryothermal energy was performed.[70]

One advantage of cryothermal energy is that it also allows for reversible "ice mapping," in which the area likely responsible for the arrhythmia can be evaluated by suppressing its electrophysiological properties before the creation of an irreversible state.[71] During cryomapping, reversible cooling is performed at tissue temperatures of approximately −28° C to −32° C without tissue destruction, whereas irreversible lesions are accomplished by achieving temperatures of less than −60° C for 2 or more minutes. The current guideline to limit cryoablation time to 4 minutes is based on the fact that the ice ball has been shown, via ultrasound visualization, to enlarge during the first 3 minutes of the freezing cycle and then remain stable.[72,73]

Application of a cryoprobe to a tissue surface results in the formation of a well-demarcated hemispherical block of frozen tissue. At the cellular level, intracellular and extracellular ice crystals form, followed by thawing, which further disrupts membranous organelles and enhances the lesion. Within 24 hours, coagulation necrosis results, with hemorrhage, edema, and inflammation. Over time, the lesion becomes sharply demarcated from surrounding tissue and is finally replaced by fatty and fibrous tissue in 2 to 4 weeks (Figure 15-6).[74] The lesion of cryoenergy is significantly less thrombogenic than that of RF energy, as a result of the preservation of endothelial cells and tissue ultrastructure.[75]

Several different catheter-based designs have been developed for the cryoablation of arrhythmias (Figure 15-7).[76] They differ among the techniques employed to achieve freezing temperatures. Some designs are based on the Joule Thompson effect, in which a pressure drop results in significant cooling or freezing, or on the Peltier effect (thermoelectric effect), in which a temperature difference is created by applying a voltage between two electrodes. Gases such as nitrous oxide or halocarbon are used as refrigerants. The size of the cryoablative lesion depends on various factors such as temperature, duration, surface area of the cooling probe, and the number of applications.

Since the time of the first transcatheter cryoablation procedure, cryoablation has been applied in the treatment of a gamut of arrhythmias. In particular, its unique safety profile has been exploited to target AV nodal re-entrant tachycardia (AVNRT) as well as arrhythmias in the young. In a prospective multi-center cohort study, FROSTY, 103 patients underwent cryoablation for AVNRT with a 4-mm tip catheter. The procedural success rate was 91%, and at 6 months, the success rate was 94% among those with initial success.[77] In spite of evidence for the greater efficacy of RF energy over cryoenergy in terms of lower arrhythmia recurrence rates, the complication of permanent high-degree AV block may be avoided when cryoapplication is promptly terminated following the observation of initial AV block.[75,78] Of note, it has been observed that accelerated junctional beats, a marker of a successful site of RF ablation, are absent during cryoablation.[79] As the catheter generates hypothermia, it adheres to tissue, which results in greater catheter stability; this is also well suited for perinodal and peri-Hisian accessory pathways. Cryoenergy has been applied to the treatment of AFL as well. Moreira et al reported the use of a 6.5-mm tip catheter, with a 91% success rate at a mean of 27 months.[80] In a small prospective randomized study of cavotricuspid isthmus ablation, it was noted that patient perception of pain was less with cryoablation than with RF ablation.[81] A disadvantage of cryoablation is the association of longer procedural times.[82]

A promising development in the delivery of cryoenergy has been in the design of a cryoablation balloon catheter for the creation of isolation of the PVs. In a prospective three-center study, 346 patients with paroxysmal or persistent AF underwent PV isolation via cryoablation. A double-walled cryoballoon, either 23 or 28 mm in diameter, was used for a maximum of five applications, at which point an 8-mm tip cryoablation catheter was introduced for those PVs that required further ablation. At 12 months, freedom from symptomatic AF was 74% in the group with paroxysmal AF and 42% in the group with persistent AF. Phrenic nerve palsy, particularly following ablation of the right superior PV with the smaller balloon, was seen in 7.5% of patients.[83] Thus far, thromboembolism or PV stenosis have not been reported with this technique.[84-87]

Ultrasound Ablation

Sound waves at frequencies of greater than 20,000 Hz are classified as ultrasound, and frequencies of 2 to 20 MHz are specifically defined as high-intensity ultrasound (Figure 15-8). Ultrasound energy causes localized hyperthermia at predictable depths without injuring intervening tissue. In addition to thermal absorption, another mechanism by which ultrasound causes tissue damage is via a process of cavitation; as the sound waves propagate through tissue, cyclical explosion and implosion of microbubbles occur in tissue. Using 10-MHz ultrasound transducers mounted on catheters, He et al created lesions up to 8.7 ± 2.9 mm in depth in the canine left ventricle.[88] Another study reported lesions up to 6.4 ± 2.5 mm deep when cylindrical ultrasound transducers mounted on a catheter were used.[89] A linear relationship was observed between increasing power and depth of lesion. Temperature also increased, and maintaining constant power increased lesion size. Although ultrasound ablation appears to be free of the "pop" phenomenon seen in RF ablation, blood coagulum formation at the tip of the catheter was reported in one study.[90] High-intensity focused ultrasound ablation has been applied from outside the beating heart to successfully create AV block in 10 open-chest dogs without damaging the overlying or underlying tissues.[91] Thus ultrasound energy may potentially allow noninvasive ablation of cardiac arrhythmias in the future.

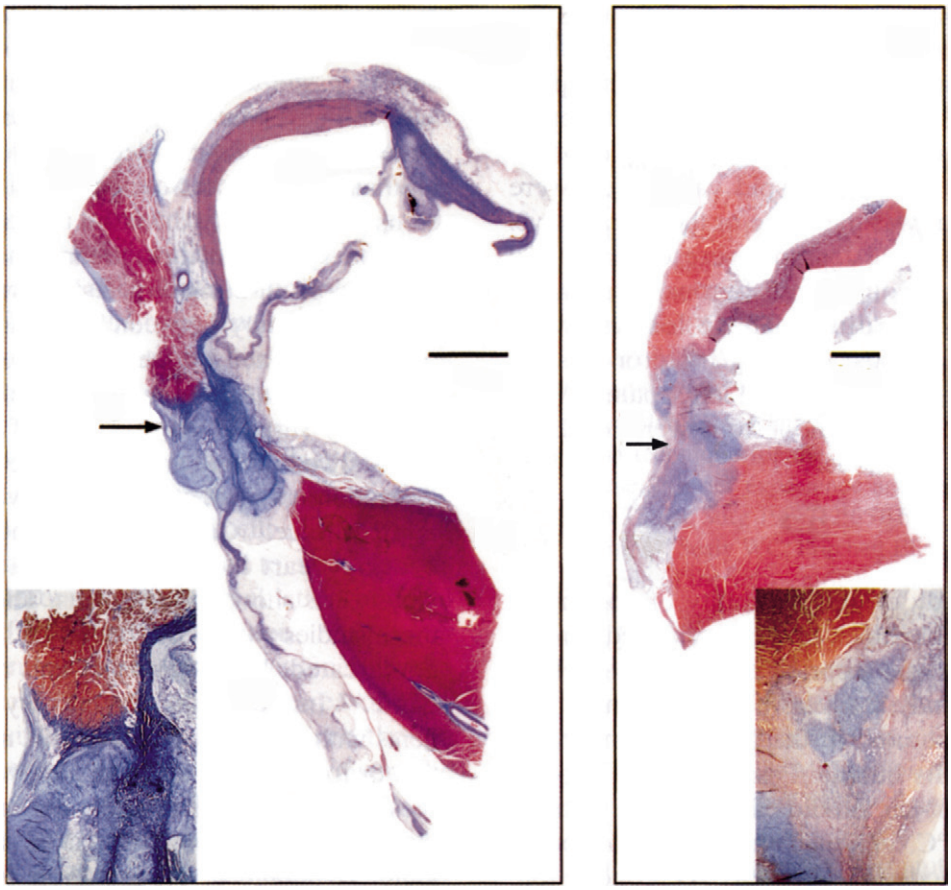

FIGURE 15-6 *Left,* Chronic cryoablation lesion of an atrioventricular (AV) node in a dog (Azan stain). Homogeneous fibrotic tissue extends from the right atrial wall across the central fibrous body to the muscular interventricular septum. *Inset,* Higher magnification: absence of viable myocardium within the fibrous strands. *Blue* indicates fibrotic tissue, and *red* indicates normal tissue. *Right,* Chronic radiofrequency lesion of AV node in dog (Azan stain). Note the presence of fibrotic tissue with scattered strands of viable myocardium. *Inset,* Higher magnification: the lesion contains inhomogeneous fibrotic tissue with strands of viable myocytes and cartilage formation. The borders are not as well demarcated as the cryoablation lesion. *(Modified from Rodriguez LM, Leunissen J, Hoekstra A, et al: Transvenous cold mapping and cryoablation of the AV node in dogs: Observations of chronic lesions and comparison to those obtained using radiofrequency ablation,* J Cardiovasc Electrophysiol *9:1055–1061, 1998.)*

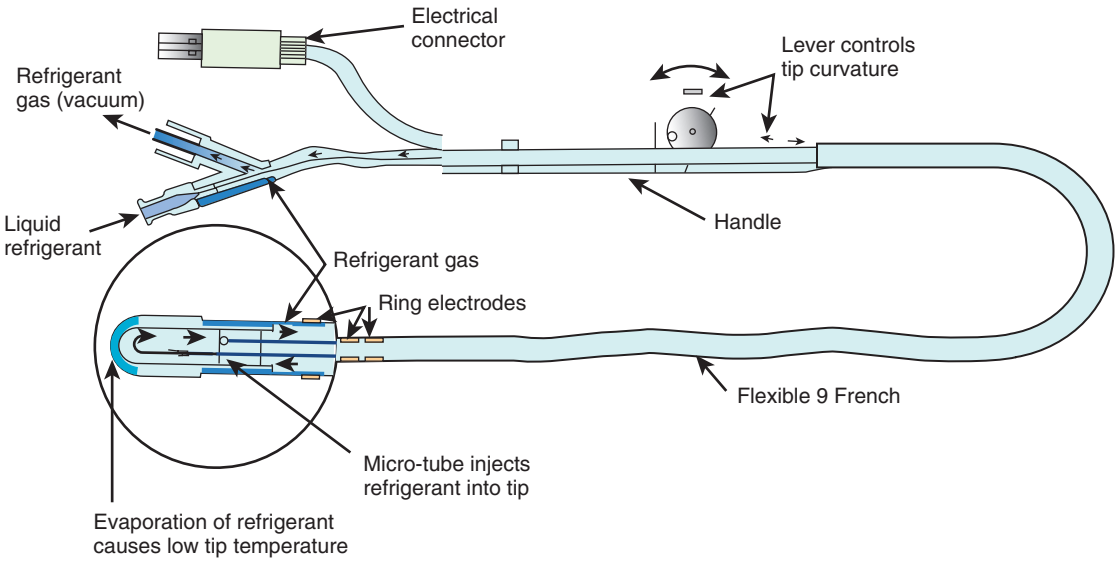

FIGURE 15-7 Schematic of a cryoablation catheter. *(Modified from Dubuc M, Roy D, Thibault B, et al: Transvenous catheter ice mapping and cryoablation of the atrioventricular node in dogs,* Pacing Clin Electrophysiol *22:1488–1498, 1999.)*

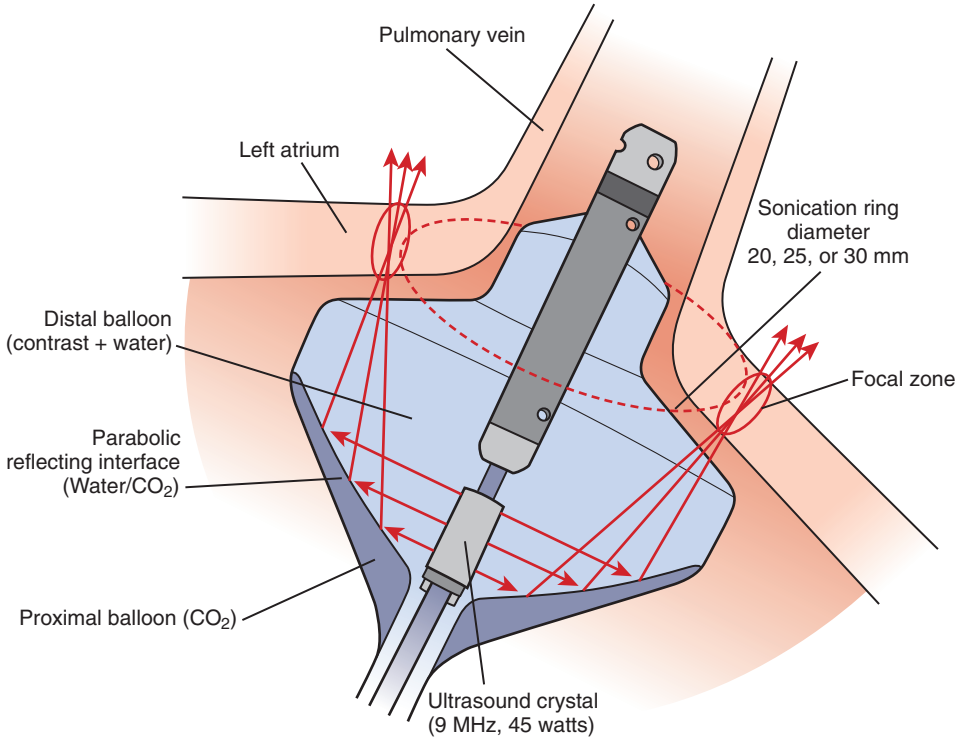

FIGURE 15-8 Schematic representation of the high-intensity focused ultrasound balloon catheter designed to focus high-intensity ultrasound circumferentially outside the pulmonary vein antrum. This system has two noncompliant balloons. A 9-MHz ultrasound crystal is located within the distal balloon filled with contrast and water. The proximal balloon, filled with carbon dioxide, forms a parabolic interface with the distal balloon to reflect the ultrasound energy in the forward direction, focusing a 260-degree ring (sonicating ring) of ultrasound energy 2 to 6 mm in front of the distal balloon surface. The distal balloon has three sizes—24 mm, 28 mm, or 32 mm in diameter—producing sonicating rings of 20 mm, 25 mm, or 30 mm in diameter. The acoustic power of the system is 45 W for all three balloons, with negligible loss of power in the balloon. The distal balloon is irrigated with contrast and water at 20 mL/min during ablation to keep the balloon cool (<42° C). *(Modified from Nakagawa H, Matthias, A, Wong T, et al: Initial experience using a forward directed, high intensity focused ultrasound balloon catheter for pulmonary vein antrum isolation in patients with atrial fibrillation,* J Cardiovasc Electrophysiol *18:136–144, 2007.)*

Combining ultrasound imaging with ultrasound ablation is yet another potential advantage of this technique (Figure 15-9).

The ability of ultrasound to remain collimated through a fluid medium has been applied to balloon technology geared toward PV isolation in AF ablation. Ultrasound waves are emitted and reflected in a forward, circumferential fashion. The theoretical advantage is that no direct tissue contact is needed to achieve a lesion, as opposed to RF ablation or cryoablation. Early clinical experience suggests that circumferential ultrasound ablation of pulmonary veins is feasible in humans. In a single-center series, a catheter with an 8-MHz transducer mounted near the tip in a saline-filled balloon was used to perform PV isolation in 15 patients. The ablation time was 2 minutes, followed by 1 minute before the balloon was deflated. A mean of 14.7 (range, 3 to 39) applications of energy were delivered per patient. Two major complications, peri-procedural stroke and phrenic nerve palsy, occurred. At a mean follow-up of 25 weeks, five patients experienced AF recurrence.[92] Saliba also evaluated the use of an ultrasound balloon catheter in the ablation of AF. In 33 patients, a total of 85 veins were ablated, with a mean of 6.7 ablations per vein and a target interface temperature of at least 60° C.[93] In more recent studies, in 39 patients, 88% of PVs were electrically isolated after a median of five energy applications of up to 90 seconds at each PV.[94,95] Notably, 8% of the patient developed permanent right phrenic nerve palsy. The technical limitations of this technique may contribute to complications are the occasionally eccentric position of the transducer in the PV and the inability to include the antrum in the lesion boundary.

Microwave Ablation

Microwaves are the part of the electromagnetic spectrum between 0.3 to 300 GHz. Microwave ablation acts mainly via di-electric heating of the myocardium. The microwave energy generates heat by producing oscillation of the water molecule dipoles within the myocardium. The microwave antenna placed at the end of a catheter radiates an electromagnetic field into the surrounding tissue and does not depend on current flow from ablation catheter to the tissue as with an RF electrode.[96] Therefore, as opposed to RF ablation, contact with the myocardium is not required to heat myocardial tissue.[22]

The microwave ablation system consists of a microwave generator and a microwave antenna incorporated into the ablation catheter. Microwave generators operate at either 915 MHz or 2450 MHz. Several measurements are used to characterize the properties of microwave systems used for myocardial ablation. A specific absorption rate (SAR) pattern provides a

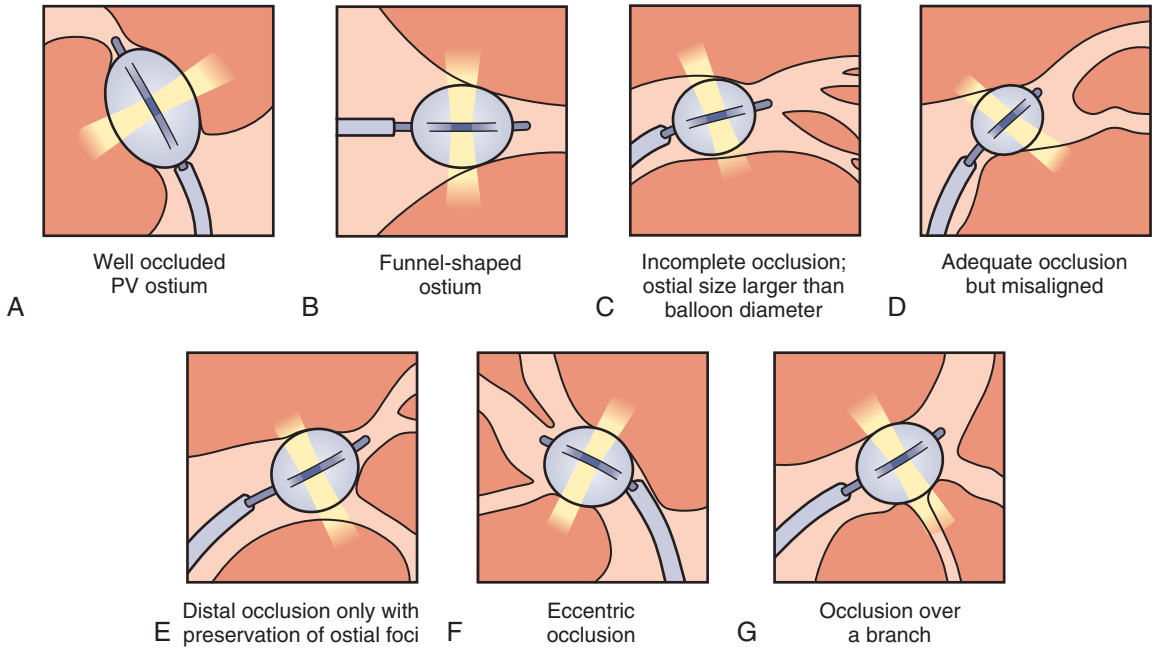

FIGURE 15-9 Some anatomic variants that are potentially responsible for ineffective delivery of ultrasound lesions. **A,** Well-occluded pulmonary vein (*PV*) ostium. **B,** Funnel-shaped ostium. **C,** Incomplete occlusion in which ostial size is larger than balloon diameter. **D,** Adequate occlusion but misaligned. **E,** Distal occlusion only with preservation of ostial foci. **F,** Eccentric occlusion. **G,** Occlusion over a branch. *(Modified from Saiba W, Wiber D, Packer D, et al: Circumferential ultrasound ablation for pulmonary vein isolation: Analysis of acute and chronic failures,* J Cardiovasc Electrophysiol *13:957–961, 2002.)*

three-dimensional picture of the electromagnetic field created during microwave ablation. SAR is measured by giving a brief energy pulse and measuring the temperature rise in three dimensions around the antenna. The ability of the energy source to deliver energy to the medium is termed "matching" of the antenna to the di-electric properties of the medium and can be measured either in terms of efficiency of energy transfer or ratio of reflected power to delivered power. When the antenna and tissue are optimally matched, high efficiency of energy transfer occurs, and very little power is reflected.

The heating pattern and efficiency of the microwave ablation system depends on the antenna design (Figures 15-10 and 15-11). The helical coil antenna generates a circumferential heating pattern, making placement parallel to the endocardial surface optimal, whereas the dipole antenna creates a heating pattern that projects the ablation energy forward. This makes the use of helical coil antennas more suitable for making long linear lesions, whereas a forward-projecting antenna is ideal for a focal target. Another version of a microwave antenna is a spiral apparatus; it was shown in vivo to create lesions that were significantly larger and deeper than the other microwave antenna systems.[97]

Microwave ablation can achieve greater temperature rise as a function of depth compared with RF ablation.[96] As the power and duration of microwave energy is increased, the lesion size also increases. Unlike RF, microwave energy is not limited by impedance rise. Microwave ablation lesion growth is considerably slower than RF ablation.[98] Whayne et al demonstrated that microwave lesion size using a 915-MHz monopolar antenna system continued to increase over 300 seconds of ablation (Figure 15-12).[33] Pathologically, microwave lesions are comparable with RF lesions. Like RF lesions, the lesions produced by microwave

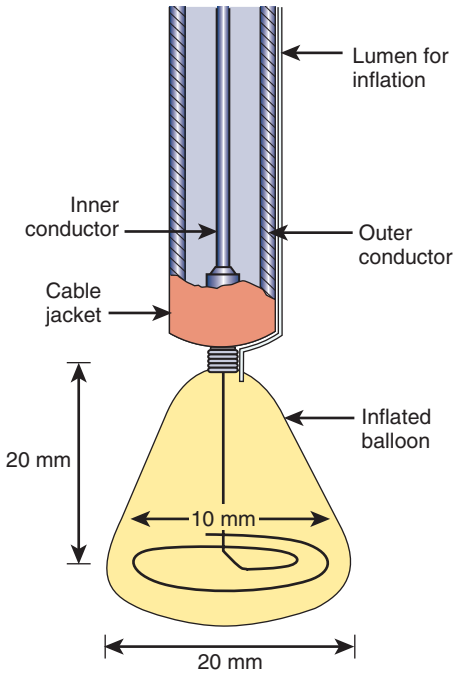

FIGURE 15-10 Schematic diagram of the spiral microwave antenna design. *(Modified from Vanderbrink B: Microwave ablation using a spiral antenna design in a porcine thigh muscle preparation: In vivo assessment of temperature profile and lesion geometry,* J Cardiovasc Electrophysiol *11:193–198, 2000.)*

ablation have greater width than depth for a given power. Acutely, they demonstrate considerable hemorrhage, but in the long term they become well-circumscribed, dense fibrous scars (Figure 15-13).

Microwave catheter ablation using a 2450-MHz generator has been demonstrated to be effective in creating chronic AV block in open-chest and closed-chest animals.[99-101] Myocardial ablation has also been used to ablate atrial myocardial tissue. Microwave energy successfully ablated aconitine-induced AT.[102] In another experiment, a deflectable microwave catheter was used to create bi-directional block at the isthmus in seven canines with an average of 2.7 ± 1.3 ablations, suggesting the potential benefit of microwave energy in creating long linear lesions.[103] Microwave ablation may also be used for ventricular myocardial ablation at either 2450 MHz or 915 MHz. In vivo experiments with canine left ventricular myocardium showed that the size of the microwave lesion increased with increasing power and duration.[100] Microwave energy, unlike RF energy, may be delivered despite

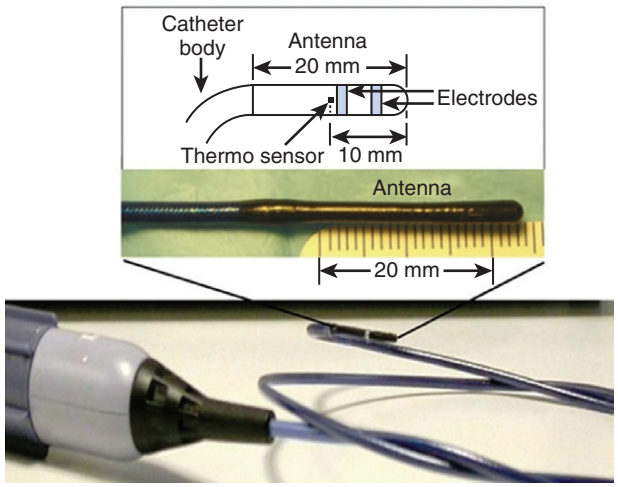

FIGURE 15-11 Microwave catheter with distal 20-mm helical coil antenna. *(Modified from Tse H, Liao S, Siu C, et al: Determinants of lesion dimensions during transcatheter microwave ablation,* Pacing Clin Electrophysiol *32:201–208, 2009.)*

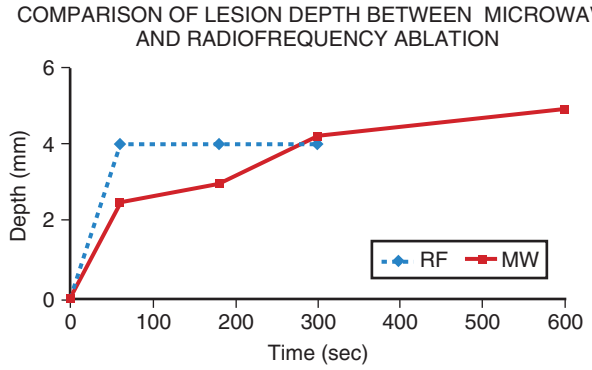

FIGURE 15-12 Comparison of lesion depth between microwave (*MW*) and radiofrequency (*RF*) ablation. Although microwave heating is considerably slower, if more energy is used, deeper lesions are created. *(Modified from Wang P, et al:* Physics and biology of catheter ablation, *Armonk, NY, 1998, Futura.)*

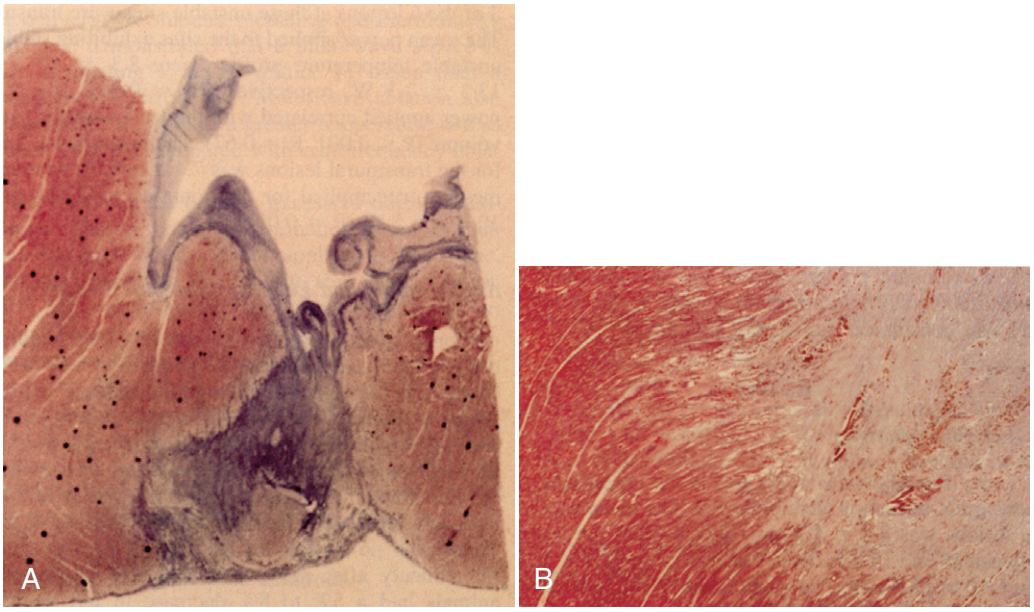

FIGURE 15-13 Histology of microwave lesion. **A,** Low-power magnification of a transmural ventricular lesion created using microwave energy. The lesion extends from the endocardial surface to the epicardium. **B,** High-power magnification of a ventricular lesion. Note the extensive fibrosis and well-demarcated lesion border zone (Masson's trichome stain). *(Modified from Vanderbrink B, Gilbride C, Aronovitz M, et al: Safety and efficacy of a steerable temperature monitoring microwave catheter system for ventricular myocardial ablation,* J Cardiovasc Electrophysiol *11:305–310, 2000.)*

tissue coagulation. Thus, temperature control of the ablation electrode may be even more important for microwave than for RF ablations to avoid thromboembolic risks.

To date, the greatest application of microwave energy in humans has been in the ablation of AF during open heart surgery.[104-108] Knaut et al prospectively evaluated 102 consecutive patients with permanent AF undergoing elective coronary artery bypass grafting surgery, concomitant valve surgery, or both, or ASD closure. Microwave energy was applied in a linear fashion in the left atrium. At 1 year, 64.7% of patients were noted to be in normal sinus rhythm, and 24% of patients required permanent pacemaker implantation. With regard to percutaneous delivery of microwave energy, thus far, only limited experience has accumulated. Chan et al demonstrated the safety and efficacy of cavotricuspid isthmus ablation for AFL with a 2-cm helical coil antenna with a unipolar electrode on a 9-Fr steerable sheath in seven patients.[109] A power setting of 21 W was used, and the mean number of energy applications was 27.4. It is postulated that inadequate catheter position and tissue contact may have contributed to the larger than expected number of lesions required for bi-directional block. Improvements in catheter design now include a bipolar electrode.

Laser Ablation

The mechanism of laser myocardial ablation is predominantly via thermal heating. Laser energy wavelength can range from 250 to 10,600 nm, and the tissue response to the laser energy depends on the wavelength delivered. Seminal work on the argon laser revealed focal thermal injury with crater formation resulting from tissue vaporization, vacuolization, and coagulation necrosis of the endocardium and the myocardium, whereas, wavelengths in the infra-red region such as with the neodymium-yttrium-aluminum-garnet (Nd:YAG) laser result in scattering of photons, causing tissue destruction via photocoagulation without vaporization.[110] Because of its low absorption in normal and coagulated myocardium, Nd:YAG laser light has the potential to reach deep intramural sites from the endocardial or epicardial surfaces. In contrast, the carbon dioxide (CO_2) laser produces predominantly absorption compared with scatter, resulting in tissue vaporization and cutting. Other laser lights such as xenon and fluoride excimer produce vaporization of tissue from absorption of energy concentrated in a thin layer.[22,111]

The laser ablation system consists of a flexible optical fiber cable housed inside a delivery catheter coupled to a laser energy source. The catheter must be continuously flushed with saline for cooling, which also helps clear the blood in front of the catheter tip. Laser is projected onto the myocardium from the fiberoptic tip. Thus, contact with the myocardium is not required. Continuous-wave laser irradiation produces gradual, dose-dependent coagulation of the irradiated myocardium.[112] Increased energy may be required to create a comparable lesion in a diseased ventricular tissue compared with normal ventricular tissue.[113] Lesion size increases with greater energy. However, laser ablation in situ results in lesions that are considerably larger compared with lesions in vitro.[114]

Lesions may demonstrate varying pathology, depending on the type of laser used. With an Nd:YAG laser, the predominant finding is coagulation necrosis with minimal vacuolization and crater formation.[115-117] Lesions are typically well demarcated. When a central vaporized crater is present, it is surrounded by a rim of necrotic tissue. Long term, the lesions are healed with a homogeneous region of fibrosis.

Laser ablation has been used successfully to create permanent AV block.[119-121] Laser catheter ablation using a preformed catheter with a pin electrode was performed in 10 patients for AVNRT, with successful outcome in all 10 patients and no adverse outcomes after a mean follow-up of 27 months.[112] Supraventricular tachycardia (SVT) in WPW syndrome has been successfully targeted via intraoperative mapping–guided argon laser ablation. In addition, laser ablation has also been used in the treatment of VT intraoperatively.[122] At the time of coronary artery bypass grafting (CABG), 9 patients who had free wall VT underwent mapping and ablation and were found to be arrhythmia free at 14 months of follow-up.[123]

More recently, a linear diffuser that delivers energy along the length of the active element has been developed. Linear endocardial laser ablation with a 980-nm infra-red laser light for the treatment of AF has been evaluated in a sheep model. Following the application of energy at a maximum of 60 W in the left atrium, electrical isolation was confirmed in all sheep. However, extensive lesions of the esophagus were noted.[124] In another attempt to treat AF, the innovation of a beam splitter has led to the design of a laser balloon that projects laser energy in a circumferential fashion for the purpose of PV isolation (Figure 15-14). An endoscopic laser balloon ablation system consisting of a compliant balloon filled with deuterium oxide to allow transmission of 980 nm laser energy has been studied in a swine model with the goal of PV

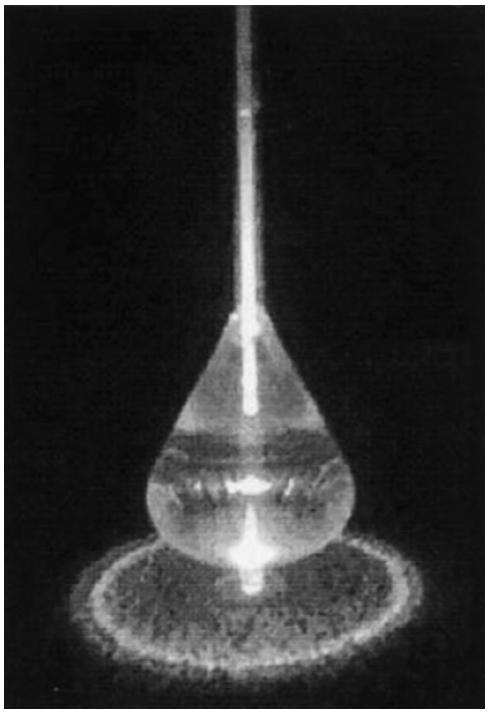

FIGURE 15-14 The laser balloon ablation catheter. The laser balloon ablation catheter filled with D20 is shown with a projected circular beam of light to simulate the photonic energy beam. *(Modified from Reddy V, Houghtaling C, Fallon J, et al: Use of a diode laser balloon ablation catheter to generate circumferential pulmonary venous lesions in an open-thoracotomy caprine model,* Pacing Clin Electrophysiol *27:52–57, 2004.)*

Table 15-1 Alternative Energy Sources for Catheter Ablation

	RADIOFREQUENCY	MICROWAVE	LASER	CRYOABLATION	ULTRASOUND
Catheter-based clinical experience	High	Minimal	Minimal	Moderate	Minimal
Lesion size	Small	Medium-large	Medium-large	Medium-large	Medium-large
Ability to create transmural lesion	Limited	Low-high	High	High	Limited
Thrombogenicity	Medium	Medium	Medium-high	Low	Medium
Lesion dependent on good contact	Yes	No	No	Yes	No
Ability to reversibly map	No	No	No	Yes	No

isolation. Laser energy was delivered under visual guidance in overlapping 30-degree arcs resulting in histologically trans-mural circumferential lesion in 7 of 8 animals.[125] A diode laser balloon ablation catheter has been tested in an open thoracotomy goat model, in which one application of photonic energy resulted in electrical isolation of 19 (70%) of 27 of the PVs.[126] The efficacy is dependent on optimal contact and orientation of its circumference with the ostium of the PV.[127]

Other Methods of Lesion Formation

Catheter chemical ablation is based on the rationale that application of cytotoxic agents such as ethanol, through the coronary circulation to selectively destroy myocardial tissue can be effective in treating various cardiac arrhythmias. Clinically, the AV node and VT have been successfully ablated using chemical ablation.[128-131] However, methods of controlling the size of myocardial necrosis as well as reflux into other vascular territories have limited the routine use of this technique.[132] It may still be considered an option for patients with septal scar, in whom standard RF energy fails.[133] Novel approaches for the ablation and modification of cardiac tissue are in development. β-Radiation has been studied as a new energy source in the creation of linear lesions in the canine atrium.[134] In addition, biologic approaches such as the implantation of autologous fibroblasts to modify AV node conduction have been studied in an animal model.[135]

Summary

Various catheter ablation techniques have been developed for the selective ablation of myocardial cells for abolition of cardiac arrhythmias (Table 15-1). Myocardial cells are destroyed by the absorption of energy or heating when RF, laser, microwave, or ultrasound is used as the energy source. Cryoablation is unique in that freezing of cells results in myocyte death. RF has emerged as the dominant energy source in clinical practice, and more recently, cooled RF has been used to target challenging substrates. Future studies are needed to determine the optimal application of each of these modalities.

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CHAPTER 16

Ablation Technologies and Delivery Systems

Paul J. Wang

Catheter ablation has been predominantly performed with a single electrode radiofrequency (RF) catheter–based system, with or without cooling; however, a number of new ablation technology and delivery systems show promise in revolutionizing the treatment of arrhythmias.

Comparison of Ablation Technologies

Each energy source used for catheter ablation has particular characteristics that determine how the energy interacts with myocardial tissue. As seen in Table 16-1, each technology is distinguished by the characteristics of the energy source. In RF energy, the 300- to 700-kHz energy source is produced by an RF generator that uses resistive heating. In contrast, the 915 to 2450 mHz microwave energy produced by a microwave generator is absorbed by substances on the basis of their di-electric properties, resulting in increased molecular motion that translates into tissue heating. Because of the differences in frequency, microwave energy uses an antenna operating at the delivered frequency, whereas RF energy may be delivered from an electrode. Cryothermia relies on the extraction of heat rather than its delivery and usually is the result of a pressure drop of a suitable gas such as nitrous oxide. Laser energy may be delivered at a range of frequencies, most commonly from 300 to 2000 nm. Each wavelength has specific absorption properties that will determine its effect on blood and body tissue. The wavelength of light is delivered via a fiberoptic, usually at a pinpoint. The fiber may be coupled to a diffusing element, which will activate to deliver the energy over a specific region, permitting the energy delivery to be adapted to the target. Ultrasound energy may be delivered using a piezo-electric crystal that converts electrical energy to mechanical energy.

The ability of each energy source to affect the properties of the ablation is illustrated in Table 16-2. Only cryothermal energy can reliably cause reversible effects for true mapping. By reducing tissue temperature to a level above freezing, it may be possible to have the bulk of the tissue be reversibly affected. Heating also has some reversible effects, but it is difficult to avoid irreversible cell death. RF energy and cryothermia are nearly completely dependent on tissue contact, whereas microwave energy, laser, and ultrasound may be delivered without tissue contact. Lesion size is considerably variable across energy sources, but in general, RF energy and cryothermia are believed to produce smaller lesions for a given maximal surface area of contact. Ultrasound and laser permit focusing of energy, which may permit controlled delivery to a specific location or even depth.

The biologic effects of the energy sources are described in Table 16-3. Heating occurs by different mechanisms, depending on the energy source. Microwave energy is absorbed by tissue, causing increased molecular motion, particularly of water molecules, which results in heating. Laser energy has several effects, including heating, vaporization, and coagulation. Ultrasound energy acts by sonication, boiling of water, and tissue heating. Cryothermia acts by its freezing the tissue, which produces ice crystals and a change in the osmotic properties of tissue. With thawing of the ice crystals, further damage and rupture of the cell may occur. Cryothermia also disrupts the vascular supply to the tissue. Overall, cryothermia is felt to result in the greatest preservation of the architecture of tissue. Cryothermia also causes the least destruction of the endothelial surface, which may help reduce the incidence of thrombus formation. Although the risk of esophageal damage is largely unknown, studies indicate that esophageal damage resulting in fistula formation may be less with cryothermia compared with other energy sources.

A summary of the advantages and disadvantages of each energy source is given in Table 16-4. RF energy has been extensively used clinically, and its relative safety has been demonstrated. The need for tissue contact and the ability of impedance rise to limit lesion formation has helped prevent complications and the destruction of collateral tissue. Microwave energy permits a variety of antenna configurations to be developed and does not require tissue contact, although the distance between the antenna and the tissue must be held relatively constant for constant energy delivery. Cryothermia's greatest advantage is the minimal disruption of tissue architecture and the endothelium and its reversible effects. In addition, tissue adherence permits excellent contact. Laser energy is capable of giving energy rapidly to create large-sized lesions and can be controlled. Ultrasound energy is capable of creating larger lesions and may permit combined imaging.

Ablation Technologies

Cooled Radiofrequency Ablation Systems

Cooling of RF ablation systems has been a major technologic advance in catheter ablation systems. The basic principle of cooling the electrode is avoidance of excessive temperatures that cause degradation of proteins and other tissue components, which leads to rises in impedance, which, in turn, prevents adequate delivery of RF energy. In addition, the avoidance of

Table 16-1 Comparison of Energy Sources

ABLATION TECHNOLOGY	MECHANISM OF HEATING	FREQUENCY	ENERGY SOURCE	ENERGY DELIVERY DEVICE
RF	Resistive	300-700 kHz	RF generator	Electrode
Microwave	Di-electric	915-2450 mHz	Microwave generator	Antenna
Cryothermia	NA	NA	Nitrous oxide or other suitable gas	Chamber permitting pressure drop in gas
Laser	Photon	300-2000 nm	Single-wavelength laser source	Fiber ± diffusing element
Ultrasound	Mechanical	500 kHz to 20 mHz	Electrical energy generator	Ultrasound piezoelectric crystal

RF, *Radiofrequency;* NA, *not applicable.*

Table 16-2 Comparison of Ablation Properties

ABLATION TECHNOLOGY	REVERSIBLE MAPPING	NEED FOR CONTACT	LESION SIZE	ABILITY TO FOCUS
Radiofrequency	0	++	++	0
Microwave	0	0	+++	0
Cryothermia		++	++	0
Laser	0	0	+++	++
Ultrasound	0	0	+++	++

++, *Medium effect;* +++, *high effect.*

Table 16-3 Comparison of Biologic Effects of Ablation

ABLATION TECHNOLOGY	MECHANISM OF CELL DEATH	PRESERVATION OF ARCHITECTURE	ENDOTHELIAL DISRUPTION	RISK OF ESOPHAGEAL DAMAGE
Radiofrequency	Heating of tissue	+	++	++
Microwave	Heating of water in tissue	+	++	++
Cryothermia	Ice crystal formation, injury of vascular supply, osmotic changes	+++	0/+	0/+
Laser	Heating, vaporization, coagulation	+	+++	?
Ultrasound	Sonication, boiling of water, heating	+	++	+++

+, *Low effect;* ++, *medium effect;* +++, *high effect.*

Table 16-4 Advantages of Energy Sources

ABLATION TECHNOLOGY	ADVANTAGES	DISADVANTAGES
Radiofrequency	Proven safety; limited ability to cause collateral damage	Limited lesion size; requires contact; charring
Microwave	Contact not required; antenna configuration may be varied for different applications	Requires control of distance to keep energy delivery constant; antenna must be efficiently coupled to tissue; heating of cable
Cryothermia	Reversible; improved safety; minimal endothelial disruption; adheres to tissue	Slow energy delivery; reversibility at margins; inability to drag lesion
Laser	Rapid delivery of high energy; large lesions; directional	No self-limiting feedback for energy delivery; risk of excessive energy delivery
Ultrasound	Large lesions; heats tissue more than blood; may permit imaging	Difficulty controlling depth; dependent on tissue properties

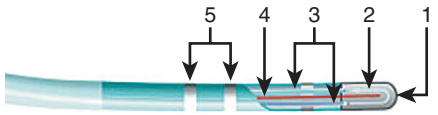

FIGURE 16-1 Saline-irrigated radiofrequency ablation catheter with internal cooling (Chilli ablation catheter). *(Courtesy Boston Scientific, Natick, MA.)*

excessive temperatures may decrease the risk of catheter ablation complications such as perforation and thrombus formation.

Cooled RF ablation systems may be divided largely into the two groups: (1) internal cooling systems and (2) external cooling systems. Internal cooling systems use saline, which circulates within the catheter to reduce electrode temperature. The dimensions of the internal cooling system limit the flow rate that may achieved during RF application. Because most catheters using current designs are limited to 7 to 8 Fr diameter size (2.33 to 2.67 mm), the flow rate is limited.

An example of the currently available internally cooled RF ablation system is the Boston Scientific (Natick, MA) Chilli Catheter (Figure 16-1). Clinical trials using this system have demonstrated that this catheter may be used effectively during the ablation of ventricular tachycardia (VT).

Externally cooled RF ablation systems use small holes in the ablation electrode to permit saline to escape the catheter and be introduced into the body. Because a return path is not required, current designs permit the forward flow to be greater compared with internally cooled RF ablation systems. In addition, it is possible that the saline that escapes into myocardial tissue directly cools the myocardium in addition to cooling the ablation electrode. Present designs incorporate several holes in the electrode that are able to cool the electrode efficiently. The Biosense Webster (Waterloo, Belgium) Thermocool (Figure 16-2) catheter and the St Jude Medical (St Paul, MN) catheter (Figure 16-3) have lateral holes at the catheter electrode. The Thermocool catheter has been approved for ablation of atrial fibrillation (AF) and VT.

Temperature sensing and power regulation during cooled ablation, whether using internally or externally cooled systems, present some particular challenges. It is generally believed that in noncooled RF ablation, the temperature measured by thermocouples or thermistors reflects the surface tissue temperature to an imperfect degree. Even in these cases, the true maximum tissue temperature is thought to be approximately 1 mm below the surface; therefore the temperature measured by the electrode tip sensors does not reflect the maximum tissue temperature. In cooled RF ablation systems, the irrigation of the electrode results in cooling at the site of temperature measurement. During irrigation, the myocardial surface is cooled, resulting in the highest temperature occurring deeper in the myocardium. Some rise in electrode temperature is observed, reflecting heat transfer from tissue to the electrode, but it is difficult to extrapolate directly from this temperature to the highest myocardial temperature.

Saline-Irrigated Needle Injection

Since creating deeper and larger lesions has been limited by the heating of the myocardial surface, using a needle to inject the saline solution, which serves as an electrolytic solution to carry the current into the myocardium, has been introduced as a new technique for the treatment of cardiac arrhythmias. Sapp et al demonstrated the ability to produce left ventricular lesions in the myocardium.[1]

FIGURE 16-2 Saline-irrigated radiofrequency catheter (Thermocool, Biosense Webster, Waterloo, Belgium) with external cooling.

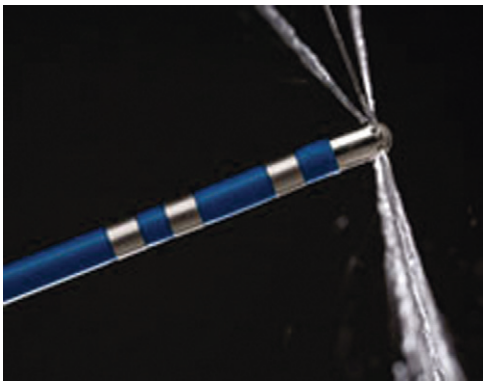

FIGURE 16-3 Saline-irrigated radiofrequency catheter with external cooling (St Jude Medical, St Paul, MN).

Cryoablation Technologies

Single-Point Cryoablation

Freezing is an effective means of killing myocardial tissue and has been successfully used in catheter cryoablation systems. Experimental studies have used several approaches to catheter cryoablation, but currently the only commercially available system is the CryoCath (Medtronic, Inc., Minneapolis, MN). Experimental

systems have included systems using the Peltier effect to achieve freezing with an electric device. Such systems have been used effectively in cooling microscope viewing stages and other controlled environments. A catheter system using the Peltier effect was designed but was not commercially pursued.

Catheter cryoablation systems may use a variety of strategies to freeze myocardial tissue at the tip of the catheter. Delivery of a cold liquid is theoretically feasible but has been limited in practice because of the exceptionally efficient insulation needed to achieve freezing at the tip. Current catheter cryoablation systems deliver nitrous oxide to the tip, where it undergoes a pressure change, causing rapid and significant cooling at the tip. Such a system requires the gas to be kept under high pressure; therefore pressure-safe systems are needed to bring the gas through the meter-long catheter.

One of the most attractive features of catheter cryoablation is the ability to cool myocardial tissue reversibly. Reversible cooling permits one to observe physiological changes transiently during cooling and to reverse these effects by rewarming the tissue. In addition, freezing of the tissue occurs gradually, initially involving the tissue closest to the catheter tip and expanding gradually in concentric circles to form an ice ball that surrounds the catheter tip (Figure 16-4).

Numerous series have studied the use of the catheter cryoablation for a variety of cardiac arrhythmias. In a series using event recordings, of the 160 patients undergoing catheter cryoablation of cavo-tricuspid–dependent atrial flutter (AFL), 80.3% remained free of AFL and 90.2% remained clinically free of AFL.[2] In a study comparing catheter cryoablation and RF ablation of cavo-tricuspid–dependent AFL, Malmborg et al found that catheter cryoablation had a lower acute success rate but had a recurrence rate similar to cryoablation and RF ablation (20% and 15%, respectively; $P = .45$).[3]

Some series have examined the role of catheter cryoablation for the treatment of atrioventricular nodal re-entrant tachycardia (AVNRT). The advantage of catheter cryoablation has been the ability to avoid permanent atrioventricular (AV) block that may occasionally occur during RF catheter ablation. Catheter cryoablation has a recurrence rate as low as 0% to 2%, but some series have reported rates as high as 10% to 15%. The reasons for these variations in outcome and recurrence have not been established. The most recent studies have shown some of the highest success rates and the lowest recurrence rates with catheter cryoablation, suggesting that over time, the success rates have improved. In a series of 312 patients with AVNRT, Bastiani et al described an acute success of 99% with a 5.8% recurrence rate.[4] In a significant number of pediatric centers, catheter cryoablation has become the standard treatment modality.

The ablation time during catheter ablation is usually longer than during RF energy. However, overall procedure time may be similar.[5] In addition, the fluoroscopy time may be decreased with catheter cryoablation compared with RF ablation ($P = .049$).[5] The need for fluoroscopy is reduced because of the adhesion of the electrode to the tissue during cryoablation.

Experience in the use of catheter cryoablation for the treatment of accessory pathways is considerably less. However, available data suggest that cryoablation is highly successful in treating accessory pathways. In the treatment of para-Hisian accessory pathways, catheter cryoablation is particularly useful and may prevent AV block. However, a higher recurrence rate may be observed. Ablation in the coronary sinus has been successfully performed, but recurrences may be more common. However, damage to the coronary arteries and the coronary sinus appears to be less of a concern.

Catheter cryoablation may also be used for focal atrial tachycardia (AT). It may be particularly useful in areas of low blood flow, which may limit energy delivery when RF energy is used.

Balloon Cryoablation

Balloon cryoablation has been introduced as a new technology for the treatment of AF. CryoCath cryoablation balloons use a "balloon within a balloon" design to prevent the leakage of refrigerant gas into the body (Figure 16-5). In balloon cryoablation, pressure change of the gas is used to achieve freezing. Transseptal catheterization is performed, and the standard sheath is exchanged for the steerable sheath over a wire placed in the left superior pulmonary vein. The balloon catheter cryoablation system is then advanced over the wire into each of the four pulmonary veins. Because freezing is optimized when pulmonary vein blood flow is minimal around the cryoablation, it is critical

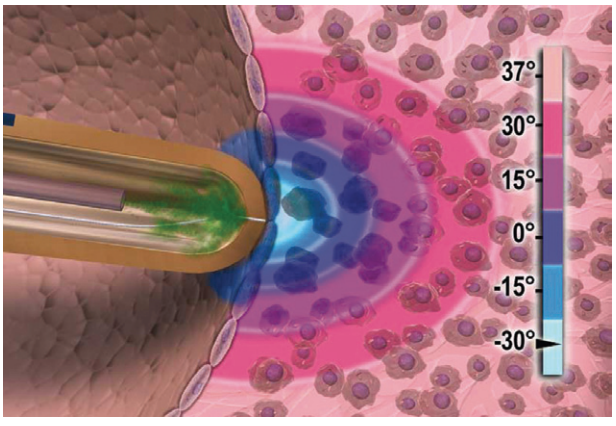

FIGURE 16-4 Demonstration of thermal profile of catheter cryoablation lesions with the CryoCath. A zone of reversible cooling surrounds the region of irreversible cell death. *(Courtesy Medtronic, Minneapolis, MN.)*

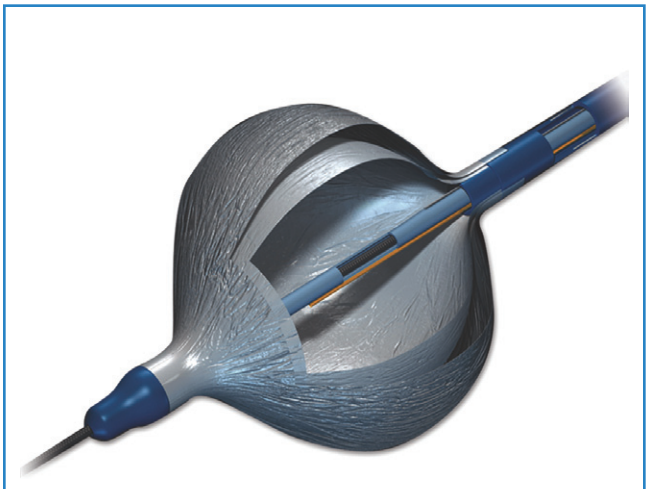

FIGURE 16-5 Arctic Front Balloon Cryoablation Catheter, in cut-away view. Note the balloon within a balloon construction. *(Courtesy Medtronic, Minneapolis, MN.)*

to obtain an excellent occlusion of the balloon outside the ostium of the pulmonary vein.

Balloon cryoablation has been successful in achieving pulmonary vein block. Acute success has been achieved in 90% to 98% of patients. Single-procedure success has varied between 60% and 80%. In the multi-center Sustained Treatment of Paroxysmal Atrial Fibrillation (STOP AF) clinical study conducted in 26 centers with 245 patients, balloon catheter cryoablation was compared with drug therapy.[6] The primary effectiveness hypothesis of the trial was that balloon cryoablation would have a significantly greater treatment success at 12 months compared with drug therapy. Patients who had two or more episodes of AF in 2 months and did not respond to one or more antiarrhythmic drugs were included in the trial. The patients were randomized in a 2:1 ratio to ablation or drug therapy. The patients were followed up at 1, 3, 6, 9, and 12 months with Holter electrocardiographic monitors and weekly with trans-telephonic monitors. The primary endpoint was freedom from detectable AF, no use of non-study drugs, and no AF interventions. The cryoablation system in the study used a double-balloon structure, with liquid-to-gas transition for cooling. The balloon was delivered using a 14 Fr deflectable sheath. The mean age of the study subjects was 56.6 years. The acute procedural success defined as three or more pulmonary veins isolated was 98.2%. Repeat cryoablation was performed in 31 (19%) of the 163 patients. After the blanking period, freedom from AF was 69.9% in the cryoablation group compared with 7.3% in the drug-treated group. No atrial-esophageal fistulas occurred, but 4 (2.5%) strokes, 3 (1.8%) transient ischemic attacks, and 1 death occurred in the cryoablation treatment arm. Among the subjects, 22 (13.5%) had phrenic nerve palsy, of whom 4 (2.5%) had phrenic nerve palsy persistent at 12 months, and one of these patients was symptomatic. Pulmonary vein stenosis (>75% change in area) was observed in 5 patients (3.1%) in the cryoablation arm.

Laser Balloon Catheter Ablation Systems

A novel laser balloon ablation system has been developed for pulmonary vein isolation as treatment for AF. The CardioFocus (Marlborough, MA) system uses a 58-W continuous 980-nm diode laser to create myocardial lesions. A console cools the balloon with circulating sterile fluid. The balloon is positioned by using a removable reusable endoscope with a 500-µm-diameter device capable of creating a wide field of view. The laser balloon uses a disposable deflectable sheath, which gives access to the four pulmonary veins. A green aiming beam is used to adjust the laser beam in arcs of approximately 30 degrees. In a recent single-center study of 27 patients, 100% of the pulmonary veins were isolated after 1.3 attempts per vein. At 3 months, 61 (90%) of 68 pulmonary veins continued to be electrically isolated.[7] The ability to visualize lesion formation using the endoscope is a novel feature of this technology (Figure 16-6).

Radiofrequency Mesh Pulmonary Vein Catheter

A 36-electrode ablation mesh is used for pulmonary vein ablation and high-density mapping. This mesh is a three-dimensional electrode array (Figure 16-7) that does not impede blood flow from pulmonary veins in the same way that a balloon ablation catheter does. In a series of patients with paroxysmal and persistent AF, 58 of 67 pulmonary veins in 17 patients were successfully acutely isolated. During a mean follow-up of 11 months, 64% of patients remained in sinus rhythm.[8]

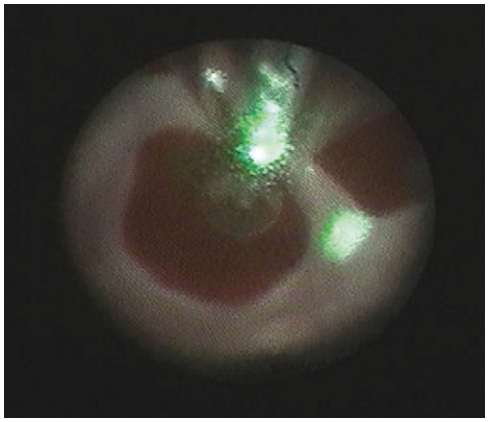

FIGURE 16-6 CardioFocus balloon ablation catheter. Endoscopic view of laser ablation of the right inferior pulmonary vein. *(Courtesy CardioFocus, Marlborough, MA.)*

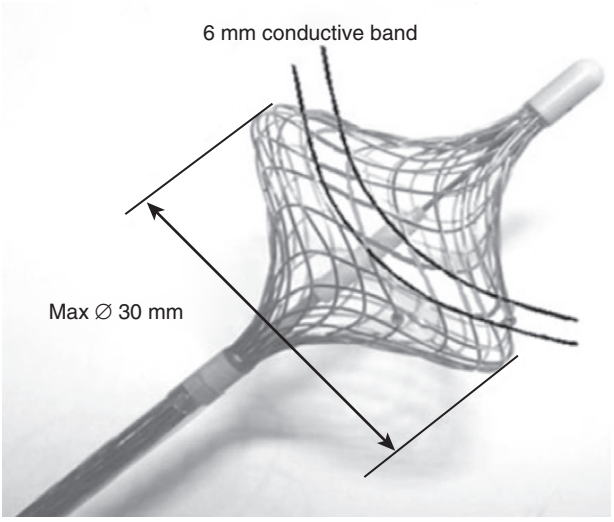

FIGURE 16-7 High-density electrode mesh radiofrequency ablation catheter (Bard Mesh; Bard Electrophysiology, Lowell, MA).

Radiofrequency Hot Ablation Balloon Catheter

Instead of using RF energy to heat atrial tissue directly, RF energy is used to heat the saline within a balloon positioned outside pulmonary veins to achieve adequate temperatures for ablation. In 100 consecutive patients, all the pulmonary vein and posterior left atrial signals were eliminated. In addition, lesions were created between the two superior pulmonary veins and the inferior pulmonary veins. In a mean 11-month follow-up, 92 patients (60 paroxysmal AF and 32 persistent AF) were free of AF.[9]

Radiofrequency Electrode Arrays

The electrode arrays are designed to permit adjustment of these multi-electrodes to deliver a series of lesions (Figure 16-8). In 98 patients over a mean follow-up of 7 months, Boersma et al

FIGURE 16-8 Electrode array catheter for ablation of atrial fibrillation. *(Courtesy Medtronic Ablation Frontiers, Carlsbad, CA.)*

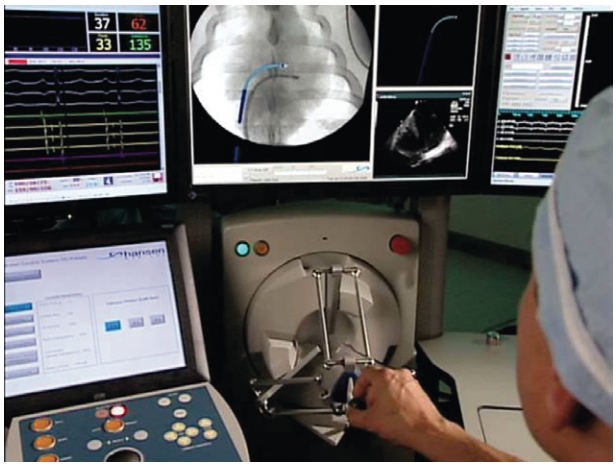

FIGURE 16-10 Composite photo of the Sensai system remote robotic navigation. *(Courtesy Hansen Medical, Mountain View, CA.)*

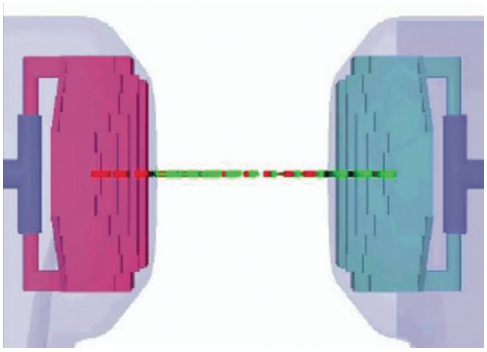

FIGURE 16-9 Schematic drawing of two external magnets used for remote magnetic navigation in the Niobe II system. *(Courtesy Stereotaxis, St Louis, MO.)*

demonstrated that 44 (83%) of 53 patients after 6 months of follow-up were free of AF on 7-day Holter monitor. After 3 months, 18% of patients had a recurrence of AF.[10]

High-Frequency Focused Ultrasound Balloon Catheter Ablation Systems

By using a reflector configuration, ultrasound is focused to create ablative lesions. In an initial series of 15 patients with paroxysmal AF, pulmonary vein isolation was achieved acutely in 89% of pulmonary veins with a power of 45 W. In median follow-up of 387 days, 58% of patients were free of AF off antiarrhythmic agents. In subsequent clinical experience, atrial-esophageal fistulas were observed, and the clinical trials were discontinued.

Ablation Delivery Systems

Remote Magnetic Navigation

Remote magnetic navigation uses large external magnets to precisely control the ablation catheter tip within the heart (Figure 16-9). This technology enables the user to perform ablation without having to manually control the catheter. In a series by Katsiyiannis et al, 20 patients undergoing ablation with a Stereotaxis (St Louis, MO) Niobe II system and a 4-mm tip magnetic catheter were compared with 20 patients undergoing ablation with an 8-mm tip manually controlled catheter.[11] In all these patients, pulmonary veins were successfully isolated along with wide-area circumferential ablation. At 1 year, a comparable number of patients were free of AF off antiarrhythmic agents, and a similar number of patients had ablation for atypical AFL. Mean procedure and fluoroscopy times were shorter in the remote magnetic navigation group.[11]

Remote Robotic Navigation

Robotic systems permit precise control of the ablation catheter remotely using a sophisticated computerized system (Figure 16-10). In one study using a combination of the Hansen Medical (Mountain View, CA) Sensai system and a 3.5-mm Thermocool catheter, all the pulmonary veins were isolated in 40 patients; at 1 year, 86% of patients were free of AF.[12] Other studies have demonstrated a significant reduction in fluoroscopy time with the remote robotic navigation system. Enhancements of this system permit assessments of catheter-tissue pressure.

Noninvasive Ablation

The use of external radiation focused on a precise region of the heart has been proposed as a method to treat arrhythmias. The use of gamma radiation is the focus of CyberHeart (Sunnyvale, CA). Early experimental data have demonstrated that it is feasible to create myocardial lesions using this approach.

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CHAPTER 17

Essentials of Imaging and Imaging Technologies Related to Arrhythmias

A. Cardiac Computed Tomography: Jasbir Sra
B. Cardiac Magnetic Resonance Imaging: Rishi Anand and Timm-Michael Dickfeld
C. Transthoracic and Transesophageal Echocardiography: Anjlee M. Mehta and Navin C. Nanda

A. Cardiac Computed Tomography

Introduction

Fluoroscopy does not provide adequate anatomic visualization because of lack of contrast between the area of interest and surrounding structures, making it difficult to precisely manipulate intracardiac catheters in complex three-dimensional left atrial (LA) anatomy in procedures such as atrial fibrillation (AF) ablation.

Recent advances in imaging technology are starting to have a profound effect on the practice of electrophysiology. Radiological scans, such as computed tomography (CT) and magnetic resonance imaging (MRI), offer high-quality anatomic visualization with high spatial and temporal resolution and can thus enhance efficacy and reduce the risks associated with procedures such as LA ablation for AF through more precise anatomic depiction, aiding accurate planning of ablation.[1]

The role of CT in cardiac arrhythmias, the focus of this chapter, has benefited from the use of electrocardiogram (ECG)-gated image acquisition, a rapid increase in gantry rotational velocity, and an increasing number and resolution of available detector rows. Recently available 64-slice scanners provide high-resolution volume and improved image quality by effectively freezing the heart's motion during acquisition and allowing scans to be performed more quickly or with fewer gantry rotations than with earlier scanners. This, in turn, has led to a reduction in errors associated with image reconstruction and segmentation, and more precise information on the position and movement of the cardiac structures throughout the cardiac cycle.

This chapter addresses the basic principles of CT imaging within the particular constraints of cardiac imaging relating to cardiac arrhythmias. Although CT imaging has been used to identify many structures in the heart, given the current interest in image-guided therapy for AF, CT imaging of the left atrium and its role in AF ablation is the main focus of this chapter.

Segmentation

Technical Considerations

Most medical images are in a digital format and are made up of an array of small square or rectangular elements called *pixels*.[2] Each pixel has associated image intensity. This provides the coordinate system of the image, and an element in the image can be assessed by its two-dimensional position within this array. For example, a typical CT slice is formed of 512 × 512 pixels, each corresponding to a portion of the cut through the patient measuring about 0.5 × 0.5 mm^2. The matrix and the pixel size are related to the display field of view (FOV). If, for example, the FOV is 25 cm, each pixel will be FOV/matrix size 25/512 = 0.48 mm^2. This dimension determines the limiting in-plane spatial resolution of the image. The two-dimensional axial slices are then stacked together to form a three-dimensional volume. Each pixel corresponds to a small volume element called a *voxel*. The height of the voxel is determined by the slice thickness. If the axial slice thickness in the above example is 1.5 mm, the voxel size would be 0.48 × 0.48 × 1.5 mm^3.

Computed Tomography Imaging

In a CT imaging system configuration, an x-ray projects a fan-shaped beam that is collimated to lie within an *x-y* plane of a Cartesian coordinate system and generally referred to as the *imaging plane*.[1,2] Thus, during CT imaging, the anatomy of interest passes through this imaging plane, and the image data of interest are acquired and reconstructed. This acquisition is typically accomplished by obtaining different views as the x-ray source and detectors rotate around the anatomy or volume. Reconstruction of these data generates a two-dimensional array of quantized grayscale values or pixels. Pixel values are a measure of the x-ray attenuation in Hounsfield units (HU), where the HU = 1000 − (4 μ/μw − 1), μ being the average linear attenuation coefficient of the volume element represented by the pixel and μw the linear coefficient of water for the effective energy at the beam exiting the patient. Thus, water has an HU number of 0, and a region with a CT number of 100 HU has a linear attenuation coefficient that is 1% greater than the linear attenuation coefficient of water.

In the most commonly used ECG-gated helical CT acquisition, the x-ray tube (and detector array) rotates continuously about the patient collecting the data, while the table (with the patient) is moved at a constant speed through the imaging plane. The helical CT thus collects a continuous sequence of consecutive axial images from a volume of the patient's anatomy. Faster scanning, as currently done with 64-slice CT scanners, allows collection of a large volume of data in short periods (<10 seconds). The factors selected in scanning a patient include slice width, FOV, gantry

rotation speed, and volume of coverage, as well as basic contrast injection protocols. Scan time is calculated from the scan volume (total distance traveled by the table) divided by table speed. Also important is the *pitch*, which is defined as a ratio of the distance the table moves per 360-degree rotation. A pitch of 1 means the patient table moves a distance of one slice. Similarly, a pitch of 0.2 means the gantry rotates five times as the table moves a distance equal to the collimator width.

Cardiac motion caused by heartbeat, respiration, and patient movement while on the table can produce artifacts that appear as blurring in the reconstructed image. Such blurring effects may make diagnosis difficult. The use of a short scan time, as can be done with current scanners, can prevent or minimize these artifacts because of the speed of acquisition. To avoid respiration artifacts, scanning is performed during the breath held in inspiration or expiration. Because of the short scan time, currently available faster scanners allow images to be acquired in expiration. The acquired data are synchronized with the collection of the ECG (QRS) signal. The ECG signal is recorded in parallel with the CT through a noninvasive monitoring device connected to the patient. The data acquired during consecutive cardiac time intervals can then be combined to produce an image of the heart at the same phase of the cardiac cycle. Retrospective gating allows alignment of images during any phase of the cardiac cycle because of continuous helical acquisition. Usually, during retrospective gating, an approximately 75% phase location is used for patients in sinus rhythm as it yields the best image quality because of diastole. During AF, because of short R-R intervals, an approximately 45% cardiac phase usually gives best results.

Once the image is acquired, it is stored in a proprietary format. The data can then be exported from the scanner. As images obtained by scanners of one manufacturer may need to be imported to that of another or to different viewing screens, a medical image standard known as DICOM (Digital Information and Communications in Medicine) has been devised and is widely used. This allows data to be exchanged between scanners and viewing consoles.

The American Radiology Society's convention is to display axial images with the right side of the patient at the left and the

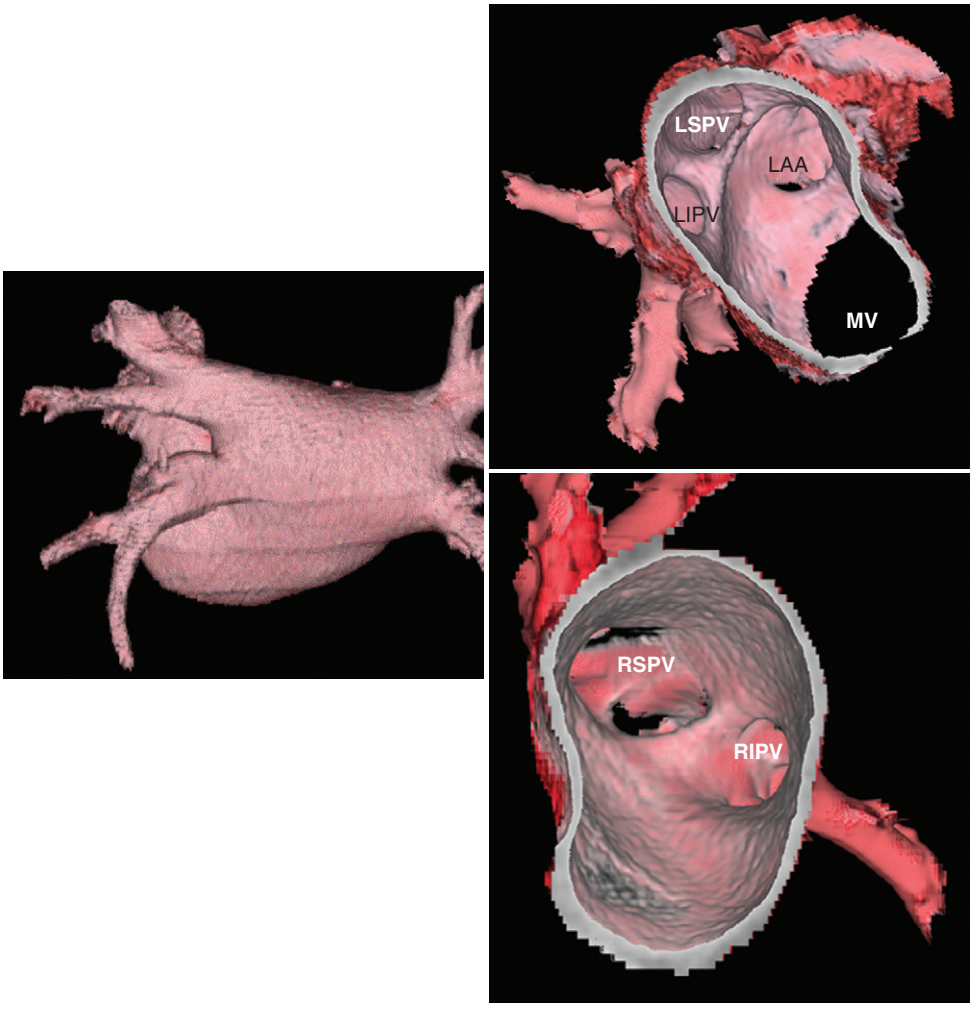

FIGURE 17-1 Left atrial three-dimensional image. *Left*, A posteroanterior view of the segmented left atrium from the computed tomography image. *Right*, Endocardial views of the left atrium. *Top right*, A right lateral view, with the medial side of the left atrium cut away, revealing the left superior pulmonary vein (*LSPV*), left inferior pulmonary vein (*LIPV*), the left atrial appendage (*LAA*), as well as the mitral valve (*MV*). *Bottom right*, Left lateral portion of the left atrium cut away, revealing the right superior pulmonary vein (*RSPV*) and right inferior pulmonary vein (*RIPV*).

posterior side at the bottom when viewed on the computer screen at the workstation.

Image Segmentation

Following scanning, cardiac images are generated by postprocessing of one phase of axial image datasets. The cardiac chamber volumes are based on the boundary between the contrast-enhanced blood pool, which is of bright appearance because of the contrast, and the endocardium, which is not contrast enhanced. This allows for clear differentiation of the lumen and the myocardial wall. The process of dividing images into different regions to visualize areas of interest is called *segmentation*.[3,4] Image segmentation methods can be grouped into thresholding, boundary detection, and region identification.

Thresholding is the simplest but most effective segmentation method. During thresholding, pixels with intensities below a threshold value are assigned a certain class and the remaining pixels a different class. Connecting adjacent pixels of the same class forms regions. Thus, boundary extraction methods use information about intensity differences between adjacent regions to separate the regions from each other. Region identification techniques then form regions by combining pixels of similar properties. The simplest region-identifying technique could start with at least one *seed* (a starting point) per region. Neighbors of the seed are visited, and the neighbors that satisfy the *predicate* (a simple predicate compares the intensity values of the pixel to the average intensity value of the region) are added to the region. Segmentation, as relevant to AF ablation, for example, can be used to identify the anatomy of the LA and its vasculature that can be viewed separately from the remaining chambers of the heart and surrounding anatomy such as the lung.

Three-dimensional endocardial views, navigator views, and various measurements can be obtained from the imaged and segmented data (Figures 17-1 and 17-2). Cut planes can be used to remove a portion of the surface. The resultant model can show endocardial surface and pulmonary veins (PVs) as if from inside the chamber. Cutting away the anterior surface, for example, gives a good view of the posterior LA endocardium. Left and right anterior views can provide excellent delineation of right and left PVs, respectively. The navigator view shows the LA from the perspective of a virtual endoscope. Several measurements such as the LA volume (Figure 17-3), PV ostium (Figure 17-4), mitral isthmus and distance between the superior PVs (Figure 17-5), and relationship of the esophagus to the LA (Figure 17-6) can be made due to their relevance to some of the linear and other lesions

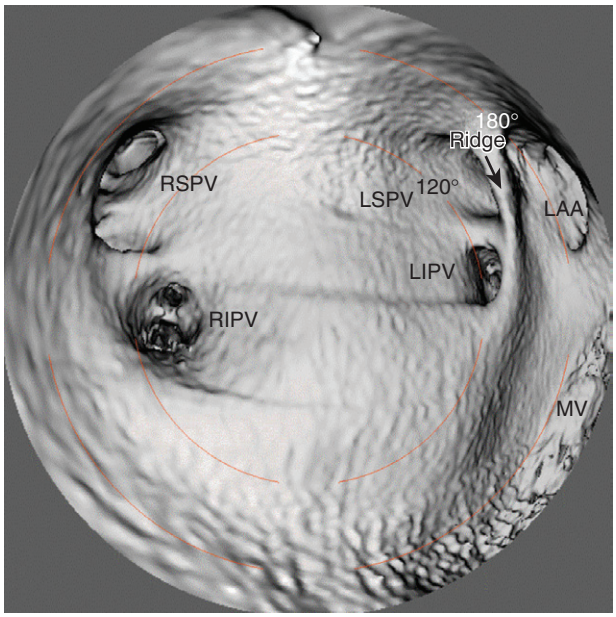

FIGURE 17-2 Navigator view of the left atrium. Polar view of the left atrium depicts the entire left atrium. *LAA*, Left atrial appendage; *LIPV*, left inferior pulmonary vein; *LSPV*, left superior pulmonary vein; *MV*, mitral valve; *RIPV*, right inferior pulmonary vein; *RSPV*, right superior pulmonary vein.

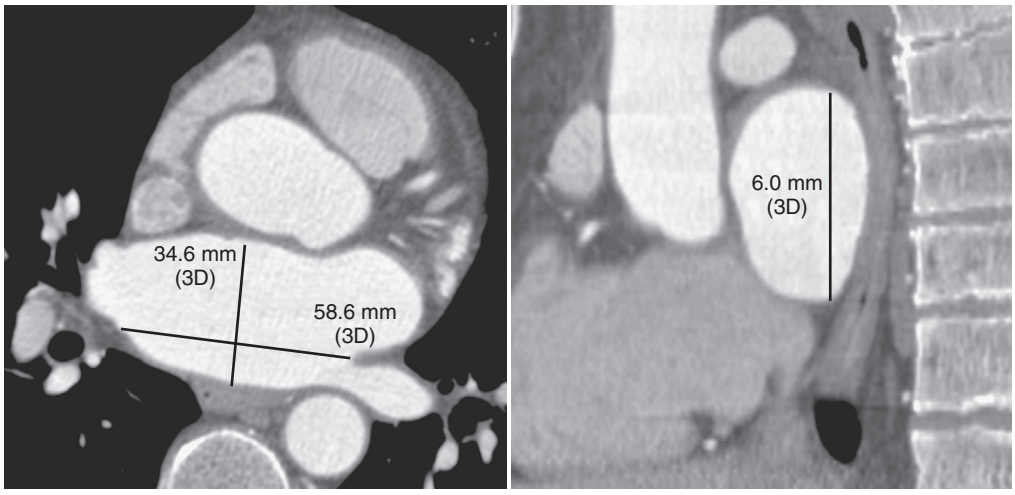

FIGURE 17-3 Left atrial measurement. Methods of measuring transverse, lateral, and anteroposterior length of the left atrium are shown. Localization of points over the three-dimensional (*3D*) computed tomography model made to create a localization line over the axial datasets is depicted. The image has been rotated to visualize all the highlighted points simultaneously.

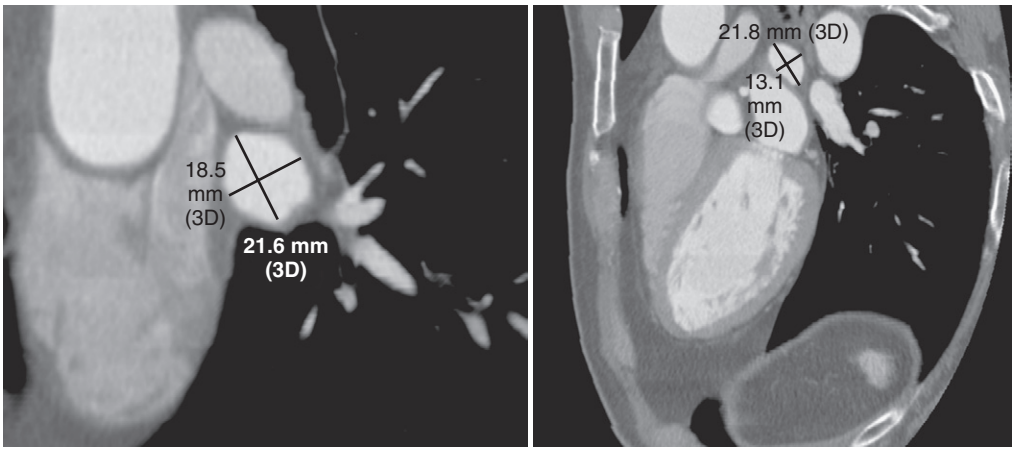

FIGURE 17-4 Right superior (*left*) and left superior pulmonary vein ostial (*right*) measurements from axial datasets. The first oblique cut creates the planes (not shown) in the figure. The second oblique shown in the left and right panel results in the cross-sections of the pulmonary veins at the ostium.

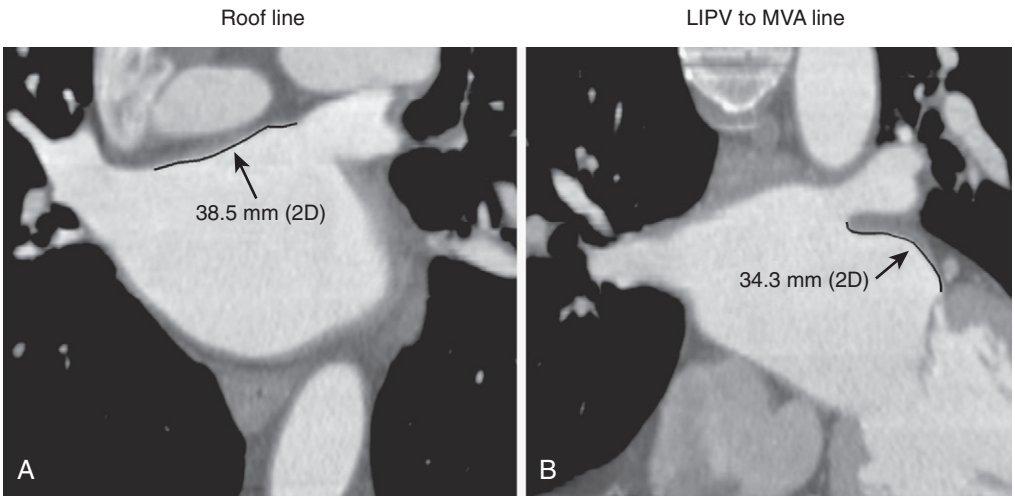

FIGURE 17-5 Measurements of strategic locations used for ablation. **A,** The roofline connecting the superior pulmonary veins. **B,** The definition of the left inferior pulmonary vein (*LIPV*) to mitral valve annulus (*MVA*) line, mitral isthmus line. **B** is an oblique cut showing the MVA and LIPV and illustrates how the line, which follows posteriorly between the LIPV and the MVA, is drawn and measured.

performed in some AF procedures in these areas. For LA dimension measurement, a series of three lines or axes are drawn in the LA to measure chamber dimensions and to serve as the basis for creating a coordinate system in the LA. First, a line is drawn near the posterior portion of the LA connecting the junction point of the right superior and inferior veins to the junction point of the left superior and inferior veins. This creates the *x*-axis. Next, a line is drawn through the mid-portion of the *x*-axis, forming the *y*-axis. Finally, drawing a line through the intersecting points of the *x*- and *y*-axes creates a *z*-axis of the coordinate system. The length of these lines serves as the LA dimensions. In the case of measuring mitral isthmus dimensions, for example, markers can be placed on the three-dimensional volume at the inferolateral aspect of the left inferior PV, the posterolateral aspect of the mitral annulus, and midway between these two points help define the optimal line. Then, a cut plane that passes through these points is defined. Finally, the distance along this surface reaching from the left inferior PV to the mitral annulus is measured. PV ostial dimensions are measured using a standard double-oblique approach. An initial oblique cut is made along the shaft or lumen of the vessel. A second oblique cut is then made and positioned orthogonally to the first cut plane. The long and short axes are then measured. For LA esophageal measurement, axial slices are scanned. A point is deposited in the center of the esophageal lumen. An oblique cut plane is then created through this point, orthogonal to the posterior LA and the esophagus. Four measurements are made of the distance between the posterior LA endocardium and the esophagus.

Imaging of the Atrium and Pulmonary Veins

A thorough understanding of the morphologic characteristics of the LA and PVs in detail will not only help achieve a more efficient ablation but also prevent procedure-related complications such as PV stenosis and others by delineating the relationship of the LA to surrounding structures such as the esophagus and by helping to choose the right tools for mapping and ablation. A survey given to task force members for the AF ablation consensus document revealed that approximately two thirds of centers are routinely obtaining MRI or CT scans in patients scheduled to have an AF ablation.[5]

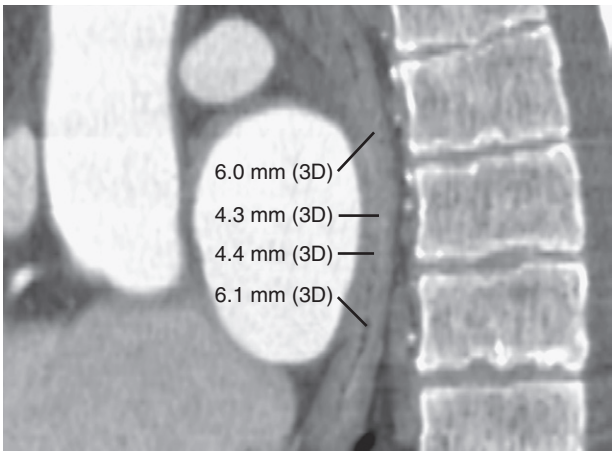

FIGURE 17-6 Relationship of the esophagus to the posterior left atrium. Left lateral three-dimensional (*3D*) computed tomography images of the left atrium are shown. The esophagus is seen as a translucent structure near the left atrial posterior wall over the left pulmonary veins. Measurements at four different locations between the left atrium and the esophagus are shown.

Detailed imaging studies have shown that anywhere from 65% to 80% of patients have four PVs, and some have left common and right middle PVs as well (Figure 17-7).[6] Part of the main trunk of the right superior PV passes immediately behind the right superior vena cava (SVC) junction. It has also been shown that the right superior PV trunk branches out significantly sooner than do the left PVs. The right inferior PV arises inferiorly and laterally to the right superior PV. It divides almost immediately, within 5 to 10 mm, into superior and inferior branches. The distance between the right superior and right inferior PVs across the canal ridge varies from 2 to 8 mm. In 18% to 29% of cases, a supernumerary right PV may arise independently on the right side.[7]

The left superior PV lies superiorly and posteriorly to the LA appendage. It enters the LA in a more vertical direction. It usually has multiple branches, which ordinarily arise 10 to 20 mm from their base. The left inferior PV enters the LA more horizontally from a posterolateral position and branches almost immediately. A common antrum of the left superior and inferior PVs is seen in 3% to 30% of patients. Some studies have suggested this number may be even higher. In a series of more than 500 CT scans done at the author's institution, in addition to the left common and right middle PVs, other unusual anatomies, including one common right PV, three PVs on the right and left, and one common ostium of the left inferior PVs, were seen.[8] Examples are depicted in Figures 17-8 and 17-9.

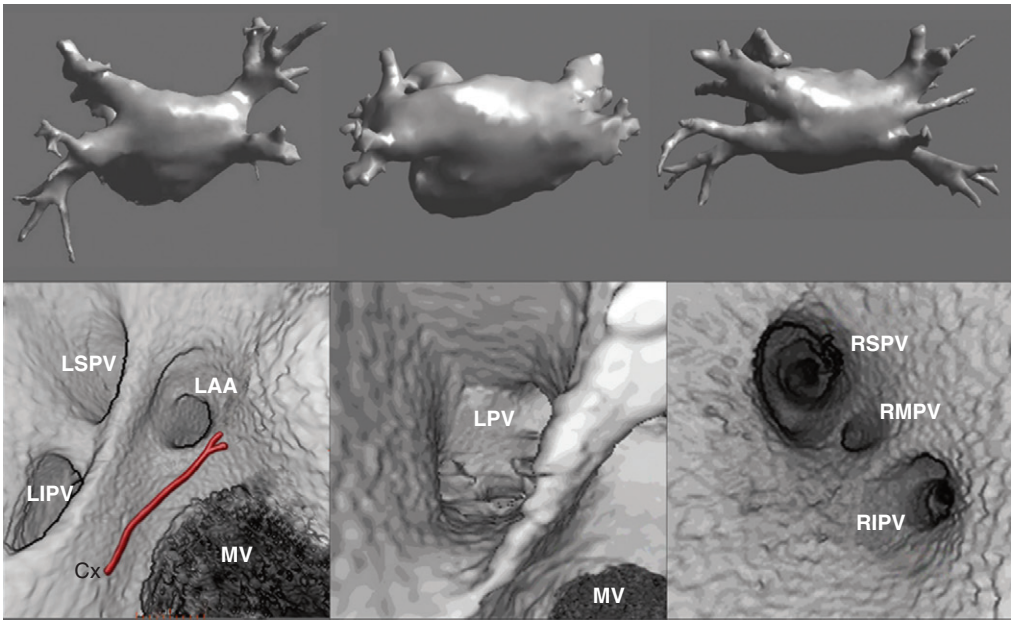

FIGURE 17-7 Three-dimensional and endocardial left atrial image reconstruction. Representative examples of three-dimensional models of three different pulmonary vein morphologies, along with endocardial views, are depicted. The standard four pulmonary veins (*top left*), a common pulmonary vein (*top middle*), and an additional right middle vein (*right*) are shown. *Bottom*, The respective endocardial views, along with the mitral valve (*MV*). *Left*, The location of the circumflex artery (*Cx*). *LAA*, Left atrial appendage; *LIPV*, left inferior pulmonary vein; *LPV*, left pulmonary vein; *LSPV*, left superior pulmonary vein; *RIPV*, right inferior pulmonary vein; *RMPV*, right middle pulmonary vein; *RSPV*, right superior pulmonary vein. *(From Sra J, Krum D, Okerlund D, et al: Endocardial imaging of the left atrium in patients with atrial fibrillation,* J Cardiovasc Electrophysiol Imag *15:247, 2004.)*

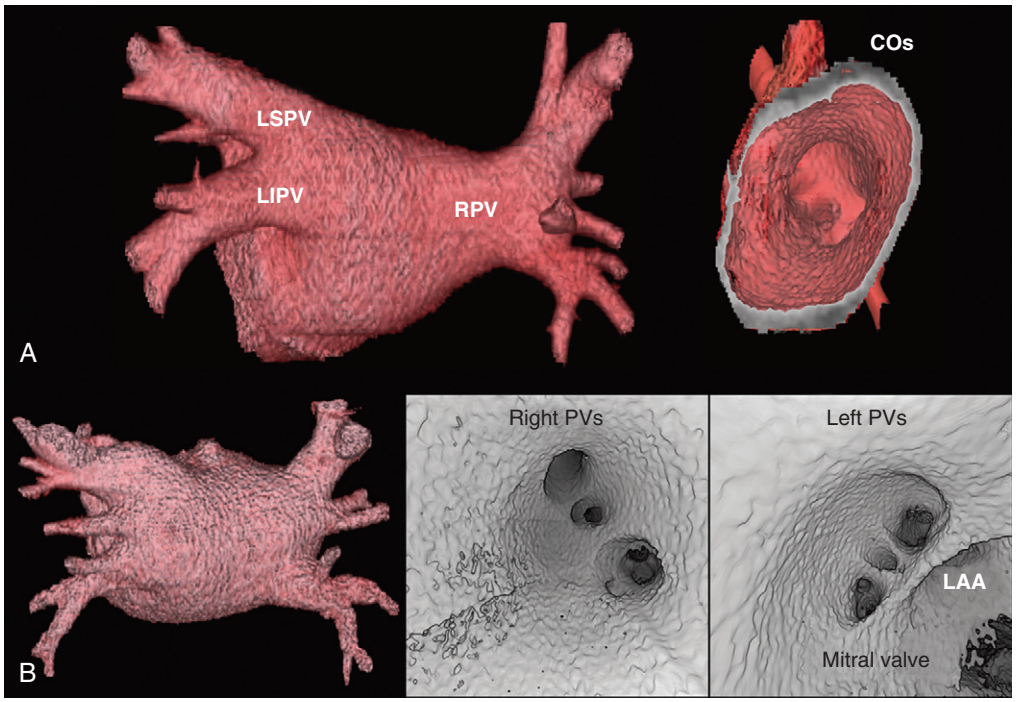

FIGURE 17-8 Different pulmonary anatomies. **A,** Common right pulmonary vein (*RPV*). Endocardial view shows the common ostium (*COs*). **B,** Reconstructed three-dimensional model of the left atrium and pulmonary veins (*PVs*). In addition to superior and inferior PVs, three-dimensional model shows middle right and left pulmonary vein. Endocardial views show right and left PVs with additional pulmonary veins as seen on the three-dimensional model. *LSPV*, Left superior PV; *LIPV*, left inferior PV; *LAA*, left atrial appendage. *(From Sra J, Akhtar M: Mapping techniques for atrial fibrillation ablation,* Curr Probl Cardiol *12:667–718, 2007.)*

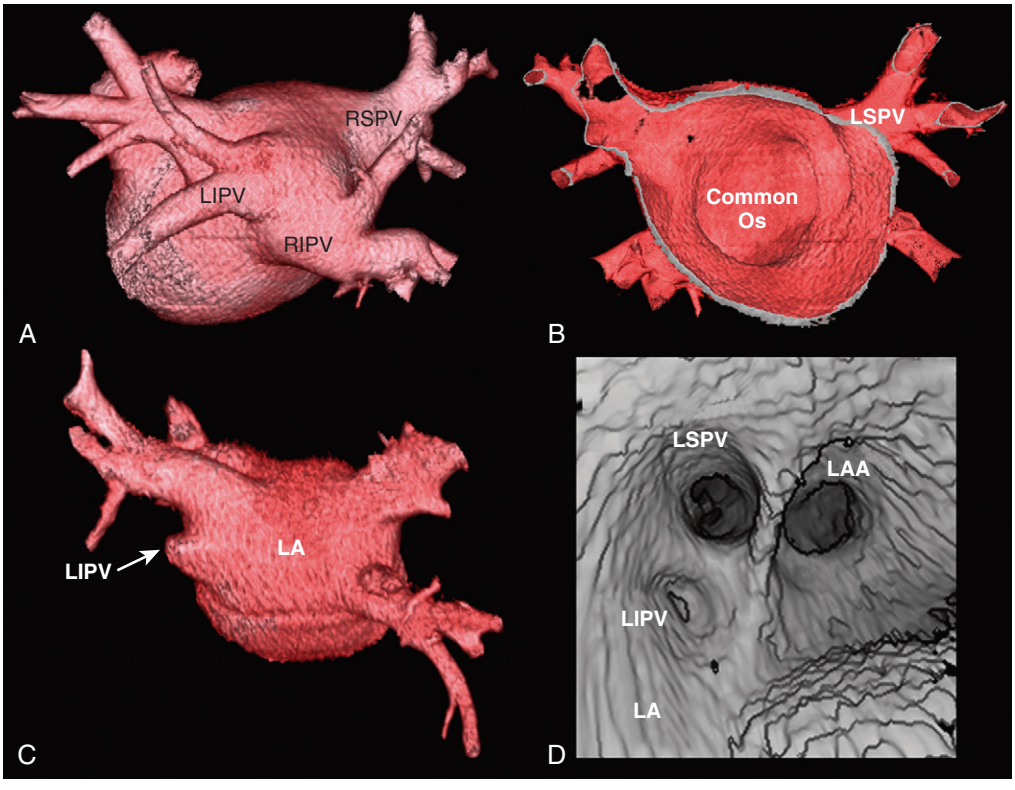

FIGURE 17-9 Unusual pulmonary vein anatomies. **A** and **B,** An unusual anatomic subtype of pulmonary vein anatomy. The left and right upper pulmonary veins (*LSPV, RSPV*) branch off from the left atrium (*LA*) in typical fashion; however, the two inferior pulmonary veins (*LIPV, RIPV*) converge near the midline of the posterior left atrium, forming a large common ostium (*Common Os*). **C** and **D,** Absent LIPV. Endocardial view is also depicted. *LAA*, Left atrial appendage. *(From Sra J, Malloy A, Shah H, et al: Common ostium of the inferior pulmonary veins in a patient undergoing left atrial ablation for atrial fibrillation,* J Interv Card Electrophysiol *15:203, 2006; and Arora V, Nangia V, Krum D, et al: Absent left inferior pulmonary vein in a patient undergoing atrial fibrillation ablation. EP images from cell to bedside,* J Cardiovasc Electrophysiol *16:924–925, 2005.)*

PV ostia are ellipsoid, with a longer superoinferior dimension, and funnel-shaped ostia are frequently noted in AF patients. PVs are larger in patients with AF versus those without AF, in men versus women, and in persistent versus paroxysmal patterns.[9] The understanding of these anatomic relationships is essential for accomplishing safe access to the LA using the trans-septal puncture, for placement of appropriate mapping tools such as a circular mapping catheter or multi-electrode basket catheter as well as Cryo balloons, and for application of energy around or outside the PV ostia. The variability of PV morphologies could substantially influence the success rate of catheter ablation if the variant veins are inadequately treated. Multiple ramifications and early branching observed in right inferior PVs possibly account for the lower incidence of focal origin of AF from this vein. These anatomic variations are important in planning catheter ablation of AF (Figure 17-10). Localization of the true LA PV, the LA appendage, and the ridge between the PV and the LA appendage in these patients can be more accurate with the assistance of three-dimensional CT images before mapping and ablation procedures.[10]

Left Atrial Registration

To improve intraprocedural guidance using current imaging techniques for ablation, cardiac image registration is currently under investigation and is in clinical use for AF ablation. Table 17-1 depicts some of the studies published in this regard. Cardiac image registration, which involves integration of two images in the context of the LA, is intermodal with the acquired image and the real-time reference image residing in different image spaces and involves optimization, where one image space is transformed into the other. Unlike rigid body registration, cardiac image registration is unique and challenging because of cardiac motion during the cardiac cycle and respiration motion. Registration algorithms involve the optimization of a cost function by the choice of a transformation, which transforms one image space into the other. The transformation can be either linear or nonlinear. Linear transformations are shape preserving and are

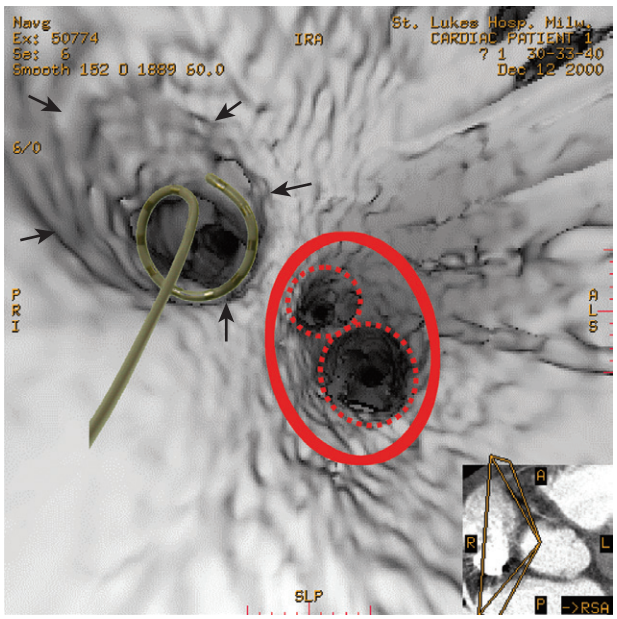

FIGURE 17-10 Endocardial computed tomography image showing pulmonary veins and different techniques of pulmonary vein isolation. A multi-electrode catheter is positioned in the upper pulmonary vein. Bottom vein shows circumferential isolation techniques used during atrial fibrillation ablation.

TABLE 17-1 Registration Techniques and Errors

FIRST AUTHOR	REFERENCE	REGISTRATION TECHNIQUE	PATIENTS/OTHER	ERROR (mm)	COMMENTS
Sra	*Heart Rhythm,* 2005	CT/ESI	Animal model	2.0 ± 3.6	Target registration error
Tops	*Heart Rhythm,* 2005	CT/CARTO	16	1.8 ± 1	Feasibility mapping points and CT surface
Dong	*Journal of Cardiovascular Electrophysiology,* 2006	CT/CARTO	16 (8 CT)	3.0 ± 0.4	Technique as above
Malchano	*Journal of Cardiovascular Electrophysiology,* 2006	CT/CARTO	13	12 ± 11 (inspiration) 4.7 ± 0.9 (expiration)	Technique as above
Kistler	*Journal of Cardiovascular Electrophysiology,* 2006	CT/CARTO	47	2.4 ± 0.4	Technique as above; CartoMerge (83% vs. 60%)
Dong	*Circulation,* 2006	CT/CARTO	Animal model	1.8 ± 1.0	Target registration error
Fahmy	*Journal of Cardiovascular Electrophysiology,* 2007	CT/CARTO	124	5.6 ± 3.2 (posterior) 9.1 ± 2.5 (anterior)	ICE-guided assessment
Zhong	*Heart Rhythm,* 2007	CT/CARTO	16	16 ± 12 (right) 11 ± 7 (left)	ICE-guided assessment
Sra	*Circulation,* 2006	CT/fluoro	Phantom, 20 patients	1.4 ± 0.5	Feasibility
Sra	*Journal of Cardiovascular Electrophysiology,* 2007	CT/fluoro	50	—	Outcome study (84% vs. 67%

CT, *Computed tomography;* ESI, *endocardial solutions; ICE, intracardiac echocardiography;* CT, *computed tomography.*

composed solely of rotations, translations, and isotropic scaling. Nonlinear transformations may deform both the shapes and sizes of images. A linear transformation between three-dimensional spaces is defined by six parameters (or degrees of freedom), where two positions of a rigid body can always be related to one another in terms of three translations and three rotations. As the voxel sizes in each image may not be similar for calibration purposes, three extra degrees of freedom, equating to scaling in each direction, are needed. A simplified rigid body registration involves translation, scaling, and rotation, where the centroid, or the center part, is aligned in each image. Subsequently, scaling is performed to calibrate both images. This is followed by rotation to align the fiducial points. A nonlinear transformation will require more degrees of freedom.

Many steps have been taken recently to develop methods of integrating three-dimensional structural details from acquired

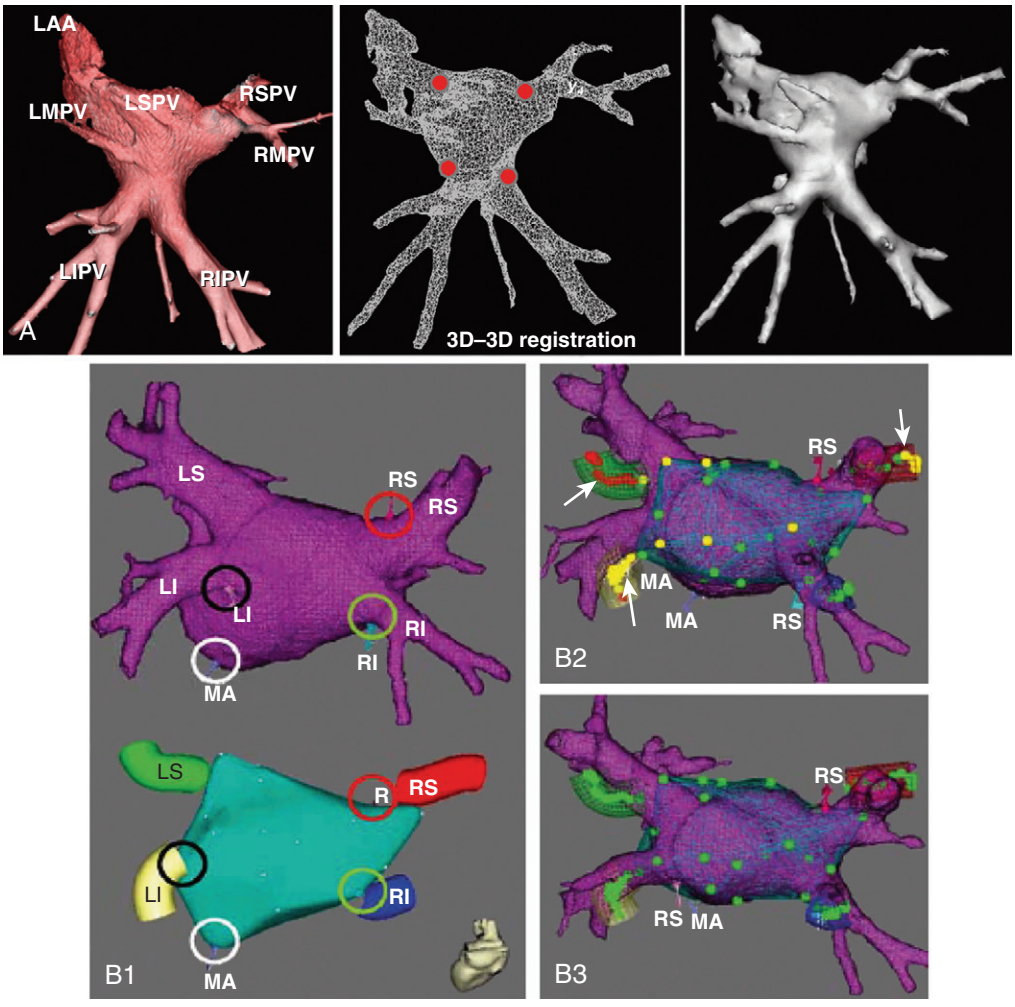

FIGURE 17-11 Registration using a multi-electrode catheter and CARTO (Biosense Webster) with computed tomography (CT). **A,** Registration of the left atrium and multi-electrode balloon. Three-dimensional (*3D*) image of the left atrium and pulmonary veins (PVs) is visualized in the posteroanterior view using CT (*left*). The location of the buried electrodes (*red circles*) are deposited at the time of segmentation. The 3D model is imported using a wireframe model (*middle*) and registered with the noncontact mapping system (*right*) using the process detailed in the text. A sinus beat is identified in the 3D registered model. *LAA*, Left atrial appendage; *LIPV*, left inferior pulmonary vein; *LMPV*, left middle pulmonary vein; *LSPV*, left superior pulmonary vein; *RIPV*, right inferior pulmonary vein; *RMPV*, right middle pulmonary vein; *RSPV*, right superior pulmonary vein. *Bottom*, Registration using the CARTO system. **B1,** Landmark pairs (*highlighted with darker circles*) at the 6 o'clock mitral annulus (*MA*) position and the junctions of the LA and right superior pulmonary vein (*RS*), right inferior pulmonary vein (*RI*), and left inferior pulmonary vein (*LI*) were annotated on the 3D CT left atrial surface reconstruction (*upper image, shown as wire frame*) and the left atrial electroanatomic map (*lower image, shown as solid shell*) with tubes representing pulmonary veins. **B2,** After landmark registration, the 3D left atrial surface reconstruction was superimposed on the electroanatomic map (*shown as mesh*). Note: The misalignment of the LS, LI, and RS between the two image datasets is indicated by the yellow or red color of the PV points (*arrows*) sampled in those PVs. **B3,** After surface registration was executed, the PV alignment between the two image datasets was significantly improved, indicated by the PV points. The electroanatomic map points indicate their distance of <5 mm, 5 to 10 mm, and >10 mm, respectively, from the registered CT reconstruction surface. *(From Sra J, Krum D, Hare J, et al: Feasibility and validation of registration of three-dimensional left atrial models derived from computed tomography with a noncontact cardiac mapping system,* Heart Rhythm *2:55–63, 2005; and Dong J, Dickfeld T, Dalal D, et al: Initial experience in the use of integrated electroanatomic mapping with three-dimensional MR/CT images to guide catheter ablation of atrial fibrillation,* J Cardiovasc Electrophysiol *17:459–466, 2006.)*

cardiac images with the real-time view of the interventional systems. The main modalities for catheter viewing, mapping systems, fluoroscopy, and ultrasound have been used in these techniques.[11] The following section describes some recent advances in the registration of acquired, structurally revealing three-dimensional images with real-time images.

Registration Using Anatomic Mapping Systems

Anatomic mapping systems provide the three-dimensional position of a navigational catheter within the cardiac chamber of interest and, in some instances, can also be used to construct three-dimensional maps of the cardiac chamber. Magellan and CARTO (Biosense Webster Inc., Diamond Bar, CA) use the electromagnetic position of the catheter tip, based on an electromagnetic locator pad, which is placed below the patient, and a reference catheter is placed at a fixed external (usually posterior) location. LocaLisa (Medtronic Inc., Minneapolis, MN) and NavX (St Jude Medical Inc., St Paul, MN) catheters are used to register the image. Previous results of this method have indicated that registration of the left ventricle alone results in inaccurate alignment. Inclusion of the aorta in the registration process rectifies this error. A clinical application of this technique that uses the CARTO system (CartoMerge), the multi-electrode catheter, and the NavX with either CT or MRI is now available.[11,12] A combination of landmark and surface registrations is used to register CT with the CARTO system. Initially, several landmarks, usually three, are manually chosen and annotated. After this, the reconstructed three-dimensional image of the LA using CT or MRI is superimposed on the electroanatomic map created by the CARTO mapping system. Figure 17-11 depicts an example of CARTO and CT registration using landmark (fiducial point) and surface registrations.

X-Ray Registration

Registration with fluoroscopy can be performed in the exported three-dimensional model by using a transformation to align the coronary sinus catheter seen on fluoroscopy with the SVC and the coronary sinus in the exported three-dimensional CT model. The author's center has recently described an implementation of a semi-automated three-dimensional/two-dimensional CT-fluoroscopy registration strategy.[13] The accuracy of this system was found to be within 1.4 mm in phantom studies. This strategy was also assessed in patients undergoing AF ablation. Twenty consecutive patients underwent ECG-gated, contrast-enhanced CT scanning. The LA and the PVs were segmented using the semi-automated method described before. The segmented images of the LA PV were then registered in real time on acquired digital cine or fluoroscopic images by superimposing the coronary sinus catheter, as seen on the cine image, over the SVC and coronary sinus as described before. Accurate registration was confirmed by PV angiography as well as by the position and recordings on a 64-pole basket catheter located in the PVs (Figure 17-12). The author's center has continued to use this strategy for PV isolation and LA linear ablation procedures on patients with AF. In a recent study, 50 patients with AF undergoing ablation were randomized to standard ablation techniques or ablation guided by CT-fluoroscopy registered images. Fluoroscopy time and total procedure time were significantly reduced in the CT-fluoroscopy group, and a trend toward better outcomes was observed. The complex translational, rotational, and

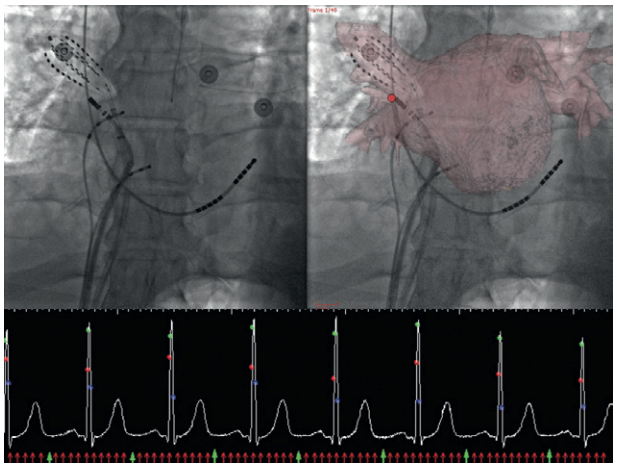

FIGURE 17-12 Electrocardiogram and respiration-gated registration. Fluoroscopic image is taken during the same cardiac cycle phase (75%, *green arrows*), and respiration gated (during inspiration) as computed tomography imaging. Accurate registration is seen. System also allows marking of the ablation site (*red circles*). *(From Sra J: Cardiac image registration,* JAFIB J Atrial Fibrillation *1:148–160, 2008.)*

conformational changes that occur with cardiac and respiratory motions will introduce error into the registration process when, as in three-dimensional/two-dimensional registration, a static image is "aligned" with the real-time fluoroscopic image. Attempts at gating the registration process so that image integration occurred during the same phase of the cardiac cycle were successfully implemented in experiments conducted in the author's laboratory; thus, fluoroscopic images can be taken at the same phase as the segmented CT images, that is, during diastole (see Figure 7-12). Synchronizing registration to the respiratory cycle during expiration or inspiration, the phase during which CT imaging has been done, could potentially eliminate movement of the LA during respiration.

Other Applications in Cardiac Arrhythmias

The ability to distinguish the dysfunctional but viable myocardium from nonviable tissue may have important prognostic implications after myocardial infarction (MI). A study by Lardo et al validated the accuracy of contrast-enhanced multi-detector CT (MDCT) for quantifying myocardial necrosis, microvascular obstruction, and chronic scar after occlusion or reperfusion MI.[14] In this study, 10 dogs and 7 pigs underwent balloon occlusion of the left anterior descending (LAD) coronary artery followed by reperfusion. Contrast-enhanced (Visipaque, 150 mL, 325 mg/mL) MDCT (0.5 mm, 32-slice) was performed before occlusion and 90 minutes (canine) or 8 weeks (porcine) after reperfusion. MDCT images were analyzed to define infarct size and extent and microvascular obstruction and compared with postmortem myocardial staining (triphenyltetrazolium chloride) and microsphere blood flow measurements. Acute and chronic infarcts by MDCT were characterized by hyper-enhancement, whereas regions of microvascular obstruction were characterized by hypo-enhancement. MDCT infarct volume compared well with triphenyltetrazolium chloride staining (acute infarcts, 21.1% ± 7.2% vs. 20.4% ± 7.4%; mean difference, 0.7%; chronic infarcts, 4.15% ± 1.93% vs. 4.92% ± 2.06%; mean difference 0.76%) and accurately

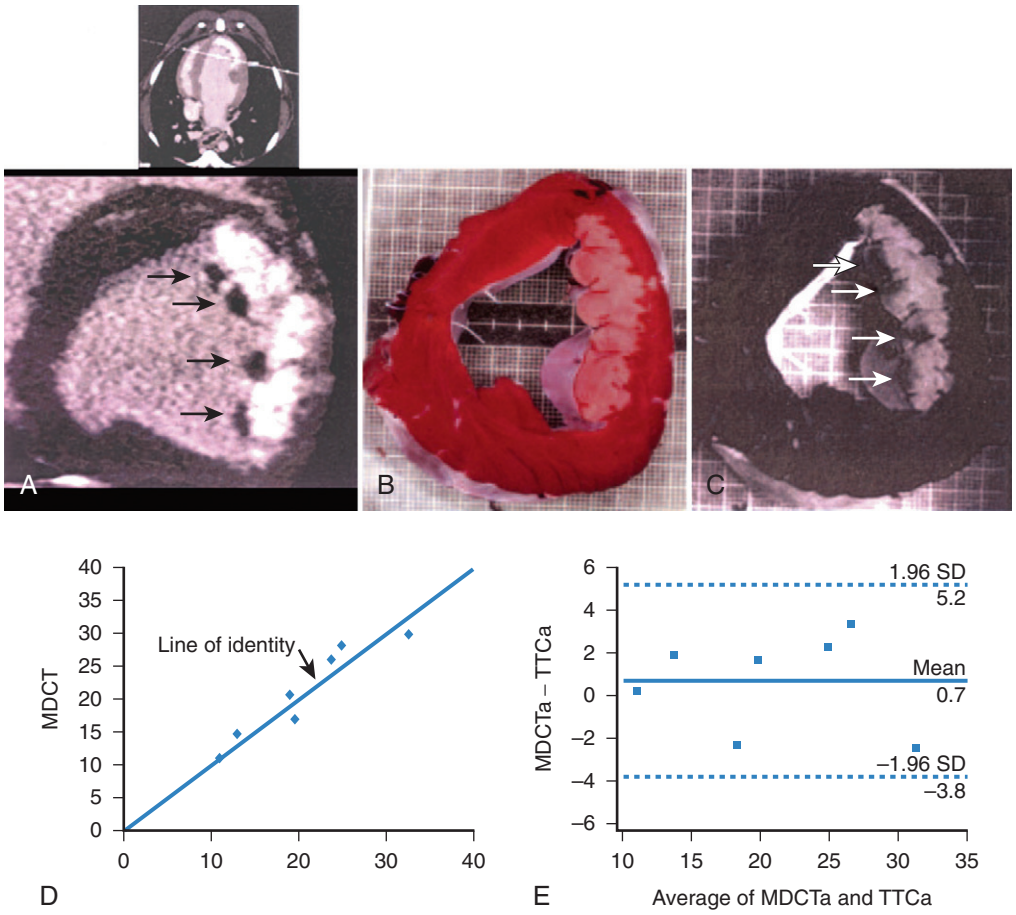

FIGURE 17-13 Multi-detector computed tomography (*MDCT*) and histopathologic staining comparison of infarct morphology. **A,** Reconstructed short-axis MDCT slice 5 minutes after contrast injection demonstrating a large anterolateral infarct (hyper-enhanced region) with discrete endocardial regions of microvascular obstruction (*four arrows*). **B,** Triphenyltetrazolium chloride (*TTC*)–stained slice. **C,** Thioflavin S and TTC staining of the same slice, which confirms the size and location of microvascular obstruction regions. **D,** Quantitative MDCT and TTC measurements of infarct size yielded good agreement, with points distributed around the line of identity. **E,** Mean difference of 0.7% by Bland-Altman analysis. *(From Lardo AC, Cordeiro AS, Silva C, et al: Contrast-enhanced multidetector computed tomography viability imaging after myocardial infarction characterization of myocyte death, microvascular obstruction, and chronic scar,* Circulation *113:394–404, 2006.)*

reflected the morphology and the transmural extent of injury in all of the animals (Figure 17-13). Peak hyper-enhancement of infarcted regions occurred 5 minutes after contrast injection. MDCT-derived regions of microvascular obstruction were also identified accurately in acute studies and correlated with reduced-flow regions as measured by microsphere blood flow. This study thus suggested that the spatial extent of acute and healed MI could be determined and quantified accurately with contrast-enhanced MDCT. This feature, combined with existing high-resolution MDCT coronary angiography, may have important implications for the comprehensive assessment of cardiovascular disease.

Other studies have shown the role of CT in imaging coronary sinus and left ventricular anatomy and function to define sites for biventricular pacing in patients with congestive heart failure (Figures 17-14 to 17-17). CT imaging has also been used to perform left ventricular functional analysis using post-processing algorithms or detailed left ventricular motion analysis, thus enabling identification of sites where left ventricular pacing should improve efficacy of biventricular pacing.[15]

Conclusion

Recent advances in imaging, especially in CT imaging, may help define anatomic structures associated with cardiac arrhythmias. This is particularly true for complex three-dimensional anatomy such as the LA. Image registration of these anatomic structures further provides a means for physicians to incorporate into a single view the varied information captured by CT, which can then be used for interventional planning and treatment of complex arrhythmias such as AF. Significant work is being done to improve imaging quality and function assessment, which should further refine the imaging of structures such as the coronary sinus and the left ventricle and the identification of myocardial scar. This should enhance efficacy of procedures such as biventricular pacing.

Acknowledgments

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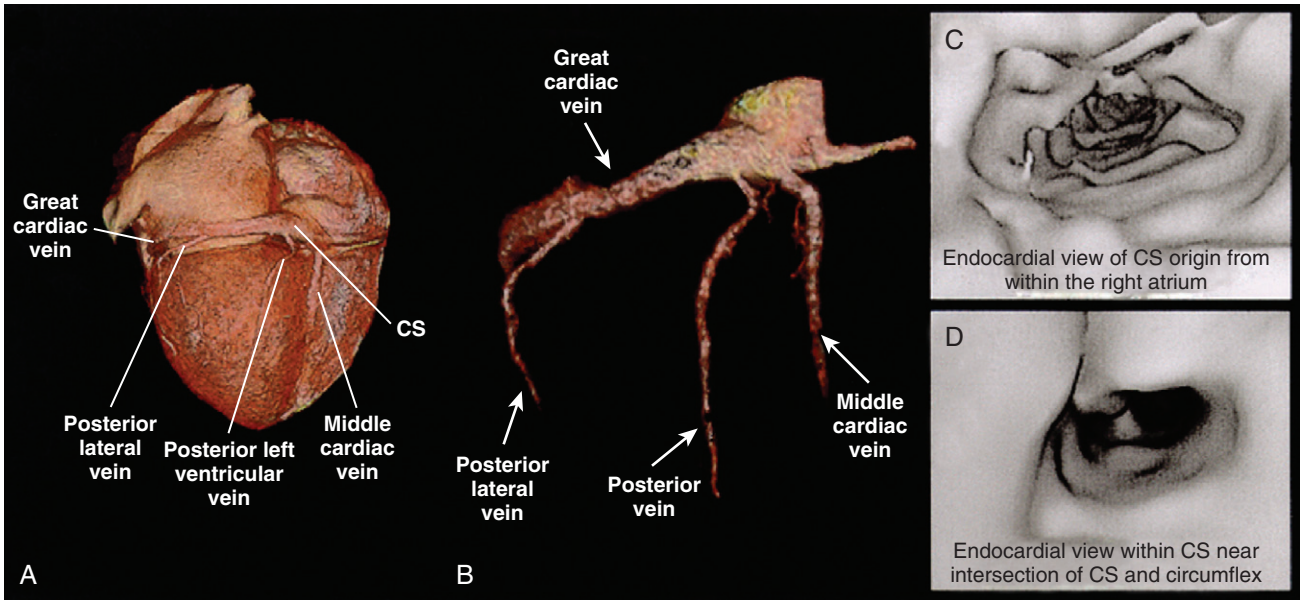

FIGURE 17-14 Three-dimensional images of the left ventricle (LV) and coronary sinus (*CS*). **A,** Endocardial images of the CS also can be obtained using post-processing segmentation algorithms. A three-dimensional image of the LV and the CS with its branches in a patient obtained using CT (16 slice, light speed ultra). **B,** Post-processing segmentation algorithms used to show three-dimensional images of the CS alone. **C** and **D,** Endocardial views of the CS at two different locations. These imaging techniques could help create a roadmap for CS lead placement in patients undergoing cardiac resynchronization therapy. *(From Sra J, Krum D, Okerlund D, et al: Three-dimensional and endocardial imaging of the coronary sinus for cardiac resynchronization therapy,* J Cardiovasc Electrophysiol *15:1109, 2004.)*

B. Cardiac Magnetic Resonance Imaging

Introduction

Improvements in understanding the arrhythmia mechanisms and the development of advanced three-dimensional mapping tools have helped create novel catheter-based ablation strategies over the past 10 to 15 years. As many of these approaches are anatomically based, cardiac imaging has been increasingly used to assist in procedural planning, guidance, and follow-up.

Three-dimensional mapping systems became available in the mid-1990s, allowing the real-time display of a catheter tip within a mathematically reconstructed cardiac chamber.[16] However, they lacked the anatomic detail desired for complex ablation procedures. Therefore, cardiac imaging was increasingly used in patients undergoing complex ablations such as AF ablations. Today, pre-procedural MRI or CT is used to characterize the individual anatomies of the LA and the PV and has become standard-of-care in many arrhythmia centers. This allows for a tailored, patient-specific ablation approach. Detailed anatomic information gained from cardiac imaging is being made available during the ablation procedure by integrating these images with three-dimensional mapping systems. In addition, imaging is used in the detection of procedural complications and postprocedural patient care.

Cardiac imaging is also increasingly used for ventricular tachycardia (VT) ablations. MRI is well validated to provide detailed information about the cardiac anatomy, the myocardial scar, or both, which are usually the targets for substrate-guided VT ablations. Current software allows the export of detailed imaging information into three-dimensional mapping systems to provide anatomic catheter guidance for patients with recurrent episodes of VT.

An emerging application of cardiac imaging is the visualization of atrial or ventricular ablation lesions using MRI. This has the potential to assess the discrepancies between intended versus actual ablation lines, delineate gaps in ablation sets, and provide a road map for additional and repeat ablation procedures.

A rapidly evolving field is real-time MRI for electrophysiology procedures, which is currently being evaluated in animal and preliminary human studies. Catheter navigation and ablation can be guided under real-time MRI visualization, which identifies the precise location of the ablation catheter tip in relation to the surrounding anatomy. This novel imaging paradigm has the potential for direct confirmation of the exact anatomic catheter location, verification of catheter-tissue contact, lesion visualization, and early detection of complications.

Current Technology of Image Integration

The ability to visualize the true three-dimensional anatomy from cardiac imaging fueled the integration of these datasets with clinical three-dimensional mapping systems to provide the electrophysiologist with patient-specific cardiac anatomy during the ablation procedure. Before the era of three-dimensional mapping, catheter navigation was guided by fluoroscopy with its known limitations with regard to visualization of soft tissue, catheter contact, and patient exposure to ionizing radiation. In the late 1990s, three-dimensional mapping systems that significantly reduced fluoroscopy time up to 82% for atrial flutter and 49% for AF became available.[17,18]

The two most commonly used three-dimensional mapping systems are Biosense Webster's CartoMerge and St. Jude

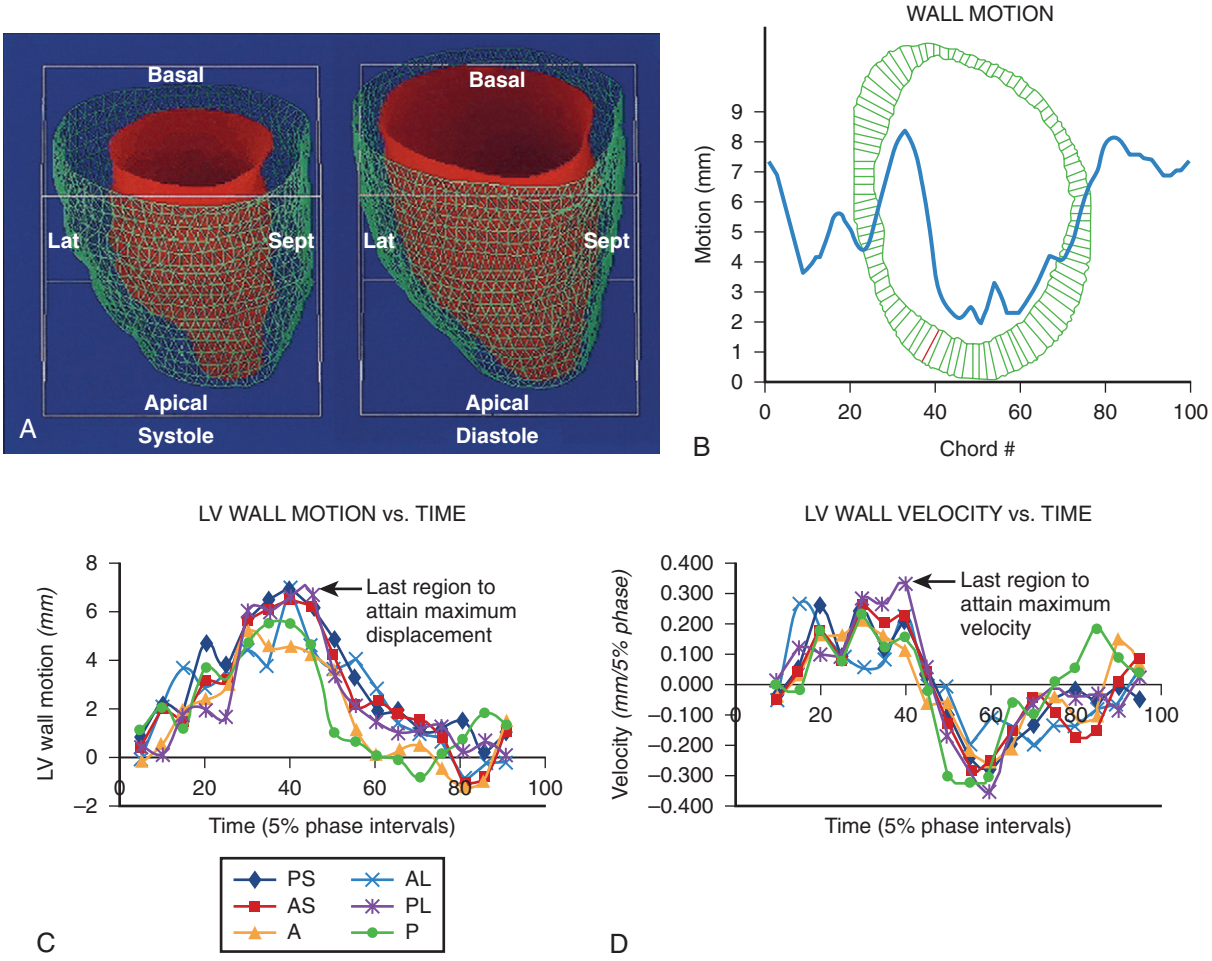

FIGURE 17-15 Ventricular wall motion using three-dimensional imaging. **A,** An example during systole and diastole, with the endocardium represented by the red mesh and the epicardium represented by the green mesh. This information can be processed to determine optimal areas for left ventricular pacing, such as the site that is the last to attain maximum displacement and the last to reach maximum velocity. Following scanning and segmentation, each axial slice (thickness, 1.25 mm) was divided into 100 chords, representing the full circumference of the axial slice. The wall motion of the endocardium at each of these chords, expressed as a displacement from end diastole was plotted throughout the cardiac cycle. Data from these chords were averaged over six areas (anterior [*A*], anterolateral [*AL*], lateral [*L*], posterior [*P*], posterolateral [*PL*], septal [*S*], anteroseptal [*AS*]) in 5% increments throughout the cardiac cycle. **B,** A plot of wall motion versus time for a slice midway between the apex and the base of the heart. LV wall motion and velocity also were determined from these data. **C** and **D,** A plot of wall motion versus time and velocity versus time for the same axial slice. By identifying areas of interest, three-dimensional cardiac imaging creates a roadmap that may help optimize cardiac resynchronization therapy. *(From Sra J, Krum D, Okerlund D, et al: Ventricular wall motion using three-dimensional imaging,* J Cardiovasc Electrophysiol *15:1110, 2004.)*

Medical's Ensite NavX navigation system. The former uses electromagnetic fields to locate an endocardial catheter, whereas the latter uses electrical signals transmitted through the patient's body. *Image integration* refers to a process in which the detailed three-dimensional anatomy from MRI or CT is extracted and superimposed on the endocardial shell created from catheter recordings (Figure 17-18). To create the endocardial shell with a three-dimensional mapping system, a roving catheter is moved sequentially along the endocardial surface, and location points are acquired. On the basis of the collected points, an electroanatomic shell which approximates the actual cardiac anatomy is mathematically reconstructed. An accurate registration (alignment of the MRI-derived dataset with the catheter-created shell) is critical for accurate anatomic catheter placement. Registration is performed by selecting several corresponding, well-defined anatomic landmarks such as the PV ostia and the posterior LA wall on the catheter-derived shell and the MRI-derived three-dimensional model. Depending on the mapping system, additional proprietary algorithms can adjust the three-dimensional model position to achieve the minimal average registration error between the shell and three-dimensional model points (surface registration) or will adjust points of the catheter-derived map to fit into the three-dimensional anatomic model (dynamic registration).[12,19] The resulting registration accuracies have been reported in the range of 1 to 4 mm.[12,19]

After successful registration, the three-dimensional mapping system displays the catheter tip location and orientation in real-time in relation to the MRI-derived cardiac anatomy. This allows the electrophysiologist to navigate to defined anatomic targets, return to specific locations, and mark the ablation locations. The use of "clipping planes" enables the creation of endoscopic views from the LA onto the PVs, and additional relevant anatomic

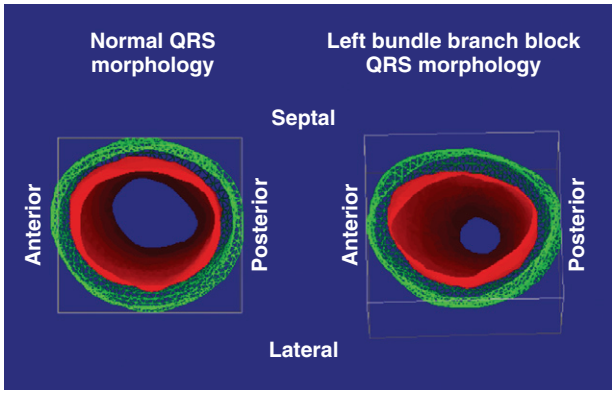

FIGURE 17-16 Ventricular wall motion during left bundle branch block and normal QRS. An example during systole and diastole is shown with the endocardium represented by the red mesh and the epicardium represented by the green mesh. *Left*, Normal QRS. *Right*, Ventricular wall motion during left bundle branch block. As opposed to normal QRS, asynchronous contraction of the ventricle is seen in left bundle branch block.

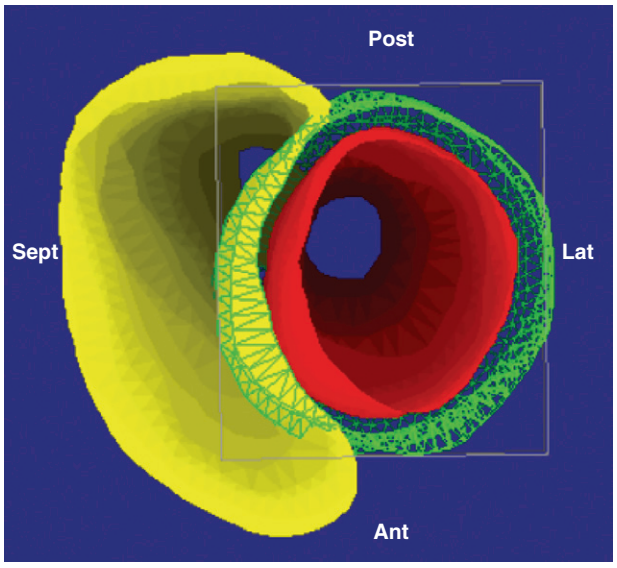

FIGURE 17-17 Right and left ventricular wall motion during left bundle branch block in the patient with left bundle branch block, as shown in Figure 17-16. The right ventricle is shown in yellow. During systole, asynchronous contraction of the left ventricle is seen. *Post*, Posterior; *Lat*, lateral; *Ant*, anterior; *Sept*, septal.

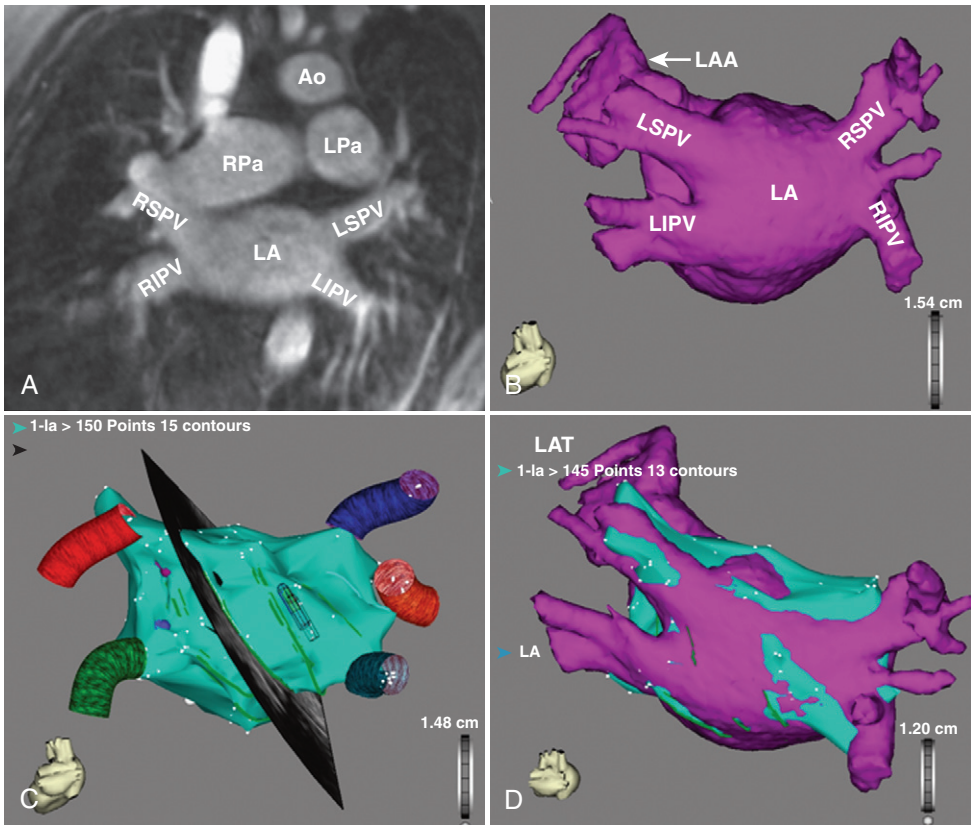

FIGURE 17-18 Image integration into clinical mapping system. **A,** Magnetic resonance angiography demonstrating anatomy of left atrium (*LA*) and pulmonary vein (*PV*). **B,** Three dimensional reconstructed anatomic shell (*MRI/CT*) demonstrating the PV ostia and branching patterns. **C,** Electroanatomic map using CartoSound. Two-dimensional ultrasound (*shown in black section*) used for reconstruction of LA. White points in the turquoise shell signify endocardial catheter positions used for validation of ultrasound-based reconstruction. Colored tubes symbolize PVs. **D,** Successful registration of electroanatomic map (*turquoise shell*) with the three-dimensional LA reconstruction (*purple shell*) demonstrating good merging of LA body and PV anatomy. *Ao*, Aorta; *CT*, computed tomography; *LA*, left atrium; *LAA*, left atrial appendage; *LAT*, lateral; *LIPV*, left inferior pulmonary vein; *LPa*, left pulmonary artery; *LSPV*, left superior pulmonary vein; *MRI*, magnetic resonance imaging; *PV*, pulmonary vein; *RIPV*, right inferior pulmonary vein; *RPa*, right pulmonary artery; *RSPV*, right superior pulmonary vein. (***A,*** *Courtesy Dr. Jean Jeudy.*)

structures such as the esophagus can be integrated in the three-dimensional anatomic map. To minimize inherent differences between the imaged volume and the catheter-derived chamber, decreased time intervals between the scan and the procedure, end-diastolic image acquisition, and end-expiratory scan time have been proposed.[20] In addition, increasing size and volume of the LA (>110 mL) are independent predictors of decreased registration accuracy.[21] Changes in cardiac rhythm such as AF versus sinus rhythm during image acquisition and procedure do not appear to significantly affect registration accuracy.[22]

Most recently, a new software module (CartoSound) that uses multiple two-dimensional intracardiac ultrasound slices to define the endocardial contours to which MRI reconstructions can be registered (see Figure 17-18, *C*) has been introduced.[23] A more accurate registration may be possible if the chamber anatomy is not deformed by catheter pressure and catheter mapping time before image registration is potentially reduced. Singh et al demonstrated that direct LA imaging (i.e., placing the intracardiac ultrasound probe within the LA) rather than imaging the LA from the right atrium (RA) resulted in less image integration error (LA = 1.83 ± 0.32 mm vs. RA = 2.52 ± 0.58 mm; $P = .004$).[24]

The obvious advantages of image integration have led to a rapid implementation of this technology. However, despite its widespread use, only limited data exist to validate its clinical superiority. Single-center, nonrandomized, retrospective trials have shown a reduction in fluoroscopy time by up to 21% and freedom from recurrence of AF following catheter ablation by up to 85%.[25,26] However, the only randomized prospective trial performed by Kistler et al did not find any benefit in image integration with respect to procedural outcomes (i.e., sinus rhythm restored by ablation of persistent AF, electrical isolation of PVs), fluoroscopy times, and procedure duration.[27]

Atrial Fibrillation

With the description of segmental PV ablation and circumferential LA ablation for AF nearly a decade ago, the importance of pre-procedural cardiac imaging to define the individual PV anatomy and its branching pattern became evident.[28,29] Knowledge of the exact anatomy is important to minimize complications such as stenosis, LA appendage (LAA) perforation, and atrio-esophageal fistula resulting from an ablation in the PVs and to avoid gaps in the ablation lines.[30,31]

Cardiac imaging studies significantly improved our understanding of the LA anatomy. Up to 38% of patients have an abnormal PV anatomy such as a common left or inferior truncus, additional right middle cardiac vein, or pulmonary roof veins.[32-34] Further imaging studies revealed abnormalities of the LA such as roof pouches in 15% of AF patients and a variable anatomy of the septal ridge between the LAA and the left superior PV in up to 32% of patients with AF.[35] Imaging studies have shown that the distance between the LA and the esophagus is only 4.4 ± 1.2 mm.[36] Furthermore, the esophagus runs close to the left superior PV in 56% of patients and obliquely from the left superior PV to the right inferior PV in 36% of patients.[37] The mean thickness of the posterior LA and anterior esophageal walls was reported as 2.2 ± 0.9 and 3.6 ± 1.7 mm, respectively.[37] Significant lateral movement of the esophagus occurs during AF procedures resulting in a greater than 2-cm lateral shift in 67% of patients during conscious sedation.[38] These anatomic considerations provide a unique insight when planning AF ablations.

Given the complex LA anatomy, post-ablation imaging is performed in patients suspected of having a procedural complication. MRI has been well validated in the diagnosis of symptomatic and asymptomatic PV narrowing and long-term follow-up.[39-43] Symptomatic PV stenosis requiring interventional therapy demonstrated a greater than 75% lumen reduction by cardiac imaging and a greater than 80% reduction in pulmonary perfusion determined with V/Q scanning.[31] Changes in ablation strategies have significantly reduced the incidence of PV stenosis to approximately 1% to 2%.[5]

Given that atrioesophageal fistulas are a rare but severe complication with a mortality rate of up to 50%, MRI or CT has the potential to delineate the course of the esophagus and potentially diagnose atrio-esophageal fistulas.[30,44,45] Frequently, air can be seen at the site of the fistula or within the cardiac chambers. Peripheral embolization to the brain or the kidneys is commonly seen.[46] Although atrioesophageal fistulas have a very high mortality rate, early diagnosis is critical as successful surgeries have been reported.[30]

Cardiac perforation with tamponade has been described in up to 6% of patients after AF ablation as a result of its technical complexity and the use of anticoagulation during the procedure.[5] Although mostly detected in the peri-procedural period with trans-thoracic or intracardiac ultrasound, cardiac effusions without hemodynamic compromise have also been documented in regular follow-up scans using MRI.

The reported incidence of thromboembolism is between 0% and 7%.[5] Emboli are thought to result from thrombus development on stationary sheaths or catheters, char formation on the ablation tip or the ablation site, or disruption of a thrombus previously present in the LA. In the presence of clinical suspicion, diagnosis is readily made by using MRI, CT, or both; this allows for early thrombolytic administration. Diffusion-weighted MRI sequences can detect early cerebral ischemia within 30 minutes.[47] In addition, air emboli could be introduced through the trans-septal sheath, via an open-irrigation ablation catheter, or as a paradoxic embolus after trans-septal access. If MRI scans are obtained promptly before the emboli are rapidly absorbed, multiple serpiginous hypodensities representing air in the cerebral vasculature may be detected with or without acute infarction.[5]

In the pre-procedural arena, delayed enhancement MRI is used in novel ways to detect and visualize LA fibrosis in patients with AF before ablation.[48] Oakes et al imaged 81 patients before they underwent AF ablation. Forty-three patients were classified as having minimal enhancement (average enhancement, 8.0% ± 4.2%), 30 as having moderate enhancement (21.3% ± 5.8%), and 8 as having extensive enhancement (50.1% ± 15.4%). The rate of AF recurrence was 14% with minimal enhancement, 43.3% with moderate enhancement, and 75% with extensive enhancement ($P \leq .001$). Preablation MRI may serve to noninvasively identify responders to AF ablation and serve as an overall metric for disease progression.[48]

Ventricular Tachycardia

Ablation of VT is the next emerging frontier in electrophysiology. Although antiarrhythmic medications are commonly prescribed as a first-line treatment, their use is frequently limited by side effects and decreasing long-term efficacy. In patients with such problems, catheter ablation has been used as an effective treatment strategy to decrease the ventricular arrhythmia burden and the number of implantable cardioverter-defibrillator (ICD)

shocks.[49-51] More recently Reddy et al demonstrated that VT ablation before the implantation of an ICD for secondary prevention could reduce appropriate ICD therapy from 33% to 12% ($P = .007$) over 22.5 ± 5.5 months of follow-up.[52]

Myocardial scar usually acts as the substrate for re-entrant VT and is present in the majority of patients with ischemic and nonischemic cardiomyopathy. The border zone between the scar and the healthy myocardium contains the exit sites for many re-entrant VTs. In patients with ischemic VT, 68% of successful ablation sites were located in the border zone, whereas 18% were in the scar, 4% in normal myocardium, and 10% on the epicardial surface.[53] Histologic and imaging studies have demonstrated that patients with scar-mediated VT frequently present with nontransmural or nonhomogeneous necrosis, which results in the formation of complex endocardial, epicardial, and intramural border zones.[54-56] Such irregular extensions and isolated islets could potentially be visualized with cardiac imaging and used to define individual ablation strategies based on pre-procedural knowledge of the complex, three-dimensional VT substrate.

The current gold standard of defining myocardial scar is based on endocardial voltage recording obtained by a roving bipolar catheter. Assuming that the voltage amplitude will be lower on scarred myocardium because of a paucity of living cells, a tiered classification with greater than 1.5 mV for normal myocardium, 0.5 to 1.5 mV for abnormal myocardium, and less than 0.5 mV for scar is generally accepted for defining scar and its border zone in the left ventricle.[49]

A purely voltage-based scar characterization has several limitations. A single endocardial voltage recording is unable to adequately represent the complex three-dimensional scar anatomy and to differentiate between different degrees of endocardial and epicardial scar components. Low-voltage recordings may represent intermittent or suboptimal catheter contact rather than true wall pathology. In addition, the spatial resolution of voltage mapping is limited by the distance between the recording electrodes, which is greater than 5 mm in the frequently used catheter systems. Finally, high-resolution voltage mapping prolongs the procedure time frequently by as much as 1 to 2 hours. However, decreased mapping density in areas not thought to participate in the tachycardia may overlook localized scar areas.

Therefore, several cardiac imaging strategies have been used to supply additional scar characterization. MRI is capable of providing more detailed post-infarct scar anatomy compared with conventional endocardial voltage mapping.[57] Delayed enhancement MRI accurately characterizes endocardial, epicardial, intramural, and transmural locations and the extent of myocardial scar both in ischemic and nonischemic cardiomyopathy.[58-61]

Certain limitations apply to the current generation of three-dimensional mapping systems. The image integration software only allows for a "surface reconstruction" of the cardiac anatomy, resulting in paper-thin anatomic shells representing the blood pool–endocardial surface.[5,62] Yet complex ablations, such as ischemic VT ablations, require detailed three-dimensional information about the myocardial scar, its transmural extent, and border zones.[49,50,53] Channels of the surviving myocardium within the scar may participate in the tachycardia circuit and represent potential ablation targets. "Volume imaging" will likely allow the next generation of three-dimensional mapping systems to integrate this information during the ablation procedure and provide additional anatomic guidance for ablations. This may also allow new treatment strategies for VT caused by cardiac sarcoidosis or arrhythmogenic right ventricular dysplasia (ARVD), in which MRI can directly visualize the involved myocardial regions and provide potential anatomic ablation targets.[63,64]

Another emerging area is the field of fusion imaging, or multimodality imaging. In this approach, several different imaging modalities are combined to allow a comprehensive evaluation for ablation procedures. An example is the fusion of cardiac MRI and positron emission tomography (PET) to allow anatomic and metabolic assessments of left ventricular scar before VT ablation (Figure 17-19). The combination of different imaging modalities has been able to identify surviving myocardial channels or nontransmural infarcts not detected by the current gold standard of voltage mapping.[65]

Recently, the importance of identifying myocardial scar with delayed enhancement MRI for further risk stratification has been recognized (Figure 17-20). Kwong et al examined 195 patients without previous MI and assessed the occurrence of major adverse cardiac events (MACEs) and cardiac mortality. The presence of delayed enhancement resulted in a hazard ratio (HR) of 8.3 and 10.9, respectively.[66] In addition, Bello et al demonstrated that delayed enhancement on cardiac MRI was a better predictor of the inducibility of monomorphic VT compared with left ventricular ejection fraction (LVEF) in patients undergoing electrophysiological testing. Patients with monomorphic VT had larger infarcts compared with patients who were noninducible (49 ± 5 g vs. 28 ± 5 g).[67] Similarly, Nazarian et al demonstrated that a nontransmural scar with a trans-murality of 25% to 75%, as visualized with delayed enhancement MRI, was significantly predictive of inducible VT in patients with nonischemic cardiomyopathy.[68]

Furthermore, several MRI studies have implicated the border zone surrounding the myocardial scar in arrhythmogenesis. Yan et al showed that a larger than median peri-infarct zone (defined as delayed enhancement from 2 to 3 standard deviations [SDs] above the normal myocardial segment) was an independent predictor of all cause-mortality (HR, 1.42) and cardiovascular mortality (HR, 1.49).[69]

Similarly, Schmidt et al demonstrated that tissue heterogeneity (defined as <50% of maximum signal intensity) at the infarct periphery was strongly associated with inducibility of monomorphic VT (noninducible vs. inducible 13 ± 9 g vs. 19 ± 8 g). Such an infarct definition as less than 50% of maximum signal intensity may help avoid overestimating infarct size, which has been reported with an intensity cut-off of two SDs.[70]

Ashikaga et al assessed the anatomic relationship between ventricular arrhythmias and MRI-defined scar or border zone by using epicardial shock electrodes and endocardial mapping in a chronic infarct model in swine. The investigators demonstrated that the re-entry isthmus was characterized by a relatively small volume of viable myocardium bound by scar tissue at the infarct border zone or over the infarct. MRI was able to identify spatial complex scar structures at the isthmus sites.[56] This could potentially enable the identification of ablation targets for unmappable VT or hemodynamically intolerable VT.

Although very promising, substrate assessment using MRI is still limited in clinical practice as the presence of a defibrillator in most patients is still considered a contraindication to MRI.[71] Metal artifacts from the ICD also significantly affect imaging quality.[72]

MRI has found increasing use in the assessment and diagnosis of ARVD. Tandri et al demonstrated that myocardial delayed enhancement MRI was able to detect increased right ventricular signal in 8 of 12 patients with clinically diagnosed ARVD compared with control subjects with no history of ARVD ($P < .001$)

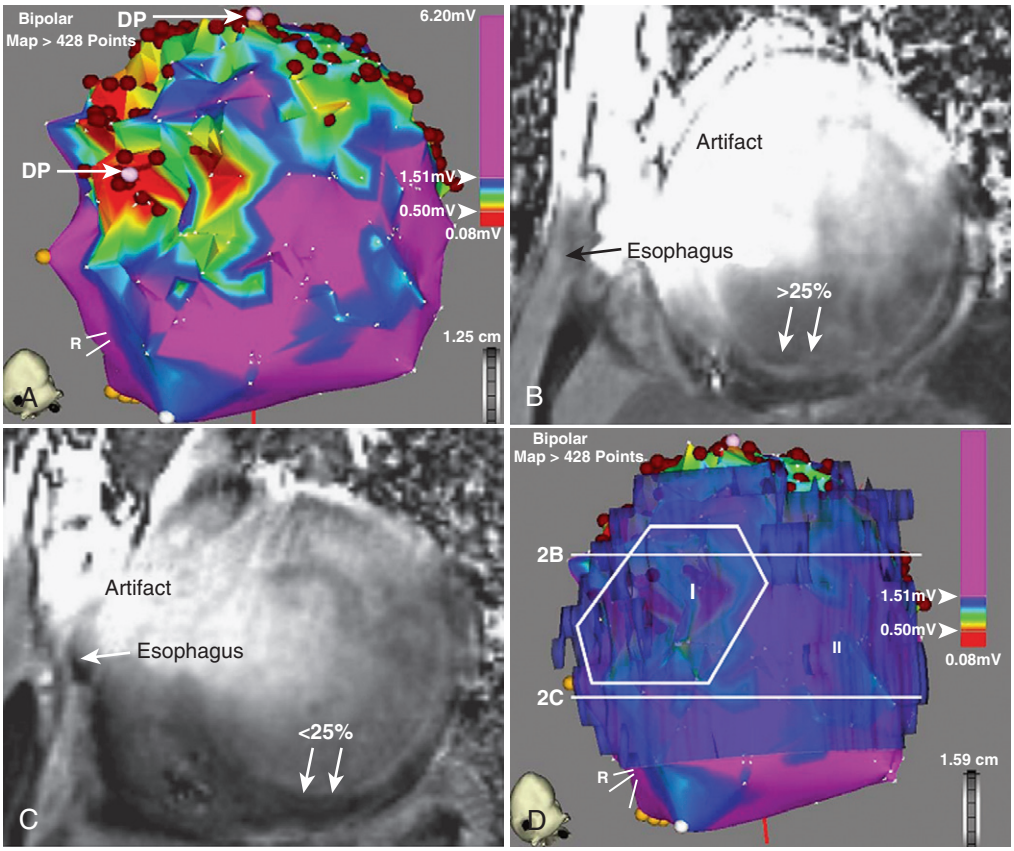

FIGURE 17-19 Positron emission tomography/magnetic resonance imaging/voltage map integration. **A,** Voltage map showing inferior scar (*red areas*) extending to lateral and septal walls and healthy myocardium (*purple areas*). *Pink markers* represent the areas of diastolic potentials (*DP*); *brown markers* indicate the ablation line. **B,** Original DE-MRI short-axis image in the plane across the voltage/FDG scar area demonstrating delayed enhancement with 25% to 50% (*black arrows*) transmurality. **C,** Original DE-MRI short-axis image in the plane across three-dimensional DE-MRI scar area that does not overlap with the voltage/fluorodeoxyglucose (*FDG*) scar with <25% (*black arrows*) scar transmurality. Bright areas in the anterior left ventricular wall represent implantable cardioverter defibrillator artifacts. **D,** Three-dimensional DE-MRI scar (*transparent blue area*) is seen in the inferior wall extending laterally and septally. Zone I and II have >25% and <25% transmurality, respectively. *White lines* labeled *2B* and *2C* represent the short-axis location of images 2B and 2C. *DE-MRI*, Delayed-enhancement magnetic resonance imaging; *PET*, positron emission tomography.

(Figure 17-21). Electrophysiological testing also revealed inducible sustained VT in 6 of the 8 ARVD patients with delayed enhancement compared with none of the ARVD patients without delayed enhancement ($P < .01$).[63] Various institutions have reported recurrence rates between 11% and 50% following VT ablation.[73,74] Delayed-enhancement MRI may be used to identify anatomic areas with increased signal that could define potential areas of ablation when planning VT ablation for ARVD patients.

Similarly, delayed enhancement MRI is finding increasing use in the evaluation of cardiac sarcoidosis.[75] MRI has the capability of identifying areas of delayed enhancement suggestive of cardiac sarcoid granulomas that may serve as potential ablation targets (Figure 17-22). Jefic et al reported in a multi-center registry that catheter ablation of VT in patients with cardiac sarcoidosis refractory to medical therapy is effective in eliminating VT or markedly reducing the VT burden.[76] Finally, recent data about patients with hypertrophic cardiomyopathy showed that myocardial fibrosis detected by delayed enhancement MRI was associated with a greater likelihood of ventricular tachyarrhythmias on Holter recordings.[77]

Imaging of Ablation Lesions

Lesion imaging may enable assessment of ablation success or search for potential gaps leading to ablation failure. Delayed enhancement is a well-validated concept to visualize myocardial scar tissue.[58] In an animal study on six mongrel dogs, Lardo et al described the ability to visualize radiofrequency (RF) ablations in the right ventricular apex after about 2 minutes with an increase in signal intensity over the first 12 ± 2.1 minutes.[78] In an animal study evaluating multiple right ventricular lesions, a characteristic four-phase delayed enhancement pattern for ablation lesions was found (Figure 17-23).[79] The first phase demonstrated a contrast void directly after injection of the gadolinium contrast in all cases. This allowed the expeditious identification of the ablation lesions. Full enhancement (i.e., "very" delayed enhancement) was seen 98 ± 21 minutes after right ventricular lesions. Lesion sizes measured during the first three phases of contrast enhancement correlate well with the histopathologic lesion sizes measured during necropsy (Figure 17-24).[79]

Given the recent reports of nephrogenic systemic fibrosis associated with gadolinium, noncontrast visualization of ablation

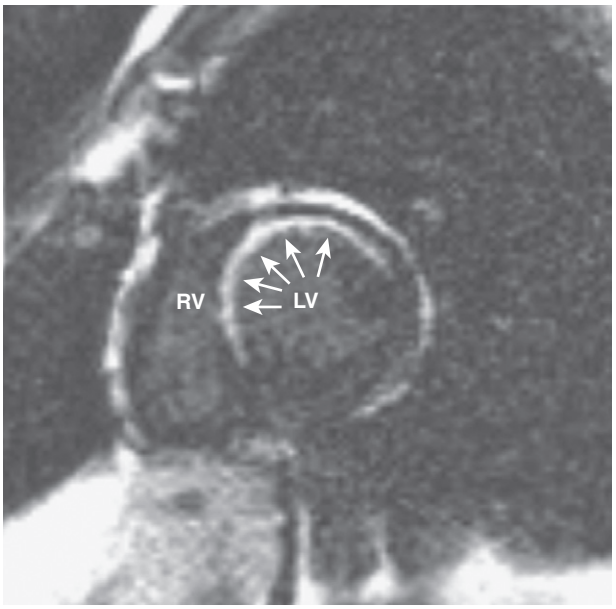

FIGURE 17-20 Ischemic myocardial scar. Delayed enhancement magnetic resonance imaging demonstrating a transmural scar (*arrows*) along the septal, anteroseptal, and anterior walls of the left ventricle. *RV*, right ventricle; *LV*, left ventricle. *(Courtesy Dr. Jean Jeudy.)*

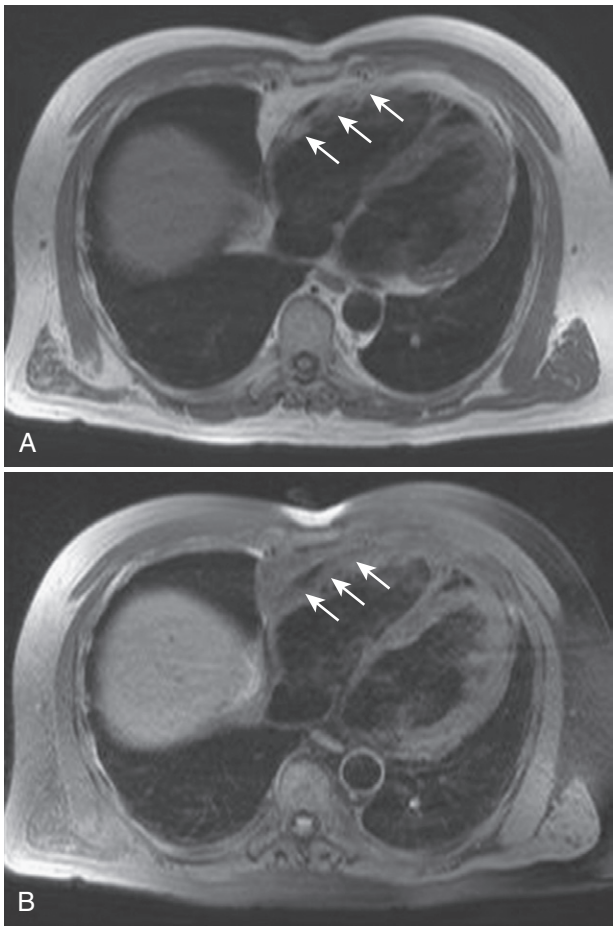

FIGURE 17-21 Arrhythmogenic right ventricular dysplasia. **A,** T1-weighted delayed enhancement magnetic resonance imaging demonstrating increased signal along the right ventricular free wall (*arrows*). **B,** Fat saturation imaging sequence confirms fatty infiltration along the right ventricular free wall (*arrows*). *(Courtesy Dr. Jean Jeudy.)*

lesions is receiving increasing interest.[80] Lardo et al showed that acute ablation lesions can also be detected in T2-weighted images as areas of increased signal intensity in the right ventricular apex in dogs about 2 minutes after ablation.[78] Animal studies demonstrated that ventricular lesions can be reliably visualized during a total follow-up time of 12 hours without contrast enhancement in T1- and T2-weighted images (Figure 17-25).[81] However, signal/noise ratio and contrast/noise ratio were lower than in the T2-weighted sequences, and the imaging quality was less consistent.[81]

Noncontrast enhanced MRI may enable evaluation of intralesional morphology and render the concept of "MRI histology" possible. When using irrigated ablation catheters at power settings of 40 W or more, pathophysiological examinations of the ablation lesions confirmed severe destruction of the intra-lesional cellular architecture, which could be visualized on MRI (Figure 17-26).[81]

Peters et al were the first to demonstrate the feasibility of LA post-ablation lesion visualization using delayed enhancement MRI (Figure 17-27).[82] McGann et al showed that PV isolation resulted in hyper-enhancement of the LA wall 3 months after the patient underwent PV isolation, which presumably represents tissue scarring. Interestingly, arrhythmia recurrence at 3 months correlated with the degree of wall enhancement with greater than 13% injury predicting freedom from AF ($P < .032$) even after adjusting for multiple variables such as age, gender, AF phenotype, LA size, and LA volume. In this study, it was possible to visualize areas of gaps in lesion sets for patients with AF recurrence.[83] The characteristic delayed enhancement MRI patterns after AF ablation were described by Badger et al. They showed that at 24 hours after ablation, delayed enhancement MRI appears consistent with a transient inflammatory response rather than stable LA scar formation, which tended to be present 3 and 6 months after ablation.[84]

Wylie et al used delayed enhancement MRI to show that catheter ablation of AF is associated with a decreased LA size and reduced atrial systolic function. Both of these measurements correlated with the extent of post-ablation LA scarring.[85]

Real-Time Magnetic Resonance Imaging

The field of real-time MRI has created significant interest in the electrophysiology community. The first human study using MRI to anatomically guide catheter navigation and ablation in real time was reported in 2008.[86] Using an MRI-compatible electrophysiology system, Nazarian et al were able to navigate to the RA, the His bundle, and the right ventricle in 10 mongrel dogs via a 1.5-tesla MRI system using rapidly acquired, fast gradient-echo images (5 frames/s). Comprehensive electrophysiology studies with recording of intracardiac electrograms and atrial and ventricular pacing were successfully performed. After proof of safety in animal studies, limited real-time MRI-guided catheter mapping studies were performed in two human patients. Adequate catheter localization was confirmed via recording of intracardiac electrograms in both patients.[86]

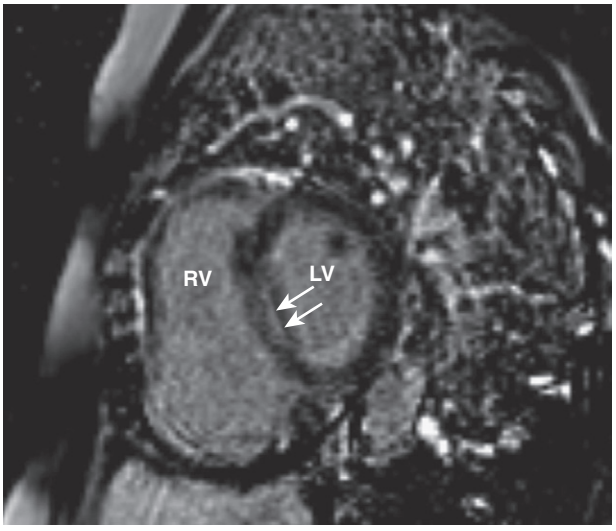

FIGURE 17-22 Sarcoidosis. Delayed enhancement magnetic resonance imaging in a patient with biopsy-proven pulmonary sarcoidosis demonstrating increased signal (*arrows*) in the interventricular septum suggestive of cardiac involvement. *LV*, Left ventricle; *RV*, right ventricle. *(Courtesy Dr. Jean Jeudy.)*

The advantages for such an approach include real-time three-dimensional imaging displaying the exact intracardiac catheter position, constant surveillance of catheter-tissue contact, potential visualization of ablation lesions and gaps, and no physician or patient exposure to ionizing radiation.

Despite the promise of real-time MRI, its use has been limited to a few academic centers.[86-88] Substantial engineering work is required to build electrophysiology platforms without ferromagnetic materials. Recently, engineering solutions have prevented parts of the catheter from functioning as an RF antenna and exposing the patient to hazardous heating effects during MRI scanning.[89] Faster imaging sequences, which were able to provide sufficient spatial and temporal resolutions, need to be developed. Given the previously mentioned complication of atrio-esophageal fistulas, real-time MRI also offers the potential for MRI thermometry.

Conclusion

MRI is well established for peri-procedural cardiac imaging, where it is frequently used interchangeably with CT, depending on local expertise and availability. Advanced image integration, volume imaging, and fusion imaging will allow the application of

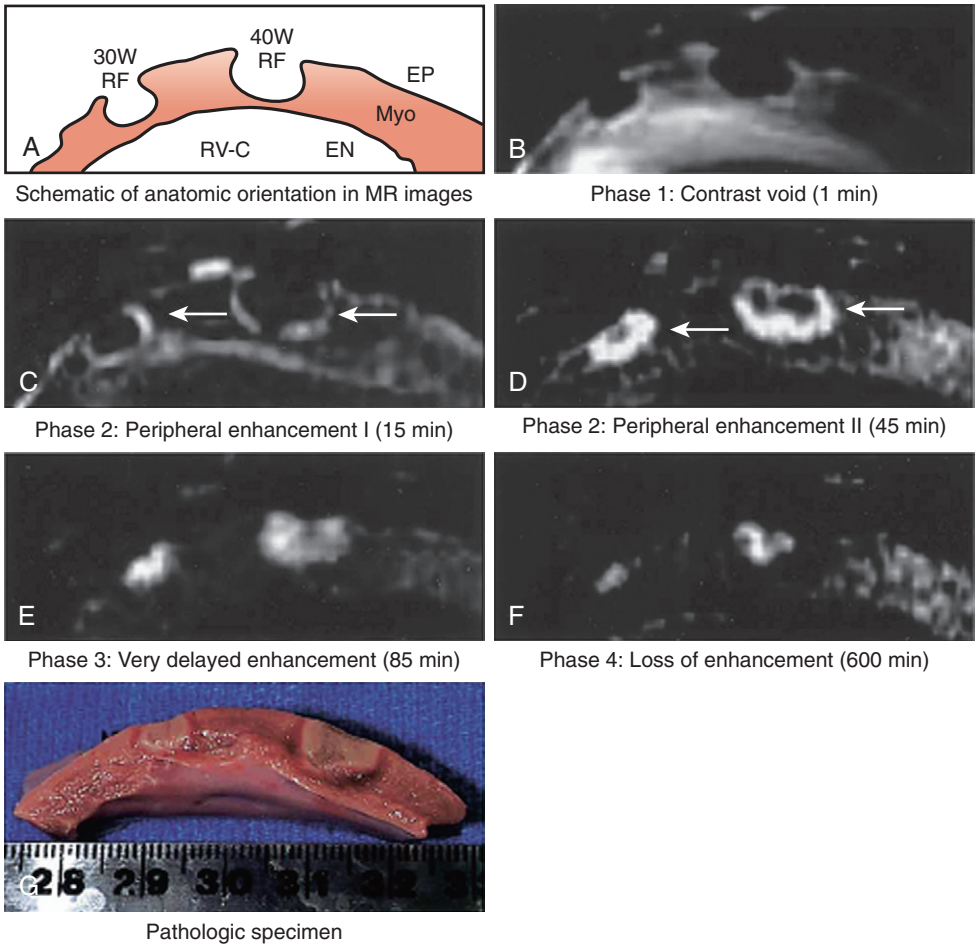

FIGURE 17-23 Visualization of radiofrequency ablation lesions using contrast-enhanced magnetic resonance imaging. Immediately after gadolinium injection ablation, lesions can be seen as areas of signal void (**B**). After increasing peripheral enhancement (**C** and **D**), complete "very delayed enhancement" can be seen approximately 90 minutes after contrast injection (**E**).

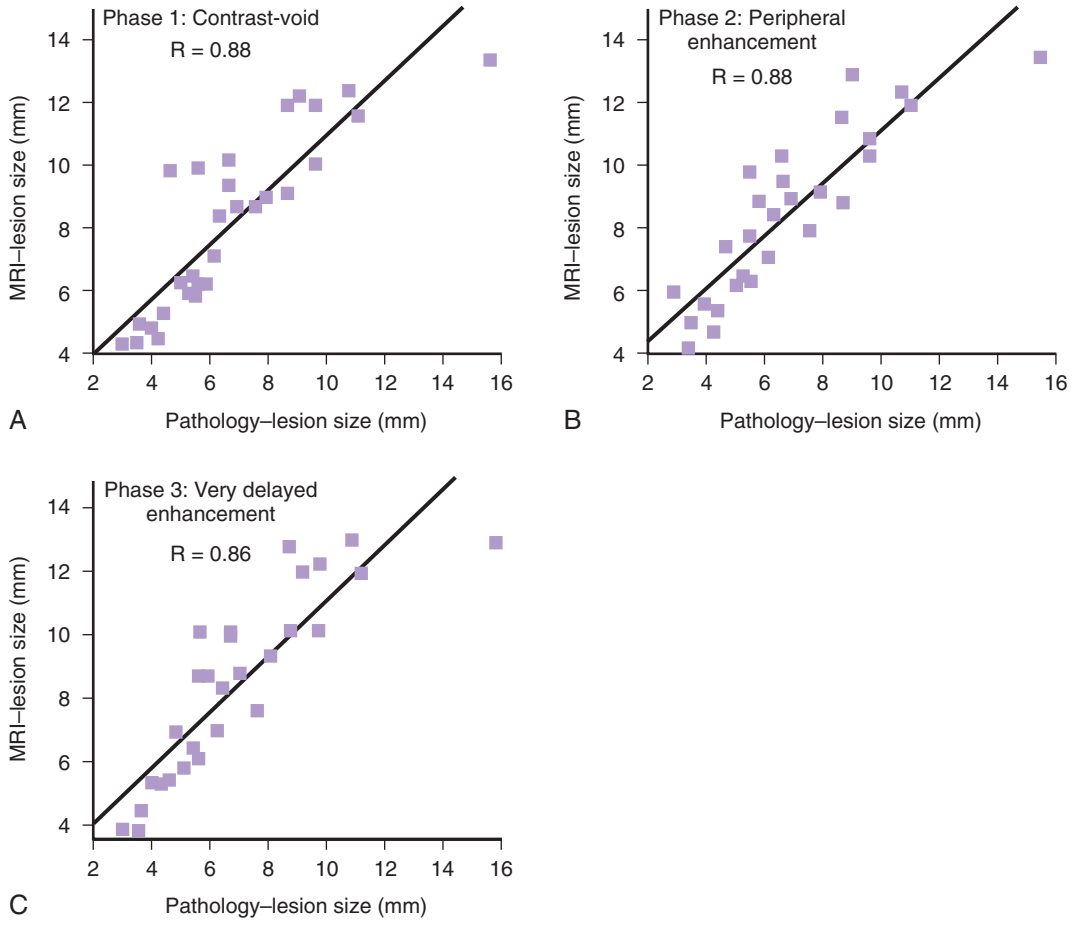

FIGURE 17-24 Lesion size assessed by and pathology. Correlation of lesion size assessed by contrast-enhanced magnetic resonance imaging versus histopathologic examination for each of the three phases of enhancement. **A,** Contrast void. **B,** Peripheral enhancement. **C,** Very delayed enhancement.

the unique features of MRI such as high soft tissue resolution to complex ablation procedures and to combine them with other imaging techniques for supplementary evaluation of ablation targets. This may be especially helpful for complex ablations such as for AF and VT. In experienced centers, imaging of ablation lesions is feasible and allows direct anatomic assessment of the ablation results. Incremental improvements move real-time MRI closer to the range of clinical applications, but further technical refinements will be necessary before widespread clinical use.

C. Transthoracic and Transesophageal Echocardiography

Principles of Echocardiography

Echocardiography, or cardiac ultrasound, is a noninvasive tool that uses the properties of ultrasound energy to study cardiac structure and function. Ultrasound is acoustic (sound) energy that occurs at frequencies much greater than the upper limit of the human auditory spectrum. Ultrasound imaging commonly uses frequencies of 1 to 20 million cycles/s (1 to 20 MHz), whereas the highest frequency detectable by the human ear is only 20,000 cycle/s (20,000 Hz). An ultrasound transducer is made up of piezoelectric elements (pressure-sensitive crystals and ceramic materials) that expand and contract on application of voltage to generate an ultrasound wave.

Ultrasound interacts with tissues in several ways. Ultrasound beams are reflected at interfaces (tissue boundaries) because of differences in acoustic impedance. Acoustic impedance equals tissue density times the speed of sound in a particular tissue; denser tissues reflect ultrasound to a greater degree. These reflections are received by the transducer and are used to form an echocardiographic image. Other interactions between the ultrasound beam and tissues that can affect image processing are scattering, refraction, and attenuation. Small structures can cause *scattering*—reflection of the ultrasound beam in all directions—and can result in reverberation artifacts. *Refraction*, or deflection, results in bending of the ultrasound beam when it encounters tissues of differing acoustic impedance. Lastly, *attenuation* occurs as various processes such as absorption remove energy from the ultrasound beam and weaken its signal strength.

Resolution, the ability to distinguish two objects that are near each other, is directly related to frequency and inversely related to wavelength. Further distinction is made between axial resolution, which defines objects on the basis of their depth from the

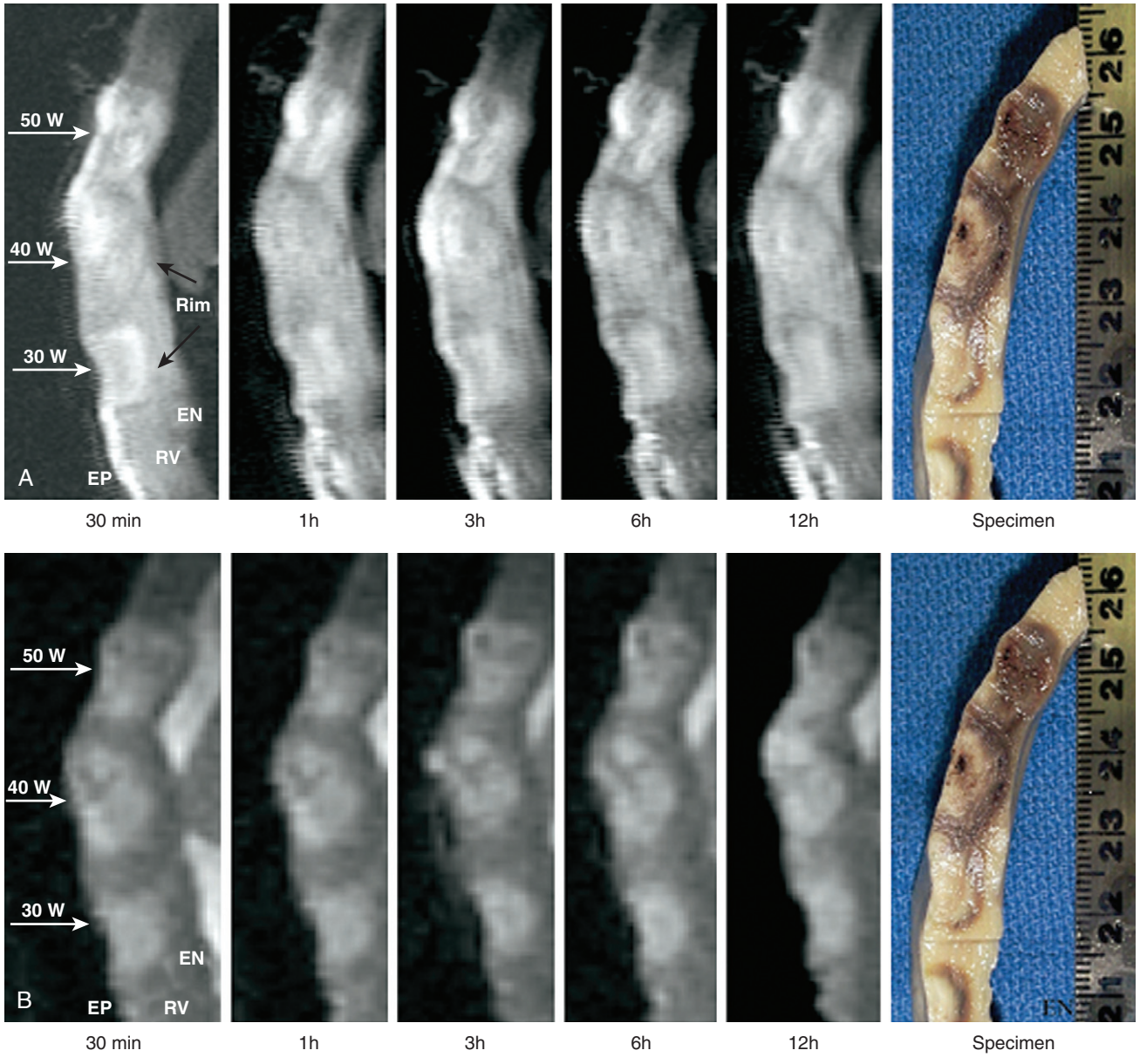

FIGURE 17-25 Appearance and time course of ablation lesions in non-contrast-enhanced magnetic resonance imaging. **A,** Typical appearance of ablation lesions using T2-weighted imaging protocols. Lesions can be seen as areas of increased signal intensity surrounded by hypodense rim. No significant change was found after a 12-hour follow-up. **B,** Corresponding images in T1-weighted images.

transducer, and lateral resolution, or differentiation of objects that lie side by side.[90]

Types of Echocardiography

Motion Echocardiography

Motion (M-mode) echocardiography is often referred to as an "ice pick" view of the heart (Figure 17-28). It is one of the earliest forms of echocardiography and helped lay the foundation for the development of multi-dimensional echocardiography. A single-crystal transducer emits an ultrasound beam directed through the heart. The transducer functions as both a transmitter and a receiver and rapidly alternates between both functions to receive returning reflected ultrasound energy at high frequencies. The information received from the reflection of ultrasound waves off various cardiac structures at different distances from the transducer is then converted into a row of spikes representing the amplitude of the reflected waves. *Amplitude*, or A-mode, is then converted into *brightness*, or B-mode, to facilitate pattern recognition. In B-mode, the height and width of each amplitude spike are represented as dot brightness and dot diameter, respectively. Finally, by plotting B-mode against time, a time-motion (M) display (M-mode) is attained. M-mode viewed in digital format produces an image that represents the anatomy along a single plane (Figure 17-29). Advantages of M-mode are that it allows for measurement of the dimensions of the structure and its motion in relation to the ultrasound beam at high temporal resolutions.[90-92]

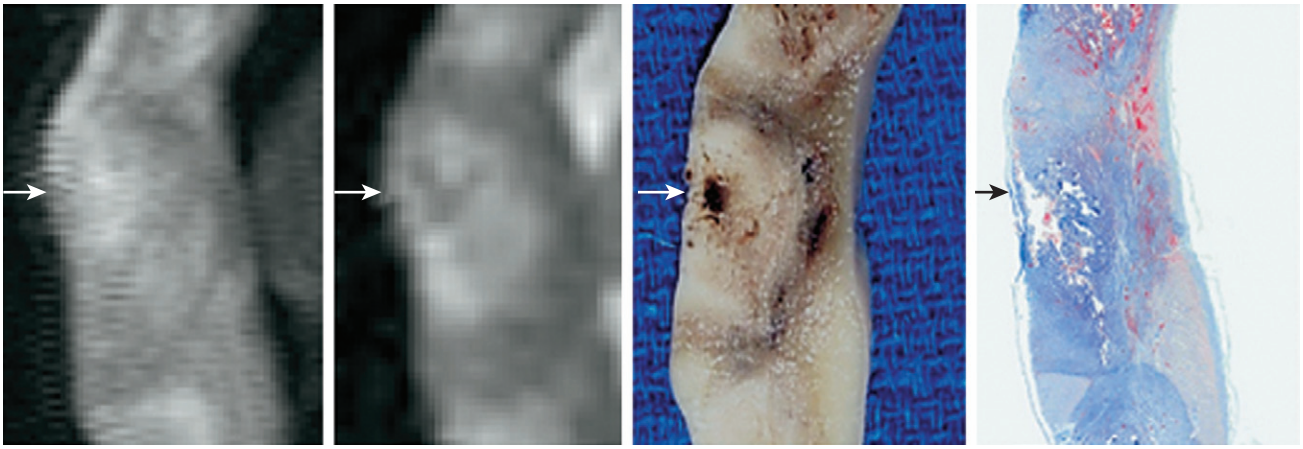

FIGURE 17-26 Assessment of intra-lesional pathology. Visualization of intra-lesional necrotic cavities of high-energy lesions as areas of low and high signal intensity when using T2- and T1-weighted imaging, respectively. *MRI*, Magnetic resonance imaging.

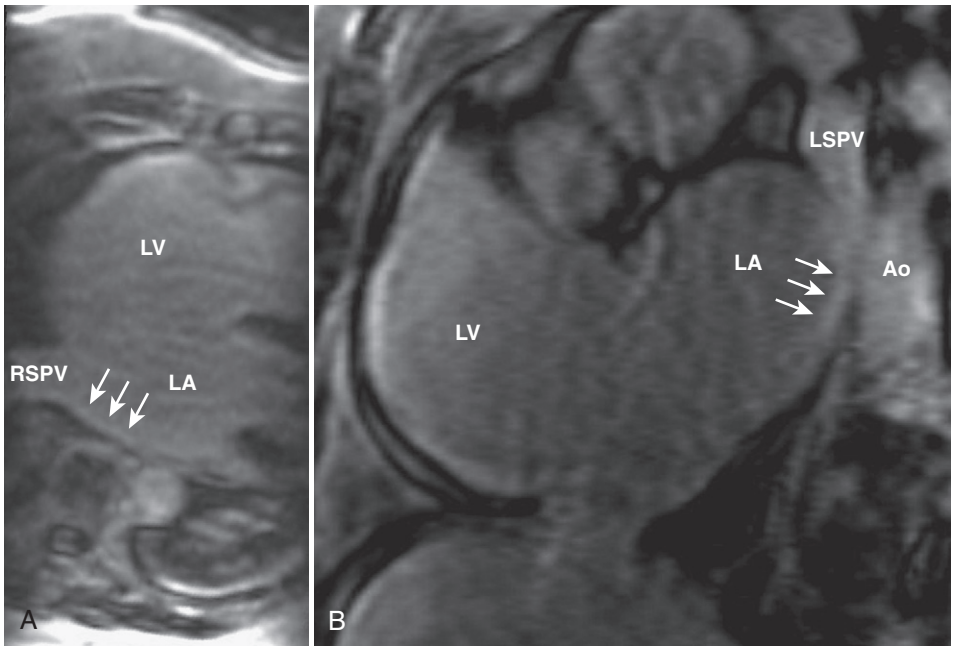

FIGURE 17-27 Left atrial ablation lesions. **A,** Horizontal long-axis magnetic resonance imaging (MRI) view of a patient 5 months after pulmonary vein (PV) isolation demonstrating areas of delayed enhancement (*arrows*) around the right superior PV (*RSPV*) representing LA scarring. **B,** Oblique short-axis MRI view with delayed enhancement (*arrows*) around the left superior PV (*LSPV*). *Ao*, aorta; *LA*, left atrium; *LV*, left ventricle. *(Courtesy Dr. Jean Jeudy.)*

Determination of an object's shape, however, is better assessed with multi-plane imaging as discussed below.

Two-Dimensional Echocardiography

Transthoracic Echocardiography

Two-dimensional transthoracic echocardiography (TTE) remains the most common modality for the initial evaluation of cardiac function. Using a mechanical or phased-array transducer to create an ultrasound beam in a sector arc creates a cross-sectional (two-dimensional), plane that, when plotted against time, allows for assessment of cardiac motion, structure, and function (Figure 17-30). By placing the transducer in various positions on the thorax, high-resolution multi-plane images of cardiac structures and their movements in real time are created.

Six main thoracic transducer positions (parasternal, apical, subcostal, suprasternal, supraclavicular, and right parasternal) are used in a standard two-dimensional TTE (Figure 17-31). With these transducer positions, various views (long-axis, short-axis, four-chamber, and five-chamber) can be obtained by rotating and

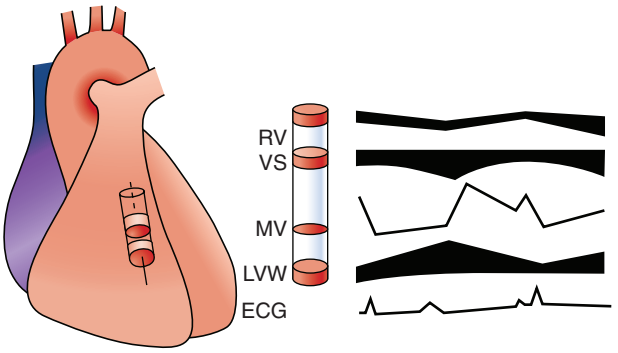

FIGURE 17-28 Motion (M-mode) echocardiography. The frontal projection of the heart demonstrates the concept that M-mode is equivalent to extraction of a plug of tissue that corresponds to the width of the beam passing through the heart. The removed plug is shown to the right and contains a portion of the right ventricle (*RV*), ventricular septum (*VS*), mitral valve (*MV*), and left ventricular posterior wall (*LVW*). A schematic of structure motion along with an electrocardiogram (*ECG*) is included. *(From Nanda NC, Gramiak R:* Clinical echocardiography, *St Louis, 1978, Mosby, p 370.)*

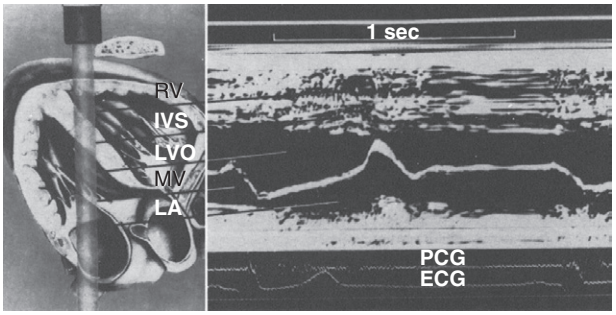

FIGURE 17-29 Motion (M-mode) echocardiography. Normal mitral valve (echocardiographic anatomy). The right ventricular (*RV*) cavity is not well represented, probably because the beam passes through it and the interventricular septum tangentially. The left atrium (*LA*) is shown behind the mitral valve (*MV*). The left ventricle may also be found behind the mitral valve when the ultrasonic beam is directed more laterally and inferiorly. *PCG*, Phonocardiogram; *ECG*, electrocardiogram. *(From Gramiak R, Shah P, et al:* Radiol Clin North Am *9:472,1971.)*

changing the angle of the transducer. For the parasternal and apical views, the patient is placed in the left lateral decubitus position, whereas the subcostal and suprasternal or supraclavicular views are obtained with the patient in the supine position. The right parasternal approach requires the patient to be placed in the right lateral decubitus position.[90]

By placing the transducer between the third and fourth left intercostal spaces and directing the ultrasound beam parallel to a line connecting the right shoulder and the left hip, a parasternal long-axis (PLA) view is obtained. This view bisects the mitral valve and the aortic valve. Rotating the transducer 90 degrees clockwise from its position in the PLA view results in a short-axis view. The most commonly used planes for the short-axis views are at the apical, papillary muscle, mitral valve, and basal levels.

Apical views are obtained by placing the transducer at the cardiac apex to produce the four-chamber view and then rotating

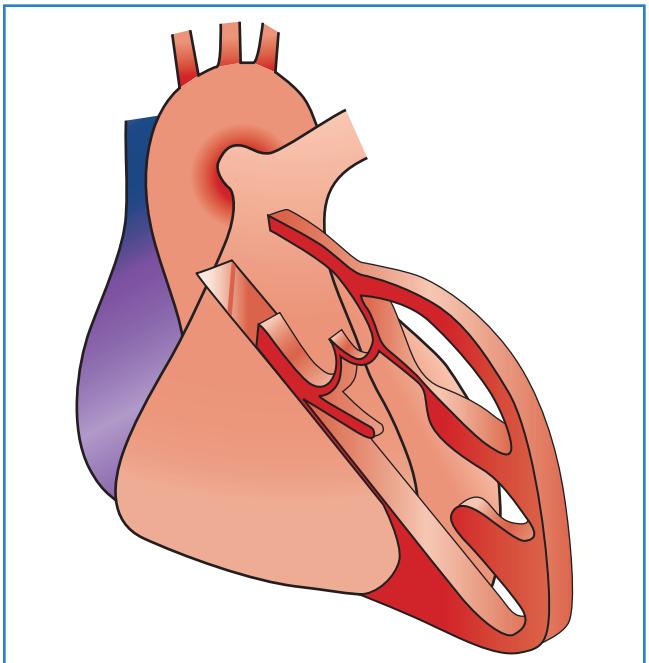

FIGURE 17-30 Two-dimensional scanning concept. Real-time, two-dimensional images are equivalent to slices of the heart that are removed and observed in motion. This illustration shows the cardiac cavities and valves viewed in the long axis of the left ventricle and the relationship of this plane to a frontal view of the heart. *(From Nanda NC, Gramiak R:* Clinical echocardiography, *St Louis, 1978, Mosby, p 371.)*

the transducer clockwise and anteriorly to produce the five-chamber view. The two-chamber view is obtained by rotating counterclockwise from the four-chamber view and continued counterclockwise rotation leads to the apical long-axis view.[91]

Placement of the transducer below the xiphoid process is required to obtain a subcostal four-chamber view. The ultrasound beam is perpendicular to the long axis of the left ventricle and rotating it 90 degrees counterclockwise creates short-axis images.

The suprasternal or supraclavicular position allows for visualization of the great vessels. Several views, including a long-axis aortic arch, short-axis pulmonary artery, short-axis aortic arch, long-axis pulmonary artery, long-axis aortic arch, and SVC planes, can be obtained. The right parasternal approach views the proximal ascending aorta, the SVC as it enters the right atrium, and the whole length of the inter-atrial septum.

Transesophageal Echocardiography

The most common indication for transesophageal echocardiography (TEE) is to evaluate for cardiac sources of emboli.[93-95] Compared with TTE, TEE provides more complete and accurate views of cardiac structures, especially on the posterior side of the heart, where it is in close relation to the esophagus. It also provides superior image quality as a higher frequency transducer can be used. However, this more invasive procedure can be uncomfortable because it requires the patient to swallow the probe. Other indications for TEE include evaluation of aortic dissections, aortic aneurysms, cardiac masses, prosthetic valve function, and endocarditis.[93]

Using multi-plane probes, transverse and longitudinal views are obtained with clockwise and counterclockwise rotation of the probe. The probe must be moved up and down to obtain

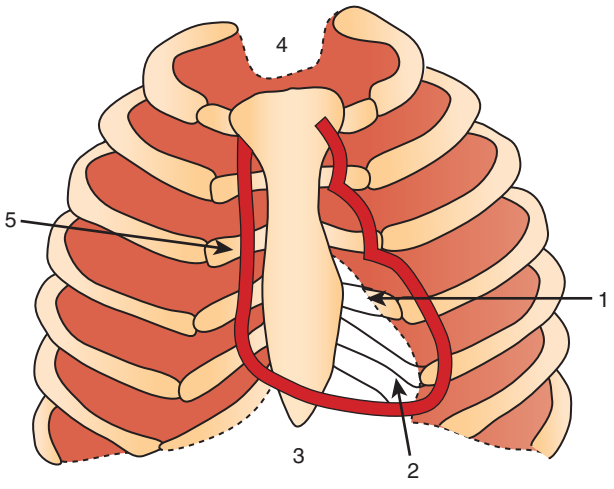

FIGURE 17-31 Cardiac window and transducer positions. This schematic frontal view of the chest shows the heart partially covered by the centrally placed sternum and the lung. The clear area over the lower portion of the heart is the cardiac window, through which ultrasonic examinations are carried out. The costal cartilages that pass across the window are generally sonolucent and do not impede the ultrasonic examination. The window varies widely, depending on the size of the heart, the shape of the chest, and body position. Since the window does not permit direct access to all portions of heart, beam angulation techniques are important to look under barriers such as bone and lung for structure detection. Numbers show various transducer positions used for transthoracic echocardiography. *1,* Parasternal widow; *2,* apical window; *3,* subcostal window; *4,* suprasternal and supraclavicular windows; *5,* right parasternal window. *(Modified from Nanda NC, Gramiak R:* Clinical echocardiography, *St Louis, 1978, Mosby, p 4.)*

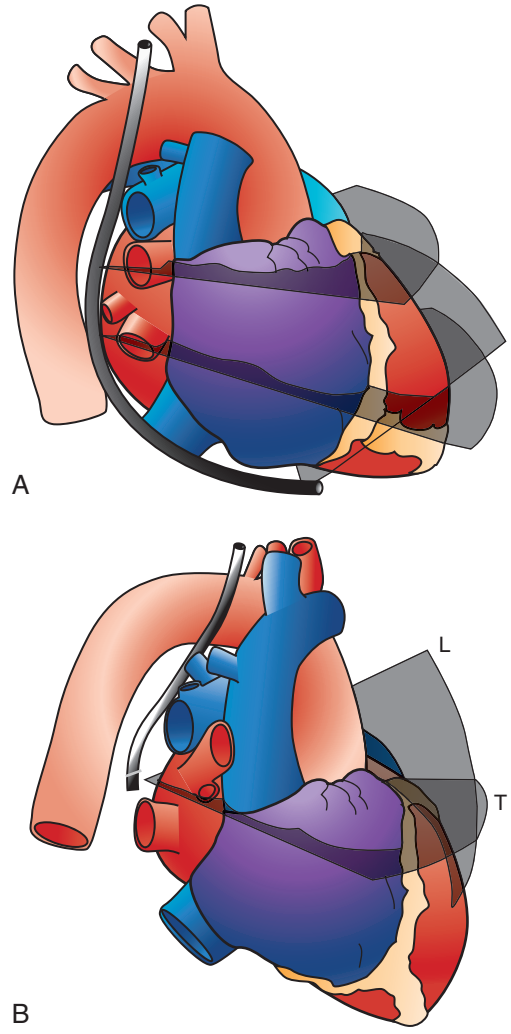

FIGURE 17-32 Transesophageal echocardiogram. **A,** Transverse and longitudinal imaging planes. Examples of transverse imaging planes that can be obtained by moving the probe up and down the esophagus. **B,** Both transverse (*T*) and longitudinal (*L*) planes. *(**A,** From Nanda NC, Mahan EF III: Transesophageal echocardiography,* AHA Council on Clinical Cardiology Newsletter *3–22, 1990. **B,** From Nanda NC, Pinheiro L, Sanyal RS, et al: Transesophageal biplane echocardiographic imaging: Techniques, planes, and clinical usefulness,* Echocardiography *7:771–788, 1990.)*

transverse sectional views of the heart at various levels but can merely be rotated to obtain longitudinal sectional views. Clockwise rotation of the probe allows for visualization of right-sided structures, and counterclockwise rotation brings left-sided structures into view. A four-chamber view of the heart can be obtained in the horizontal plane. An apical four-chamber view provides a detailed view of the mitral valve that can allow visualization of specific characteristics and evaluation of the function of both of the mitral valve leaflets (Figures 17-32 and 17-33).[94]

Another advantage of TEE is the superior visualization of the LA and the LAA. The LAA is a small outpouching of the LA that is between 1.2 and 4.5 cm long and lined by pectinate muscles. Although TTE can provide views of the LA and the LAA, the internal structures and the presence of thrombi, masses, and tumors in the LA and the LAA are more readily detectable by TEE (Figures 17-34 and 17-35). However, as studies by the authors' center have shown, simply assessing the LAA even with two-dimensional TEE for thrombi can result in prominent pectinate muscles being mistaken for clots. With three-dimensional TTE, these pectinate muscles can be differentiated from thrombi. Three-dimensional TTE can also provide information on the presence or absence of clot lysis, which can be used to assess the efficacy of anticoagulation therapy. A study by the authors' center suggests that in the future, combining two-dimensional TTE with three-dimensional TTE may be an alternative to two-dimensional TEE for the evaluation of LA and LAA thrombi and could spare the patient from having to undergo the more invasive TEE.[96]

Contraindications to TEE include esophageal strictures, diverticulum, tumors, fistulas, and prior esophageal surgery. Relative contraindications include esophageal varices and severe cervical spine problems. Risks include esophageal bleeding or rupture, arrhythmias (e.g., SVT), oropharyngeal injury, laryngospasm, methemoglobinemia, and oversedation.

Doppler Echocardiography

The Doppler effect, the observation of changes in frequency that occur when a sound source is moving toward or away from an observer, forms the basis for Doppler echocardiography. These principles are used to record the patterns, direction, and velocity of blood flow in the heart, thus allowing for assessment of insufficient or stenotic valves and detection of cardiac shunts. The Doppler shift is the observation of changes in frequency that

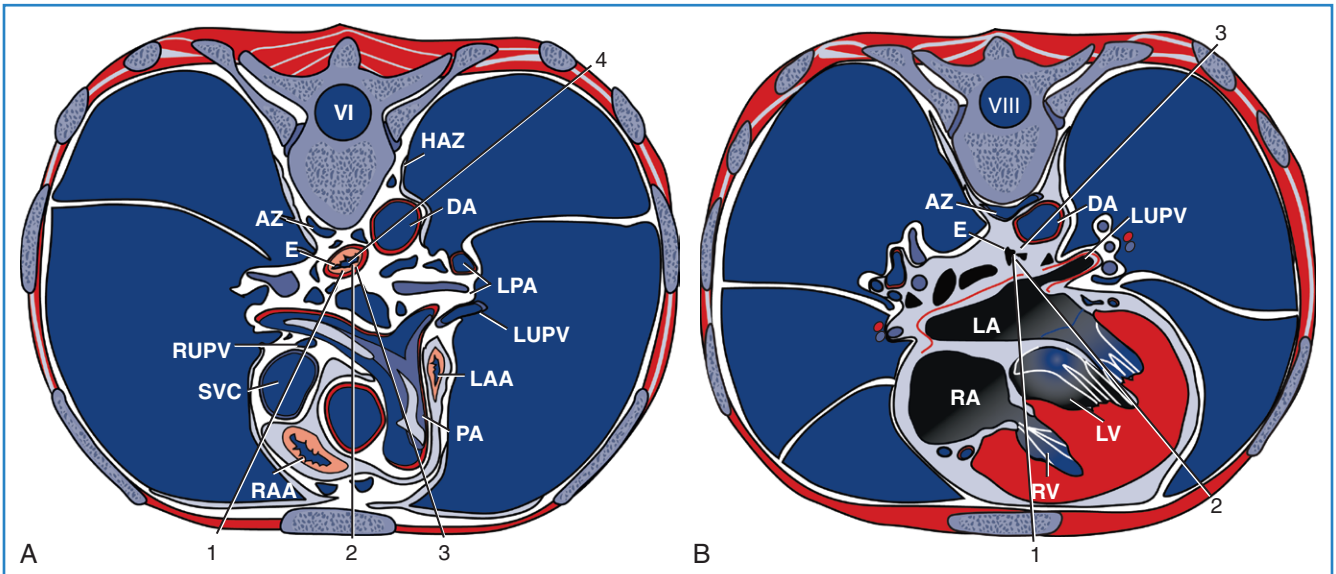

FIGURE 17-33 Transesophageal echocardiogram. Transverse sections. **A** and **B,** Sections obtained at the level of the sixth (**A**) and eighth (**B**) vertebrae. *AZ*, Azygos; *DA*, descending thoracic aorta; *E*, esophagus; *HAZ*, hemiazygos vein; *LA*, left atrium; *LAA*, left atrial appendage; *LPA*, left pulmonary artery; *LUPV*, left upper pulmonary vein; *LV*, left ventricle; *PA*, main pulmonary artery; *RA*, right atrium; *RAA*, right atrial appendage; *RUPV*, right upper pulmonary vein; *RV*, right ventricle; *SVC*, superior vena cava. *(From Nanda NC, Pinheiro L, Sanyal RS, et al: Transesophageal biplane echocardiographic imaging: Technique, planes, and clinical usefulness,* Echocardiography *7:771–788, 1990.)*

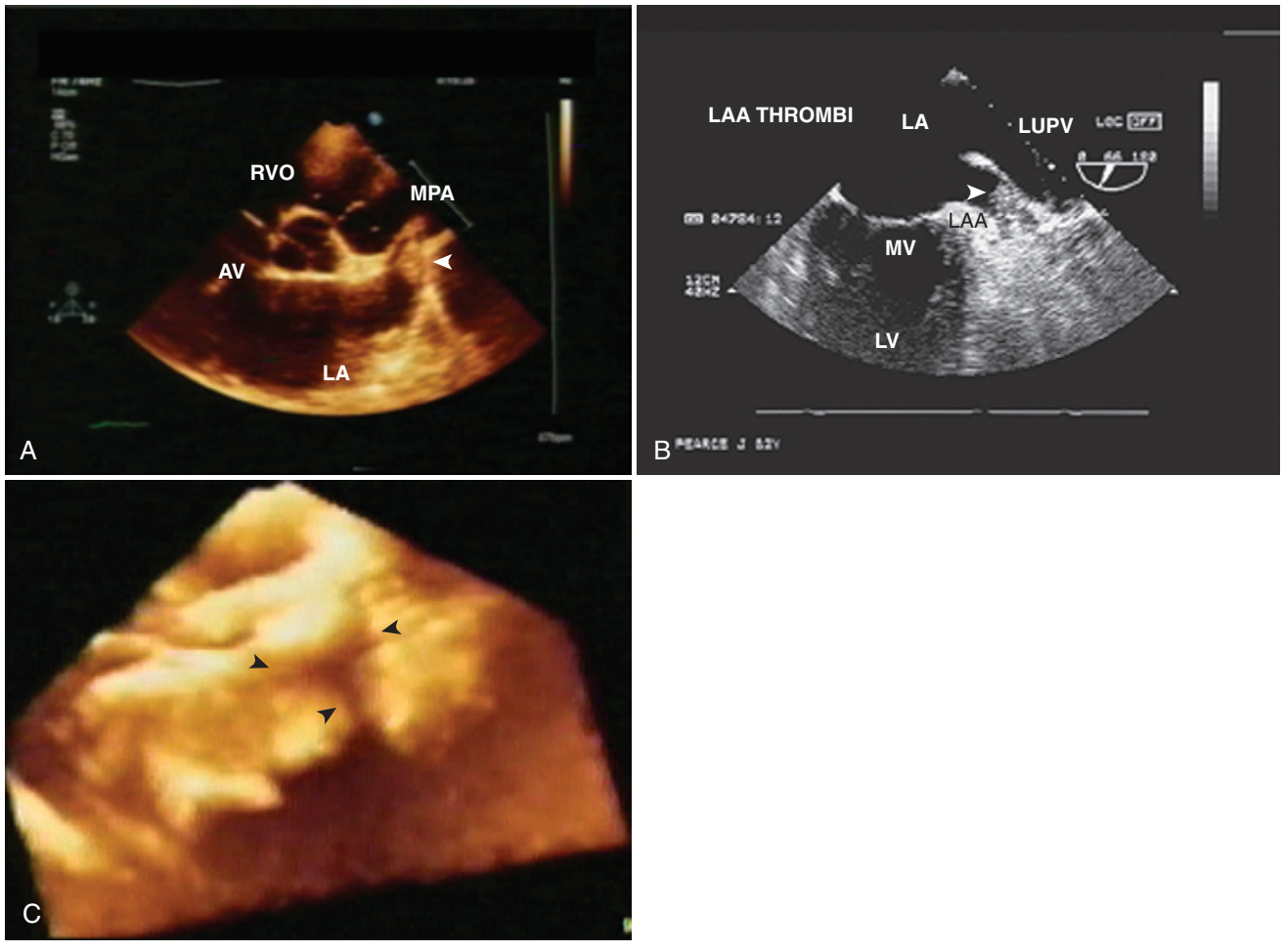

FIGURE 17-34 **A,** Two-dimensional transthoracic echocardiogram. *Arrowhead* points to a thrombus within the left atrial appendage (*LAA*). **B,** Two-dimensional transesophageal echocardiogram. The *arrowhead* points to a thrombus in the left atrial appendage. **C,** Three-dimensional transthoracic echocardiogram. *Arrowheads* point to individual lobes of the LAA visualized by cropping a three-dimensional dataset. *AV*, Aortic valve, *LA*, left atrium, *MPA*, main pulmonary artery; *RVO*, right ventricular outflow tract; *LV*, left ventricle; *LUPV*, left pulmonary vein; *MV*, mitral valve. *(**A,** From Nanda NC, Domanski M:* Atlas of transesophageal echocardiography, *ed 2, Baltimore, 2007, Lippincott, Williams and Wilkins, p 78. **B** and **C,** From Karakus G, Kodali V, Inamdar V, et al: Comparative assessment of left atrial appendage by transesophageal and combined two-and three-dimensional transthoracic echocardiography,* Echocardiography *25:918–924, 2008.)*

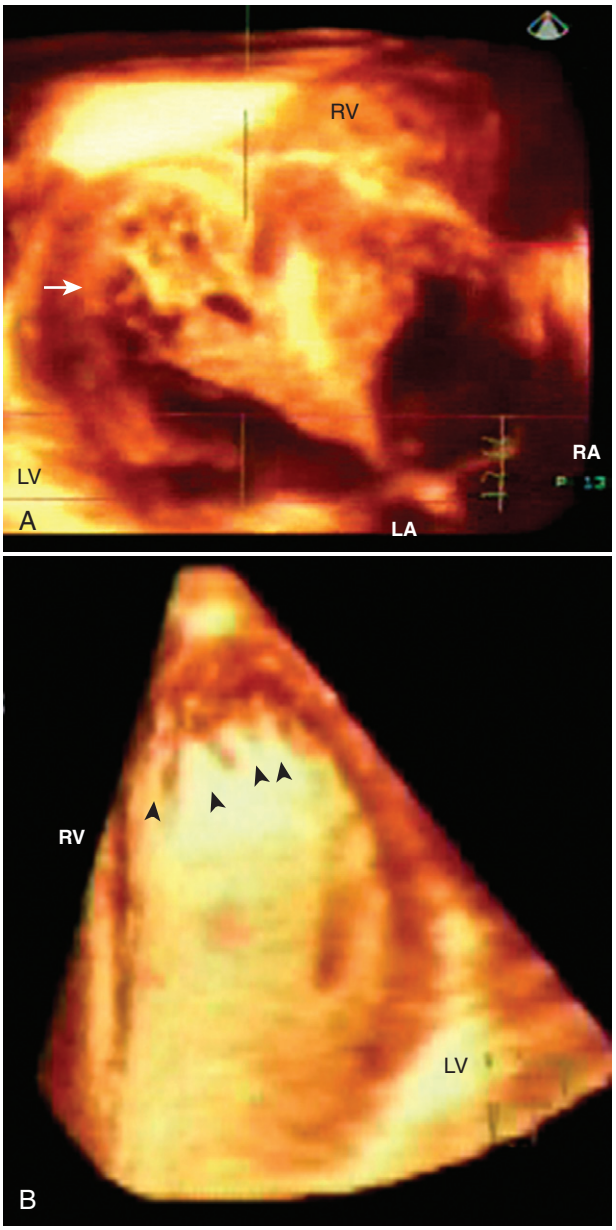

FIGURE 17-35 Live three-dimensional transthoracic echocardiography in left ventricular noncompaction. **A,** Transverse cropping of left ventricle (*LV*) apical area shows a honeycomb-like appearance (*arrow*) typical of noncompaction. **B,** Echo contrast study using perflutren lipid microspheres (Definity) shows filling of intertrabecular recesses with the contrast agent (*arrowheads*). *RV*, Right ventricle; *RA*, right atrium; *LA*, left atrium. *(From Bodiwala K, Miller AP, Nanda NC, et al: Live three-dimensional transthoracic echocardiographic assessment of ventricular noncompaction,* Echocardiography *22:611–620, 2005.)*

occur when a sound source is moving toward and away from a stationary observer.

The most accurate calculation of blood flow occurs when the ultrasound beam is parallel to the direction of blood flow. As the angle of incidence between the beam and the blood flow increases, the calculation of velocity becomes less inaccurate, and it becomes necessary to use a correction factor, the cosine of the angle of incidence, in the Doppler equation.

Doppler has several forms in clinical use, including continuous-wave, pulse-wave, color-flow, and tissue Doppler. Continuous-wave Doppler uses two ultrasound crystals for sending and receiving ultrasound waves simultaneously. Its main advantage is that it can measure high-velocity flows such as those in valvular or congenital heart diseases, and it has proven useful in the quantitation of abnormal flows. The disadvantage is that the Doppler data obtained occur throughout the length of the ultrasound beam and thus cannot be obtained from a specific area.

Pulse-wave Doppler transmits short "pulses" of ultrasound to a designated point, the sample volume, thus allowing data retrieval from a specified structure or segment of a blood vessel. It can also be used in combination with a mechanical or phased-array system to allow two-dimensional guidance.[97]

Doppler color flow imaging is a form of pulsed-wave Doppler, in which multiple bursts of ultrasound are transmitted along multiple scan lines to obtain Doppler data. All the frequency shifts obtained are averaged and used to calculate the velocity and direction of blood flow. The velocities are displayed on a color scale, with red indicating flow toward the transducer and blue indicating flow away from the transducer.[98]

Tissue Doppler combines various Doppler modalities used for assessing blood flow and applies these to the determination of myocardial velocities. Calculation of the lower velocities of myocardial motion provides a more objective measure with which to assess LV function that is not based on visualization of the endocardial excursion and wall thickening. Tissue Doppler imaging also has usefulness in assessing the longitudinal motion of the heart and in the diagnosis of left ventricular diastolic dysfunction, especially when combined with mitral inflow Doppler waveforms.[99]

Contrast Echocardiography

Contrast echocardiography involves intravenous injection of microbubbles that produce opacification of the heart chambers. It has been used to detect intracardiac shunts, enhance Doppler evaluation of cardiac chambers, and evaluate myocardial perfusion. Many different types of contrast agents have been studied in an attempt to find the ideal contrast agent that is small enough and persists long enough to cross the pulmonary circulation so that left heart structures can be evaluated. Other features that can be adjusted to improve contrast opacification include harmonic imaging and low mechanical index imaging. With these advances, contrast echocardiography provides improved left ventricular endocardial border imaging, resulting in better detection of wall motion abnormalities, ventricular volume, and ejection fraction. The result is a more accurate estimate of LV function.[100]

Stress Echocardiography

Stress echocardiography uses two-dimensional TTE before and after stress testing (exercise or pharmacologic) to detect coronary disease by showing wall motion abnormalities induced by the stressor. The extent of ischemia is determined by observation of induced dyskinetic, hyperkinetic, and akinetic segments of the myocardium and provides data that can be used to predict the likelihood of future cardiac events.[101]

Three-Dimensional Echocardiography

Three-dimensional echocardiography is an area of increasing research and clinical application. In the past, three-dimensional images were obtained by the reconstruction of two-dimensional

images, but the creation of three-dimensional transducers composed of arrays of crystals has allowed for real-time three-dimensional imaging.[102,103] These transducers scan a pyramidal wedge of the heart, and the image can then be cropped to view specific structures of interest. It appears that three-dimensional imaging can more accurately measure chamber volumes and better visualize valve architecture in some cases. Studies show that compared with two-dimensional imaging, three-dimensional imaging is better at measuring LV volume and mitral valve area in mitral stenosis and provides better quantitation of valvular regurgitant volumes. It has also proved useful in the assessment of intracardiac masses and can more accurately diagnose and characterize other cardiac disease entities such as ventricular noncompaction, aortic dissection, and aortic valve stenosis (see Figure 17-35).[104]

Echocardiography in the Evaluation of Cardiac Arrhythmias

Cardiac imaging has unveiled a new way of studying arrhythmias by allowing physicians to see structural and functional defects, which would help delineate the etiology of these arrhythmias.

Atrial Fibrillation

AF is one of the most common arrhythmias encountered in clinical practice. It is also one of the most common indications for referral for echocardiography. As studies continue to show, AF and other atrial arrhythmias can be strongly linked to underlying cardiovascular disease secondary to structural and functional abnormalities. M-mode echocardiography can reveal coarse undulations secondary to AF when the ECG is not definitive (Figure 17-36). TTE allows for the evaluation of the LA size, mitral valve structure and function, and LV function. In addition to the evaluation of the parameters already mentioned, TEE results in better detection of thrombi in the LA and the LAA.[93] Clinically, both modalities provide information that can help determine the underlying etiology of arrhythmia and identify patients at risk for a thromboembolic event before cardioversion.

The LA size is typically obtained using the parasternal long-axis view at end-systole. The measurement is made from the trailing edge of the posterior aortic wall to the leading edge of the posterior LA wall. Measurements should also be taken in the apical view from the tip of the mitral valve to the posterior wall of the LA, since LA size can be underestimated using the parasternal view secondary to longitudinal enlargement of the atrium.

LA enlargement is a common finding in patients with AF. The normal value for LA dimension in adults is less than 4 cm (<2 cm/m^2 body surface area). The Stroke Prevention in Atrial Fibrillation study showed that LV systolic dysfunction and LA enlargement are the strongest independent predictors of future thromboembolic events.[95] LA size has also been used to predict the success of maintenance of sinus rhythm after cardioversion; a larger size is a poor prognostic indicator for restoration of normal atrial function.

Determination of the LVEF is another major reason for referral for echocardiography.[105] Area and length measurements taken from apical long-axis views and apical short-axis views can be used for the calculation of LV systolic and diastolic volumes. Stroke volume (the difference between LV diastolic and systolic volume) and ejection fraction (stroke volume divided by end-diastolic volume) can subsequently be derived. As mentioned, the presence of LV dysfunction is related to increased risk of stroke in patients with AF. Knowing the degree of dysfunction is also useful for deciding which pharmacologic regimen would be optimal for controlling the ventricular rate in these patients.

Mitral valve dysfunction, including stenosis and regurgitation, is often associated with AF. Elevated LA pressure caused by impedance of flow at the mitral valve level can lead to enlargement of the LA, stasis, and subsequent increased risk of thromboembolism and AF. The valve can be visualized with M-mode echocardiography and two-dimensional TTE views, including the apical four-chamber, parasternal long-axis, and parasternal short-axis views.

Evaluation of the LAA by TEE and three-dimensional TTE was briefly mentioned in the section on TEE. In patients with AF, thrombus has a tendency to form in the LAA. Doppler echocardiography has shown that low LAA flow velocity is one risk factor for thrombus formation. Spontaneous echo contrast (smokelike echoes) in the LA, LAA, or both, which is thought to be a sign of abnormal atrial flow and uncoordinated atrial systole, has also been shown to be a risk factor for thrombus formation.

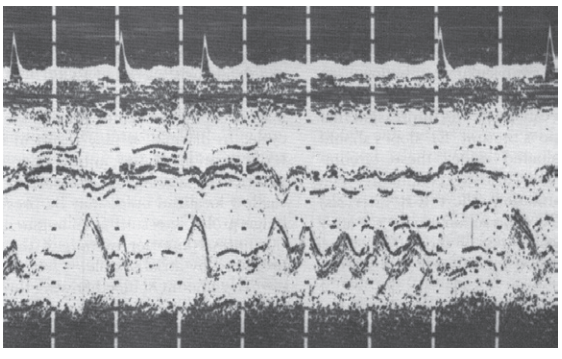

FIGURE 17-36 Mitral valve recording in atrial flutter or atrial fibrillation. Both leaflets of the mitral valve (*MV*) show coarse undulations in diastole resulting from rapid and irregular atrial activity. *ECG*, Electrocardiogram. *(Courtesy Cardiology Division, Genesee Hospital, Rochester, NY.)*

Ventricular Tachycardias

Two-dimensional echocardiography is useful in the evaluation of wall motion and valvular function in VT.[106] Combined with Doppler and color flow, echocardiography has been used to detect the presence of variable mitral valve leaflet excursions and mitral blood flow during VT.

Echocardiography in the Evaluation and Management of Cardiomyopathy

It is relevant to mention the increasing usefulness of echocardiography in the evaluation and management of cardiomyopathies, since they can often result in sudden death from fatal ventricular arrhythmias if not addressed in a timely manner. Quantitation of systolic and diastolic function can be done by echocardiography in dilated, hypertrophic, restrictive, arrhythmogenic RV, and unclassified cardiomyopathies. In dilated cardiomyopathy, the presence of left ventricular spherical dilation, reduced systolic wall thickening, enlarged atrial cavities, right ventricular enlargement, wall motion abnormalities, dilated mitral annulus,

incomplete coaptation of mitral valve leaflets, and apical mural thrombi are some of the characteristics that can be seen on echocardiography.[91] Doppler can supplement both M-mode and two-dimensional echocardiography by providing information about cardiac output, mitral inflow patterns, left ventricular filling pressures, and dyssynchrony. Doppler can also help guide the timing of diastolic filling to optimize cardiac output after placement of a biventricular pacemaker. In hypertrophic cardiomyopathy (HCM), some of the findings demonstrable by echocardiography include a hypertrophied LV, asymmetric septal hypertrophy, systolic anterior motion of the mitral valve, left ventricular outflow tract (LVOT) obstruction, notching of the aortic valve, mitral regurgitation, and LA enlargement. In addition to more common echocardiographic features similar to those mentioned above, cardiac amyloidosis (a form of restrictive cardiomyopathy) produces echogenic "speckling" secondary to the presence of amyloid in the myocardium.[91] Prominent left ventricular trabeculations and intertrabecular spaces that fill with blood on color-flow imaging or with contrast echocardiography are findings in ventricular noncompaction, an unclassified cardiomyopathy, which can be more accurately diagnosed with three-dimensional TTE (see Figure 17-35).[104] Endomyocardial fibrosis, also an unclassified cardiomyopathy, can have mass-like apical lesions on echocardiography. In arrhythmogenic right ventricular cardiomyopathy, right ventricular enlargement is one of the most common echocardiographic findings. Other findings on echocardiography include right ventricular systolic dysfunction, right ventricular wall motion abnormalities, thinning of the RV free wall, right ventricular aneurysm, segmental right ventricular dilation, an abnormal hyper-reflective moderator band, right ventricular trabecular derangements, and echogenicity of the RV free wall secondary to the presence of fat and fibrous tissue.[107]

Echocardiography for the Evaluation of Pacemakers

Localization of Pacemaker Leads

Echocardiography can be used in some situations when an ECG does not definitely rule out misplacement of a pacemaker lead. For example, 11 years after placement of a right ventricular VVI pacemaker for a patient with third-degree atrioventricular block, it was found by two-dimensional TTE that the pacing lead had mistakenly been placed from the right atrium, across the interatrial septum, through the mitral valve, and along the posterior wall of the LV. Although this patient's ECG at the time of placement did show a right bundle branch block indicative of misplacement of the pacing lead in the LV, this finding has been noted in up to 10% of patients with normal pacemaker lead placement in the RV. In the above case, the apical and parasternal views on two-dimensional TTE showed the exact course of the pacemaker lead through the atrial septum and its contact with the posterior wall of the LV.[108] Two-dimensional echocardiography has also been used to help differentiate between placement of RV and coronary sinus pacing catheters when this is unclear from ECG or fluoroscopy.

Acoustic artifacts can often incorrectly mimic other structures or objects in the heart. Experience helps avoid mislabeling these artifacts; however, this continues to be a challenge even for the most experienced. Intracardiac catheters are hyperechoic and often create a tail-like reverberatory artifact.[109] Sometimes these artifacts are easily identifiable and can even help confirm the location of the catheter. However, depending on various factors such as echogenicity and the presence of artifacts in a different scan line, artifacts can sometimes be mistaken for other objects, as in the case of an artifactual image of LA catheter being mistaken for a catheter in the left ventricle.[110]

Optimization of Pacemaker Parameters

Continuous-wave Doppler echocardiography and pulsed Doppler echocardiography have been shown to be effective in the determination of pacemaker settings that can optimize a patient's hemodynamics. Although the pacing mode and AV interval length cannot, by themselves, reliably predict the degree of mitral regurgitation, Doppler studies can be used to optimize stroke volume and assess and minimize the degree of mitral regurgitation in sequential pacing. Because aortic diameter is constant in a given patient, peak aortic flow velocity can be used as a surrogate for stroke volume. As a result, peak aortic flow velocity and analysis of diastolic trans-mitral flow patterns to determine atrial capture in various pacing modes have also been assessed with Doppler to determine ideal pacemaker settings and modes for desired hemodynamics with improved atrioventricular synchrony (Figure 17-37).[111]

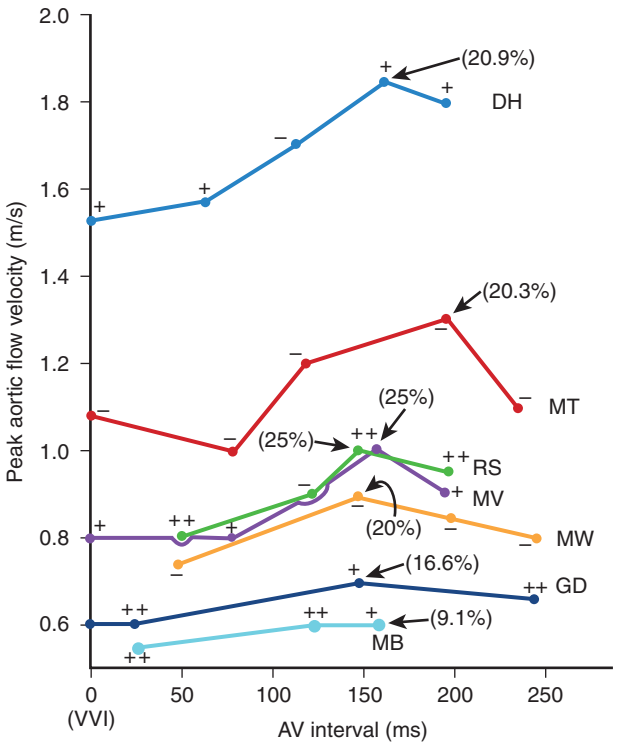

FIGURE 17-37 Peak aortic flow velocity at different atrioventricular (*AV*) intervals (7 patients). *+*, Mitral regurgitation present; *++*, increased mitral regurgitation; *–*, mitral regurgitation not evaluated by Doppler. The number in parentheses indicates the maximum percentage change in peak aortic flow velocity obtained in a given patient as compared with the VVI value or value at the shortest AV interval (in patients in whom VVI values were not available). Note that the maximum percentage change occurred with pacing at AV intervals between 150 and 200 ms. Patient initials are at the right of each Doppler flow velocity curve. *(From Zugibe FT, Nanda NC, Barold SS, et al: Usefulness of Doppler echocardiography in cardiac pacing: Assessment of mitral regurgitation, peak aortic flow velocity and atrial capture,* PACE *6:1350–1357, 1983.)*

Detection of Pacemaker Complications

Echocardiography has proven to be a valuable tool in the diagnosis of pacemaker complications such as perforations, thromboses, and vegetations.[112-114] Direct evidence for pacer perforation by echocardiogram was noted in a study of several patients who initially presented with indeterminate evidence for abnormal location of their right ventricular pacing catheters. This indeterminate evidence consisted of findings such as increased pacing threshold, loss of sensing, new pericardial rub, catheter malposition on chest radiograph, and right bundle branch block on ECG. Echocardiography was used to show the movement of the catheter tip from an extracardiac region, intraseptal location, or the LV into the RV or RA during withdrawal of the catheter, thus proving its abnormal location.

Two-dimensional TTE has been successfully used in the detection of pacing catheter–induced thrombosis as well as in the detection of vegetations on pacing catheters. Studies now show increasing clinical application of three-dimensional TTE over two-dimensional TTE and two-dimensional TEE in the detection of vegetations on pacemaker leads. The pyramidal wedge obtained with three-dimensional TTE can be manipulated to obtain any desired plane and angulation to view the location, attachment, and size of a lesion, whereas two-dimensional TTE only provides a thin-slice view of the cardiac anatomy.

Echocardiography in the Evaluation of Fetal Arrhythmias

Fetal tachycardia, bradycardia, and a persistent irregular rhythm on a screening ultrasound examination are all indications for further evaluation of the fetal heart with echocardiography. Echocardiography provides a noninvasive, nonteratogenic method for the evaluation of fetal cardiac arrhythmias and the structural defects that may be responsible for these arrhythmias.[115]

M-mode echocardiography has been used extensively in the evaluation of fetal arrhythmias. By directing the ultrasound beam through both the fetal atrium and ventricle, the relationship of atrial and ventricular contractions can be observed. Pulsed Doppler can also indirectly evaluate arrhythmias by evaluating intracardiac blood flow. An apical four-chamber view allows visualization of flow into and out of the ventricle.

Studies at the authors' center have shown the application of various modalities of fetal echocardiography in the detection of reduced stroke volumes in fetuses with ventricular ectopy as well as tricuspid regurgitation and pericardial effusion with heart block. Three-dimensional echocardiography has also been shown to provide en face views of atrial and ventricular septal walls and valves, which are not attainable with two-dimensional echocardiography. Fetal three-dimensional imaging continues to be a rapidly evolving area with increasing clinical value.

All references cited in this chapter are available online at expertconsult.com.

CHAPTER 18

Principles of Hemodynamics Applied to Cardiac Arrhythmias

Kevin P. Jackson, Donald D. Hegland, and James P. Daubert

The hemodynamic consequences of cardiac arrhythmias depend on various factors, including the filling and emptying capacity of the atrium and the ventricle, the duration and relative timing of systole and diastole, as well as neurohormonal influences on cardiac contractility and peripheral tone. Early studies examined these effects in various arrhythmias, including atrial fibrillation (AF), Wolff-Parkinson-White syndrome, and ventricular tachycardia (VT).[1,2] This chapter expands on this pioneering work to provide a current framework for considering the important hemodynamic consequences of cardiac arrhythmias.

Atrial Mechanics

Pressure and flow recordings from the right and left atria under normal conditions consist of two major positive deflections: (1) the "a" wave and (2) the "v" wave (Figure 18-1). The a wave results from atrial contraction and is immediately followed by the "x" descent, representing atrial relaxation. A small "c" wave in the right atrial tracing occurs during the x descent and represents tricuspid valve closure. The atrial v wave occurs during ventricular contraction, which results in the descent of the tricuspid valve annulus and the passive filling of the atrium from the venous system. As the right ventricular pressure falls below that of the atrium, the tricuspid valve opens, and atrial blood is emptied into the ventricle, resulting in the "y" descent.

Early studies by Gesell and Wiggers estimated the contribution of atrial systole to overall cardiac output to be between 10% and 35%.[3,4] Subsequent studies have shown that the atrial contribution to left ventricular (LV) performance operates via a Frank-Starling relationship, whereby cardiac output is augmented by an increase in end-diastolic volume (preload) of the ventricle.[3] Loss of atrial systole results in a decrease in cardiac output by causing a downward shift of the Frank-Starling curve; that is, the smaller left ventricular end-diastolic diameter from diminished filling results in a smaller stroke volume. This relationship is independent of changes in systemic afterload.

Although less well studied than ventricular mechanics, left atrial (LA) pump function has been characterized in both normal and pathologic states.[4] In the early stages of LV dysfunction, atrial contraction is augmented via an upregulation of β-myosin heavy chains in response to the increased afterload from worsening LV compliance. This improvement in LA mechanical work may aid in initial compensation of heart failure symptoms. As ventricular pressure and volume continue to increase, however, intrinsic atrial contractility deteriorates, and circulatory failure progresses. As heart failure progresses and, consequently, LV end-diastolic pressure increases, the capacity of atrial systole to augment cardiac output diminishes.

The reservoir function of the left atrium, which includes the passive, early-phase filling during atrial relaxation and the late-phase filling during ventricular systole, has been shown to be an independent determinant of cardiac output.[5] Disease states that reduce atrial compliance, including conditions of chronic pressure overload such as mitral stenosis, hypertrophic cardiomyopathy, or advanced LV systolic dysfunction, may result in decreased cardiac output despite preserved atrial contraction. The loss of atrial systole or atrioventricular synchrony in the background of such diseases may result in the sudden deterioration of previously well-compensated cardiac function. The effects of specific atrial arrhythmias on atrial and ventricular hemodynamic functions are discussed below.

An important but perhaps under-recognized component of atrial mechanical function is the conduction between the right and left atria. The classic electrocardiographic criteria established for LA enlargement correlates with elevated pulmonary capillary wedge pressure only in patients with cardiomyopathy or rheumatic mitral valve disease.[6] In patients without cardiomyopathy, the electrocardiogram pattern of LA enlargement may represent a prolongation of interatrial conduction time (IACT), often with normal LA size and pressures. Disease states such as AF, hypertension, and mitral regurgitation are associated with adverse atrial myocyte remodeling. Abnormalities in IACT are also common in these conditions, but whether remodeling leads to interatrial conduction delays or is a result of incoordinate atrial contraction is unknown. In patients undergoing cardiac resynchronization therapy for cardiomyopathy, those with an IACT greater than 100 ms have had larger LA volumes and lower indices of LA function at follow-up compared with patients with normal IACTs.[7] The presence of severely prolonged IACT in this population has important implications for optimal programming of the atrioventricular delay as AV nodal conduction may be more rapid than right-to-left atrial conduction in up to 30% of patients.

Prolongation of the P-wave duration and IACT is common in patients with AF.[8] Slowed conduction in the setting of increased atrial dimension increases the number of wavelets that coexist, thereby increasing the likelihood that AF will be sustained. In addition to prolongation of the normal right-to-left atrial route of conduction via Bachmann's bundle, atrial fibrosis and remodeling

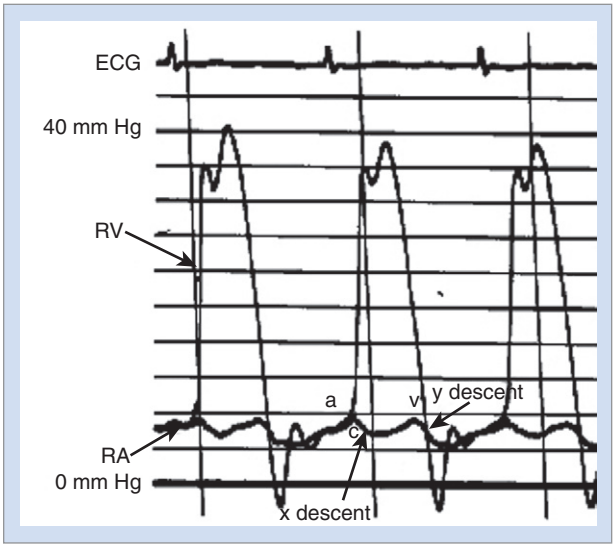

FIGURE 18-1 Simultaneous pressure tracings of the right atrium (*RA*) and the right ventricle (*RV*) during normal sinus rhythm.

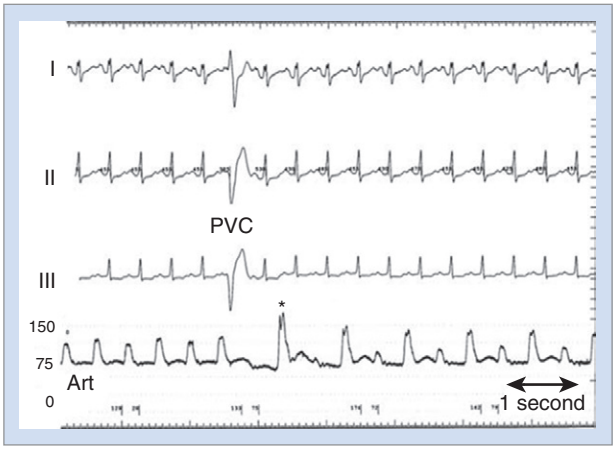

FIGURE 18-2 Sinus tachycardia is present and is interrupted by a single premature ventricular contraction (*PVC*). The sinus beat following the PVC generates a high-amplitude pulse (*asterisk*) because the ventricle has a long filling time, which results in a higher ventricular end-diastolic volume and an increase in contractility because of the Frank-Starling mechanism. After the PVC, perpetuation of the pulsus alternans is present for several cycles. *(From Panutich MS, Knight BP: Augmentation of pulsus alternans by a premature ventricular beat,* J Cardiovasc Electrophysiol *17:918, 2006.)*

often result in alternative conduction pathways to the LA, such as the margin of the fossa ovalis or coronary sinus ostial connections. Shortening of the IACT via bi-atrial epicardial pacing after coronary artery bypass grafting has been shown to decrease the incidence of AF as well as to improve pulmonary capillary wedge pressure and cardiac output. The complex interplay of atrial hemodynamics and geometry on IACT and susceptibility to arrhythmia warrants further study.

Premature Contraction

Cardiac arrhythmias generally considered benign in nature, such as premature atrial contractions (PACs) or premature ventricular contractions (PVCs), may still have important hemodynamic consequences and therefore warrant therapy. The stroke volume of a given ectopic beat is proportional to its prematurity, with blocked or nonconducted PACs resulting in zero stroke volume. In normal conditions, a temporary loss or decrease in cardiac output is unlikely to result in clinical deterioration. However, in patients with underlying cardiomyopathy, blocked PACs may further impair cardiac efficiency.

Closely coupled PACs result in incomplete ventricular filling and lower-than-usual left ventricular end-diastolic volume. Immediate postectopic beats, however, demonstrate augmented filling and, thus, increased stroke volume. In addition, postextrasystolic potentiation, which is the increased contractility seen in postectopic beats, may further enhance cardiac output. Hemodynamic studies have shown that in the majority of patients with PACs, cardiac output is not significantly changed.[9] In those with more frequent PACs, however, cardiac output may decrease by as much 25%.

The effect of PVCs on LV stroke volume is often more profound than that of PACs. The shortened end-diastolic filling time as well as the compensatory pause before the postectopic beat can set up profound changes in LV contractility, such as those seen in pulsus alternans (Figure 18-2). Similar to the effect of PACs, the immediate effect of PVCs on arterial blood pressure is related to the coupling interval of the ectopic beat, with extremely short-coupled PVCs often resulting in no discernible arterial pressure. The site of origin of PVCs, on the other hand, does not appear to affect the relative cardiac output.[10]

Frequent PVCs can lead to deterioration of cardiac function in an otherwise structurally normal heart. Patients with the highest percentage of PVC beats (>20% of total daily beats) show evidence of reverse LV remodeling, reduced ejection fraction, and a greater amount of mitral regurgitation compared with those with infrequent PVCs. Over time, these patients may show evidence of progression of heart failure, with worsening New York Heart Association (NYHA) functional class, elevated brain natriuretic peptide, and elevated baseline heart rate (HR). The mechanism for LV dysfunction with frequent PVCs is likely multifactorial. In patients whose PVCs originate in the right ventricular outflow tract, the left bundle branch block (LBBB)–type beat results in septal dyskinesia as well as abnormal basal-to-apical ventricular activation. Cumulatively, these effects, over time, may lead to inefficient myocardial contraction, with progressive LV stiffening, elevated LV end-diastolic pressure, and ventricular dilation. Closely coupled PVCs cause calcium release, which results in postsystolic potentiation and improvement in ejection fraction in the beat immediately thereafter. In the long term, however, chronic calcium overload might result in cellular dysfunction and worsening of cardiac performance. The cause of LV dysfunction is likely unrelated to elevated HR, as mean HR has not been found to significantly affect the degree of ventricular dysfunction in patients with frequent PVCs.[11]

Reversal of adverse hemodynamic and ventricular remodeling effects of frequent PVCs is possible with the use of antiarrhythmic medications or catheter ablation targeting the PVC focus.[12,13] A randomized, controlled study examining the use of class IC antiarrhythmic drugs to suppress asymptomatic or minimally

symptomatic PVCs in patients after myocardial infarction was terminated early because of increased mortality in the treatment arm.[14] The impact of these medications on mortality among patients without coronary disease has not been well studied.[15] Studies of catheter ablation for frequent, monomorphic PVCs in patients with structurally normal hearts have shown the most common site of origin to be the outflow regions of the right ventricle (RV) and the LV or, more rarely, in the posteroseptal region of the LV chamber.[16] Acute and midterm success rates for catheter ablation of these foci are excellent, although no long-term, prospective data are yet available. Recently, catheter ablation of post-infarction PVCs in patients with ischemic cardiomyopathy and greater than 5% daily PVC burden was shown by cardiac magnetic resonance imaging to be highly successful with an improvement of cardiac function to near-normal in patients without high-density scar.[17] While these data demonstrate that elimination of the PVC focus results in reversal of LV dilation and improvement of ejection fraction (EF), no evidence that this has a beneficial impact on mortality has yet been presented.

Atrial Fibrillation

The atrial chamber serves as a conduit between the venous bed and the ventricles. More than that, however, atrial systole also contributes importantly to ventricular filling. Early animal studies found that atrial systole increased ventricular filling by roughly 35% and that the magnitude of the effect depended on both the strength of the atrial contraction as well as relative timing during ventricular diastole.[18] In addition to augmenting forward ventricular stroke volume, atrial systole is also important in maintaining a low mean atrial pressure by allowing properly timed closure of the mitral valve during LV diastole (Figure 18-3). The contribution of atrial systole appears to be particularly important at higher heart rates.

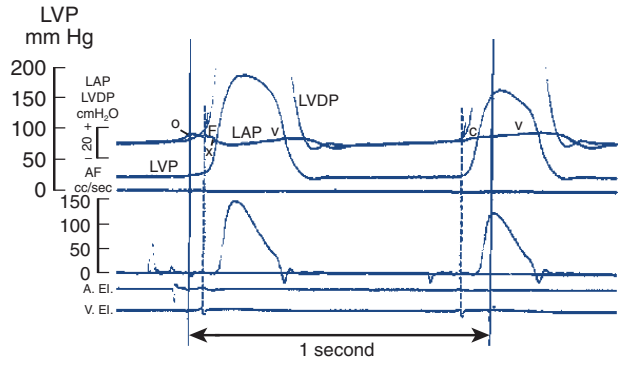

FIGURE 18-3 Effect of atrial systole on mean left atrial pressure (*LAP*) and left ventricular stroke volume. The first ventricular contraction in the tracing is preceded by atrial systole, whereas the second is not. Note the increase in LAP as well as the decrease in left ventricular pressure (*LVP*) that occurs with the loss of atrial systole in the second beat. *LVDP*, Left ventricular diastolic pressure; *A. EI*, left atrial bipolar electrogram; *V. EI*, left ventricular bipolar electrogram. *(From Mitchell JH, Shapiro W: Atrial function and the hemodynamic consequences of atrial fibrillation in man,* Am J Cardiol *23:556–567, 1969.)*

Loss of Atrial Systole in Normal Hearts

The occurrence of AF can have significant hemodynamic consequences in structurally normal hearts. The irregularity of the rhythm, independent of HR, has been shown to decrease cardiac output in experimental models.[19] The most likely explanation for this finding is that beat-to-beat changes in ventricular filling alter myocardial contractility via the Frank-Starling mechanism. The beats with longer R-R intervals do not entirely compensate for those beats with short R-R intervals, and an overall loss of cardiac output ensues. A second possible mechanism for this finding is that sudden changes in ventricular cycle length cause inefficient ventricular mechanics and wasted energy because of incomplete cellular restitution during an abbreviated ventricular diastole. In support of the independent deleterious effect of heart rate irregularity, a small trial of atrioventricular junction ablation in patients with chronic AF and a normal range of HR (60 to 100 beats/min) showed improvement in EF and heart failure symptoms at 1-year follow-up. In contrast, relative regularization of the R-R intervals using ventricular rate-smoothing algorithms in patients with AF and permanent pacemakers has failed to show significant symptomatic improvement.[20]

Incessant rapid ventricular rates during AF can lead to ventricular dysfunction and progressive congestive heart failure (CHF). Hemodynamic changes, characterized by markedly elevated ventricular filling pressures and impairment of LV contractility, are seen after as little as 24 hours of rapid ventricular pacing in animal models. As cardiac output diminishes, systemic vascular resistance is typically increased, and mitral regurgitation may develop as a consequence of increased afterload. Calcium overloading of myocardial cells during chronic tachycardia may also lead to impairment of LV relaxation and progressive diastolic dysfunction. With ongoing high-rate pacing, ventricular filling pressures continue to rise with a plateau at about 1 week. Cardiac output may continue to deteriorate for up to 5 weeks, with eventual development of symptoms of CHF.[21]

Unique to the tachycardia-induced cardiomyopathy of AF is the rapid and dramatic recovery of LV function with restoration of sinus rhythm. Animal models have shown that within 48 hours after termination of pacing, mean arterial pressures, cardiac output, and peripheral vascular resistance normalize. Left ventricular EF recovers after 1 to 2 weeks; however, LV volumes may take up to 3 months to return to baseline because of extensive ventricular remodeling. Similarly, human studies of rapid AF have shown that restoration of normal sinus rhythm with direct-current cardioversion (DCCV) results in early return of atrial transport (days) and delayed recovery of LV function (weeks). The delayed improvement in global cardiac function following DCCV suggests that LV stroke volume depends significantly on the reversal of intrinsic cardiomyopathy from calcium overloading rather than from the immediate restoration of atrial systole.

Neurohormonal activation during AF may have additional deleterious hemodynamic effects in patients with otherwise normal cardiac function. HR irregularity and sustained tachycardia lead to increased sympathetic nerve activity. This, in turn, may result in an increase in right atrial pressure and decreased systemic blood pressure because of cardiopulmonary baroreceptor activity (Figure 18-4).[22] Prolonged neurohormonal activation with elevated levels of catecholamines and angiotensin II may promote long-term structural changes to the LA because of atrial fibrosis.[23] In addition, atrial stretch from chronically elevated pressure is thought to activate cardiac mechano-receptors, which, in turn,

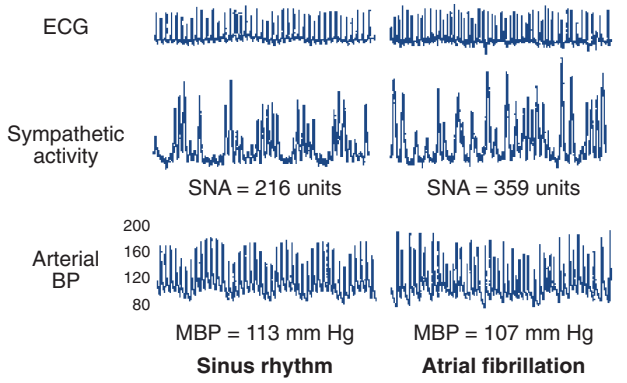

FIGURE 18-4 Surface electrocardiogram (*ECG*), sympathetic nerve activity (*SNA*), and blood pressure (*BP*) tracings from a patient during normal sinus rhythm and atrial fibrillation. SNA increased during atrial fibrillation compared with normalsinus rhythm. *(From Chen J, Wasmund SL, Hamdan MH: Back to the future: The role of the autonomic nervous system in atrial fibrillation,* PACE *29:413–421, 2006.)*

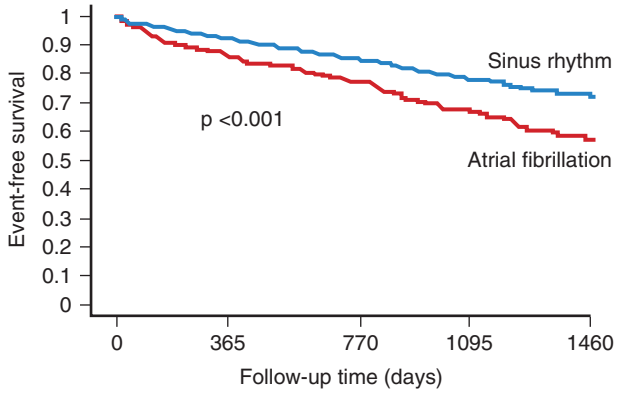

FIGURE 18-6 Effect of atrial fibrillation on survival in patients with severe left ventricular dysfunction. Kaplan-Meier event-free survival curves for the endpoint of all-cause mortality comparing those with atrial fibrillation (*red line*) and those patients in sinus rhythm (*blue line*) at baseline in patients with ejection fraction (EF) ≤35%. *(From Dries DL, Exner DV, Gersh BJ, et al: Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: A retrospective analysis of the SOLVD trials,* J Am Coll Cardiol *32:695–703, 1998.)*

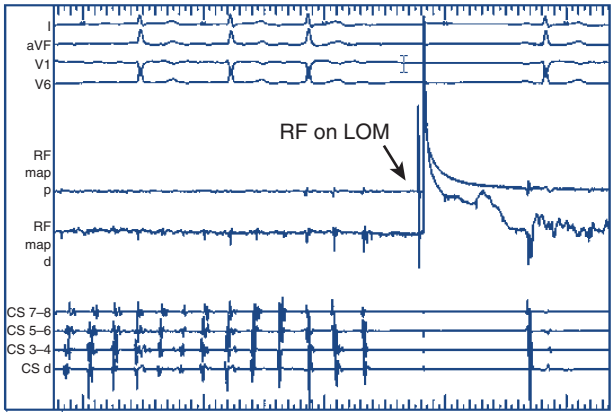

FIGURE 18-5 Demonstration of catheter stimulation of vagal nerve fibers on the ligament of Marshall (*LOM*) during catheter ablation of atrial fibrillation (AF). Atrial asystole occurred immediately after catheter positioning with subsequent termination of AF during radiofrequency (*RF*) ablation.

leads to increased cardiac vagal activity. Vagotonic effects in the cardiac conducting system include a shortening of the atrial effective refractory period, which is conducive to the initiation and maintenance of AF.[24] Interestingly, catheter ablation of the vagal nerve fibers during pulmonary vein isolation (PVI) may reduce the recurrence of AF after ablation, perhaps because of attenuation of these adverse parasympathetic effects (Figure 18-5).[25]

Loss of Atrial Systole in Diseased Hearts

Both systolic and diastolic dysfunction of the LV may lead to LA dilation and increased dispersion of refractoriness because of the stimulation of stretch-activated receptors. This, in turn, leads to a high prevalence of AF in both these disease states. The occurrence of AF is related to the degree of systolic dysfunction as well as CHF functional classification, with a prevalence of up to 50% in patients with NYHA class IV symptoms. About 25% of patients with new diastolic CHF present with recent-onset AF with rapid ventricular rates.[26] The loss of atrial systole in this setting leads to a compensatory rise in LA pressure to maintain cardiac output. In addition, the presence of rapid ventricular rates further shortens diastolic filling of the LV. New-onset AF in patients with previously well-compensated CHF may lead to a functional deterioration because of a reduction in cardiac output, increase in LA size, and pressure, and worsening of mitral regurgitation. The occurrence of AF in patients with LV dysfunction has been independently associated with mortality in multiple clinical trials (Figure 18-6).[27,28]

The prevalence of AF is greater in patients with valvular heart disease. In patients with mitral stenosis (MS), in particular, the occurrence of AF may have significant deleterious effects because of the abbreviated diastolic filling times from rapid, irregular ventricular rates. The effect of the loss of atrial systole during AF in patients with MS is less clear. With severe stenosis, loss of early diastolic filling occurs despite elevated LA pressures. In patients with mild or moderate MS, atrial systole makes a greater contribution to ventricular filling, and its loss during AF may have more profound hemodynamic consequences (Figure 18-7).[29] Concomitant restoration of sinus rhythm during surgical or percutaneous correction of MS has been shown to result in further improvements in symptom status, exercise capacity, and quality of life.

Hemodynamic Consequences of Catheter Ablation for Atrial Fibrillation

Patients with AF who undergo serial electrical DCCV have shown a reduction in LA size after restoration of normal sinus rhythm. Similarly, patients who undergo PVI and maintain sinus rhythm

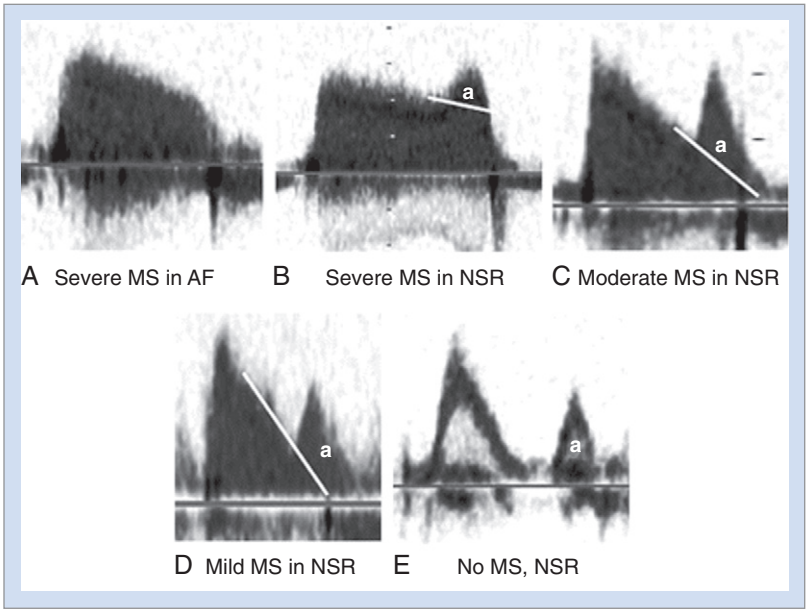

FIGURE 18-7 The relative contribution of atrial systole to ventricular filling with varying degrees of mitral stenosis (*MS*). Echocardiographic Doppler recordings of mitral inflows are shown. *A* demonstrates mitral flows with loss of a wave during atrial fibrillation (*AF*). *B* through *D* show the increasing proportion of atrial filling from atrial systole with less severe forms of MS during normal sinus rhythm (*NSR*). *(From Karthikeyan G: The value of rhythm control in mitral stenosis,* Heart *92[8]: 1096–1101, 2006.)*

at follow-up are shown to have reduced LA volumes compared with patients with recurrent AF.[30] Despite extensive radiofrequency ablation within the LA, PVI does not seem to result in a deterioration of atrial contractility. Small studies measuring LA ejection fraction after PVI have, in fact, shown a significant improvement following ablation.[31] This is an important issue, as a lack of recovery of atrial mechanical function may predispose the patient to thromboembolism despite the elimination of AF. The measurement of LA ejection fraction after PVI may be an inaccurate marker of true LA function, however, as worsened pulmonary venous regurgitation created by ablation of the PV muscle sleeves can result in overestimation of the systolic flow into the LV.

While the amount of radiofrequency ablation time during PVI does not seem to impact LA function, the impact of linear lesions, multiple ablation procedures, or PVI on patients with a preexisting atrial myopathy is unknown. In addition, small studies have suggested that LA ablation may have differential effects on atrial transport function, depending on the burden of AF before the procedure.[32] In patients with persistent or chronic AF, in whom atrial remodeling has occurred, LA systolic function improves after PVI, likely because of the beneficial effects of the restoration of normal sinus rhythm on atrial reverse remodeling. In contrast, patients with paroxysmal AF and preserved LA volumes may show a mild decrease in LA transport function after PVI. What impact these findings have on long-term LV hemodynamics or thromboembolic risk is unknown.

Ventricular Tachycardia

The spectrum of clinical symptoms during VT varies widely—from asymptomatic or minor palpitations despite hours of persistent arrhythmia to immediate and complete hemodynamic collapse at rhythm onset. The hemodynamic tolerability of a given patient's ventricular arrhythmia depends on the interplay between the underlying heart disease and the functional consequences introduced by the rhythm (Table 18-1). After VT onset, an initial decrease in cardiac output may be followed by progressive hemodynamic recovery as the peripheral vascular resistance increases as a consequence of reduced systemic blood pressure.[33] Failure of hemodynamic recovery may result in degeneration of the VT into ventricular fibrillation.

Table 18-1 Baseline and Arrhythmia-Specific Factors Influencing the Hemodynamic Tolerability of Ventricular Tachycardia

BASELINE INFLUENCES	ARRHYTHMIA INFLUENCES
Ejection fraction	Heart rate
Left ventricular dyssynchrony	Incoordinate left ventricular contraction
Myocardial ischemia	Impaired ventricular filling
Autonomic function	Impaired ventricular relaxation
	Loss of atrioventricular synchrony
	Mitral valve regurgitation

The rate of the tachycardia has been identified as one of the most predictive factors of hemodynamic stability during VT.[34] Cardiac output augments with moderate increases in HR over baseline; however, stroke volume diminishes once the rate of tachycardia begins to impair LV filling time. In patients with depressed baseline EF, higher HRs during tachycardia result in an exaggerated loss of cardiac output (Figure 18-8). Antiarrhythmic medications such as amiodarone or procainamide may be used to prolong the tachycardia cycle, thereby converting a nontolerated VT into a hemodynamically stable rhythm. These medications can be used as adjuncts before and during catheter ablation to allow tolerability of sustained VT and to aid mapping during tachycardia.

The mechanism for diminished cardiac output during VT likely varies between patients with preserved baseline EF and those with reduced baseline EF.[35] In patients with normal LV function, a decrease in ventricular cavity size cause by incomplete filling and impaired relaxation may lead to a rapid decrease in stroke volume during VT (Figure 18-9, *A*). In contrast, patients with a reduced EF often have preserved LV cavity size but dyssynchronous ventricular activation (Figure 18-9, *B*). Thus, in addition to the deleterious effects of a sudden increase in HR on ventricular filling, incoordinate ventricular contraction during VT can lead to sudden hemodynamic collapse. Pacing models in humans have demonstrated a greater drop in cardiac output with RV apical stimulation versus outflow tract; however, data regarding the importance of the LV VT exit site on hemodynamics are scarce.[36] Small imaging studies have demonstrated the appearance of functional LV aneurysms during VT with exit sites of the tachycardia often adjacent to these areas.[37] Altered ventricular activation during VT may also lead to papillary muscle dysfunction with subsequent mitral regurgitation. These effects are likely to be more detrimental at higher HR.

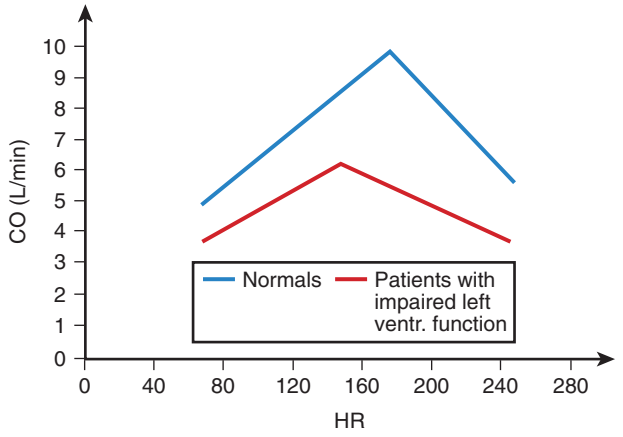

FIGURE 18-8 Relationship between heart rate (*HR*) and cardiac output (CO) in patients with normal hearts and patients with impaired left ventricular function. *(From Steinbach KK, Merl O, Frohner K, et al: Hemodynamics during ventricular tachyarrhythmias,* Am Heart J *127:1102–1106, 1994.)*

Hemodynamic compensation after the onset of VT requires both α-adrenergic vasoconstriction and β-adrenergic augmentation of LV contraction. The response of the peripheral vasculature to diminished blood flow is an initial, rapid activation of α-adrenoreceptors, likely mediated by baroreceptor reflexes. This is followed by a slower, catecholamine-dependent response, which results in both α-mediated vasoconstriction and β-mediated inotropic augmentation of LV function. Blunted HR variability and decreased baroreflex sensitivity, both markers of cardiovascular autonomic modulation, correlate with higher mortality after myocardial infarction, perhaps because of hemodynamic deterioration during ventricular arrhythmia.[38] In addition, blunted sympathetic responses present in older adults may account for an increase in hemodynamically unstable VT seen in this population.

Another important hemodynamic factor during VT is the presence or absence of atrioventricular (AV) synchrony. During VT with ventriculoatrial dissociation, the effective AV interval is either absent or occurs at random durations. The loss of AV conduction during sustained VT results in a decrease in cardiac output and a rise in venous pressures. When atrial activity fortuitously establishes a near-normal AV interval, stroke volume increases and RA pressure falls (Figure 18-10). Two-dimensional and Doppler echocardiographic studies have demonstrated variable mitral valve excursion during VT with AV dissociation, with maximal flow occurring when atrial systole is timed well before the QRS complex.[39] Small studies have examined the effect of synchronized atrial pacing during sustained VT.[40] These studies have shown that re-establishment of a physiologically normal AV interval with ventricular-triggered, sequential atrial pacing during

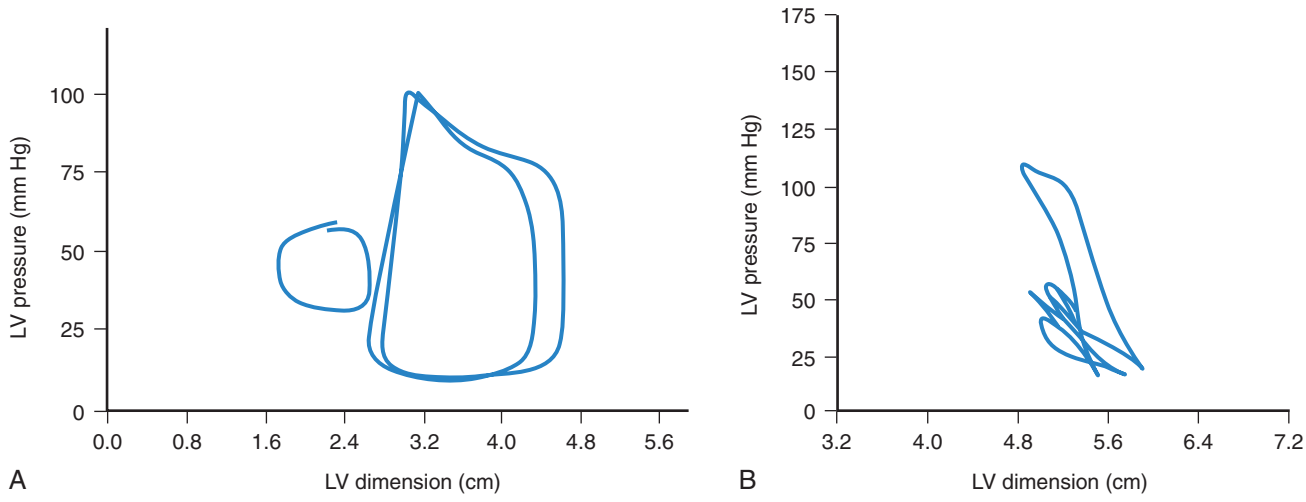

FIGURE 18-9 **A,** Pressure-volume loop during sinus rhythm (*right*) and ventricular tachycardia (*left*) in a patient with normal baseline ejection fraction (EF) demonstrating severely reduced left ventricular (LV) cavity size and elevated LV end diastolic pressure (LVEDP) during tachycardia. **B,** Pressure-volume loop in a patient with depressed EF at baseline. Note the absence of appreciable change in LVEDP but evidence of discoordinated contraction. *(From Lima JA, Weiss JL, Guzman PA, et al: Incomplete filling and incoordinate contraction as mechanisms of hypotension during ventricular tachycardia in man,* Circulation *68:928–938, 1983.)*

VT may have a dramatic effect on the hemodynamics during the arrhythmia.

RV hemodynamic monitoring has been proposed as a method for the discrimination of VT from supraventricular tachycardia (SVT) in patients with implantable cardioverter defibrillators.[41] Small studies using simultaneous pressure monitoring of both ventricles during VT have demonstrated a blunted decrease in systolic pressure and dP/dT of the RV compared with those of the LV; however, a modest correlation does exist. Incorporation of direct hemodynamic monitoring for VT discrimination, however, would require implantation of a separate pressure transducer. Alternatively, local impedance changes at the tip of the RV pacing electrode have been shown to correlate well with acute changes in RV systolic pressure and may present a means of indirect pressure monitoring in future implantable cardioverter-defibrillator platforms.[42]

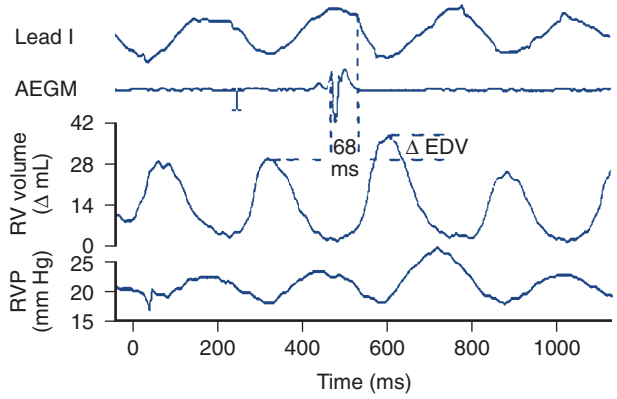

FIGURE 18-10 Recording of an episode of ventricular tachycardia with atrioventricular (AV) dissociation. The presence of atrial activity established an AV interval of 60 ms and resulted in an increase in right ventricular (RV) volume and pressure compared with ventricular contraction in the absence of atrial contribution. *AEGM,* atrial electrogram; *RVP,* right ventricular pressure; *EDV,* end-diastolic volume. *(From Maloney J, Khoury D, Simmons T, et al: Effect of atrioventricular synchrony on stroke volume during ventricular tachycardia in man,* Am Heart J *123:1561–1568, 1992.)*

Hemodynamics During Catheter Ablation

Maintenance of stable VT allows precise mapping of the ventricular chamber, including entrainment pacing to determine critical isthmus sites within the re-entrant circuit. In patients presenting for catheter ablation of scar-related VT, however, the minority of induced arrhythmias are hemodynamically well tolerated.[43] Various methods for augmenting cardiac output during VT exist (Table 18-2).

As discussed previously, loss of synchronization between the atrium and the ventricle can result in rapid hemodynamic collapse during VT. With intact, one-to-one ventriculoatrial conduction, a markedly premature atrial contraction can further worsen cardiac output because of venous regurgitation and paradoxical vasodilation triggered by atrial stretch reflex arcs.[44] Prior studies have shown proper timing of atrial systole to be between 60% and 75% of the R-R interval. When triggered from the right ventricular electrogram, the initiation of atrial pacing during VT can result in dramatic hemodynamic recovery (Figure 18-11). Mechanisms

Table 18-2 Techniques for Maintaining Stable Hemodynamics During Catheter Ablation of Ventricular Tachycardia

Slowing of tachycardia cycle length using antiarrhythmic medications
Synchronized atrial pacing at physiologic AV interval
Augmentation of SVR with vasopressor infusion
Augmentation of CO with intra-aortic balloon pump or percutaneous LVAD

AV, atrioventricular; SVR, *systemic vascular resistance;* CO, *cardiac output;* LVAD, *left ventricular assist device.*

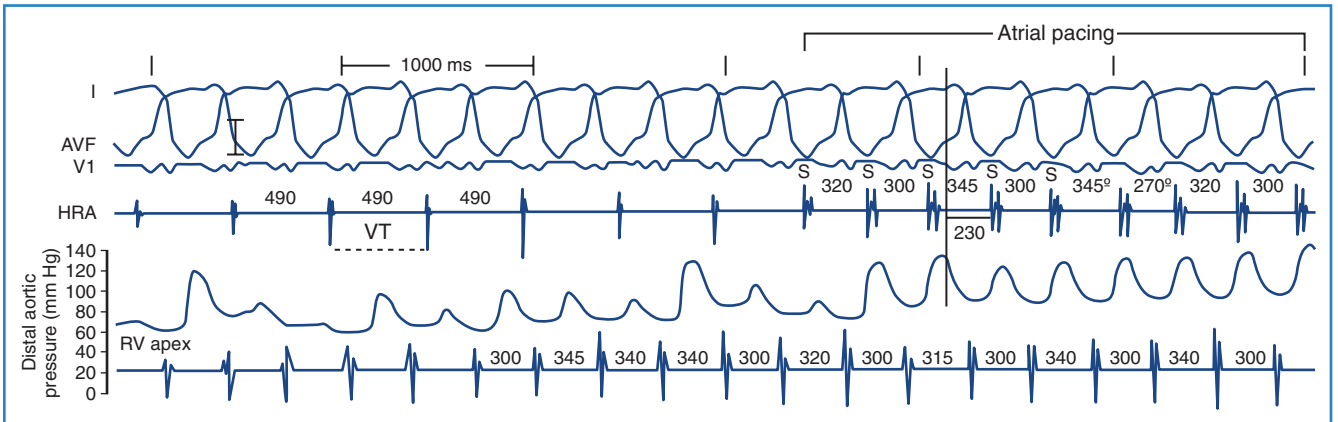

FIGURE 18-11 Effect of atrial pacing on arterial blood pressure during ventricular tachycardia (VT). The panel is arranged with surface electrocardiographic leads I, aVF and VI above an endocardial recording from the high right atrium (HRA), a pressure recording from the distal aorta, and a recording from the right ventricular (RV) apex. On the left side of the panel, the VT has a cycle length of 295 to 320 ms with dissociated atrial activity at a cycle length of 490 ms. Atrial pacing is begun, timed from the electrogram in the RV apex recording. This example shows the optimal coupling interval of the atrial stimulus (S) 230 ms after the onset of the QRS (*horizontal dotted line*), equivalent to 73% of the R-R interval. As a result of atrial pacing, arterial blood pressure increases from a variable systolic pressure between 70 and 125 mm Hg (average 98 mm Hg) to a more consistent pressure between 125 and 145 mm Hg, later averaging 149 mm Hg, which exceeded the systolic pressure in sinus rhythm (120 mm Hg). *(From Hamer AW, Zaher CA, Rubin SA, et al: Hemodynamic benefits of synchronized 1:1 atrial pacing during sustained ventricular tachycardia with severely depressed ventricular function in coronary heart disease,* Am J Cardiol *55:990–994, 1985.)*

behind this effect likely include improved ventricular filling, reduction or elimination of AV valve regurgitation, and maintenance of systemic vascular resistance because of the blunting of atrial stretch receptors.

In the past decade, ablation techniques have evolved for treating "unmappable," hemodynamically unstable VT. These techniques include creation of a voltage map of the ventricular chamber with identification of scar and low-voltage border zones with pacemapping and ablation at putative VT exit sites. While this approach allows treatment during normal sinus rhythm, the elimination of VT with this procedure alone is likely worse than that with the use of entrainment and activation mapping. The addition of peri-procedural mechanical support such as intra-aortic balloon pump or percutaneous left ventricular assist device may allow successful mapping and ablation of VT. Despite initial hemodynamic stability with mechanical support, however, subsequent deterioration may occur because of right ventricular fatigue.[45] Patients who have had catheter ablation using mechanical support for maintenance of cardiac output have a fourfold greater risk of mortality.[37]

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CHAPTER 19

Principles of Clinical Trials

Ruth McBride and April Slee

Introduction

A clinical trial is a medical study in humans. Typically, these studies are conducted to determine the efficacy and the safety of a drug or medical device. Patients are assigned to one of possibly many prespecified treatments, and their outcomes are recorded.

Clinical trials are different from other types of human studies because the exposure or the intervention is prospective and controlled. For example, if the goal of the study is to determine the relationship between niacin use and high-density lipoprotein (HDL), you can do one of the following:

1. Find a sample of people on the basis of some HDL criteria or threshold and gather information about historical niacin use (case-control study)

2. Find a sample of people and collect information about HDL and niacin use over time (cohort study)

3. Control niacin use by randomizing a population to niacin use or no niacin use, and monitor the effect of the randomized treatment on HDL over time (randomized controlled trial [RCT])

In items 1 and 2, the intervention, niacin use, is not under the control of the investigators. Clinical factors such as age, smoking status, and other comorbidities as well as HDL levels may affect the physician's choice to prescribe niacin, so the statement that can be made on the basis of these studies is that niacin use is associated with changes in HDL. In contrast, when the intervention is randomized, factors that could be related to HDL and clinical characteristics that influence the decision to prescribe niacin are ignored. As a result, the statement that niacin use causes changes in HDL is valid. The causal relationship between a test treatment and an outcome is called *efficacy* when it is measured in clinical trials and *effectiveness* when it is measured in a routine care setting. RCTs are the gold standard for evidence of the efficacy of a drug or other intervention, and this evidence is used by the U.S. Food and Drug Administration (FDA) to determine whether new medical treatments should be approved.[1]

Hypothesis Testing

Successful clinical trials begin with a clearly stated hypothesis, or a statement about the effect of an intervention on a population. The design of the study is usually dictated by the hypothesis, which consists of two mutually exclusive statements. Usually, one statement describes a clinically meaningful effect of an intervention (*alternative hypothesis*), and the other describes harm, no effect, or an effect too small to be clinically meaningful (*null hypothesis*). In the spirit of scientific inquiry, the goal is not to prove the alternative hypothesis but to disprove the null hypothesis. Continuing with the niacin example, a hypothesis might be:

> Niacin use raises HDL by at least 10% on average
> *and*
> Niacin use raises HDL by less than 10% or lowers HDL on average

Note that every possibility of a relationship between niacin use and change in HDL is covered by one of these two statements. Note also that the measurement used to evaluate change in HDL is also defined in the hypothesis: Conclusions will be based on the mean percentage change in HDL.

Types of Comparisons

Hypotheses usually involve demonstrating that one treatment is significantly better than another (superiority) or that one treatment is not meaningfully worse than another treatment (non-inferiority, equivalence) (Figure 19-1). When testing an active drug or treatment compared with placebo, the study should be designed to detect the smallest clinically meaningful improvement as well as the cost and side effects of the drug. Placebo-controlled trials should always be superiority trials if the goal is to test the efficacy of the new drug. Sometimes non-inferiority placebo-controlled trials are used to establish the safety of a new drug.

It is important to determine, a priori, if the goal is to prove superiority or non-inferiority. If the new drug has efficacy comparable with that of an accepted treatment but a secondary property such as side-effect profile or cost is reduced, then demonstration of non-inferiority would likely be acceptable. If a study designed as a non-inferiority trial shows superiority, then the superiority of the new drug can be the stated result. However, it is important to remember that a failed superiority trial is not a non-inferiority trial. Non-inferiority trials are much larger than superiority trials by design. The driving factor that makes non-inferiority trials large is the non-inferiority margin, or the amount that the new drug could differ from the accepted one before claiming that the new drug is not worse than the accepted one.

Other Design Parameters

It is possible to be "unlucky" in a clinical trial in two key ways, which means that the result of the clinical trial leads to a conclusion that does not hold in the general population of patients.

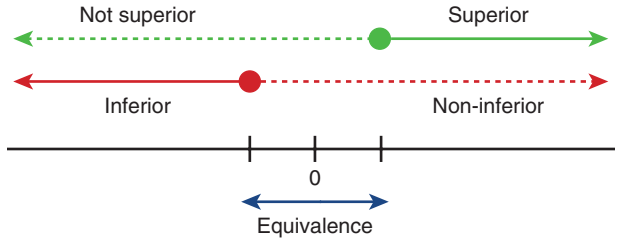

FIGURE 19-1 Types of comparisons.

Table 19-1 Human Phase of Development for a Drug or Intervention

PHASE	GOALS	EXAMPLES OF OUTCOMES
I	Maximum tolerated dose, toxicity, and safety profile	Pharmacokinetic parameters, adverse events
II	Evidence of biological activity	Surrogate markers* such as CRP, blood pressure, cholesterol, arterial plaque measure by intravascular ultrasound, hospitalization for CHF
III	Evidence of impact on hard clinical endpoints	Time to death, myocardial infarction, stroke, hospitalization for CHF, some combination of these events
IV	Postmarketing studies collecting additional information from widespread use of drugs or devices	Death, myocardial infarction, lead fracture, stroke, heart failure, liver failure

CRP, C-reactive protein; CHF, congestive heart failure.
**A surrogate marker is an event that precedes the clinical event, which is (ideally) in the causal pathway to the clinical event. For example, if a drug is thought to decrease risk of myocardial infarction (MI) by reducing arterial calcification, changes in arterial calcification might be used as a surrogate endpoint because these changes should occur sooner than MI, leading to a reduction in trial time. Hospitalization is a challenging surrogate marker because it is not clearly in the causal pathway; hospitalization does not cause MI, but heart failure worsening to the degree that hospitalization is required is in the causal pathway. When hospitalization is used as a measure of new or worsening disease, it is important that the change in disease status and not just the hospitalization event is captured.*

These are given the non-mnemonic names *type I error* and *type II error*. Type I error, often denoted *alpha*, is basically the chance that a difference is detected for the patients in the experiment but that difference does not hold for patients in general. It is common to set this error tolerance to 5%. Type II error, often denoted *beta*, is basically the chance that no difference is detected for patients in the experiment, but a difference exists for patients in general. The power of a study, or 1 minus beta, is basically the chance that if a treatment difference exists, the experiment will detect it.

Primary Outcome

The human phase of development for a drug or intervention is divided into four parts, and each part has unique objectives (Table 19-1). The choice of the outcome measure should be based on the goals of the development phase.

Randomization

Randomization is the process of "randomly" assigning individuals or groups of individuals to one of two or more different treatment options. The term *random* means that the process is governed by chance. Different trial designs may implement randomization in different ways as will be described below. The simplest design randomly allocates study participants between one of two treatment arms. A particular participant is equally likely to be assigned to one or the other arm.

Why Randomize?

The notion of randomly assigning individual observational units to one treatment modality or another was first discussed by R.A. Fisher in the 1920s.

Randomization, then, tends to even out any differences between the study participants assigned to one treatment arm compared with those to the other. The Coronary Artery Surgery Study (CASS) randomly assigned patients with stable class III angina to initial treatment with bypass surgery or medical therapy.[2] If this trial had not been randomized and treatment assignment had been left to the discretion of the enrolling physician, it is likely that these physicians would have selected patients who they believed would be "good surgical candidates" for the bypass surgery arm. This would have led to a comparison of patients who were good surgical candidates receiving bypass surgery with a group of patients who, for one reason or another, were not good surgical candidates receiving medical treatment. It is likely that the medically selected patients would have been sicker, with more comorbidities than the patient selected for surgery. This design would not result in a fair comparison of the two treatment strategies. Randomization levels the playing field.

Intention to Treat

To make randomization work, analysis of RCT data needs to adhere to the principle of "intention to treat." In its purest form, this means that data from each study participant are analyzed according to the treatment arm to which they were randomized, *period*. In the case of the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial, this meant that data from patients randomly assigned to the implantable defibrillator arm were analyzed in that arm, whether or not they ever received the device.[3] Data from patients randomly assigned to the antiarrhythmic drug treatment arm were analyzed with that arm, even if they had received a defibrillator. This may not make obvious sense, and many trial sponsors have argued that their new treatment just could not show an effect if the patient never received the new treatment. However, the principle of "intention to treat" protects the integrity of the trial by removing a large source of potential bias. In a trial to examine the efficacy of a new antiarrhythmic drug for preventing sudden cardiac death (SCD), for example, a sponsor might be tempted to count events only while the patient was still taking the drug. How, they would argue, could the drug have a benefit if the patient was not taking it? But, if, as has happened, the drug exacerbates congestive heart failure (CHF), then patients assigned to the experimental drug would be likely to discontinue taking the drug. And any subsequent SCD or cardiac arrests would not be attributed to the drug. In fact, it could be

argued that the drugs led to a situation where the patient was more likely to die of an arrhythmia.

Stratification and Site Effect

Although randomization is quite effective in evening out differences between populations assigned to one treatment arm versus another, it is not a perfect method. In some instances, important clinical differences have appeared between the two treatment arms. At one interim analysis of the Cardiac Arrhythmia Suppression Trial (CAST) (personal communication), one treatment arm had a markedly lower mean ejection fraction than the other. This difference evened out before the trial was stopped, but if it had not, adjustments would have been required to analyze the data accounting for this very important prognostic difference between the treatment groups.

When an important clinical factor or a potential differential effect of therapy on one group versus another exists, stratification is used to balance the number of patients assigned to each treatment arm within strata. The AVID trial and many other multicenter RCTs are stratified by clinical site. In the case of arrhythmia trials, the skill and experience of the arrhythmia teams or the availability of particular devices at the sites may vary, leading to different outcomes, depending on where the participants are randomized. By stratifying by site, it can be ensured that participants at each site have an equal probability of being assigned to surgical treatment versus medical treatment. Other important differences may vary by clinical site, for example, in surgical trials where the skill and experience of the surgeon can have an effect on the outcome.

Some investigators get carried away with the concept of stratification to try to design randomization in such a way that all possible factors are balanced. It is easy to design a trial with too many strata. Take, for example, a trial stratifying on the basis of ejection fraction at baseline (<30%, 30% to 50%, and >50%) and a required history of myocardial infarction (MI) being "recent," that is, within the past 6 months, or distant, that is, more than 6 months ago. With this, six strata have been created, a reasonable number for a sample size of, say, 200 or more subjects, randomized to one of two treatment options (Table 19-2). But if the decision is made to stratify by site, with 10 sites, for example, more strata than expected patients would be created. It has been shown that as the number of strata in a conventional randomization design is increased, the probability of imbalances between treatment groups is, in fact, increased as well.[4]

It is important to adjust for stratification factors in the analysis of clinical trials. Failure to adjust for the "nonrandomness" in the randomization will influence the results.

Table 19-2 History of Myocardial Infarction

EJECTION FRACTION	<6 MONTHS AGO	>6 MONTHS AGO	OVERALL
<30%	25: 12 active and 13 placebo	25: 13 active and 12 placebo	50
30%–50%	37	38	75
>50%	38	37	75
Overall	100	100	200

Types of Randomization Designs

The most commonly used and most straightforward randomization design is a "permuted block" design. Using this method, a trial for any number of treatment arms can be designed and the proportion of patients assigned to each treatment arm can be set. Randomization does not mean that it is necessary to have equal numbers of patients assigned to each arm. In many trials of new drugs, in order to gain information on side effects in early-phase studies, the sponsor may decide to allocate twice as many patients to the new treatment as to the control (a 2:1 allocation).

Permuted block randomization can best be described as constructing small decks of cards, shuffling the cards, and then dealing them out. For a design with two treatment options, two decks with two types of cards (say, hearts and clubs) would be created. For equal allocation, each deck would contain an equal number of hearts and clubs. The size of each deck, or block, would depend on stratification and other factors. The deck is shuffled and as each patient is randomized, the next card is dealt. When all of the cards in the deck have been dealt, a new deck is shuffled and the process is repeated. The size of each deck needs to be an even multiple of the number of treatment arms and can vary over the course of the randomization sequence. In actual practice, the size of the decks is determined in advance, and the decks are shuffled in advance.

Permuted block designs can lead to the same problems as with too many strata. For this reason, adaptive randomization is sometimes used. Several types of adaptive designs exist. Basically, the next randomization assignment is dependent, in some way, on the characteristics of the patients who have been randomized so far. Baseline adaptive techniques adjust the probabilities of assigning the next patient to one treatment arm or the other on the basis of the baseline characteristics of the patient compared with other patients already randomized.[5] In the study design described above where randomization will be stratified by the class of angina, recent or distant history of MI, and ejection fraction, the objective is to keep a balance of treatment assignments within each stratum. So, as each patient is randomized, the randomization algorithm will look at the existing balance in that stratum and assign treatment on the basis of a biased coin toss.

Blinding or Masking Therapy

Ideally, all clinical trials should be double-blind or double-masked studies. That is, neither the patient receiving the treatment nor the medical staff treating the patient should have knowledge of the patient's treatment assignment. In this way, bias in outcome assessment can be minimized. If the patient is aware of receiving the experimental treatment, he or she may be more likely to report side effects than those who believe that they are receiving placebo or do not know which treatment they are receiving. Similarly, an investigator who knows that the patient has received the experimental treatment may be more likely to see a benefit than if the investigator believes that the patient is receiving a placebo.

Ethically and logistically, many trials cannot be conducted as double-blind trials. For example, trials involving surgical intervention for only one of the study arms cannot, in almost all cases, be conducted as a double-blind study. In a single-blind trial, the patient is unaware of the treatment assignment, but the treating physician is aware of the assignment. Trials of pacemakers might be conducted in a single-blind fashion where participants know

that they have a pacemaker but are unaware of the programming mode.

Since the purpose of blinding or masking of therapy is to minimize bias in outcome assessments, a strategy to minimize bias in an unblinded trial is to make use of a blinded event assessor. The Stroke Prevention in Atrial Fibrillation studies used a neurologist unassociated with the routine care of the patient to evaluate the patient in the event that symptoms of stroke were reported. The blinded event assessor was presented with medical records masked to therapy, in this case warfarin versus aspirin. The blinded event assessor evaluated the patient and drafted a narrative based on his or her clinical findings.

In a triple-blind study, the patient, the treating medical staff, and the data coordinating center are all masked to individual treatment assignments. Where the data coordination is being provided by a commercial sponsor, the sponsor can elect to remain blinded to interim study results because of the apparent conflict of interests in making decisions regarding study endpoints. Clinical trials rely on scientific equipoise. As soon as a trend favoring one of the treatment assignments is evident, sponsors and clinicians may make decisions different from what they would make if they had no knowledge of the emerging trend. Early trends often do not pan out, and the experiment can become compromised. It is advisable, whenever possible, to keep the sponsor blinded.

Accuracy of Measurement and Event Ascertainment

Endpoint selection is one of the most critical components of trial design. In considering primary and secondary outcomes, the following principles are important to remember:

1. The outcome should be measurable.
2. It should be possible to define the outcome clearly and unambiguously.
3. The experimental treatment should have a measurable effect on the outcome measure, and the outcome should be important to the patient population being studied.

Principles of Outcome Selection

The Outcome Should Be Measurable

In designing a trial to decrease the frequency of episodes of paroxysmal arrhythmias, measurement of the outcome would be a challenge. From an experimental standpoint, every study participant should be outfitted with a telemetry system that would constantly monitor heart rhythm and report any episodes of the arrhythmia. This is not possible practically. Thus, most studies of antiarrhythmic drugs have used 24-hour Holter recordings as a way of sampling the patient's heart rhythm and concluding whether the frequency of episodes of atrial fibrillation (AF) or ventricular tachycardia (VT) has decreased or the episodes have stopped.

The FDA now advocates the use of patient-reported outcomes in the case of chronic diseases. Patient-reported outcomes include standardized quality-of-life questionnaires, symptom questionnaires, and electronic or paper patient diaries. The outcome measure is usually a computed scale derived from the patient report. One motivation for the use of such instruments is that it enables the patient to contribute to determining whether the treatment is working or not.

To be convincing as measurable outcomes, such questionnaires need to be validated. Some key components to validation of such questionnaires are as follows: (1) Does the instrument reliably measure what it is intended to assess? In a questionnaire used to assess pain or discomfort, the instrument needs to reveal the presence and intensity of pain as reported by a variety of patients. (2) Are the results reproducible? That is, if the questionnaire is administered several times to a person with the same level of pain or discomfort, will the questionnaire give similar results?

The Outcome Should Be Unambiguously Defined

The American College of Cardiology (ACC) has devoted much effort to standardizing the definition for MI. Whereas earlier trials such as CASS had to define MI for their trials, current studies refer to the ACC definition.[6]

Suppression of arrhythmia as an endpoint is not clearly defined unless the investigators add to the protocol specifics such as the following definition from CAST:

- ≥80% suppression of the frequency of ventricular premature depolarizations (VPDs) and
- ≥90% suppression of episodes of unsustained VT
- As measured on a 24-hour Holter monitor[7]

The Outcome Should Be Important to the Patient Population

For a patient with AF, what is important? Clearly, avoiding death or disability caused by a stroke or other cardiovascular cause is most important. Thus, some of the most critical trials in patients with AF were the Atrial Fibrillation Follow-up Investigation of Rhythm Management trial (AFFIRM), which examined the effect of two treatment strategies, heart rate control, and restoration of sinus rhythm, to prevent overall mortality in patients with atrial fibrillation,[8] and the Stroke Prevention in Atrial Fibrillation (SPAF),[9] Aspirin vs. Warfarin Standard Dose (AFASAK),[10] and other trials of anticoagulation to prevent stroke.[11] Then, is functional status important? The AFFIRM study attempted to measure change in functional status using the New York Heart Association (NYHA) functional class scale, Canadian Cardiovascular Society Angina Classification, a Mini-Mental State Examination, and a 6-minute walk test.[12] The investigators in the study were able to detect a difference in functional status related to the presence or absence of AF. In contrast, inflammatory measures such as C-reactive protein and degree of stenosis may be good measures of disease burden, but changes in these measures may not be identifiable to patients.

Overreads and Clinical Endpoint Adjudication

As clinical trials have to reach further and include many more sites to recruit enough patients, the study is dependent on the clinical judgment of a large number of physicians to assess study endpoints. In the AFFIRM trial, for example, the more than 200 clinical sites were located primarily in cardiology practices. One of the important endpoints was cardioembolic stroke. Although

the patients were, of course, treated by neurologists, the study physicians were, in almost all cases, not neurologists. To make sure that all of the strokes included in the study-defined endpoint met the protocol definition for cardioembolic stroke, the investigators used a clinical events committee (CEC) to evaluate each potential study endpoint by reviewing collected medical records. These records were masked to anything that could reveal the patient's assigned treatment arm (rhythm or rate control). Two separate CEC neurologists examined records that included imaging reports, hospital discharge summaries, and a narrative discussion provided by the local physician. Concordance was required between two CEC neurologists or consensus by the committee in order for an event to be "ruled in" (E. Nasco, personal communication). In the final analysis, only events confirmed by the CEC were included. In the AFFIRM trial, only 171 of 247 reported strokes were ruled in. In the Trial With Dronedarone to Prevent Hospitalization or Death in Patients with Atrial Fibrillation (ATHENA), an events adjudication committee categorized the causes of death using a modification to a previously published classification scheme that standardized the criteria for determining arrhythmic, nonarrhythmic cardiac, noncardiac vascular, or noncardiovascular death.[13]

Some of the reasons to use CECs are (1) The assessment of an endpoint event is done without the knowledge of treatment assignment, and (2) the assessment is done consistently by a small group of trained physicians. The use of CECs can thus minimize bias and inconsistency in determining whether a study-defined endpoint has occurred.

Interim Analyses and Adaptive Designs

In the simplest approach, a clinical trial would be designed, the trial would be launched, and participants would be enrolled, treated, and followed up. Follow-up would continue up to a prespecified endpoint, such as 6 months after the last patient was treated. While the trial is ongoing, data would be collected, but no one would look at the results. At the end of the trial, the data would be completed, closed, and analyzed. However, for many trials conducted these days, investigators have valid reasons to look at the data even while the trial is ongoing. In the case of experimental treatments, the sponsor may want an independent group monitoring the trial to make sure that participants are not exposed to undue risk or harm from the adverse effects of the treatment. In the case of trials with long-term follow-ups, it may be possible to reach a reasonable conclusion about the treatment that is being evaluated without continuing the trial to its planned conclusion. For these reasons, many trials are planned with "interim analyses." Further, regulatory agencies have, in some situations, strongly recommended the use of external, independent monitoring committees, commonly referred to as Data Monitoring Committees (DMCs) or Data and Safety Monitoring Boards.[1,14] Although the specific charge of DMCs will vary from one trial to another, in general, DMCs are charged with monitoring the trial for the following reasons:

- To protect the safety of the participants
- To protect the scientific integrity of the trial
- In some cases, to monitor for unexpected early demonstration of conclusive efficacy or lack of efficacy

The DMC works in an advisory capacity to the sponsor. That is, the committee makes recommendations to the sponsor about continuing the trial as designed, continuing with changes, or prematurely discontinuing the trial. The actual decision to continue, change, or discontinue is made by the sponsor; however, it is rare that a sponsor would not accept the recommendations of the DMC.

Much has been written about DMCs, which are being used more frequently for late phase II and phase III trials. Ellenburg and colleagues make the following recommendations regarding when a DMC should be used[15]:

- Phase IIb, III, and IV in life-threatening diseases or in diseases causing irreversible and serious morbidities
- Trials of novel treatments with potentially life-threatening complications
- Trials in emergency settings where individual consent is not possible
- Trials involving vulnerable populations (e.g., children)

In some other situations such as early-phase trials where dose selection would best be made by a group of experts independent of the investigators or sponsor, an independent DMC might be recommended.

In some trials, it is not practical to implement the interim reviews of data, for example, trials with short-term outcomes such as surgical studies of 30-day mortality rate that have a quick enrollment period. If it is expected that all or most of the patients would be treated in a short period, all of the patients would have been treated by the time data could be collected and reported to a DMC for review; the DMC would not be able to protect patients from exposure if the treatment shows evidence of harm. This is why some device trials are deliberately designed with a pause in recruitment. Such a pause would allow a DMC to examine the results of treatment of the first cohort of patients before proceeding to treat more patients.

For a DMC to adequately monitor a trial, the committee needs information that is sufficiently complete and current so that valid conclusions about the study can be made. The DMC's most important responsibility is to ensure the safety of the trial participants. For this, complete reporting of adverse events is vital. The evaluation of safety will be made by the DMC in the context of risk/benefit. That is, the DMC and the trial sponsor may be more tolerant of moderate to severe adverse events *if* the benefit expected is great and the disease is severe. Cancer therapies commonly have a more severe adverse effect profile than do cardioprotective drugs such as β-blockers or statins.

Reports to DMCs should be succinct but give a clear and complete picture of the risks and benefits of the study treatment. It is important to understand that DMC reports are not the same as full, final study reports. They should be focused on the areas that the DMC is charged to review, such as enrollment and performance of the clinical sites in treating and monitoring appropriate study participants, safety of the treatment, adherence of patients to treatment protocols as it would affect the power of the trial, and important measures of efficacy.

The practicalities of collecting and cleaning study data put constraints on the DMC report. While the DMC needs to have data that are as accurate and complete as possible, access to

information that is as current as possible is also important. It is common practice to create a snapshot of the study data to prepare reports for the DMC. When to create that snapshot in relation to the planned meeting depends on the mode of data collection and other logistic issues. In general, the snapshot should be made no more than 6 weeks in advance of a DMC meeting where paper case report forms are used and no more than 4 weeks in advance of a DMC meeting where electronic CRFs are utilized.

During the CAST I study, the DSMB was concerned that the reports contained information about all of the deaths that had occurred. For this reason, the coordinating center organized and performed an "events sweep." During a 2-week period, research coordinators at each of the clinical sites were instructed to call all of their participants to find out, primarily, if they were still alive.[16] This ensured that the DMC had current (within the past 4 weeks) follow-up data on all randomized participants. This information supplemented the data from a normal database freeze.

Interim monitoring can be classified into two types. (1) In the first type, the DMC is solely concerned with the safety of the patients in the study. Safety data are reviewed periodically during the study, and the DMC may recommend that the trial stop for qualitative safety reasons or futility if something about the execution of the trial suggests that the experiment will not be able to test the hypothesis in question. (2) The second type of DMC includes group sequential trials and many adaptive designs; the DMC may stop the study if sufficient evidence of efficacy based on preset stopping rules exists, or the committee may make modifications to the study design.

When the DMC is charged with making recommendations regarding early termination of a trial for early demonstration of efficacy, certain statistical techniques guide the analyses that are presented to the DMC. Several approaches are commonly used. Why are these statistical adjustments made? Recall that the alpha level of a trial is the probability that a particular treatment effect is being observed purely by chance. The more often that a treatment effect is looked for, the more likely it is that it will be seen, even if that effect is not real. For this reason, the *P* value or alpha level is adjusted while taking interim "looks" at the data. The *P* value is not relevant if the trial does not reach a positive conclusion, so the adjustment is based on the efficacy boundary, which is the criterion at any point in time for claiming success. The DMC can recommend stopping for safety at any time, regardless of whether a boundary has been crossed.

In "group sequential" study designs, the trial is designed and conducted assuming a clinically important treatment effect; this is accompanied by a sample size and follow-up to ensure that if things turn out as expected, enough information will be available at the end of the trial to detect that treatment effect if it is present ("power") at the significance level ("alpha") selected. Built into a group sequential design are pre-planned interim examinations of data. At prespecified times, data are analyzed (by treatment group) and a *P* value for the treatment comparison is made. If the results indicate that the treatment is effective with a sufficiently small *P* value, the DMC might recommend that the trial be discontinued and results disclosed.

A number of approaches to the group sequential study design exist. Basically, they each take a different approach to the *P* values or alpha levels that will be used to determine whether or not to recommend curtailment of the trial. At the interim analysis, data are analyzed by the treatment group, and the appropriate statistic is computed. The *P* value associated with that statistic is compared with a prespecified alpha. If the computed *P* value is smaller than the prespecified alpha for the boundary at that look, the DMC might conclude that efficacy has been proven and might recommend that the trial be curtailed. Each time that the DMC formally examines the data, the trial "spends" alpha. This is because the chances that the expected treatment effect is observed by chance alone increase, roughly by the alpha level used as the boundary at that look. So, at the end of a trial, instead of using a *P* value, for example, of 0.05 to determine if the trial was successful, the data would have to result in a slightly smaller *P* value to say that the results were significant.

The various approaches to a group sequential design can best be illustrated by Figure 19-2, which depicts a typical O'Brien-Fleming boundary. The O'Brien-Fleming approach is very conservative at early looks at the data and is less conservative as more information is available. The Pocock approach assigns the same alpha level at each look. The actual shape of the O'Brien-Fleming boundary can be adjusted based on the risk tolerance and objectives of the sponsor. The decisions regarding the number of formal interim analyses and the shape of the boundary are important for management to consider carefully.

The same approach can be taken to monitor for lack of efficacy. While few trials continue long enough to prove "harm," many are designed with guidance for the DMC so that the trial could be curtailed if the experimental treatment is much less effective than expected or the trial is unlikely to show a benefit for the treatment. In this case, a second boundary is selected to monitor for lack of efficacy. The Multicenter Automatic Defibrillator Implantation Trial (MADIT) describes a "triangular" design. In the design of this trial, early examinations of the data should have shown definite harm in order to suggest a recommendation to stop the trial for lack of efficacy. But, as the trial progressed, this boundary for inefficacy approached the boundary for efficacy, that is, if the results were not trending to a sufficiently large benefit, the investigators would not have wanted to continue to the end of the trial. CAST was designed with a symmetric boundary; that is, the alpha level at each interim analysis was the same whether the direction of treatment effect was benefit or harm. CAST I was discontinued early because the results exceeded the boundary for harm. In hindsight, CAST might have been designed

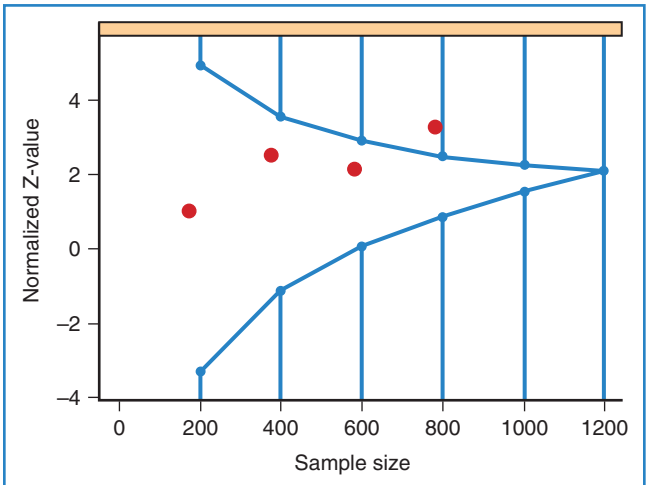

FIGURE 19-2 Normalized *Z* value is the computed statistic that will correspond to a *P* value. The larger the *Z* value, the smaller will be the *P* value. The upper boundary corresponds to efficacy and the lower boundary to lack of efficacy.

with an asymmetric bound, that is, a more conservative boundary for efficacy than for lack of efficacy. As it was, the results were so conclusive that class III antiarrhythmics are no longer used for post-MI ventricular arrhythmias such as those studied in CAST.

Adaptive clinical trials are basically a class of trial where some aspect of the design is modified on the basis of accumulated data within that trial. One of the oldest examples of an adaptive trial is a study to determine the maximum tolerated dose. For this experiment, three patients are started on a low dose, and if no side effects occur, the dose is increased for the next three patients and so on until side effects emerge. The dose for the next three patients is always determined by the result of the three previous patients, so the dose is adapted on the basis of accumulated data. A second example is when phase II is started with placebo compared with high-dose and low-dose medications. The goal is to determine which dose should be taken into phase III. In a traditional model, the investigators stop after phase II, choose the dose to take forward, and begin a new study. An adaptive model might allow the decision to be made within the study or pause for an interim analysis between phases II and III, but enrollment is never stopped (the latter is called a "seamless" trial).

It is not uncommon to test patients in phase II who are from a population different from patients in phase III. For example, phase II might enroll patients with permanent AF, and phase III might enroll patients with permanent or paroxysmal AF. Because the patients are different, the rates observed in phase II are not likely to be correct for phase III. Phase III could be started using the phase II rates, and then after 10% of the information is collected, the sample size calculation could be done again with the rate seen so far in phase III to get a more accurate sample size. Most of these adaptive designs cost something in terms of type I error, and controversy surrounds the interpretation because the design of the experiment is not fixed a priori (although this is true for group-sequential trials as well). The most important point is that adaptations must be specified before the trial begins; adaptive trials are not a remedy for poor planning.

Issues Related to the Conduct of Clinical Trials

Recruitment

In designing a trial, delineating the population to be studied requires careful thought. These definitions will ultimately define the conclusions that can be drawn from the trial. For example, the Physicians Health Study studied 22,017 male physicians in the United States.[17] By excluding women from their study, the investigators were limited in any conclusions that could be drawn from their data as they related to women.

The inclusion criteria define the disease condition to be studied. For example, in CAST, the inclusion criteria stated that potential participants should have had an MI 6 months to 2 years before enrollment and should have demonstrated sufficient ventricular arrhythmia to warrant treatment (≥6 VPDs per hour on a 24-hour Holter monitor). The investigators gave considerable thought to setting a cutoff of 6 or more VPDs per hour. Would 10 or more VPDs have defined a population that would have better benefited from the treatment? Would a cutoff of 10 VPDs per hour have excluded too many patients? The Cardiac Arrhythmia Pilot Study (CAPS) was designed as a feasibility study to see if a long-term trial could be conducted to test the hypothesis that suppression of ventricular arrhythmias in a post-MI population would decrease the rate of arrhythmic and overall death.[18] Data from CAPS provided needed information about the proportion of patients likely to be excluded if a cutoff of 10 VPDs per hour was used.

Exclusion criteria specify (1) participants in whom the planned treatments would be contraindicated, (2) those who would be unlikely to benefit from the planned treatment, or (3) those who could not be adequately followed up to ascertain outcome.

It has been said that as soon as a trial begins, the prevalence of the disease decreases. In some respects, this is true about trials in cardiology. Over the past 20 years, the rate of death from cardiovascular cause has decreased to the point that it is expected that cancer will exceed cardiovascular disease as the primary cause of death in the United States.[19] The number of clinical trials being conducted in the United States has increased in the past 20 years to such an extent that in any community more competition occurs for the pool of available patients. Nearly all large clinical trials have struggled with recruitment.

In recent years, more and more trials have expanded into Europe, Asia, and South America to find sufficient numbers of patients to meet enrollment targets. Global trials certainly have their logistical challenges. But, more importantly, they increase the heterogeneity of the population studied and the background care that participants receive. In the United States, for example, patients with even slightly elevated cholesterol have been treated with statins and other lipid-modifying drugs for many years. While these drugs are available in many nations, they are not as widely prescribed for a variety of reasons, including regional differences in diet and general access to medical care to monitor their use.

The ATHENA trial was a multicenter randomized trial of dronedarone in patients with AF.[20] Patients with paroxysmal or persistent AF were eligible if they were older than 70 years or had at least one risk factor for cardiac complications (arterial hypertension, diabetes mellitus, previous stroke, transient ischemic attack or systemic embolism, enlarged left atrium, or depressed ejection fraction). As the trial proceeded, overall mortality rates were lower than expected. For this reason, the investigators modified the entry criteria to increase the risk profile of patients enrolled. Patients between ages 70 and 75 years were eligible only if they had one or more of the above risk factors for cardiac death. Patients younger than 70 years were no longer eligible.

Adherence

Adherence describes the ability of the trial participants to "adhere to" the study protocol. It includes both their ability to continue to take a prescribed medication or treatment as part of the trial and to come to follow-up visits as well as their participation in any patient-reported outcome measures and other activities that might be part of the study protocol. Inherent in sensible trial design is a buffer for expected lack of adherence. In real life, things happen that prevent participants from taking their medication as prescribed, from attending every follow-up visit, and from having the required blood draws done. The poorer the expected adherence, the higher the number of participants who need to be enrolled and followed up to collect enough information to draw a valid conclusion. The effect on sample size can be considerable. Recruitment of additional participants is expensive. It is a lot cheaper to put efforts to improve adherence than it is to enroll a sufficient number of participants to overcome poor adherence.

In drug trials, adherence to treatment is frequently measured by counting tablets returned at follow-up. This method of ascertaining whether the participant took the study drug as prescribed is an accepted measure, even though it has its problems. Depending on the medication, if participants take 75% or more of expected doses of study drug, they are considered to be "good" adherers.

In the ATHENA study, the study drug was discontinued in 696 (30.2%) of 2301 patients assigned to dronedarone and 716 (30.8%) of 2327 patients assigned to placebo. This trial was designed with 80% power to show a 15% reduction in mortality and hospitalization rates for cardiac cause. If all of the patients had remained on their assigned study drug, the trial could have been completed with far fewer participants.

Conclusion

Well-designed clinical trials are powerful tools for advancing medical science. The conduct of trials presents challenges to the study leadership, sponsors, recruiting sites, and study participants. The true benefit from a clinical trial, however, cannot be realized without clear, accurate, and complete dissemination of the results, whether positive or not.

Medical journals publishing the results of clinical trials have set certain standards for reporting these results. This is been done to prevent the publication of false or misleading reports.[21] Consolidated Standards of Reporting Trials (CONSORT) is an organization that has examined the quality of reporting of medical studies.[22] CONSORT was formed by a group of clinical trialists and journal editors who originally met in 1993 to set a scale for evaluating published results from clinical trials. As a result of their examination, CONSORT has published standards for results manuscripts, which include the following key points:

- Clear definition of the inclusion and exclusion criteria and settings in which participants were recruited
- Clear definition of the primary and secondary objectives and outcome measures, including any measures taken to enhance the quality of the measures
- Description of treatment allocation and randomization as well as masking of therapy
- Succinct summary of participants as they flowed through the study from recruitment through randomization, treatment, follow-up, and drop-out
- Description of the sample size determination, interim analyses, and statistical method for comparing treatment groups and for measuring effect size
- Summary of baseline and demographic characteristics of the participant population by treatment group

The primary results from the ATHENA trial is a good example of adherence to CONSORT. In addition to the points listed above, the publication includes a study diagram clearly depicting the disposition of all patients randomized.

The real result of clinical trials research is improvement in the way that diseases are treated and prevented. If the results of a clinical trial are not published or disseminated in a trustworthy manner, it is unlikely that the practice of health care professionals will change on the basis of trial results. It has been estimated that it takes, on average, 17 years for the results of a clinical trial to bring about an effect in general practice.[23] The Beta-blocker Heart Attack Trial (BHAT) in 1982 showed that treatment with β-blockers after an MI would significantly decrease mortality in this at-risk population.[24] And yet, the widespread use of β-blockers did not become the standard of care until the AHA/ACC published guidelines for the use of β-blockers in 1996 that this class of drug became standard of care.[25,26] The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) trial was a National Heart, Lung, and Blood Institute sponsored trial of antihypertensives and lipid-lowering treatment to reduce the rate of cardiac death and nonfatal MI in participants with hypertension and at least one other risk factor for cardiovascular disease.[27,28] The trial showed that aggressive treatment with antihypertensives could significantly decrease the mortality rate in this population. Following the conclusion of the trial and the publication of the initial results, the study group for ALLHAT embarked on a project to focus on the dissemination of the study results in such a way as to maximize the impact of the trial's results.[29] Their dissemination plan included the usual press releases, presentations at national medical meetings, and refereed articles in major medical journals. In addition, they targeted the "determinants of clinician behavior" to communicate more directly with clinicians about the implications of the ALLHAT results. They took their message to places where physicians routinely went to get information and conducted numerous in-person, interactive sessions. Their approach included, among other strategies, Web forums, online continuing medical education sources, and other more immediately available media.

Thus, if medical practice is to improve, well-controlled as well as well-conducted clinical trials and clear, accurate, and complete reporting of their results are needed.

All references cited in this chapter are available online at expertconsult.com.

CHAPTER 20

Clinical Electrophysiology Techniques

John D. Fisher and Andrew Krumerman

The term *technique* implies an objective. The electrophysiological techniques described in this chapter have the objective of determining whether a patient's condition is electrophysiologically normal, adequate, or abnormal. Tests have been developed to assess the multiple electrophysiological levels of the heart ranging from the sinus node to the atrium, the atrioventricular node (AVN), the His-Purkinje system, the ventricle, and associated structures such as pulmonary veins. Abnormalities that can be associated with bradycardias or tachycardias are sought to be identified at any of these levels. Other chapters in this textbook detail the various types of abnormalities that can be found at each of these levels as well as appropriate therapies for them. This chapter will cover the elements of a *complete electrophysiological study* (EPS).

Indications for an Electrophysiological Study

Not everyone with a known or suspected arrhythmia needs an EPS. A simple electrocardiogram (ECG) or one of the many noninvasive tests may provide definitive information. Guidelines on the indications for EPS and ablation are published from time to time by the American College of Cardiology and the American Heart Association with input from the Heart Rhythm Society.[1] These guidelines are likely to be updated in the near future.

Preparing for an Electrophysiological Study

The Electrophysiologist

Performing an EPS is not a routine procedure but must be tailored to the individual patient. As the study proceeds, the electrophysiologist must recognize the implications of each finding and adjust the remainder of the study accordingly. All of this implies an intimate knowledge of the patient and the indications for this specific EPS as well as knowledge of clinical electrophysiology (EP) and testing techniques, including the risks and benefits associated with each test or maneuver. Clinical electrophysiology is recognized as a subspecialty of cardiology that requires substantial training and experience. Diagnostic and therapeutic (interventional or device) EPS should be performed only by physicians who have such a background.[2,3]

Electrophysiology Laboratory

A detailed list of the requirements for an adequate EP laboratory is beyond the scope of this chapter. A summary of the needs of an adequately equipped EP laboratory would include the following: an imaging/fluoroscopy system, with pulsed fluoroscopy or other means of limiting radiation exposure, especially for laboratories performing ablation; a suitable amplifier-recording system; a programmable electrophysiological stimulator; a selection of EP catheters, introducers, connectors, and so on; an ablation system (typically a radiofrequency generator); a selection of antiarrhythmic medications that can be delivered intravenously; and equipment for defibrillation and Advanced Cardiac Life Support. Provisions for monitoring blood pressure, oxygen saturation, and expired CO_2 must be present.

Catheter Electrode Insertion and Positioning

No single "correct rig" exists. Only the use of the Seldinger technique is virtually universal. Sites of insertion include brachial, subclavian, internal and external jugular, and femoral veins. The number of catheters used and the insertion sites also depend on the purpose of the EPS and on any intention of retaining one or more catheter electrodes ("wires") for subsequent use another day. Some of the common variations are shown in Figure 20-1.

Subclavian and Internal Jugular Approaches

Both these approaches have their advocates. The internal jugular approach has a lower risk of pneumothorax, but it may be somewhat more difficult to maneuver the wire and to maintain sterility during a longer procedure or with a retained wire because of proximity to the hair. The subclavian approach, particularly on the left, permits the wires to follow a smooth arc toward the heart. In the authors' lab, the preference is the subclavian approach, in part because sometimes the wires are retained overnight after certain ablation procedures for confirmation testing before discharge the following morning.

Femoral Approach

The femonal approach is the most common approach for all EPSs; some electrophysiologists use it almost exclusively. Multipolar catheters can help keep the number of punctures to the minimum. For example, octopolar and decopolar catheters with

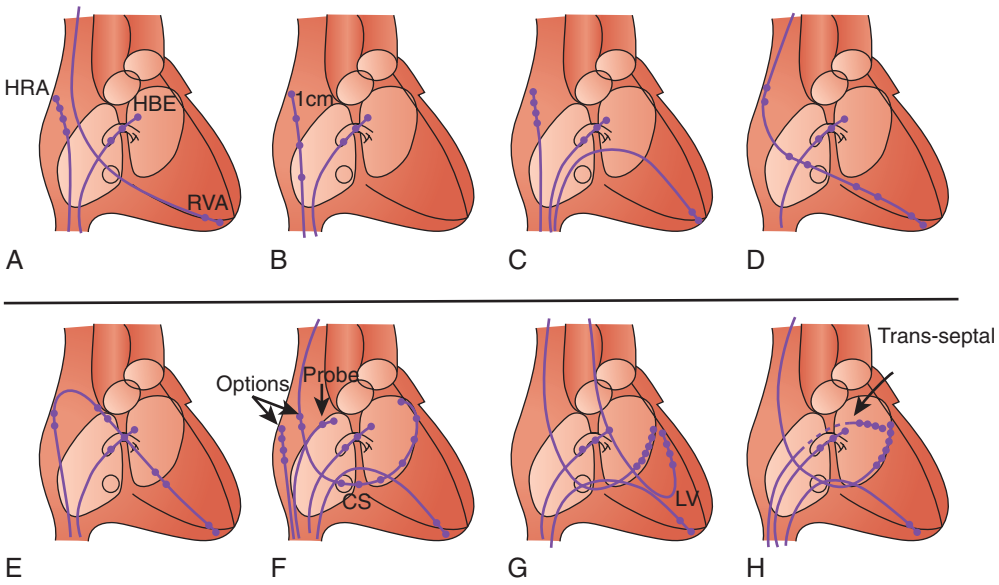

FIGURE 20-1 Common electrophysiology wire rigs. The number and type of electrode catheters used for an electrophysiology study (EPS) is determined by the type of study, the preferences of the physician and the laboratory, and patient-specific issues. *A,* A setup for a standard diagnostic EPS. Note that the quadripolar catheter in the high right atrium (*HRA*) has closely spaced poles. This allows stimulation through the distal end recording of the resulting electrograms through the proximal pair of poles that are still in or near the HRA. *B,* Use of a catheter with 1 cm or more interelectrode distance for this purpose no longer allows recordings from the HRA. In *A,* one catheter was inserted from above, that is, from an arm or subclavian or jugular vein. *C,* A comparable rig with all catheters inserted from below. *D* and *E,* Somewhat comparable effects obtained using a multi-polar catheter, eliminating the need for separate HRA and right ventriculoatrial (*RVA*) leads. As shown, both stimulation and recording in the HRA would need to be done through the same catheter. This is possible with some, but not all, recording systems and often results in the ability to record only those beats that are not directly stimulated. *F, G,* and *H,* Options for more complex studies. *HBE,* His bundle electrocle.

appropriately spaced poles can be positioned so that a single wire can perform pacing and recording from the right atrium and from both the right ventricular septum and the apex. Such a wire together with another for recording the His bundle potential is all that is needed for most comprehensive diagnostic EPSs.

Trans-septal Puncture and Catheterization

This technique dates back to the l950s but has become important to the electrophysiologist for its role in the ablation of arrhythmias on the left side of the heart. The classic procedure uses a Brockenbrough needle, which is advanced through a special long sheath. For electrophysiology purposes, the classic Mullins sheath with a distal curve (i.e., like an umbrella handle) has largely been supplanted by sheaths with special shapes to facilitate placement in the desired portions of the left atrium. The more current steerable sheaths provide greater flexibility when performing left atrial catheter ablation.

The biggest danger associated with the trans-septal technique is tamponade caused by perforation of the left atrium, usually posteriorly. Several techniques have been used to reduce this risk. The literature suggests a comparably low incidence of complications with most techniques.[4-6] Approaches to the pulmonary veins, presently a matter of interest in atrial fibrillation ablation, are almost exclusively via the trans-septal route, often with several punctures. It must be emphasized that the trans-septal technique is fraught with many subtleties and potential complications. The details are far beyond the scope of this section, and no one should attempt the technique only on the basis of general experience and a reading of this part of the text.

Retrograde Approach

For certain types of ablations, the retrograde (femoral artery to aortic valve to left ventricle) approach may be used. Ablation of left-sided Wolff-Parkinson-White (WPW) syndrome can be accomplished using either the trans-septal approach or the retrograde approach. Endocardial ablation of ventricular tachycardia (VT) may also be performed using either of the aforementioned methods.

Epicardial Catheterization

Patients with tachycardia originating from the epicardial surface of the heart require mapping within the pericardial space. This technique was initially described by Sosa et al.[7] When performing epicardial ablation, patients typically require general anesthesia. A coronary angiogram is required to avoid ablation of areas adjacent to the coronary arteries. The operator must also be cognizant of the course of the phrenic nerves so as to avoid diaphragmatic paresis.

Stimulation Techniques

Incremental/Decremental: How Fast Is That?

Unfortunately, mutually contradictory terms are in widespread and general use. The use of the terms *intervals* or *cycle lengths* (CLs) in milliseconds between successive beats or stimuli allows a more precise description of specific events and their

consequences. However, an inverse relationship exists between rate in beats per minute and CL. This leads to descriptions of *incremental* (progressively faster) pacing coupled with extrastimuli delivered at *decremental* (faster/shorter) intervals, with the electrophysiologist observing for *decremental* conduction (longer/slower CLs). Usually, the meaning is clear from the context, but it is probably wise to provide clarification through terms such as *rate incremental pacing.*

Rate and Frequency

Beats per minute is commonly described as *rate*. Frequency usually refers to (1) how often an arrhythmia occurs spontaneously, or (2) the signal filtering settings in hertz. In other languages, *frequency* often means "rate in beats/min," which can introduce confusion in some communications.

Straight Pacing

Pacing stimuli are delivered at a constant rate or CL. The duration may be indefinite as with temporary pacing, but for EPSs, it is usually for a specified number of stimuli or seconds. As indicated in the previous paragraph, progressively faster pacing can be described as "incremental" (beats/min) or "decremental" (CL).

Ramps

With pacing, a series of stimuli is delivered, with each interstimulus interval successively differing from its predecessor. Most often, the interval decreases, resulting in progressively faster pacing during ramps.[5] For example, stimulation could begin at a CL of 400 ms (150 beats/min), with each of 10 successive intervals shortening by 10 ms so that at the end of the ramp, the CL would be 300 ms (200 beats/min). Clinically, ramps are used for the assessment of conduction and for the initiation and termination of tachycardias. Ramps that start fast and then slow down are occasionally used in the treatment of tachycardias. The various uses of ramp pacing will be detailed in the sections below.

Extrastimulus Technique

After a series of spontaneous or paced beats at a constant CL (a type of straight pacing, designated S1-S1), an extrastimulus is introduced at a somewhat shorter CL that is designated S1-S2. After observing the response, the process is repeated, with the S1-S2 intervals progressively shortened. Sometimes, double or triple extrastimuli (S3-S4) are introduced. The extrastimulus technique is used for the assessment of refractory periods (see below), for initiation and termination of tachycardias, and as a diagnostic tool during ongoing tachycardias.

Stimulus Amplitude and Pulse Duration

These are particularly important during extrastimulus testing. Higher amplitudes and longer pulse durations permit more closely coupled stimuli to "capture" (depolarize) the heart.[8,9] Excessively large stimuli may cause fibrillation. For these reasons, most EPSs involve stimuli at two to four times the diastolic threshold (in milliamperes or volts) and 1- to 2-ms pulse duration.[10]

Ultra-Rapid Train Stimulation

A series of stimuli are delivered at such a rapid rate (typical CLs are 10 to 60 ms) that it is not expected that each of these will capture the tissue being stimulated. The method helps assess vulnerability to inducible ventricular fibrillation (VF) by using progressively higher stimulus amplitudes with successive trains. With stimulus amplitudes in conventional pacing ranges, trains have been used for both initiation and termination of regular monomorphic tachycardias. At very low (subthreshold) amplitudes, trains have been used as a tool to alter local tissue responses, which, in turn, can affect certain tachycardias.[11,12]

Stimulation Protocols

Protocols did not come fully formed right at the beginning of clinical EP. Different centers around the world developed their own EP protocols. In general terms, broad differences are present in what constitutes a "complete" EPS. In more specific terms, differences exist in the sequence in which extrastimuli are delivered and in the stimulus amplitudes and pulse durations used. These differences can affect the sensitivity and the specificity of protocols and also the time required to complete a protocol. Over the years, demands for a "universal protocol" have been made, but such a protocol is not likely to come any time soon. Guidelines suggest that a given stimulation protocol must be able to reproduce clinical arrhythmia in at least 90% of cases.[10]

Effect of Signal Filtration and Interelectrode Spacing

During EPSs, the scale of interest ranges from macro-events (When does the QRS complex start, or what is the QRS duration?) to micro-events (How many milliseconds does it take for a wavefront to move from the His bundle to the right bundle branch?) (Figure 20-2). The ability to distinguish between macro-events and micro-events is based on the effects of signal filtration and interelectrode spacing.

Low and Wide

Macro-events such as the QRS duration are best measured with electrograms filtered at about 0.5 to 100 Hz. Most of the electrical energy of the heartbeat occurs in these low-frequency ranges, and low-frequency signals also propagate over greater distances than do high-frequency signals. The archetype of these recordings is the surface ECG. The recommended filtration is 0.5 to 100 Hz, but very little difference is noted in the appearance of the QRS complex when filtration is set as low as 0.5 to 20 Hz. Interelectrode distances are also relatively great, for example, arm to arm, or arm or chest to leg. With intracardiac catheter electrodes, inclusion of the lower frequencies (starting at 0.5 Hz) and relatively wide interelectrode spacing will maximize inclusion of "far-field" signals from parts of the heart that are not close to the recording electrodes.

For example, with filtering at 0.5 to 100 Hz, the lead in the ventricle will record a relatively broad electrogram, possibly with a low-amplitude atrial wave followed by a higher-amplitude ventricular signal, followed, in turn, by a broad, gently rounded T wave. The ventricular deflection will usually show several components. As the wavefront approaches the electrodes from afar, a progressively steeper deflection will culminate in a point. At this point, as the wavefront passes by the recording electrodes, a very

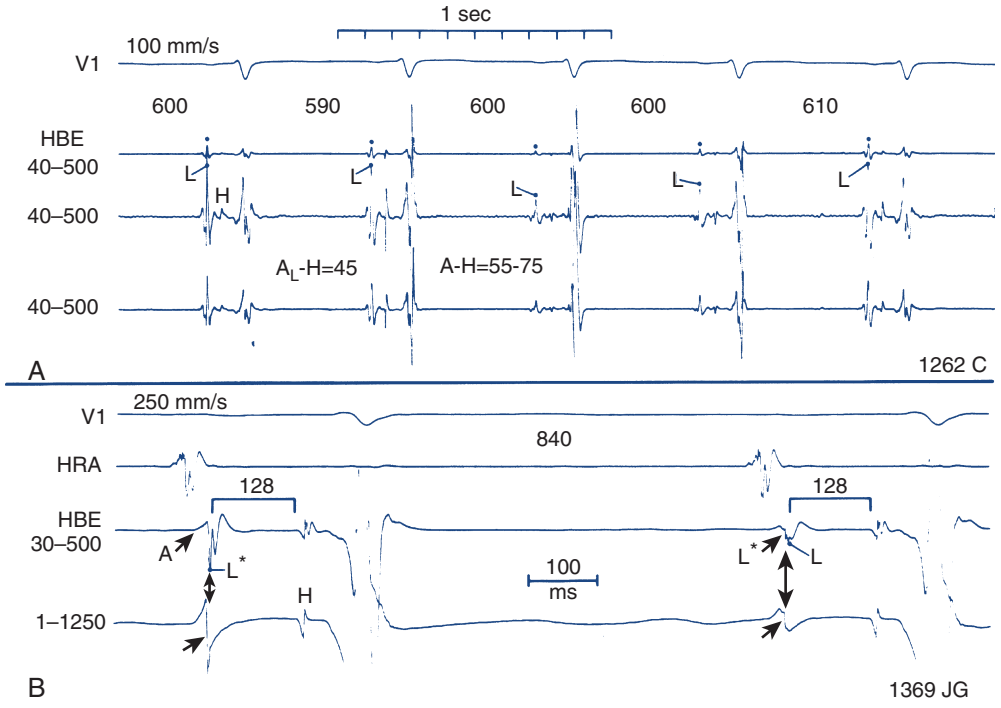

FIGURE 20-2 Beat-to-beat variation during normal sinus rhythm. **A,** Electrocardiogram (ECG) lead V1 is displayed together with the His bundle electrogram (*HBE*) lead filtered at 40 to 500 Hz and recorded simultaneously at three gain settings. Paper speed is 100 mm/s. Beat-to-beat variation can materially affect the slope of the "first rapid deflection." In the 5 beats shown, these variations resulted in a 20-second spread in traditionally measured A-H intervals. A_L (local atrial activity) is designated by an L connected by a line to a dot at the point in the upper low-gain HBE tracing. A_L was easy to measure throughout the changes in amplitude and remained in constant relationship to the H deflection. **B,** Atrial electrograms during normal sinus rhythm at paper speed 250 mm/s. The onset of the first rapid deflection changes from beat to beat. Measurements of A_L-H is constant at 128 ms. Local atrial activity L and L* on the HBE at 30 to 500 Hz was determined by using a simultaneously unfiltered tracing at 1 to 1250 Hz. *A*, onset of atrial activity as conventionally measured and designated by an *arrow* from the letter A to the site measured; L is the timing of local activity on electrograms filtered at 30 to 40 to 500 Hz. The letters L, L* are connected by a line to a dot at the designated site of the tracings; L* is the timing of the electrogram that corresponds most closely to the local electrogram recorded on the unfiltered lead. On the tracings, the timing of the local deflection is indicated by an *arrow*. *(From Fisher JD, Baker J, Ferrick KJ, et al: The atrial electrogram during clinical electrophysiologic studies: Onset versus the local/intrinsic deflection,* J Cardiovasc Electrophysiol *2:398–407, 1991.)*

rapid reversal in slope occurs, making a near-vertical deflection that has the highest dV/dt of the entire electrogram, which is known as the *intrinsic deflection*. This culminates in another reversal of direction as the wavefront continues to move away from the recording electrodes and inscribes a deflection that is a mirror image of the curve inscribed by the approaching wavefront.

Higher and Closer

"Local" events such as the precise timing of a His bundle deflection are best accomplished by filtration settings beginning at 30 or 40 Hz and going up to 500 Hz or higher. This takes advantage of the fact that higher frequencies do not propagate as well and that many of the structures of interest (such as the His bundle) contain relatively few cardiac fibers and, thus, relatively low amounts of energy. Close interelectrode spacing (2 to 10 mm) and filtering at 30 to 500 Hz combine to maximize recording of local "micro-signals" and exclude far-field or macro-signals. It is possible to focus even more closely on local events by filtering at 100 to 1000 Hz. However, so little energy is present at these frequencies that the recorder-amplifier system must be used at high gains, where the signal-to-noise ratio tends to eliminate any potential benefit.

In the case of signal filtration, the terminology again becomes somewhat confusing, rather like the alternative meanings for incremental and decremental pacing. With filtration, the "high-pass" level is *not* the higher end of the frequency range but, rather, the hurdle above which frequencies are recorded. Similarly, the "low-pass" level is the frequency below which a signal will be recorded. Thus, interestingly, for a typical 30- to 500-Hz filtration range, the high pass is 30 Hz, and the low pass is 500 Hz.

Timing of Electrical Events

Conduction in the heart is ionic rather than electronic or photonic. This means that conduction does not proceed at the speed of light but at millimeters to meters per second. This, in turn, means that it is possible to measure sequences of depolarization rather easily using simple calipers or rulers. As indicated in the previous section, filtration and interelectrode distance affect the ability to record events at varying distances from a given point

within the heart. All recorded signals will have characteristics such as duration and amplitude. As a general rule, if one is looking for the first evidence of an electrical event, several simultaneously recorded leads are observed for the *onset* of a deflection that is used for the relevant measurement, and far-field signals are welcome in some instances. The *local timing* of an event is important during mapping studies, when the timing of an event at the site where the mapping electrode or probe is located is of interest. Here, far-field signals are unwelcome, and closely spaced electrodes filtered at 30 to 500 Hz are critical. However, for some measurements (e.g., the atrial deflection in the His bundle region) the *local* timing at 40 to 500 Hz corresponds to the intrinsic deflection of "less filtered" recordings (see Figure 20-2).[13]

Several factors can alter the shape of a wavefront. If the recording electrodes are close to the initial site of ventricular repolarization (e.g., near the site of initial depolarization during sinus rhythm, or at the site of a tachycardia focus), the intrinsic deflection may come very early in the overall complex. This is particularly notable if *unipolar* recordings are made; an initial rapid negative intrinsic deflection is evidence that a recording electrode is *at* the initial site of depolarization. Unipolar stimulation is generally undesirable because the larger field (usually intracardiac—the "unipole"—to a surface electrode) creates a large stimulus artifact that can obscure the recordings.

When filtered at 30 to 500 Hz, the recorded electrograms take on a more jagged appearance, often with several sharp changes in direction. The total duration of the electrogram is less than that recorded at 0.5 to 100 Hz because less-far-field information is included. However, as previously indicated, the timing of the maximum or peak deflection can be similar for electrograms recorded at 0.5 to 100 Hz and 30 to 500 Hz.[13] Similarly, if recordings are made in areas that are scarred or damaged, overall signal amplitude may be low (<1.0 mV), and a series of low amplitude deflections may be present, and none of them fulfills the criteria for local or intrinsic deflection. Usually, the first of the relatively larger deflections (this can be quite subjective) is used for local timing.

Clipping and Limiting

In some instances, very large gains are necessary to focus on an area of interest. For example, recordings in the His bundle region typically include the low medial right atrium, the His bundle deflection, and the right ventricular inflow region. If only a very small His bundle deflection can be recorded, the gain may be increased on the recording system. This may make the atrial and right ventricular inflow deflections so large that they would cover much of the screen, overlapping with other simultaneous recordings. In such instances, *clippers* or *limiters* that electrically chop the maximum amplitude of signals are applied so that they remain within designated bounds.

Notch Filters

During the construction of an EP laboratory, it is important to have significant bioengineering input to ensure that electromagnetic interference with the recording apparatus is minimized. Nevertheless, some interference from alternate current is virtually unavoidable, creating the telltale 50- to 60-Hz pattern that can render recordings almost unreadable. Notch filters that are optimized for 50 or 60 Hz can go far to mitigate the interference problem. Although the notch is optimized at 50 or 60 Hz, some attenuation of signals at nearby frequencies is present. In most instances, this does not have a clinically important effect on the recorded electrograms.

Electrophysiology Study

Choice of Surface Electrocardiogram and Intracardiac Recordings

It is cumbersome to display all 12 leads of the regular surface ECG. One option is to use mutually perpendicular leads (I, aVF, and V1), often supplemented by lead II, which gives an indication as to the presence of abnormal left-axis deviation. Many electrophysiologists have their own personal favorite lead selections. Orthogonal lead systems (X, Y, Z) are logical but not commonly used.

Intracardiac leads are placed strategically at various positions within the heart to record *local* events in the region of the lead, rather than far-field events. This is accomplished by filtering intracardiac electrograms.

Monophasic Action Potential Recordings

Monophasic action potential (MAP) recordings provide information about local transmembrane depolarization and repolarization. An MAP catheter has 5-mm–spaced, silver-silver chloride matrix electrodes that may be positioned into the atrium or the ventricle. Standard EP recording systems should be set to 0.05 to 1000 Hz to capture lower-frequency components of the action potential. Currently, MAP recordings provide insight into cellular EP and are largely used in clinical research (Figure 20-3).[14]

Extrastimulus Technique

The extrastimulus technique (briefly introduced above) is the heart of EPSs used primarily for assessing refractoriness and tachycardia induction. Typically, the baseline drive comprises 8 beats, which may be sinus rhythm but are usually delivered at a constant CL (S1-S1) by a stimulator. The drive is then followed successively by single, double, and triple extrastimuli, which are designated S2, S3, and S4. Generally, the extrastimuli are initiated at 80% to 90% of the drive CL. All these stimuli are delivered with uniform specifications, usually 1- to 2-ms pulse duration and an amplitude two to four times the diastolic threshold. Of the various methods for shortening (decrementing) S1-S2 intervals and subsequently S2-S3, and S3-S4, most are variations of either the *tandem method* or the *simple sequential method* (Figure 20-4).[15,16]

Tandem Method

The S1-S2 is decremented in 10-ms steps until S2 does not capture; the S1-S2 interval is then increased by 40 to 50 ms. A late S3 is then introduced and the S2-S3 interval decremented until S3 fails to capture. Then, the S1-S2 and S2-S3 intervals are alternated (tandem) until S3 fails to capture. S3 is then moved out by 40 to 50 ms and the process repeated with S4. Some laboratories do use an S5 or S6 as well, but stopping with triple extrastimuli (S4) is more typical.

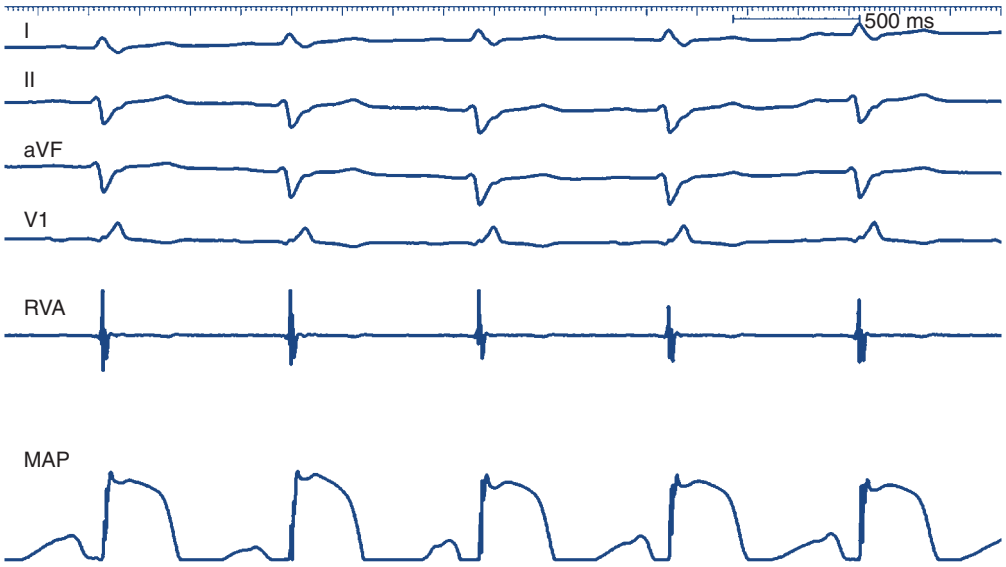

FIGURE 20-3 Monophasic action potential recording from the right ventricle. *Leads from top to bottom*: Electrocardiogram surface leads I, II, aVF, and V1, bipolar endocardial right ventricular (*RVA*) electrogram, and monophasic action potential (*MAP*).

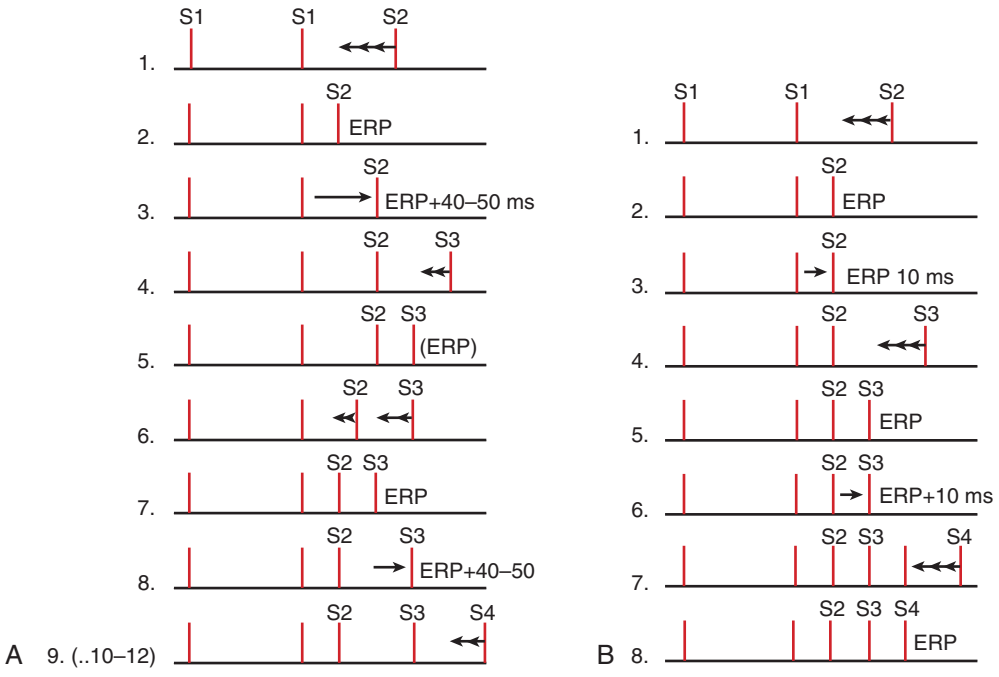

FIGURE 20-4 Method of introducing extrastimuli. **A,** The tandem method; after the first extrastimulus (S2) reaches the effective refractory period (*ERP*), it is moved out 40 to 50 ms. The second extrastimulus (S3) is introduced and the S2-S3 interval is decremented until S3 fails to capture. The S1-S2 interval is then decremented until S3 again captures. Decrements of S2 and S3 continue in this tandem fashion until the shortest intervals where S2 and S3 capture are reached. For the third extrastimulus (S4), S3 is moved out 40 to 50 ms, and the process is repeated for S3 and S4. **B,** Simple sequential method; the S1-S2 interval is decremented until the ERP of S2 is reached. S2 is then placed 10 to 20 ms later to ensure capture, and the process is repeated with S3 and then S4. Clinical results are comparable with the two methods (P = NS). *(From Fischer JD, Kim SG, Ferrick KJ, Roth JA: Programmed ventricular stimulation using tandem versus simple sequential protocols,* Pacing Clin Electrophysiol *17(3 Pt 1):286–294, 1994.)*

Simple Sequential Method

The S1-S2 interval is decremented in 10-ms steps until S2 fails to capture. It is then moved 10 ms later or until reliable capture is attained. At that point, the second extrastimulus (S3) is decremented similarly and finally a third (S4).

A prospective randomized trial has demonstrated that the tandem method and the simple sequential method produce comparable results in terms of inducibility of the clinical arrhythmia, inducibility of "nonclinical" arrhythmias, and noninducibility.[15] The simple sequential method takes significantly less time to perform.[15]

Refractory Periods and Conduction Intervals

These closely interwoven concepts often create some level of confusion. At the simplest level, refractory periods are established by responses to extrastimulus testing, and conduction is accessed by rate incremental pacing. Details are provided below.

Refractory Periods

The classic technique is to deliver eight drive stimuli, all designated as S1. After the last S1, an extrastimulus (S2) is delivered at an interval somewhat shorter than the S1-S1 interval. The process is repeated with decrements in the S1-S2 interval, usually until S2 reaches refractoriness, that is, fails to capture. The S1-S2 interval is usually decremented in 10-ms steps, although 20-ms or even 30-ms steps may be used in clinical laboratories for very long S1-S2 intervals. Refractory periods tend to be shorter with shorter S1-S1 intervals. An exception is sometimes seen in the AV node, where refractory periods may be prolonged as the S1-S1 is decreased from 1000 ms to 600 ms but thereafter usually tend to shorten as the S1-S1 is further decreased (Figure 20-5).

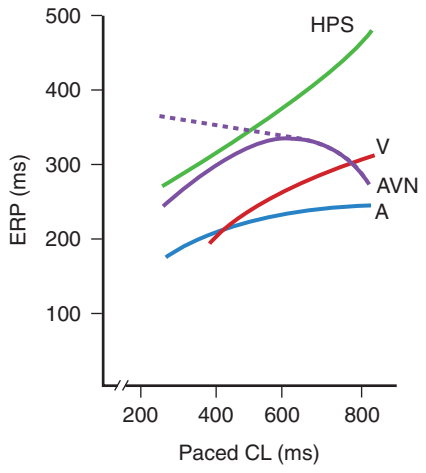

FIGURE 20-5 Effective refractory period (*ERP*) variability in different parts of the atrioventricular conduction system. In the case of the His-Purkinje system (*HPS*), atrium (*A*), and ventricle (*V*), the ERP consistently shortens with shorter paced cycle lengths (*CLs*). The atrioventricular nodal (*AVN*) ERP may initially prolong with shorter paced CLs, and this trend can continue (*dashed line*) or the AVN ERP can shorten as the paced CL is further shortened. *(From Fisher JD: Primer of cardiac electrophysiology, Armonk, NY, Futura, In press.)*

Depending on the objective of the EPS, refractory period testing may be carried out with stimulation at several atrial or ventricular sites and at two or more drive (S1-S1) CLs. Several different refractory periods warrant further discussion (see below).[17-25]

Absolute Refractory Period

The absolute refractory period (ARP) is the longest S1-S2 interval that fails to capture, *even at the maximum available S2 stimulus amplitude*.

Effective Refractory Period

The effective refractory period (ERP) is the longest S1-S2 interval that fails to capture or depolarize the tissue of interest, at the designated stimulus amplitude and duration used for the EPS or delivered remotely by the cardiac tissue. Note that the ERP is defined by stimulus-stimulus (S1-S2) intervals. The definition becomes somewhat problematic when double (S3) or triple (S4) extrastimuli are introduced and ERPs are defined for them. In this case, the definition is altered slightly, and the ERP of the first extrastimulus is set as the *shortest* coupling interval that *does* result in capture. Such an ERP should thus be 10 ms longer than the longest S1-S2 that *fails* to capture; but if the earlier extrastimuli failed to capture, responses to the later extrastimuli would have little meaning.

A *downstream effect* with ERPs occurs. If measured at the site of pacer stimulation, the interval set in the programmable stimulator can be read directly to determine the ERP. Suppose, however, one is interested in the ERP of the His bundle. If stimulation is delivered to the high right atrium (HRA) as is conventional, it may be necessary to reduce the S1-S2 interval to the point where the relative refractory period (RRP) (see below) of the atrium is reached, resulting in a prolonged conduction time from the HRA to the AVN–His bundle region. The impulse may also encounter the RRP of the AVN, further delaying the arrival of the wavefront generated by S2 at the His bundle. Thus, the H1-H2 interval will be substantially longer than the S1-S2 interval. Since in this case the tissue of interest is the His bundle, its ERP is defined as the longest H1-H2 interval that fails to propagate. As indicated, this may differ substantially from the S1-S2 delivered in the HRA. Often, the ERPs at a proximal site (e.g., the HRA) are longer than at distal sites, making it impossible to determine the ERP distally.[17-25] The importance of taking the extra steps to correctly measure depends on the nature of the EPS.

Relative Refractory Period

Just longer than the absolute refractory period, in the RRP the stimulated tissue has repolarized just enough to permit depolarization in response to a stimulus. However, because repolarization is not yet complete, the action potential amplitude and dV/dt (slew rate) are also low. This results in a slowly conducting wavefront that has a low "safety factor" for propagating to nearby cells.

Functional Refractory Period

Functional refractory period (FRP) is defined as the *shortest* coupled response-response time at the tissue of interest as a result of an S1-S2. Again, interestingly, depending on the tissue of interest, the shortest stimulation intervals may not produce the shortest response intervals. For example, when assessing the AVN, 10-ms decrements in the S1-S2 stimuli delivered to the HRA may produce substantially longer increments in AVN conduction as accessed by the resulting H1-H2 intervals. Thus, the FRP of the

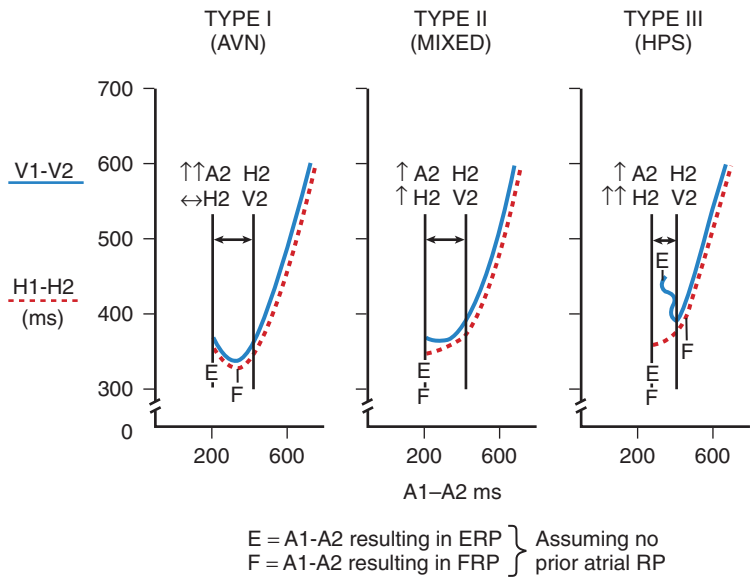

FIGURE 20-6 Patterns of atrioventricular node (*AVN*) conduction and refractoriness. In response to decremental extrastimulus testing, conduction over the AVN (A2-H2) and the His-Purkinje system (H2-V2) may differ substantially from each other. Major delays may be encountered at the A2-H2 level with minimal H2-V2 prolongation (type I); at the H2-V2 level (type III); or at both levels (type II). *ERP*, Effective refractory period; *FRP*, functional refractory period; *RP*, refractory period. *(From Fischer JD, Zhang X, Waspe LE, et al: Tests of refractoriness and conduction during clinical electrophysiologic studies: yields and roles,* J Electrophysiol *2:175, 1988.)*

AVN may occur at S1-S2 intervals that are longer than the S1-S2 intervals needed to reach the ERP of the AVN.[18] Normal variations in these relationships were identified early on and are summarized in Figures 20-5, 20-6, and 20-7.

Conduction

Conduction is usually defined as the ability of (a string of) tissue to propagate a wavefront in response to increasingly faster pacing rates.[18-20,26-30] No extrastimuli are involved. Straight pacing and slow ramp techniques can both be used for this purpose.[18] With straight pacing, the first several beats involve stimuli at CLs substantially shorter than the resting CLs, so that a period of "accommodation" occurs, and in some instances, it takes as long as 45 seconds to resolve, although 10 to 15 seconds are usually sufficient.[29,30] The ability of an impulse to conduct from the HRA to the ventricle is often tested with straight incremental pacing, often simultaneously with the same type of pacing used for the assessment of sinus node recovery times. A slow ramp (rate increasing by 2 to 4 beats/sec or 10-ms interstimulus decrement) results in accommodation on a beat-to-beat basis and allows assessment of AV and ventriculoatrial (VA) conduction in a total of 10 to 15 seconds.[15,26-28,31] The ramp technique is, therefore, useful as a screening tool and as a means of assessment after interventions such as catheter ablation. Some phenomena can be seen more readily with the ramp technique. For example, in patients with dual AVN physiology, a sudden discontinuity or "jump" in the A-H interval can often be observed during a ramp but much less often with straight pacing because the stepped series of CLs used in straight pacing are not close enough together to identify a jump.

Conduction Intervals

It is routine during EPS to indicate the CLs at which AV or VA Wenckebach or other block occurs. These conduction intervals are usually defined in terms of the stimulation CLs and

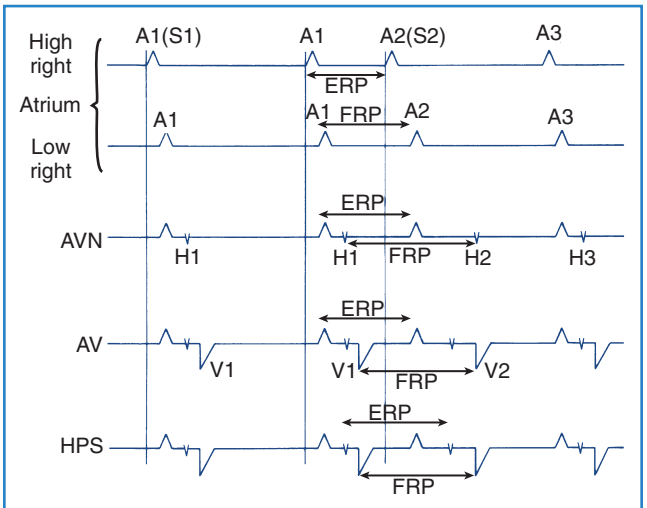

FIGURE 20-7 Effective and functional refractory periods (*EPR, FRP*) in the atrioventricular conduction system. A1 (S1), H1, and V1 represent baseline depolarizations. A2 (S2) in the high right atrium represents an extrastimulus with the responses A2 in the low right atrium, H2 in the His-Purkinje system (HPS), and V2 the ventricle. A3 is the recovery beat. At each level of the conduction system, the ERP is the longest stimulus-to-stimulus interval that fails to capture or conduct, and the FRP is the shortest result of such conduction in the specified tissue. Note that the ERPs are, therefore, specified not by the timing of the stimulus in the high right atrium, but by the component of the conduction system that is acting as the stimulus for the next step. Hence, at the bottom of the cascade, the ERP of the HPS is defined in terms of the H1-H2 interval. Note that in the atrioventricular node (*AVN*) line, the H1-H2 interval should be shorter, identical to that of the following two lines. *(From Fischer JD, Zhang X, Waspe LE, et al: Tests of refractoriness and conduction during clinical electrophysiologic studies: yields and roles,* J Electrophysiol *2:175, 1988.)*

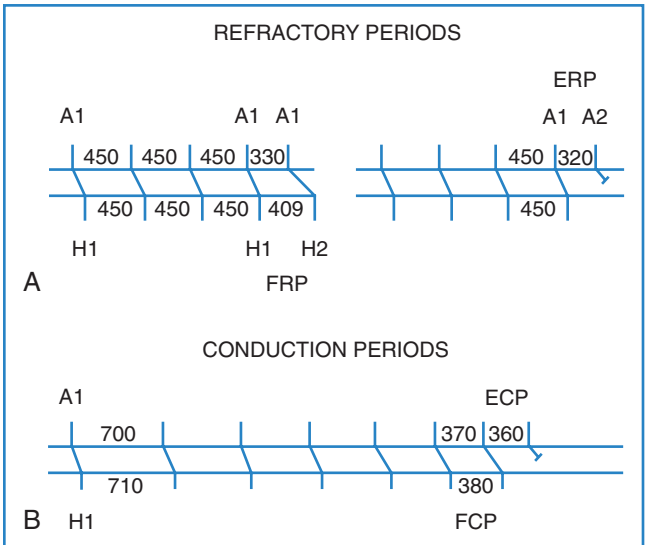

FIGURE 20-8 Schematic comparison of refractory and conduction periods. **A,** Atrioventricular nodal refractory periods. Impulses in the low right atrium at regular intervals of 450 ms (A1-A1) are followed by an extrastimulus (A2) with an A1-A2 interval of 330 ms. The resulting H1-H2 interval of 409 ms is the shortest achieved and represents the atrioventricular node functional refractory period (*FRP*). To the right in **A,** an extrastimulus at A1-A2 = 320 ms fails to conduct and represents the effective refractory period (*ERP*). The A1-A2 intervals resulting in the fact that FRP and ERP are not always juxtaposed. The FRP is typically much longer than the ERP. **B,** Atrioventricular nodal conduction periods. Pacing at progressively shorter cycle lengths ultimately results in block. The shortest resulting H-H interval is the functional conduction period (*FCP*), and the longest A-A failing to conduct is the effective conduction period (*ECP*). The intervals are typical, with relatively little difference between ECP and FCP. *(From Fisher JD, Zhang X, Waspe LE, et al: Tests of refractoriness and conduction during clinical electrophysiologic studies: Yields and roles,* J Electrophysiol *2:175, 1988.)*

thus are analogous in some ways to ERPs. The timings of depolarizations are downstream from the site of stimulation and are analogous to FRPs. Because of accommodation with straight pacing and near-elimination of this factor with ramp pacing, effective and functional *conduction* periods are usually much nearer to each other than the comparable *refractory* periods (Figure 20-8).[18,31]

"Problem-Oriented" Versus "Complete" Electrophysiological Study

Sometimes, limited or problem-oriented indications for EPS are present. Typical examples are assessment of the effects of an antiarrhythmic drug on inducibility of any arrhythmia or on defibrillation threshold in a patient with an implantable cardioverter-defibrillator (ICD). Sometimes, scheduling or workload issues dictate a limited study, with the option for a more complete study at a later time if the clinical situation warrants it.

Generally, it is preferable to plan for a complete diagnostic EPS with or without ablation of known or suspected arrhythmias. The reason is that patients with indications for an EPS are often found to have multiple abnormalities. Thus, patients being studied for syncope of undetermined origin may have abnormalities of the sinus node, AV node, and His-Purkinje system; inducible arrhythmias; or some combination of these abnormalities that could affect the choice of treatment. For example, sinus node abnormalities identified in a patient with VT would suggest the use of a dual-chamber ICD as part of therapy. As an additional example, in the case of supraventricular tachycardias, about 15% of patients have more than one reproducibly inducible mechanism; hence it is not uncommon to find arrhythmias related to accessory pathways and dual AVN physiology in the same patient. Often, these arrhythmias have somewhat similar rates, and previous documentation is often unable to definitively rule out both arrhythmias as a source of patients' clinical tachycardias. Thus, many electrophysiologists believe that after ablating what they think is the main arrhythmia, it is wise to proceed and ablate other inducible arrhythmias so that the patient will not need to return to the laboratory for another invasive procedure. Except for induction of heart block, the major risk of additional procedures is related to the instrumentation process, so eliminating arrhythmias that seem likely to be clinically relevant should be done, if possible, during a single EPS.

Complete Electrophysiological Study

A complete diagnostic EPS should include assessments of the sinus node, atrium, AVN, His-Purkinje system, retrograde conduction, and inducibility of supraventricular and ventricular arrhythmias. In many cases, a single set of stimulation sequences provides information about a broad range of cardiac chambers and conduction system components. For example, rate-incremental atrial pacing can be used to assess sinus node recovery times (SNRTs) as well as conduction at the AVN and His-Purkinje levels. Atrial extrastimulus testing can provide information on the sinoatrial conduction time (SACT), vulnerability to atrial tachycardias, evidence of normal or dual AV node physiology, and vulnerability to induced AVN re-entry tachycardia, as well as refractory period data on the atrium, AVN, and His-Purkinje system. Similarly, ventricular pacing can provide information on retrograde conduction as well as vulnerability to ventricular arrhythmias.

Top-to-Bottom Report

If one conceptualizes the heart as starting at the sinus node and ending at the ventricle, with testing of the various structures in between, organization becomes rational and simple. An EPS report should comment on each of these steps or levels, indicating normal, borderline, or abnormal findings. Many of the same stimulation processes accomplish several tests at once. Other chapters in this textbook provide details on some of the testing methods mentioned only briefly in the present section.

Baseline Intervals

These are obtained from the *passive His recording*, that is, from the combination of the surface ECGs and catheters that allow timing of the intra-atrial, atrial-His bundle, His bundle, and His-ventricle intervals in the resting state without simulation or additional medications (Figure 20-9). Normal intervals are listed in Table 20-1.[13,23,32-40] The electrophysiologist should indicate whether the intervals are normal, borderline, or abnormal.

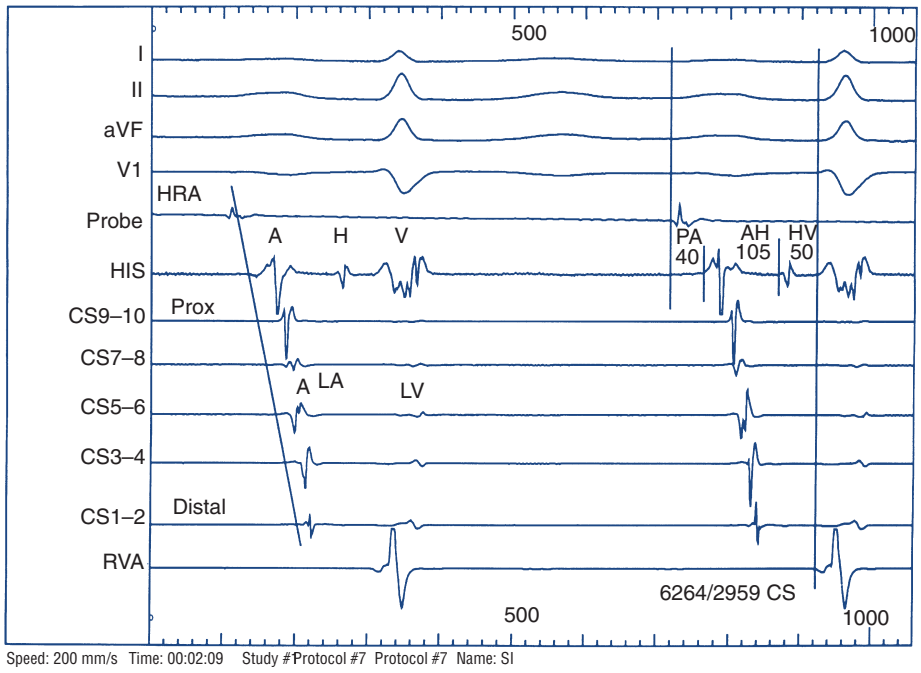

FIGURE 20-9 Normal intracardiac electrograms. This is a passive His bundle electrogram with accompanying recordings during sinus rhythm with no ongoing manipulations, stimuli, or intentional stresses. Semi-orthagonal leads II, aVF, and V1 are used together with lead 2, which is helpful in determining the axis. The measurement of intervals is demonstrated. The coronary sinus (*CS*) poles 1 to 2 (distal) to 9 to 10 (proximal) represent left atrial (*LA*) and ventricular (*LV*) events. HRA, *High right atrium*; Prox, *proximal*; HIS, *His bundle*.

Table 20-1 Normal Conduction Intervals in Milliseconds (±2 SD)

	INTRA-ATRIAL	AV NODE	HIS	HIS-VENTRICLE	INTER-ATRIAL
Passive/baseline	10–45	55–130	<25	30–55	40–130
Atrial paced	10–75	*	<25	30–55	65–150

**Progressive prolongation; see Figure 20-12.*
SD, *Standard deviation;* AV, *atrioventricular.*

Sinus Node Function Tests

These tests include SNRTs and SACTs, using either the Narula or Strauss or direct methods.[22,23,41-78] Sinus node tests and tests of other structures will be discussed in greater detail in later chapters.

Intrinsic Heart Rate

The sinus node is the archetype of the automatic focus but is heavily influenced by neurohumoral tone. It is sometimes important to distinguish whether inappropriate sinus rates, or responses to SNRT or SACT testing, is caused by intrinsic sinus node dysfunction or by extrinsic influences. To achieve autonomic blockade, divided doses of medications are given over a few minutes, including propranolol 0.2 mg/kg and atropine 0.04 mg/kg. After these medicines, the intrinsic heart rate = 118.1 – (0.57 × Age); normal values are ±14% for age younger than 45 years and ±18% for age older than 45 years. Interpretation of SNRTs and SACTs after neurohumoral blockade is uncertain.

Carotid Sinus Massage

The effects of carotid sinus massage can be assessed particularly well in the EP laboratory. Pauses of 3 seconds or longer (cardioinhibitory response) are abnormal because of sinus node arrest or atrioventricular block (the latter at the AH level). If sinus arrest is present, atrial pacing will give some inkling as to whether the AVN is also affected. Blood pressure measurement during carotid sinus massage may identify a *vasodepressor* effect.[75-81]

Atrium

The atrium is assessed for conduction, refractory periods, and induction of arrhythmias. Intra-atrial conduction is determined from the intra-atrial interval (see Figure 20-9). The intra-atrial interval is measured from the first onset of evidence of sinus node depolarization (either a normal-appearing P wave or a deflection on the HRA intracardiac lead) to the first rapid deflection of the atrial depolarization seen on the intracardiac electrodes recording

the His bundle deflection. The inter-atrial conduction time between the right atrium and the left atrium is generally measured between the HRA and a mid-distal coronary sinus lead and should not exceed 130 ms. The routes of interatrial conduction in humans are complex and are still a subject of investigation.

Atrial extrastimulus testing is used for refractory period assessment and induction of arrhythmias. Atrial fibrillation can be induced in virtually any patient with atrial stimulation that is both very prolonged and rapid. Induction of an organized regular atrial tachycardia or flutter is much less likely to be a normal variation, particularly if the arrhythmia is sustained.[35,39,82-96]

Atrioventricular Node

The AVN competes with the sinoatrial node for being known as the part of the heart most influenced by the neurohumoral tone. The AVN is the chief arbiter of the P-R interval on the surface ECG, which prolongs or shortens in response to physiological needs. As a general rule, sympathetic tone—as seen in exercise, anxiety, and similar situations—tends to shorten the atrial-His bundle interval, which is a reflection of AVN conduction. The parasympathetic (vagal) tone tends to prolong AV conduction at the AV level and may even cause nocturnal block in normal hearts or block during low-level activities in highly trained athletes. Atropine and adenosine are commonly used pharmacologic probes in the assessment of both sinus node and AVN function.[23,82-114]

Dual or Multiple Atrioventricular Node Pathways

Humans do not have the very discreet internodal pathways that can be identified in some animals. However, remains of these pathways may exist in the *slow posterior*, *fast anterior*, and *left atrial input* fibers entering the AVN. This is a simplification of very complex anatomy, but it means that a possibility exists that the electrophysiology of all these pathways may differ somewhat, so entrance into the AVN may be blocked by refractoriness at the same interval, which allows entrance through an alternative pathway. Among the possible effects of such alternative entry ways into the AVN are a discontinuity in the atrial-His interval in response to rate incremental pacing or extrastimulus testing. Such discontinuities or "jumps" are defined as an increase in the usually smooth prolongation of the atrial-His interval by 50 ms or more in response to a decrease of 10 ms in the pacing stimulus interval (e.g., during a ramp) or the extrastimulus interval. Such jumps are almost routinely observed in patients with AVN re-entry tachycardia.

His-Purkinje System

His bundle responses are also observed during passive recordings, rate incremental pacing, and extrastimulus testing and in response to pharmacologic probes (Figure 20-10).[22,51,81,113,115-134]

Longitudinal Dissociation and "Normalization" of Left Bundle Branch Block

Some anisotropic conduction exists between the longitudinal fibers in the His bundle that are destined to become the right and left bundle branches (RBB, LBB). However in some patients with left bundle branch block (LBBB), pacing the His bundle will normalize the QRS complex (Figures 20-11 and 20-12). If the stimulus to ventricle time is longer than the baseline His-ventricle interval, normalization of the QRS may be caused by

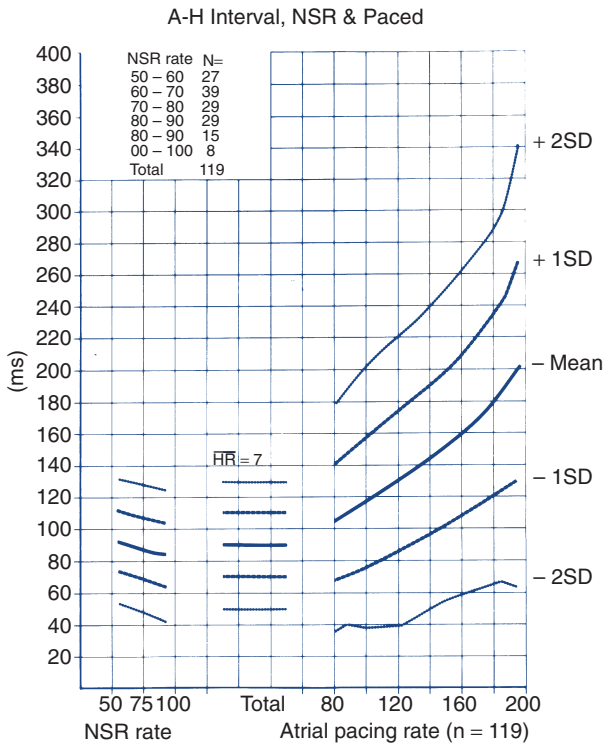

FIGURE 20-10 The atrial-His bundle (*A-H*) interval during normal sinus rhythm (*NSR*) and during high right atrial pacing. Mean and standard deviations (*SDs*) are shown for subjects without evidence of atrioventricular nodal disease. *(Modified from Fischer JD: Role of electrophysiologic testing in the diagnosis and treatment of patients with known and suspected bradycardias and tachycardias,* Prog Cardiovasc Dis *24:25, 1981.)*

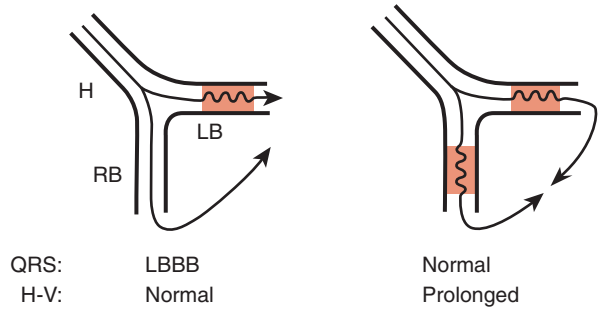

FIGURE 20-11 Balanced bilateral first-degree bundle branch block. *Left,* Delay in the left bundle (*LB*) is shown, whereas the right bundle (*RB*) conducts normally. This results in a left bundle branch block (*LBBB*) morphology on the surface electrocardiogram and a normal His-ventricle (*H-V*) interval. *Right,* A patient with balanced first-degree bundle branch block. Equal delays in both the right and the left bundle branch results in a prolonged H-V interval but a normal QRS morphology. *(From El Sherif N, Amay-Y-Leon F, Schonfield CA, et al: Normalization of bundle block patterns by distal His bundle pacing. Clinical and experimental evidence of longitudinal dissociation in the pathologic His bundle,* Circulation *56:996–1006, 1977.)*

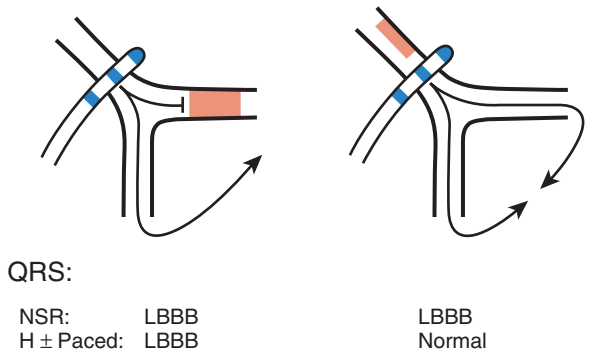

FIGURE 20-12 Proximal versus distal disease causing left bundle branch block (*LBBB*) pattern. *Left,* Disease in the LBB creates an LBBB pattern on the surface electrocardiogram (ECG) and also during pacing of the His bundle, which is proximal to the site of block. *Right,* Disease is present in those fibers of the His bundle destined to become the LBB. In patients with such longitudinal dissociation, the surface ECG will also show an LBBB pattern. However, during His pacing at a site distal to the block, the paced wavefront will propagate down both the right and left bundle branches with a normal stimulus-ventricle time (equivalent to the H-V interval), and a normal QRS morphology. *(From El Sherif N, Amay-Y-Leon F, Schonfield CA, et al: Normalization of bundle block patterns by distal His bundle pacing. Clinical and experimental evidence of longitudinal dissociation in the pathologic His bundle,* Circulation *56:996–1006, 1977.)*

balanced first-degree block in the bundle branches, with prior first-degree LBBB now matched by pacing-induced first-degree right bundle branch block (RBBB). When the stimulus to ventricle is equal to the His-ventricle interval, this may indicate disease in the His bundle, with block in fibers committed to become the LBB; pacing depolarizes the His bundle below the level of block. This is potentially the more serious scenario because progression of the lesion could cause complete heart block at the His-ventricle level.

Catheter Bumping

The His-ventricle interval can be affected by trauma during the placement of EP catheters. Most often RBBB is seen but rarely persists more than a few hours. Complete heart block is uncommon. A notable exception is seen in patients with pre-existing LBBB; in these patients, trauma to the His bundle or the RBB can produce complete AV block.

Response to Stimulation

Rate incremental atrial pacing and atrial extrastimuli most often have negligible effects on the His-ventricle interval. If the patient has a good AVN, then sequential impulses may reach some part of the His-Purkinje system within its ERP. The most typical example is RBBB observed with increasingly premature atrial extrastimuli and often seen with short cycles during atrial fibrillation as the *Ashman phenomenon.* As a rule of thumb, block at the His-ventricle level is uncommon in response to incremental pacing or extrastimulus testing with H-H interval 400 ms or longer. Block at the His-ventricle interval during straight pacing at CLs not producing Wenckebach at the AVN level is distinctly abnormal and an indication for pacing.[119]

Pharmacologic Probes

Isoproterenol has a minimally positive effect on conduction to the His-Purkinje system. Lidocaine and procainamide as well as ajmaline have been used as part of the assessment of "suspect" His-Purkinje conduction.[51,121-123,130-135] Block or prolongation of the His-ventricle interval by more than 30% in response to these agents is abnormal. In the case of lidocaine, typical doses are 75 mg delivered twice over a period of 30 seconds; procainamide is usually given as 10 mg/kg with a delivery rate of about 25 to 50 mg/min. At the end of the drug infusions, rate incremental pacing may help by precipitating heart block.

Retrograde (Ventriculoatrial) Conduction

During clinical EPSs, 20% to 50% of patients with apparently normal anterograde conduction have no retrograde (ventriculoatrial) conduction. This is a normal variation. In many of these, administration of isoproterenolol results in a normal pattern of retrograde conduction. In those with normal retrograde conduction, earliest atrial activation occurs in the atrium, specifically the relatively anterior septal portion that records the His bundle deflection as well. Occasionally, the earliest activation will occur more posteriorly, presumably because of the use of the slow pathway. If the earliest atrial depolarization occurs elsewhere, this is sometimes referred to as an "eccentric" pattern, which may imply the presence of an accessory pathway. As with other portions of the EPS, note that basic technique is a combination of rate incremental pacing and extrastimulus testing, this time from the ventricle.[136-143]

Unusual Phenomena

Various types of *gap phenomena* are described with retrograde as well as anterograde conduction.[91,144-153] One should keep in mind that these are, indeed, unusual phenomena, rather than abnormalities. *Retrograde jumps* during ventricular stimulation may also occur for several reasons: (1) dual AVN physiology that may only be apparent during retrograde conduction; (2) conduction using an accessory pathway which then blocks, with subsequent conduction switching to the normal pathway, or the reverse of this process; (3) block of ventriculoatrial conduction in the RBB, resulting in transventricular septal conduction and retrograde conduction up the LBB. In some instances, this latter phenomenon results in *bundle branch re-entry*, in which the impulse traveling retrograde in the LBB continues retrograde to the atrium via the His bundle but also reaches a turnaround point at the bundle branch bifurcation region and travels anterogradely down the RBB to the ventricle.[154,155] Demonstration of a few beats of bundle branch re-entry is classified as a normal phenomenon, which is to be distinguished from sustained bundle branch re-entry tachycardia (described elsewhere in this textbook). *Supernormal conduction* occurs when a precisely timed beat results in conduction in a previously blocked area.[156] Other phenomena such as phase 3 and phase 4 blocks, supernormal excitability, and others are discussed elsewhere in this textbook.

Ventricle

With regard to the ventricle, the most important question is whether sustained monomorphic VT is inducible, particularly *reproducibly* inducible. Given enough stimulation and enough

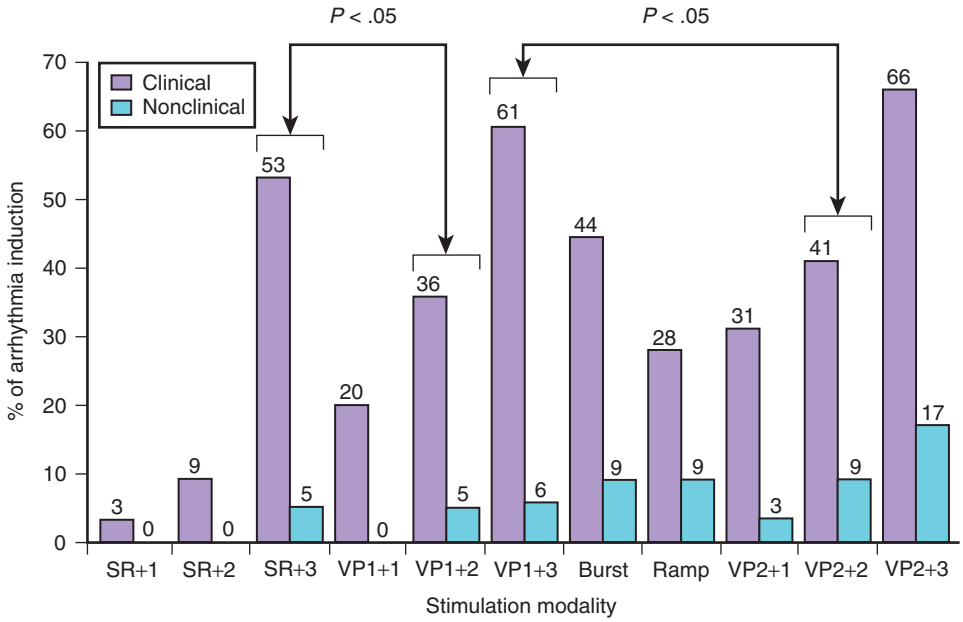

FIGURE 20-13 Frequency of induced clinical and nonclinical arrhythmia with each stimulating modality (protocol step) in a consecutive series of patients with inducible ventricular tachycardia. All patients received *all* steps. The sequence actually used is displayed on the abscissa. The ordinant indicates the percent of uses of each modality that resulted in a clinical (*purple*) or nonclinical (*blue*) arrhythmia. Each of the bars is capped by the more precise percentage of arrhythmias induced. Note that SR + 3 was more efficacious than either VP1 + 2 or VP2 + 2 and that VP1 + 3 was superior to VP2 + 2. In addition to the *P* values indicated, VP2 + 3 was more likely to induce nonclinical arrhythmias than NSR + 3 or VP1 + 3 ($P < .05$). *SR*, Sinus rhythm; *VP1*, the slower paced drive rate; *VP2*, the faster rate; *1*, *2*, and *3*, number of extrastimuli. *(From Artoul SG, Fisher JD, Kim SG, et al: Stimulation hierarchy: Optimal sequence for double and triple extrastimuli during electrophysiological studies,* Pacing Clin Electrophysiol *15:790–800, 1992.)*

electricity, it is possible to fibrillate anybody (except in special circumstances detailed elsewhere in the textbook), so the induction of VF is considered nonspecific. As mentioned earlier, no universal stimulation protocol exists (Figures 20-13 and 20-14; also see Figure 20-4). Virtually all techniques in common clinical use involve the serial introduction of single, double, triple, and occasionally quadruple extrastimuli during at least two drive rates and at two ventricular sites at the minimum. Rapid pacing in the form of bursts and rapidly increasing ramps are also used in many centers. Isoproterenol or psychological stresses are needed in some patients. The definition of *sustained tachycardia* varies somewhat from center to center, with some laboratories using 15 seconds, others 30 seconds, and most accepting need for rescue cardioversion or termination. Sustained monomorphic VT implies that the rhythm has a shape or morphology that can be described in terms of BBBs (with the understanding that these are not truly related to AV conduction difficulties). Examples of such descriptions are given in Table 20-2.

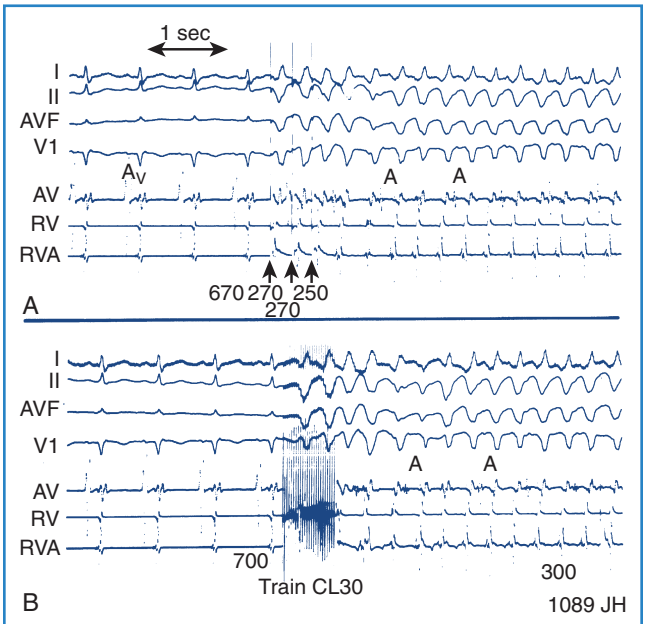

FIGURE 20-14 Programmed stimulation and ultra-rapid trains for induction of ventricular tachycardia (VT). **A,** After a series of baseline (S1) beats in sinus rhythm, triple extrastimuli are introduced at the coupling intervals shown, and VT is induced. **B,** In the same patient on the same day, an ultra-rapid train at cycle length 30 ms produces three captures and the same VT as in **A**. *AV*, Intracardiac electrogram recording atrial (*A*) and ventricular (*V*) signals; *RV*, right ventricle; *RVA*, RV apex.

SUMMARY

The techniques described in this chapter for setting up and performing a *complete diagnostic electrophysiological study* contain the components that are essential to all EPSs: selection of stimulation sites and recordings; methods of stimulation including stimulus characteristics, patterns (straight, ramp, extrastimulus); timing of overall sequence and local events; and the use of pharmacologic probes. Other chapters will expand on these basics for the differential diagnosis of complex arrhythmias, and for therapeutic or interventional electrophysiology.

Table 20-2 Description of Ventricular Tachycardia Morphologies in Terms of Similarity to Bundle Branch Block Morphologies

		QRS IN LEAD			
BBB		**I**	**II**	**AVF**	**VI**
TWO-CHOICE AXIS					
RBBB	Superior	+, –	–	–	+
RBBB	Inferior	+, –	+	+	+
LBBB	Superior	+, –	–	–	–
LBBB	Inferior	+, –	+	+	–
FOUR-CHOICE AXIS					
RBBB	RBNA	+	+	+	+
RBBB	RBLA	+	–	–	+
RBBB	RBRA	–	+	+	+
RBBB	RBXA	–	–	–	+
LBBB	LBNA	+	+	+	–
LBBB	LBLA	+	–	–	–
LBBB	LBRA	–	+	+	–
LBBB	LBXA	–	–	–	–

RB, *Right bundle;* LB, *left bundle;* RBBB, *right bundle branch block;* LBBB, *left bundle branch block;* NA, *normal axis;* LA, *left axis;* RA, *right axis;* XA, *extreme axis ("Northwest");* +, *positive;* –, *negative.*

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All references cited in this chapter are available online at expertconsult.com.

CHAPTER 21

The Electrophysiological Laboratory: Technologic Advances and Future Development

Sabine Ernst

Introduction

Crossover or hybrid laboratories were common in the early days of invasive electrophysiology (EP), when the electrophysiological study (EPS) was performed late in the afternoon at the end of the coronary catheterization laboratory (cath lab) list. As the field of EP grew, more and more departments decided to equip dedicated EP labs that would be exclusively designed to support the special needs of an arrhythmia service. Because device implantation does not need any specific equipment besides a C-arm fluoroscopy, many large EP services have decided to transfer these procedures to a lesser specialized area, such as a hybrid operating room (which also meets the requirements for sterile implantation of devices).

Newly Designed or "Retrofit"?

Many considerations need to be taken into account when deciding to either design a state-of-the-art cath lab in a newly constructed area or renovating an older lab with up-to-date technologies (Figure 21-1). One of the biggest problems is having enough space to fit not only all the equipment necessary for the procedure (Figure 21-2) but also equipment needed only in an emergency. In addition, ample space for moving the patient into and out of the room via stretcher or patient bed and sufficient in-room storage are essential. Normal items such as telephone lines, a data point for the hospital information system (HIS), sufficient lighting, and easy access from the sink to the sterile field are involved as well. The placement of gases and suction outlets in the procedure room should also be given attention.

Minimal Standards for Invasive Electrophysiology ("The Must Have")

To visualize catheter positioning, a fluoroscopic imaging system with at least a single C-arm is necessary. The system should be programmable to a certain extent to control radiation exposure (Figure 21-3).[1] Because comparably less radiation exposure is needed to image the metal electrodes of a catheter compared with the resolution required for lesion assessment in coronary artery interventions, a special setting should be reserved for EP procedures. The C-arm should be rotatable by at least 90 degrees in both the right anterior oblique and the left anterior oblique positions, and cranial or caudal angulations are not often necessary.

To reduce radiation exposure to the operator, proper Plexiglas lead protection, both "under the table" (closest position to the x-ray beam) and "over the table" against scattered radiation from the patient is a legal requirement. In addition, the image should, whenever possible, be centered on the chamber of interest and the table should be locked in the optimal position for all angulations to avoid unnecessary radiation exposure. Finally, collimation and "fencing in" of the lung fields should be routine, and any unnecessary metallic devices should be removed from the area to be imaged because they result in an automatic intensification of radiation exposure (e.g., transesophageal echocardiography probes should be removed from view). European laws require the documentation of both total exposure time and dosage of the overall deployed radiation. In regard to applied fluoroscopy, the ALARA (as low as reasonably achievable) principle should be followed, and unnecessary imaging should be avoided.[1] If available, the "last image hold" option should be used.[2]

Electrophysiology Recording System (Including Intracardiac Pressure Recordings)

The minimal requirements for EP recording systems are fairly subjective. Although some operators work with only 32 channels, at least 64 channels seems to be the current standard. In addition to the standard display of the 12-lead electrocardiogram (ECG), bipolar and unipolar signals should be programmable.[3] The gain applied to any given recording should be individually adjustable, and electrodes belonging to one catheter are usually grouped (e.g., by color). Although the order of the displayed signals is a question of personal preference and training, the signal accuracy is of utmost importance. Too large a noise level is unacceptable because it could mislead the operator during the mapping process. Signal quality during energy application also is important, and every effort should be made to achieve clean signals to allow drag lesions rather than sequential point-by-point applications. In addition to the electrical signals, the recording of at least one invasive pressure should be possible (e.g., for emergency percutaneous transluminal coronary angioplasty or hemodynamic monitoring).

Cardiac Stimulator

To allow diagnostic pacing maneuvers from various electrodes, a programmable cardiac stimulator is necessary. The properties and pacing output of these stimulators vary; however, the adjustable

FIGURE 21-1 Retrofit of a conventional catheter laboratory. **A,** The old equipment is removed. **B,** The examination room's walls are fitted with special shielding.

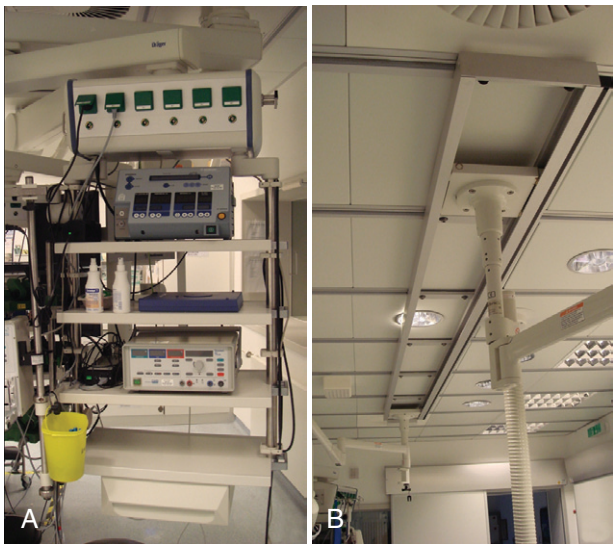

FIGURE 21-2 A, Ceiling-suspended racks allow plenty of storage for generators, patient interface units, and more equipment. Power outlets on top and electrical cabling through cabling tunnels inside the ceiling are seen. **B,** Rails along the ceiling allow for flexible solutions for monitors and racks as well as radiation protection shield and operation lamp.

FIGURE 21-3 A, Monitor gantry with six monitors arranged to allow the best orientation for the operator, with live monitors for fluoroscopy and intracardiac signals side by side. **B,** Controls of the fluoroscopy system (AXIOMS Artis; Siemens, Munich, Germany) positioned at the table side to allow rapid navigation through recorded scenes, again supporting single-operator functionality.

or programmable timing of the pacing impulses, the pacing output, and the pulse duration are crucial. Automatic sensing of the intrinsic rhythm on the selected pacing electrode allows assessment of the contact of the pacing electrode to the cardiac tissue.

Radiofrequency Generator

In most laboratories, unipolar radiofrequency (RF) current is the routine ablation energy for catheter ablation. Several devices are available, differing mostly in the ability to connect to accessories such as cool flow pumps or to integrate three-dimensional mapping systems. The operator should have the option to start and stop the energy delivery, such as by pressing a foot pedal, because catheter dislodgment is felt first through manual feedback. Any delay in stopping the energy delivery, such as that

caused by a second person who has to hear and react appropriately to the operator's verbal command to stop, may have detrimental effects (e.g., atrioventricular [AV] node block, "pop" formation).

Monitoring Unit for Vital Signs

Monitoring of the basic vital signs such as noninvasive blood pressure, heart rate, and oxygen saturation should be performed during every EP procedure, allowing instant reaction to changes in hemodynamics and safe monitoring of anesthesia.

Cardiac Defibrillator

Because fast arrhythmias may result in instant hemodynamic deterioration, rapid electrical defibrillation must be accessible at any time during EPS. A cardiac defibrillator should be at hand and turned on at the beginning of the procedure. The batteries should be routinely checked and the device tested for appropriate function on at least a weekly basis. The energy level should be adjustable and R-wave triggering possible in a stable arrhythmia; however, during ventricular fibrillation (VF), the R-wave trigger must be deactivated to avoid any delay in shock delivery. Nowadays, biphasic waveform shocks are the gold standard, with defibrillation energies of up to 360 J. The choice of patch versus direct paddle shock delivery is again a matter of debate; the first has the advantage of being fast with no impairment of the sterile field, whereas the paddles are less expensive.

Emergency Equipment

Ventilator

In case of the somewhat rare event of an emergency such as respiratory compromise of the patient, a portable ventilator system should be part of the crash cart in the EP lab. Logically, all necessary tools for intubation must be readily available, and training the staff for such scenarios should be performed regularly.

Anesthesia Equipment

In addition to the minimum crash cart equipment, some departments elect to have a complete anesthesia setup available in the EP lab to give optimal support. Children are investigated only under general anesthesia in some countries, whereas other countries allow a more liberal handling of patient sedation.

Equipment for Advanced Electrophysiology Labs

Although most simple EP substrates can be readily treated by using conventional two-dimensional fluoroscopy in conjunction with intracardiac signals, catheter ablation of complex arrhythmias such as ventricular tachycardia, incisional atrial tachycardia, or atrial fibrillation are facilitated by three-dimensional mapping systems. Following the cardiac activation across a complex three-dimensional geometry of a given cardiac chamber can be extremely helpful in performing confirmative diagnostic pacing maneuvers (e.g., entrainment in the critical isthmus of a re-entry). Because the ablation catheter usually is depicted in a real-time fashion, roaming inside the chamber of interest, three-dimensional movements are possible without controlling the movement with fluoroscopy. Although three-dimensional mapping systems should reduce overall fluoroscopy exposure, some investigators did not observe any change in their practice, whereas others relying completely on the real-time depiction of the mapping catheter demonstrated significant reductions after a learning curve.[4-6] For reduction of radiation exposure, however, the accuracy with which the catheter position is displayed is key. Two different systems have established themselves as routinely used three-dimensional tools in most cath labs performing advanced EP procedures.

NAVx and EnSite

The concept of the original LocaLisa system (now implemented in the NAVx system; St Jude Medical, St Paul, MN) is based on real-time display of all intracardiac electrodes using surface patches in all three spatial directions, which act like condensators.[7] By emitting a small current between opposite patches, any interposed catheter changes the received current and thereby becomes locatable. After reconstruction of the geometry, sequentially acquired activation information can be superimposed on the three-dimensional shell to delineate the arrhythmia substrate.

The EnSite balloon (St Jude Medical) works on the same platform by using essentially the same patches and concepts.[8] In addition to the sequentially acquired three-dimensional geometry, simultaneously acquired unipolar electrical information can be projected from the multi-electrode array using an inverse solution to the Laplace equation. This system has been reported to be of additional benefit, especially in transient and nontolerant arrhythmias.

Electroanatomic Magnetic System: CARTO

The CARTO system (Biosense Webster, Inc., Diamond Bar, CA) acts on a concept similar to that of a global positioning system, in which a small sensor on the tip of the ablation catheter is located in three different ultra-low-energy magnetic fields encoding the chest of the patient via electromagnets positioned below the patient table (so-called *location pad*).[9] Through visual display of sequentially acquired sites (and their corresponding electrical information, e.g., voltage amplitude or activation time), a color-coded map is created. Because the mapping electrode is displayed in real time, nonfluoroscopic mapping ideally is enabled, but in clinical practice some fluoroscopy is still required.

Image Integration

Currently, all three-dimensional mapping systems are able to integrate previously acquired three-dimensional DICOM-standard (Digital Imaging and Communications in Medicine) information derived from either computed tomography or cardiac magnetic resonance imaging scans.[10-11] However, accurate merging requires careful registration (e.g., to contrast injection or distinct anatomic landmarks) to obtain optimal results without the operator being misled. Knowing the targeted chamber ahead of time may lower overall radiation exposure and allows specific planning of the procedure (e.g., larger catheter curves in cases of enlarged cardiac chambers). The display of the acquired three-dimensional map

on top of the fluoroscopy reference pictures allows even better orientation during the case.

Alternative Ablation Energy Sources

As an alternative to the commonly used RF current, other ablation sources such as cryothermia techniques have been introduced in recent years.[12] Besides balloon devices for pulmonary vein isolation, some operators choose cryothermia for anteroseptal accessory pathways to use the transient freezing option (approximately −10° C), so-called *cryo-mapping,* in selected cases.[13]

Further alternative energy sources are laser energy, microwave, and ultrasound energy, modalities mostly reserved for study protocols at this time.[14]

Advanced Technologies in the Electrophysiology Lab

Remote Navigation

Remote navigation is the umbrella term for two recently introduced technologies. By using computerized workstations from within the control room, investigators are no longer exposed to scattered radiation (Figure 21-4).

Two remote catheter navigation systems have been introduced into clinical practice, both enabling remote control of the ablation catheter.[1-3] One is based on an electromechanical concept in which two steerable sheaths guide a conventional catheter; the other is based on a steerable, permanent magnetic field in which a magnetically equipped catheter must be aligned in a parallel position (Figure 21-5).

The electromechanical robotic system (Sensei; Hansen Medical, Mountain View, CA) consists of a "master" input that transmits the operator's movement with a joystick via an electromechanical "slave" at the patient's side (Artisan; Hansen Medical).[15] This remote catheter manipulator controls the tip of two guiding sheaths (14 and 11.5 Fr) that fit any conventional standard ablation catheter. The guiding sheaths (inner lumen of 8.5 Fr) work on mechanical pull-wire mechanisms that steer the catheter in a fashion similar to that of conventional guiding catheters.

Magnetic Navigation

Magnetic navigation works on the concept of small magnets, integrated in the tip of a soft ablation catheter that can be moved with a well-defined outer magnetic field (0.08 T). By changing the orientation of the outer magnets, the catheter tip will align parallel to this outer magnetic field direction. The combination with a mechanical motor drive allows operating the magnetic mapping and ablation catheter in a fully remote-controlled fashion.[16] The specialized, magnetically enabled ablation catheter was initially equipped with a solid 4-mm tip ablation electrode; an irrigated tip version has recently been introduced.

Both remote navigation systems are compatible with three-dimensional electroanatomic mapping systems, with the NAVx system being directly integrated in the robotic system and the CARTO system being integrated into the magnetic system. All image integration features of the three-dimensional mapping systems also are available.

Other Image Integration Technologies

Intracardiac ultrasound catheters have recently been introduced in an attempt to integrate three-dimensional echocardiographic information to reduce mapping time further, thus facilitating trans-septal punctures and eventually directly depicting the lesion formation during energy delivery.[17] Although these systems are quite popular in the United States, the European experience has been significantly sparse.

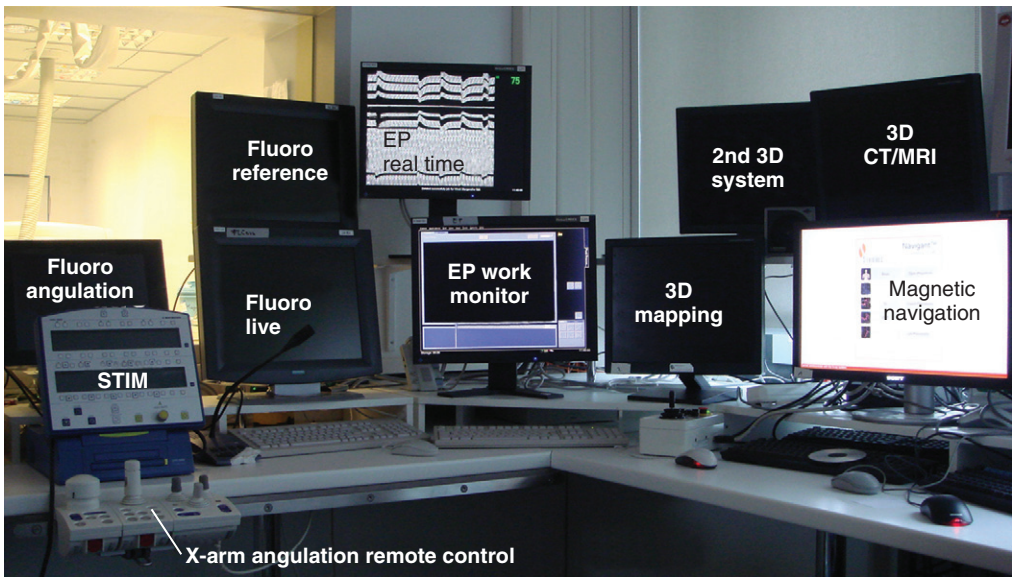

FIGURE 21-4 View of the control area of a catheter laboratory using remote control by magnetic navigation (at St. Georg Hospital, Hamburg, Germany). The monitors are arranged as in a cockpit, allowing a single operator to lead the investigation. *Fluoro*, Fluoroscopy system; *STIM*, cardiac stimulator; *EP*, electrophysiology recording system; *3D,* three-dimensional; *CT*, computed tomography; *MRI*, magnetic resonance imaging.

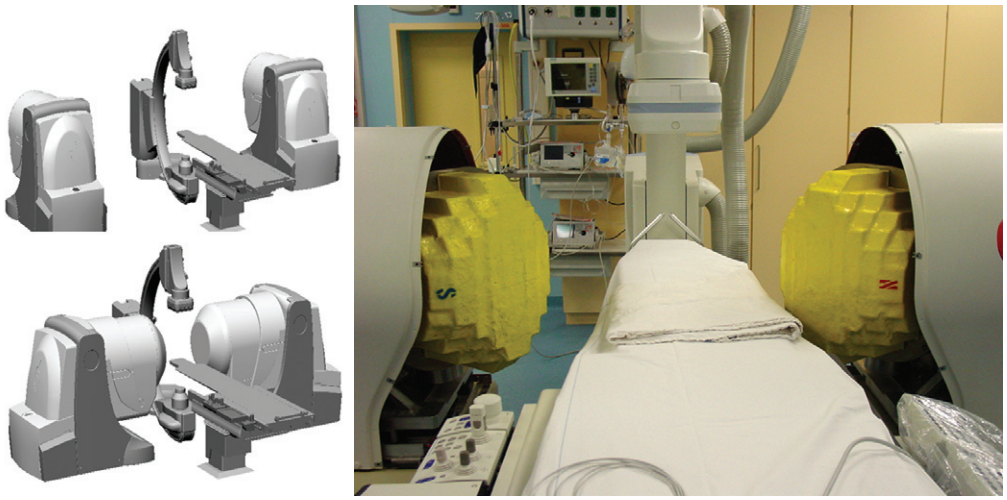

FIGURE 21-5 *Left,* Magnetic navigation system in "park" (*top*) and "navigate" (*bottom*) positions. *Right,* The system in "navigate" position, with the covers removed to show the permanent magnets exposed with their magnetic field directions (*N,* north; *S,* south).

To overcome the possible problem of pre-procedural three-dimensional imaging in different cardiac rhythms, volume load, and patient positioning, rotational angiography has been successfully implemented in the EP labs. While a timed contrast injection is performed, the C-arm rotates around the patient and acquires computed tomographic–like images that can be computed to three-dimensional DICOM formats.[18] These three-dimensional datasets can be transferred to the three-dimensional mapping systems as well as to a "ghost" picture-in-picture display on the live fluoroscopy screen (e.g., iPilot, Siemens Medical Solutions, Munich, Germany).

For a perfect overview of the different systems commonly used in an EP laboratory, the ODYSSEY system (Stereotaxis Inc., St Louis, MO) serves as a common platform on which all video signals of the different systems (e.g., EP recording, fluoroscopy, three-dimensional mapping system, ultrasound system, generator data, magnetic navigation) can be simultaneously displayed. Instead of using multiple keyboards together with the corresponding mouse for each, ODYSSEY automatically switches all the keyboard functions to the system, which is activated by one mouse. In addition, it facilitates display of the cross-talk by superimposition of three-dimensional mapping data and real-time locations of the mapping electrode on reference fluoroscopy pictures.

Because EP systems have become more and more technique oriented, with a multitude of options for the operators, remote technical and clinical support for these advanced systems poses a significant challenge for the future. One of the possible solutions could be a closed network of linked systems that allow remote expert advice for clinicians who are at the beginning of their learning curve with a given system. Review, data storage, and shared cases could be made possible (e.g., ODYSSEY Cinema, Stereotaxis, Inc.).

Outlook on Future Developments

Future EP lab systems should be able to address fundamental problems encountered in today's clinical routine. Although lesion formation currently is only indirectly monitored (irrespective of the type of energy delivered), future tools should enable the operator to see and measure lesion trans-murality to avoid excessive or too little ablation at a given site. Direct feedback between contact force and amount of energy delivered should be implemented in the next generation of ablation generators to improve lesion formation and widen the safety margin at the same time.

Any improvement that would lead to further reduction of radiation exposure for patients and operators will be greatly welcomed because a growing number of complex AF ablations have significantly lengthened the exposure times in recent years.

Conclusion

Although multiple new and sophisticated systems have been introduced to invasive EP in the past decade, the baseline EPS that allows the identification of the underlying arrhythmia substrate is still the key to success in any given case. Basic conditions such as signal quality and angulated fluoroscopic images must be ascertained, together with basic life support equipment and adequate protection against the detrimental effects of fluoroscopy. Advanced technologies such as three-dimensional mapping systems are now routinely used in more complex ablation programs (e.g., for atrial fibrillation). Remote navigation systems, together with their image integration features, have already demonstrated their ability to reduce fluoroscopy exposure for both operators and patients.

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CHAPTER 22

Imaging in the Electrophysiology Laboratory: Intracardiac Echocardiography

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Introduction

With the increase in number and variety of percutaneous intracardiac procedures, as well as the advance in intracardiac echocardiography (ICE) technology, the applicability and utility of ICE are steadily growing. This chapter discusses the use of ICE during cardiac electrophysiology (EP) procedures. To start, comparison of available ICE technologies and acquisition of baseline images are discussed. Next, the use of ICE is discussed for the following procedures: evaluation for the presence of thrombus in the left atrial appendage (LAA), placement of percutaneous LAA occlusion devices, trans-septal catheterization (TSC), and catheter ablation for atrial fibrillation (AF) and ventricular tachycardia (VT). Finally, the integration of ICE imaging with other imaging modalities and with EP mapping is described.

Comparison of Intracardiac Echocardiographic Technologies

ICE systems use miniaturized piezo-electric crystal transducers mounted on a fixed-shaft, deflectable, or mechanically driven catheter body and a computer platform for image processing, display, recording, editing, and analysis. The features and capabilities of these systems are, in substantial part, determined by the transducer technology and partly by the catheter body and platform technology. As a result, each type of system has distinct abilities and limitations. Furthermore, advances in image acquisition and processing have laid the foundations of three-dimensional reconstruction of imaged structures in the heart. To appreciate these aspects, it is necessary to briefly revisit the essential principles of sonography and ultrasound image construction.

Principles of Intracardiac Echocardiographic Imaging

Piezo-electric crystals in transducers generate ultrasound waves and receive the reflected echoes from the target. Current ultrasound transducers use either miniature crystals in a series, commonly referred to as *phased-array systems*, or a single crystal rotated by a mechanical system, aptly referred to as a *mechanical* or *rotational transducer system*. These crystals produce vibrations in response to voltage gradients as polarized molecules in the crystal distort the crystalline surface to produce sound waves. These waves propagate through the body in a longitudinal fashion and, like light energy, undergo reflection, refraction, absorption, and scatter. Reflection of ultrasound waves can occur at the surface and within tissue planes with differing acoustic impedances. Their angle of incidence on tissue planes can determine the nature and intensity of reflection. Reflection is maximal at the tissue surface and increasingly attenuated because of scatter and refraction in deeper tissue planes. The acoustic properties of tissues can also determine the degree of reflection, with greater disparities between adjoining tissues providing greater reflection, such as heart and lung tissues. The frequency of generated ultrasound energy also determines the extent of tissue penetration. Reflected waves are received by the transducer crystal and generate an electrical signal that is amplified and processed. Amplification of signals varies depending on their magnitude and is designed to allow low-amplitude signals to be registered. They are filtered, and the ultrasound signal is displayed in different scan formats such as two dimensional, in which sequential echoes are made over a 90-degree sector using up to 100 scan lines displayed at rapid frame rates that give the impression of a constant image. Other display formats used include M-mode scans, which result from repeated scanning along a single axial array displayed sequentially from left to right to envelope the time element. The Doppler principle can be used to quantify blood flow velocity across cardiac structures by the ICE probe. The shift in transducer frequency generated by the moving elements, such as blood cells and their contents, is generated by the ultrasound beam hitting the element and repeating on beam scatter. In pulsed Doppler, brief bursts of ultrasound (<5 ms in duration) are delivered and received, but undersampling may occur with potential for aliasing. Continuous-wave Doppler involves constant emission of ultrasound energy and provides a more accurate velocity measure, particularly if high velocities are present. Color-flow Doppler imaging adds processing to display velocities during a Doppler sector scan to show their distribution in the scanned region. This is useful for assessing regurgitant jets, septal defects, and stenoses. It is also subject to aliasing because of the pulsed nature of the measurements.

Comparison of Mechanical and Phased-Array Intracardiac Echocardiographic Transducers and Systems

Mechanical transducers are mounted perpendicularly on a 6 to 10 Fr catheter body with a single rotating piezo-electric crystal in the transducer that rotates at 1800 rpm (Boston Scientific, Natick, MA). This allows a circular, 360-degree scan giving a cross-sectional view of the surrounding structure. These transducers are driven at higher frequencies (9 to 20 MHz), which reduce the depth of ultrasound beam penetration into tissue. Thus these systems can produce high-quality near-field images but with limited imaging depth (4 cm). Thus far, field image resolution is poor. Furthermore, the catheter body has limited or no deflection capability and is not flexible because of the rotational mechanism in its core. Because of these features, these ICE systems must be passed into the chamber of interest. For example, satisfactory left atrial visualization is achieved only after trans-septal placement in the chamber, unlike phased-array systems. They can be used to visualize right-sided structures such as the crista terminalis, fossa ovalis, superior vena cava, or tricuspid valve.

Phased-array systems use either a linear array of crystals (Viewmate, St Jude-EP Med Systems, Berlin, NJ; AcuNav, Acuson Division, Biosense Webster, Diamond Bar, CA) parallel to the catheter body or radially arranged crystals at the catheter tip (JOMED). The first two use 64 to 128 crystal elements and operate at frequencies ranging from 5 to 10 MHz. These can operate at variable (Acuson) or four different frequencies (Viewmate) to produce a sector scan parallel to the long axis of the catheter. The catheter body ranges from 7 to 10 Fr and is typically deflectable over an arc of 90 degrees. These systems produce two-dimensional and M-mode images with high resolution over depths up to 12 cm. This permits imaging of the left-side chambers from the right heart without trans-septal puncture. In general, these systems have become more popular in clinical electrophysiological procedures. More detailed features of each of these systems are shown in Figure 22-1. Platforms can provide more enhanced imaging features such as harmonic imaging for producing improved gray-scale image presentation, adaptive color Doppler to select the optimal frequency for improved resolution, and tissue Doppler imaging to assess direction and timing of myocardial function and pulsed-wave tissue Doppler for velocity mapping during cardiac and vascular imaging. Fusion of two-dimensional ICE images into a static electroanatomic map using the CARTO system (Biosense Webster) is now commercially available (discussed later and elsewhere in this text).

Three-dimensional reconstruction has now been performed with offline and real-time reconstruction of serial images and by overlay of electrical activation sequences on the images. Simon et al initially demonstrated electroanatomic mapping by using serial sections from a rotational ICE transducer and electrical recordings from a basket catheter in the right atrium in patients with atrial flutter, which were processed offline (Figure 22-2, *A*).[1] With this approach, they could demonstrate macro–re-entrant activation sequences in common atrial flutter on a three-dimensional anatomic ICE image. Smith et al used a phased-array system to reconstruct a real-time three-dimensional anatomic ICE image with up to 60 volumetric scans per minute and superimposed activation maps on these images. In a sheep model, they demonstrated right and left atrial intracardiac structures, including pulmonary veins and the right ventricle, and pacing sequences could be accurately visualized in the reconstructed anatomy.[2] Pulmonary veins, antral regions, and right atrial structures have been reconstructed in early three-dimensional image efforts (see Figure 22-2, *A*).[3] Knackstedt and colleagues reported a close to real-time technique using an AcuNav ICE catheter with a motorized sector scan and reconstruction of serial two-dimensional images. Animal and clinical testing validated the visualization of anatomic structures.[4] Okumura and colleagues applied online imaging and offline reconstruction of ICE imaging of pulmonary veins by using a pullback technique during ablation procedures in 29 patients.

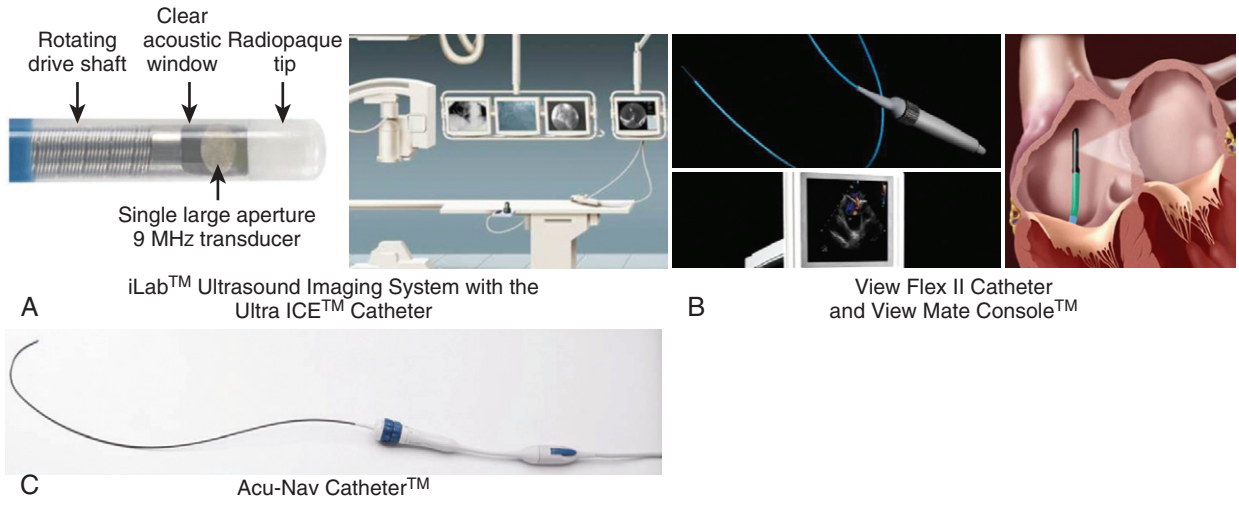

FIGURE 22-1 Three commercially marketed ultrasound systems with associated platforms and ultrasound catheters. **A,** Boston Scientific rotational mechanical ultrasound catheter (*left*) and display screen (*right*) in an interventional laboratory. The construction of the transducer and its elements are shown at *left*. **B,** St Jude Medical View Flex II phased-array catheter (*upper left*) and display console (*lower left*) with schematic of deflectable catheter in the right heart for left heart imaging (*right*). **C,** Biosense Webster AcuNav Steerable phased-array ultrasound catheter.

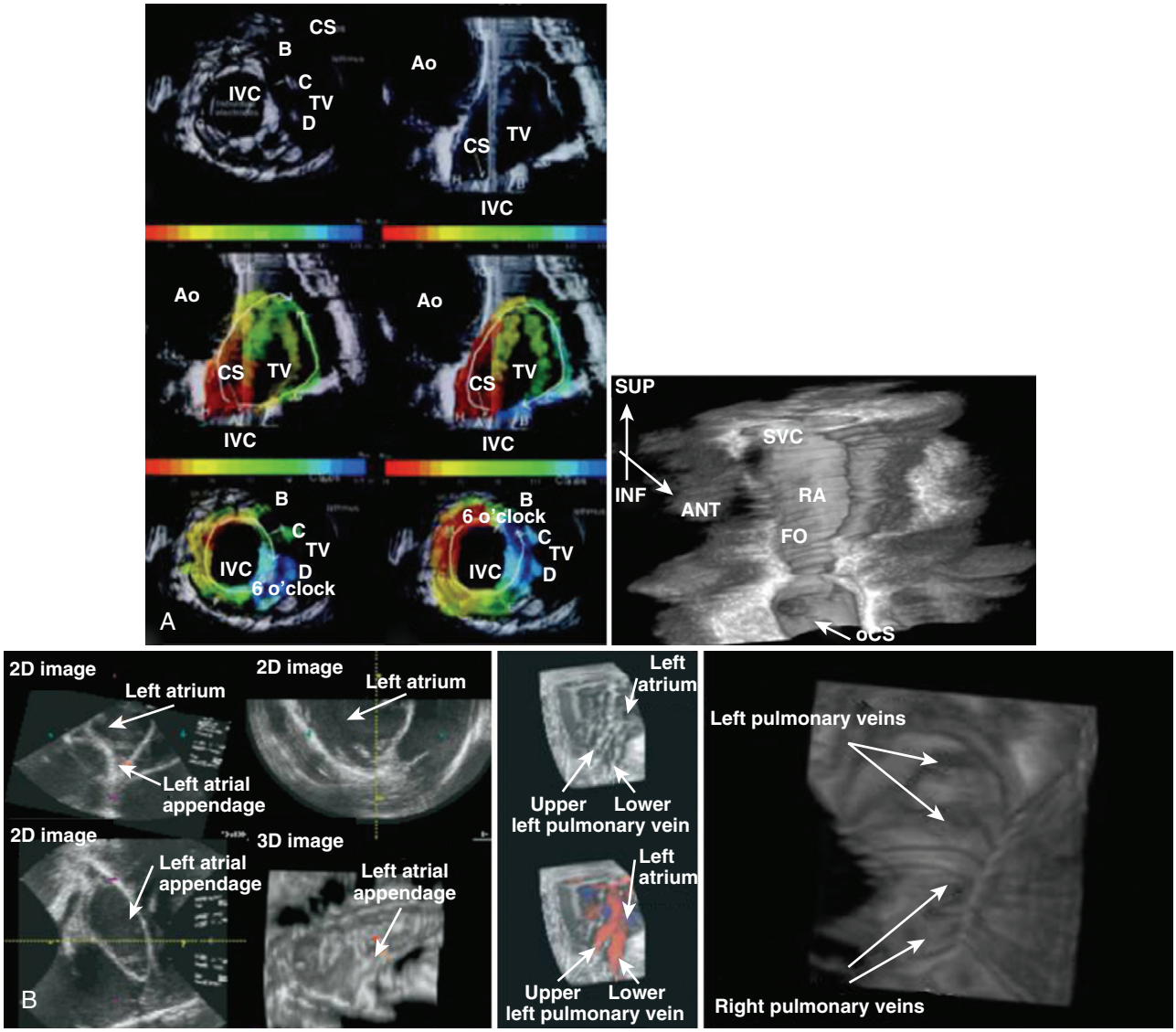

FIGURE 22-2 Three-dimensional reconstruction of right and left atrial and pulmonary vein regions with rotational and phased-array systems. **A,** Short- and long-axis sections of the right atrium displayed from a three-dimensional (*3D*) reconstruction of serial intracardiac echocardiography images using a rotational transducer combined with activation mapping overlap from a basket catheter in common atrial flutter *(left)*. The basket splines are shown in alphabetical order and the macro–re-entrant circuit is clearly visualized. *Right,* 3D reconstructed image of the right atrium showing the coronary sinus en face. **B,** Real-time two (*2D*) and (3D) images of the left atrium obtained with a motorized phased-array system *(left)*. Left atrial structures are visualized in a typical 2D view (*top, bottom left*), and reconstructed 3D view shows the left atrial appendage visualized in three dimensions (*bottom right*). Pulmonary veins, their ostia, and their antra are well shown in this 3D reconstruction of the anatomic interfaces of these structures *(right)*. *SUP*, Superior; *INF*, inferior; *ANT*, anterior; *SVC*, superior vena cava; *RA*, right atrium; *FO*, fossa ovalis; *oCS*, ostium of the coronary sinus. *(Modified from Simon RD, Rinaldi CA, Baszko A, Gill JS: Electroanatomic mapping of the right atrium with a right atrial basket catheter and three-dimensional intracardiac echocardiography,* Pacing Clin Electrophysiol *27:318–326, 2004; Smith SW, Light ED, Idriss SF, Wolf PD: Feasibility study of real-time three-dimensional intracardiac echocardiography for guidance of interventional electrophysiology,* Pacing Clin Electrophysiol *25:351–357, 2002; and Knackstedt C, Franke A, Mischke K, et al: Semi-automated 3-dimensional intracardiac echocardiography: Development and initial clinical experience of a new system to guide ablation procedures,* Heart Rhythm *3:1453–1459, 2006.)*

The images were computer reconstructed to visualize the entire length of pulmonary veins with a three-dimensional full motion image being developed. Radiofrequency (RF) lesions could be visualized and the extent of ablation between extensive and segmental ablation procedures assessed. The superior pulmonary veins were visualized in virtually all patients; the ablation sites were identified, pulmonary vein stenosis excluded, and comparable lesions sizes noted with both approaches.[5]

Baseline Image Acquisition Using Intracardiac Echocardiography

ICE catheters range in size from 7 to 10 Fr and can be inserted from a femoral or subclavian venous approach. Typically, right atrial entry is achieved under fluoroscopic guidance, although ultrasound-guided placement from a subclavian approach has

been used in some centers. In general, given the catheter dimensions and flexible yet firm tip, fluoroscopic guidance is strongly recommended to avoid vascular damage. In our experience, 3% of ICE catheter placements could not be achieved from a femoral approach, even with fluoroscopy, because of venous tortuosity. Although direct right atrial placement is feasible, left atrial and right ventricular placements typically require guiding sheaths. The former requires TSC, usually with a puncture of the interatrial septum at the fossa ovalis. The latter requires placement of a Mullen's sheath over a guidewire in the right ventricle.

Passage of the ICE catheter into the right atrium allows the initiation of baseline imaging of cardiac structures.[6] Baseline imaging requires visualization of the right atrium, the tricuspid valve, and the right ventricular inflow tract in the first image set. This is usually accomplished from a low to mid-right atrial placement of the phased-array transducer with the catheter body parallel to the spine. Tricuspid valve motion and trabeculation of the right ventricle and its inflow tract are identified. The coronary sinus ostium, the triangle of Koch, and the crista terminalis can also be imaged by sweeping and torquing the transducer viewing sector. The transducer can then be deflected and retroflexed to a septal imaging view in this location. On occasion, the transducer may need to be advanced or withdrawn to achieve good septal imaging. The fossa ovalis and its muscular margins are clearly seen. Aortic root and valve imaging is usually best achieved in a more superior right atrial location with retroflexion of the ICE transducer. Transducer imaging depth may be adjusted to achieve imaging of the left atrial pulmonary vein and LAA as well. Left atrial wall thickness and change in tissue image may be used to assess the extent of ablation, as can microbubble formation. The transducer may have to be deflected to visualize the ostia of the pulmonary veins and the appendage. It is important to torque the ICE catheter body to fully scan the left atrium from the superior to the posterior aspect to the inferiorly located mitral valve to look for thrombus, intracavitary echoes or "smoke," and septation such as in cor triatriatum. Pulmonary vein antra and ostia require care and imaging depth adjustment for optimal visualization from the right atrium. In contrast, rotational ICE catheter systems require a systematic scan from the superior to inferior right atrium for right atrial structure identification. Trans-septal puncture is not required for phased-array systems, but rotational ICE catheters need to be placed in the left atrium for adequate imaging, and the phased-array catheter may need trans-septal placement for mitral valve or left ventricular interventions. Right ventricular placement is useful for left ventricular imaging as well as in ventricular wall motion analysis, optimization of cardiac resynchronization therapy, and smoke or thrombus identification.

A complete ICE evaluation includes physiological information obtained from Doppler studies of the septum, including color-flow imaging, mitral, aortic and tricuspid valves, as well as pulmonary vein and LAA flow velocity measurements. A saline contrast injection may be performed to assess left-to-right shunts. Anatomic abnormalities such as an inter-atrial septal aneurysm may be more clearly defined with contrast or flow imaging. Additional views for imaging the LAA may be achieved from the coronary sinus or left pulmonary artery. In ventricular studies, septal to posterior wall motion delay can be used to assess intraventricular dyssynchrony. Intracavitary smoke and thrombi can be detected. Ascending and descending aortic imaging can be performed from the aortic valve and left atrial imaging sequences for plaque. Doppler flow in the ascending aorta can be used to optimize cardiac resynchronization therapy.

Anatomic accuracy has been judged by comparing ICE imaging to computed tomographic (CT) angiography. Jongbloed et al noted a high degree of concordance between the two methods for left atrial structural anatomy such as pulmonary vein anatomy and ostial and antral configurations and dimensions.[7] One prospective clinical trial has assessed ICE imaging compared with transesophageal echocardiography (TEE).[8] In unpaired analyses, an atrioseptal aneurysm was detected by TEE in 4 (9%) of 45 patients with TEE and in 5 (15%) of 34 patients with ICE. In paired analyses, there was no atrioseptal defect identified by either technique. The percentage concordance in paired analysis for the presence of a patent foramen ovale was 100% and 96% for atrioseptal aneurysms with the two techniques, respectively. Ascending aortic plaques were more often visualized by TEE, but descending aortic plaques were more often visualized by ICE. However, concordance between the two methods was quite modest, especially when plaque size was considered. Dense smoke, thrombus, or aortic plaque can potentially influence interventional procedures and should be carefully examined.

Use of Intracardiac Echocardiography to Guide Electrophysiological Procedures

Evaluation of the Left Atrium and Left Atrial Appendage

ICE can be used for anatomic and functional evaluation of the left atrium and its appendage with ultrasound imaging and Doppler flow measurements. For phased-array systems, imaging frequency must be optimized by the operator by using adjunctive gain, depth, and focal length controls to define anatomic structures and to minimize noise. Imaging can be performed at different levels in the right atrium if needed. Intracardiac physiology in the region of the appendage, mitral valve, and interatrial septum is examined with color-flow and spectral Doppler. Rotational systems require trans-septal puncture for imaging these structures. ICE can be used for evaluating chamber structure, malformations, spontaneous echo contrast, and thrombus. In addition, pulmonary vein antra and ostia as well as mitral valve function can be evaluated anatomically and functionally with Doppler flow measurements.

The left atrial cavity is visualized as an echo-free chamber, and the appendage is typically seen arising at the inferolateral aspect of the sector. Muscular ridges and trabeculation may be seen at the appendage base or even body. These must be carefully differentiated from thrombi. The pulmonary veins arise in the superior and inferior aspects. The pulmonary vein ostia are clearly seen, and flow rates and patterns in the veins can be defined. For example, mitral regurgitation can reverse flow in the veins during color-flow mapping. Pulmonary vein stenosis can increase flow rates because of stenotic obstruction. Thus changing flow velocity is a useful adjunct in the diagnosis of this condition. Actual visualization of the stenosis is more difficult and requires contrast studies.

Left atrial visualization for chamber diameter or wall thickness is not routinely performed with ICE, but very large chamber dimensions may preclude complete ICE imaging. Importantly, the proximity of the esophagus and the left atrium can influence posterior left atrial interventions. The esophagus can be visualized in posterior left atrial imaging when torquing the catheter to a medial view. The cavity of the left atrium is well visualized by ICE. The most common abnormality is the presence of

spontaneous echocardiographic contrast, which is defined as slow-moving, continuous echoes, indicating a low-flow state, swirling slowly within the structure cavity. When present, the gain should be systematically decreased to exclude noise artifacts caused by excessive gain. This contrast can be graded as *dense contrast* when contrast continuously fills the entire cavity of the structure and does not clear with cardiac cycle or as *mild contrast* when intermittent contrast is seen, often in only part of the structure. Intracavitary thrombi can be visualized. A thrombus in the left atrium or appendage can be seen as a dense well-circumscribed mass, which is usually immobile or can show varying degrees of mobility with a pedicle. It is acoustically distinct from the underlying endocardium or trabeculations. A thrombus is definitely present when it is well visualized in two or more views or may be suspected when seen only in one view. To fully visualize the LAA, two or more views are preferred, and it may be necessary to open the mouth and body of the appendage for inspection. Trabeculations may be common at the mouth and mimic a thrombus. Comparison among views is important for the accurate differentiation of thrombi from muscular ridges and trabeculations.

In the Intra-Cardiac Echocardiography–Guided Cardioversion to Help Interventional Procedures (ICE-CHIP) study, comparison with TEE showed no significant difference in the presence of spontaneous echo contrast between ICE and TEE during left atrial imaging, but there was a significantly greater incidence of spontaneous echo contrast in the appendage detected with TEE compared with ICE ($P = .005$).[8] Percentage concordance for the presence of spontaneous echo contrast was 65% for the two techniques for the left atrium and 60% for the two techniques of the LAA. Dense contrast was seen in the left atrium in 12.5% of ICE studies and 16.9% of TEE studies. In the LAA, dense contrast was less common with ICE (ICE, 5.3% vs. TEE, 15.7%). The LAA is visualized with both techniques, and the presence of spontaneous echo contrast in both the left atrium and the LAA is clearly seen. Intracardiac thrombus was uncommonly seen with both techniques (TEE, 6.9% vs. ICE, 5.2%) with a percentage concordance for the presence or absence of thrombus of 97% in the left atrium and 92% in the LAA. Probable thrombus in the left atrium was actually detected more frequently by ICE, but the presence of thrombi in the appendage was more frequently detected or reported with TEE. In view of this, ICE should be complemented with TEE for LAA thrombus, particularly if limited views and poor-quality images are obtained. Other approaches, such as coronary sinus placement of the ICE probe, have been suggested to improve appendage imaging, particularly if ablation or cardioversion of AF is contemplated.[9]

Other findings may have implications for thrombus presence or development after intervention or cardioversion. In the ICE-CHIP study, all patients with left atrial or appendage thrombus had dense or moderate smoke in the cavity. Thus the absence of spontaneous echo contrast is an important negative finding in assessing thrombotic risk. Low appendage flow velocities are typically present in patients with thrombi. Thus a Doppler flow measurement would have value in assessing risk.

Percutaneous Left Atrial Appendage Occlusion

Approximately 90% or more of thrombi formed in patients with AF arise in the LAA. Although effective in reducing the risk of thrombus formation, anticoagulation therapy can be onerous and associated with significant risk. As such, LAA occlusion devices are being investigated as possible alternatives to anticoagulation for thromboembolic risk reduction in patients with AF.[10,11]

These devices are membrane-covered, flexible, nitinol cages designed to expand to completely occlude the LAA ostia. Each device is delivered percutaneously from a femoral vein, across the interatrial septum, into the LAA. Multiple imaging modalities, including fluoroscopy/angiography, TEE, and ICE, are used during device implantation. Imaging is required to rule out LAA thrombus; to evaluate the size, shape, and orientation of the LAA ostium; to guide proper positioning and orientation of the occlusion device before deployment; to confirm appropriate device position after deployment; and to assess for complete occlusion of the appendage after deployment.

To date, ICE has been used primarily to guide trans-septal puncture with imaging from the right atrium. However, one study compared imaging with ICE versus TEE in 10 patients undergoing placement of the percutaneous LAA transcatheter occlusion (PLAATO, ev3, Plymouth, MN) device.[12] ICE and TEE images were found to be comparable, especially when ICE imaging was performed from the coronary sinus and the proximal pulmonary artery. In particular, the absence of LAA thrombus was confirmed by ICE imaging along with TEE imaging, and LAA ostial dimensions measured by ICE were comparable to those measured by TEE.

Certainly, larger scale studies are required to confirm the safety and efficacy of ICE imaging without TEE imaging to guide LAA occlusion device placement procedures. Because the use of TEE usually requires the two additional operators (echocardiographer and anesthesiologist), ICE and fluoroscopy or angiography, alone, could potentially simplify the logistics and reduce the cost of this procedure.

Trans-septal Catheterization

TSC has become an integral component of many EP procedures, including ablation for AF, atrial tachycardia (AT), accessory pathways, and VT. Historically, fluoroscopy alone was used to guide TSC.[13] However, with the advent and advance of technology, ICE has allowed more nuanced and detailed imaging during TSC.

To begin, ICE allows a survey of the baseline anatomy, as previously discussed. With ICE, an operator can document the presence or absence of pericardial fluid as well as the relationship of critical cardiac structures—such as the aortic root and the posterior or lateral wall of the left atrium—to the fossa ovalis, which is the target of TSC. The fossa ovalis itself can be well characterized in terms of its length and thickness, which can be especially useful for cases requiring repeat TSC in which areas of thickening or scar can be more readily identified. As well, the presence of a patent foramen ovale may be suggested by the fossa ovalis morphology and confirmed with the application of color-flow Doppler.

During TSC itself, ICE more clearly delineates the relationship between the TSC apparatus (needle, dilator, and sheath) and the fossa ovalis. ICE allows optimal positioning of the tip of the apparatus in the fossa ovalis, away from surrounding structures such as the aortic root and the non-fossa aspects of the interatrial septum. Small adjustments away from these critical structures can be made with relatively direct visualization with ICE. ICE also provides more selective location of TSC, that is, more mid to inferiorly versus superiorly in the fossa. Once the trans-septal apparatus is optimally positioned, the fossa ovalis can be seen to "tent." Once the needle has successfully crossed, resolution of the

tenting can be visualized, as can nonagitated saline injected into the left atrium to confirm successful crossing.

Finally, ICE, unlike fluoroscopy alone, can display catheter-related and sheath-related thrombi, which may allow for timely removal. Fluoroscopy, angiography, and pressure monitoring remain indispensable to guide TSC, and ICE has become a remarkably useful tool in guiding crossing of the interatrial septum.

Catheter Ablation Procedures

ICE is potentially useful during catheter ablation of supraventricular and ventricular arrhythmias.[14,15] The images obtained by ICE provide detailed anatomic information in real time. Such detail is not possible by fluoroscopy and is not associated with radiation exposure. The addition of intravenous contrast for angiography does not generally provide the same degree of detail as ICE, the images are no longer available in real time, and radiation exposure is increased. In addition, the intravenous contrast necessary for angiography may be problematic for patients with renal insufficiency or pre-existing allergy to the contrast agent. ICE imaging during EP procedures may also help detect complications such as pericardial effusion and tamponade and thrombus formation or char on the catheter. Thus ICE has several potential advantages over conventional forms of imaging for EP procedures and may therefore be a valuable tool.

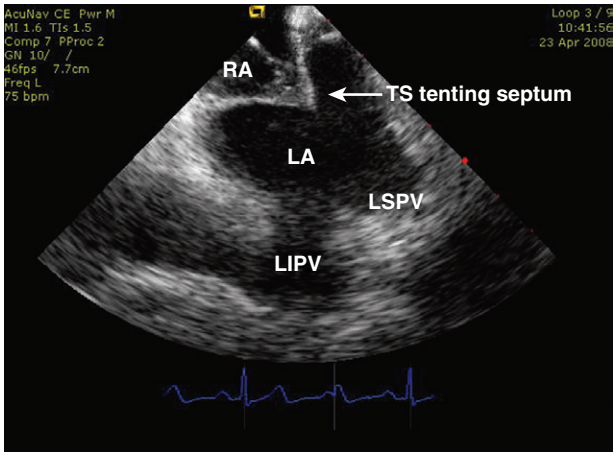

FIGURE 22-3 Intracardiac echocardiography image of the atrial septum, left atrium (*LA*), and proximal left pulmonary veins during trans-septal puncture. Note the trans-septal sheath apparatus (*TS*) tenting the atrial septum with the left pulmonary veins in the same imaging plane to help cross the septum sufficiently posterior. *LIPV*, Left inferior pulmonary vein; *LSPV*, left superior pulmonary vein; *RA*, right atrium.

Intracardiac Echocardiography Guidance During Catheter Ablation of Atrial Fibrillation

Many of the applications of ICE have specific benefits in catheter ablation of AF. In fact, ICE has become an invaluable tool for many interventional electrophysiologists involved in AF catheter ablation.[16,17] Applications of this technology for AF catheter ablation are numerous and include guidance of the trans-septal puncture(s), evaluation for LAA thrombus, evaluation of left atrial dimensions and anatomic features, monitoring of the catheter-tissue interface, visualization of adjacent structures, and monitoring for complications. The Doppler features may be used to evaluate flow in the pulmonary veins, LAA, and cardiac valves.

The use and potential benefit of ICE for the guidance of trans-septal punctures has already been discussed. This is particularly important for operators who perform the procedure without interruption of oral anticoagulation (e.g., warfarin). Performing the procedure without interruption of such anticoagulation has been shown to be safe and avoids the issues that may be encountered with the interruption of warfarin, such as the need for TEE to exclude atrial thrombus and the need for "bridging" with intravenous or subcutaneous heparin after the procedure.[18] In addition, for AF catheter ablation, the importance of avoiding a puncture too far anteriorly on the atrial septum should be emphasized because an anterior puncture may result in difficulty reaching the pulmonary veins with the catheter, particularly the right inferior pulmonary vein. Some electrophysiologists therefore target the posterior portion of the atrial septum by using an ICE imaging plane that contains the left pulmonary veins to ensure a sufficiently posterior puncture (Figure 22-3).

The phased-array technology for ICE imaging provided a distinct advantage over the radial technology. The main advantage of phased-array systems is the ability to image a much greater depth of field. For AF catheter ablation, this allowed visualization of left atrial structures, including the proximal portions of the pulmonary veins, with the imaging catheter remaining within the right atrium (see Figure 22-3). This is particularly important for AF catheter ablation techniques that already use two catheters in the left atrium because it avoids the need for a third catheter in the left atrium for ICE imaging, as would be required for radial technology ICE imaging.

A valuable application of phased-array ICE imaging during AF catheter ablation is the ability to visualize the proximal portions of the pulmonary veins. All the pulmonary veins may be visualized with very little manipulation of the ICE catheter other than rotation. The left pulmonary veins are generally viewed in a longitudinal view. The right pulmonary veins may be easily viewed in a cross-sectional plane, but the ICE catheter may be manipulated with relative ease to provide longitudinal views. This requires a varying degree of retroflexion of the ICE catheter and placement of the catheter just superior to the tricuspid valve. The longitudinal view of the pulmonary vein is best to determine the position of the circular mapping catheter relative to the os and vestibule or antrum of the vein. The importance of such positioning is considered by many operators to be crucial for AF catheter ablation; the application of RF ablation energy within the pulmonary vein was associated with an unacceptably high incidence of pulmonary vein stenosis and a lower rate of efficacy because of lack of ablation of more proximal trigger sites.[19] Figures 22-4 and 22-5 show examples of ICE and fluoroscopy images of the circular mapping catheter positioned at the antrum of various pulmonary veins. The longitudinal view of the right pulmonary veins is especially helpful to avoid delivering ablation lesions too far distally within the pulmonary vein (Figure 22-6, *A* to *D*).

With the advent of newer balloon-based catheter ablation systems for pulmonary vein isolation, ICE imaging may be useful to verify proper contact and alignment of the balloon with the antrum or os of the pulmonary vein and, with the use of Doppler, verify proper contact with the tissue by demonstrating lack of blood flow around the balloon from within the pulmonary vein.

ICE imaging is also potentially valuable for the detection of complications during interventional EP procedures. As previously

discussed, AF catheter ablation is performed at many centers without interruption of oral anticoagulation, in addition to administration of intravenous heparin throughout the procedure, often to aggressive levels of anticoagulation. Taking this into consideration, perforation and tamponade are an even greater concern, especially when maneuvering the catheters in potentially fragile areas such as the LAA. The ICE catheter can be quickly moved to the right ventricle to obtain excellent images of the left ventricle and the pericardial space, quickly providing an evaluation for the presence of pericardial effusion (Figure 22-7). This may rapidly distinguish between hypotension related to sedative medications or anesthesia versus that related to cardiac tamponade. In addition, a pericardial effusion may be detected prior to any hemodynamic compromise, allowing more expeditious treatment.

Other complications that ICE may detect include thrombus or char formation on the catheters or intravascular sheaths (Figure 22-8).[14,16] This complication may be less likely to occur with more aggressive anticoagulation regimens and perhaps with

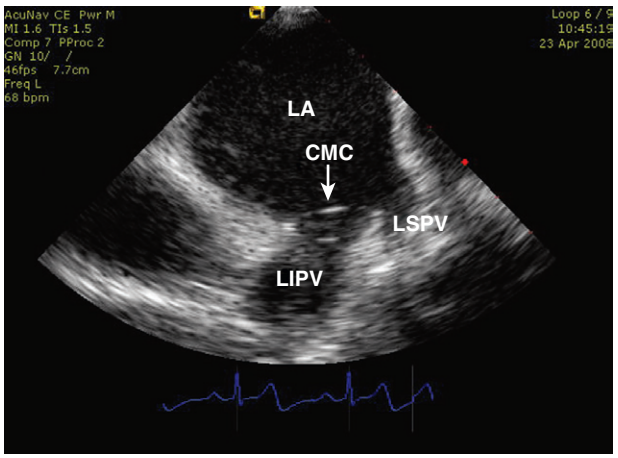

FIGURE 22-4 Intracardiac echocardiography image of the left atrium (*LA*) and left pulmonary veins demonstrating a circular mapping catheter (*CMC*) positioned at the antrum of the left inferior pulmonary vein (*LIPV*). *LSPV*, Left superior pulmonary vein.

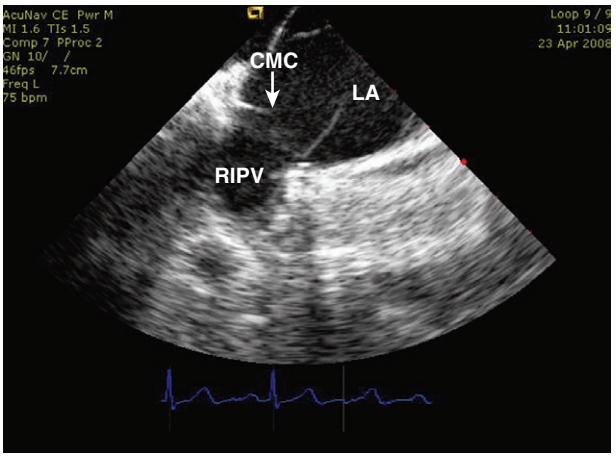

FIGURE 22-5 Intracardiac echocardiography image of the left atrium (*LA*) demonstrating the circular mapping catheter (*CMC*) at the antrum of the right inferior pulmonary vein (*RIPV*).

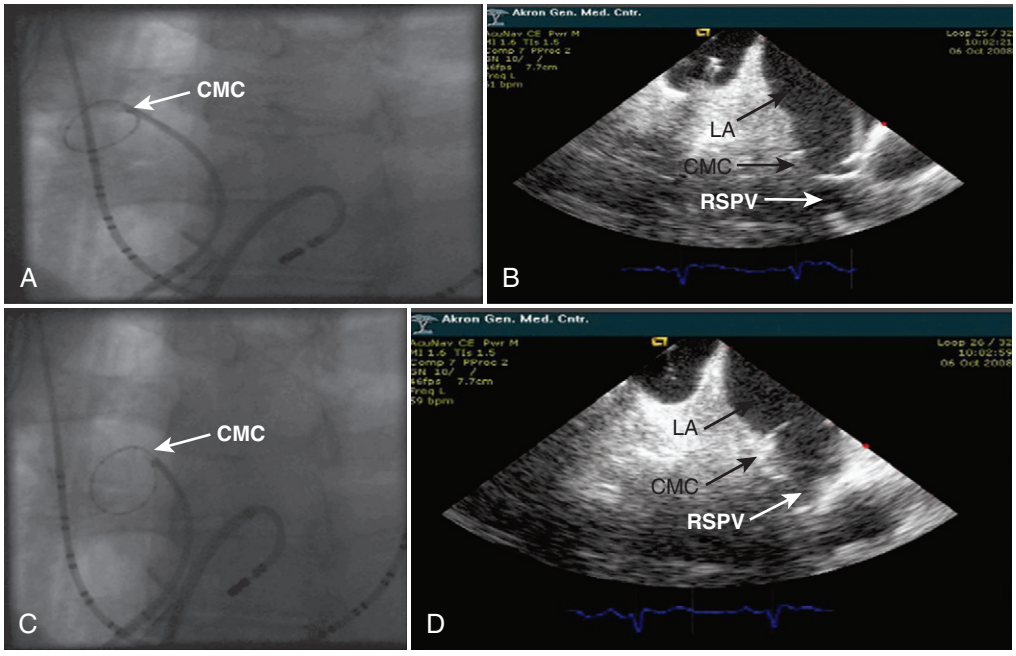

FIGURE 22-6 Intracardiac echocardiography (ICE) and corresponding fluoroscopic images demonstrating a distal location of the circular mapping catheter (*CMC*) within the right superior pulmonary vein (*RSPV*) (**A,** fluoroscopic image; **B,** ICE image) and a more proximal location of the CMC appropriately at the antrum of the right inferior pulmonary vein (**C,** fluoroscopic image; **D,** ICE image). The fluoroscopic images are in a left anterior oblique projection. The ICE images show the right inferior pulmonary vein in a longitudinal view. *LA*, Left atrium.

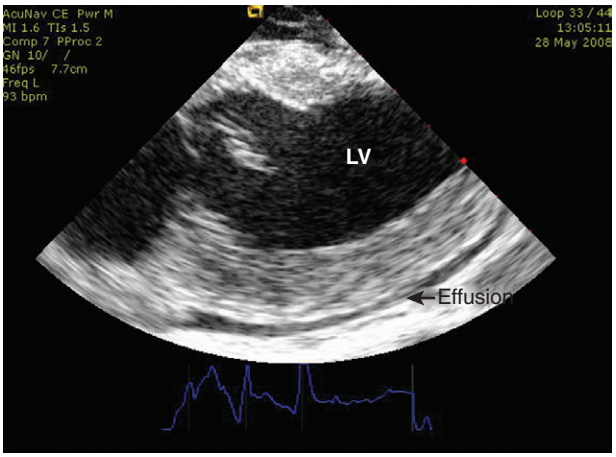

FIGURE 22-7 Intracardiac echocardiography (ICE) image of the left ventricle (*LV*) in longitudinal view, demonstrating a pericardial effusion that appears as a hypoechoic region outside the ventricular myocardium (*arrow*). This image is obtained by retroflexion of the ICE catheter and positioning the catheter across the tricuspid valve and within the right ventricle.

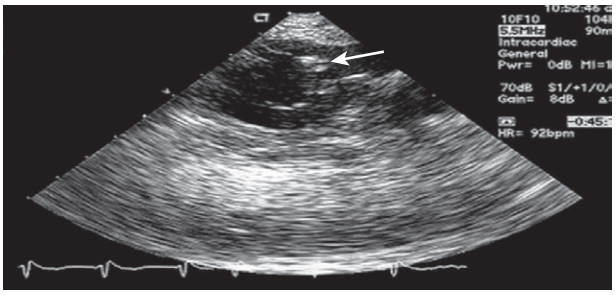

FIGURE 22-8 Intracardiac echocardiography image of a circular mapping catheter within the left atrium. A mobile echodensity is demonstrated on the catheter (*arrow*).

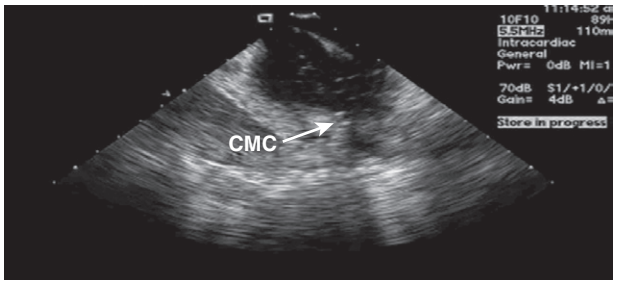

FIGURE 22-9 Intracardiac echocardiography image of the left atrium. An ablation catheter is delivering radiofrequency ablation energy near the circular mapping catheter (*CMC*). Formation of microbubbles is demonstrated.

open-irrigation ablation systems. Also, there has been increased attention on the avoidance of esophageal complications during catheter ablation of AF.[20] The esophagus may be imaged with ICE, which may help guide the AF catheter ablation procedure.[14,16,20]

ICE has been used to monitor the ablation catheter-tissue interface and guide the application of ablation energy. Before the advent and popularity of the use of open-irrigation RF catheter ablation systems, many operators were concerned about the potential adverse effects of overheating of tissue at the catheter-tissue interface when using conventional nonirrigated tip ablation catheters. With such systems, overheating could lead to coagulum and char formation at the tip of the ablation catheter and also at the adjacent circular mapping catheter. Severe overheating could also result in damage to adjacent structures such as the esophagus or result in an atrial tissue explosion. The latter event could increase the risk for embolic stroke during the procedure. A technique in which ICE imaging is used to guide power titration during the application of ablation energy such that the presence of microbubbles was considered indicative of tissue overheating has been developed.[19] Therefore, the technique involved continuous ICE monitoring of the catheter-tissue interface during the entire period of ablation energy delivery, with titration of power output performed such that power output was maximized to just under the power that caused microbubble formation (Figure 22-9). This technique was shown to be associated with a higher degree of safety and efficacy compared with traditional catheter ablation techniques.[21] Overheating of the esophagus was demonstrated to be less likely with this technique of power management.[20] However, this technique has more recently fallen out of favor with the increasing use of open-irrigation RF catheter ablation systems, in which the active irrigation of saline at the catheter tip obscures the delineation of microbubbles. Fortunately, the open-irrigation ablation technology seems to substantially reduce the problem of overheating at the catheter-tissue endocardial interface, so the perceived need for monitoring of microbubbles has lessened.

Thus ICE imaging has many potential applications in the catheter ablation of AF. The use of new techniques and technologies in the catheter ablation of AF will most likely continue to be enhanced and complimented by the use of ICE imaging.

Intracardiac Echocardiography Guidance During Catheter Ablation of Ventricular Arrhythmias

ICE imaging may be helpful for catheter ablation procedures targeting ventricular arrhythmias.[14,22-24] First, it can help with access to the left ventricle if a trans-septal approach is needed rather than a retrograde aortic approach. As previously mentioned, ICE can guide trans-septal puncture. The trans-septal approach allows the mapping or ablation catheter to obtain access to the left ventricle without the need for arterial access. This could be important for patients with severe peripheral vascular disease, an aneurysmal or heavily calcified aorta, or a diseased or prosthetic aortic valve. Also, some operators using newer robotic catheter ablation systems may favor or even require a trans-septal approach to the left ventricle. However, if an operator is using a retrograde aortic approach and is having difficulty with crossing the aortic valve with the catheter, ICE is capable of providing imaging of the aortic valve and the proximal aorta and may therefore provide insight into any structural abnormalities that could be impeding access. ICE can be used to monitor for complications such as tamponade and may also provide images of the catheter-tissue interface.

Perhaps the most common type of ventricular arrhythmia catheter ablation in which ICE may provide additional guidance is the aortic cusp variant of outflow tract VTs.[24] ICE is capable of providing images of the aortic valve, sinuses of Valsalva, the aortic

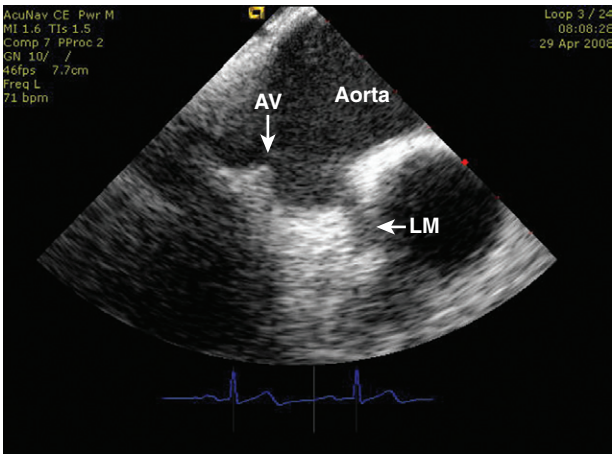

FIGURE 22-10 Intracardiac echocardiography image of the aortic valve (*AV*) and proximal aorta in longitudinal view. Note the left main coronary artery (*LM*) arising from the left coronary cusp.

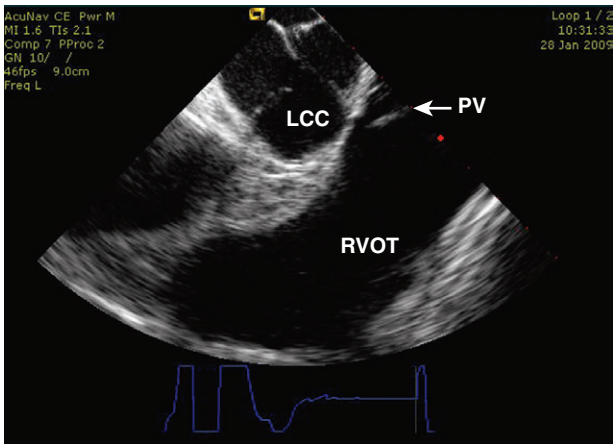

FIGURE 22-12 Intracardiac echocardiography (ICE) image of the aortic valve in cross-sectional view. Note the demonstration of the close relationship of the right ventricular outflow tract, pulmonic valve (*PV*) and the aorta, particularly the left coronary cusp (*LCC*).

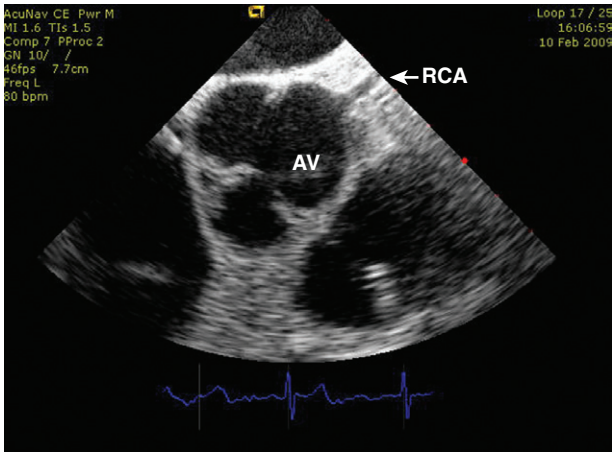

FIGURE 22-11 Intracardiac echocardiography image of the aortic valve (*AV*) in cross-sectional view. Note the right coronary artery (*RCA*) arising from the right coronary cusp.

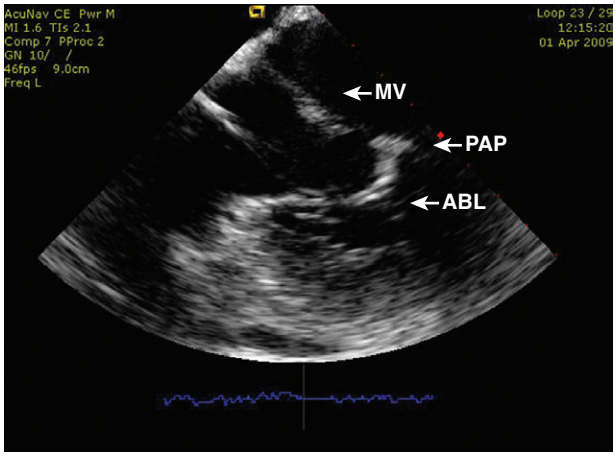

FIGURE 22-13 Intracardiac echocardiographyimage of the left ventricle in longitudinal view. Note the mapping or ablation catheter (*ABL*) crossing the mitral valve (*MV*) with its tip in contact with a papillary muscle (*PAP*).

root, and the proximal portions of the coronary arteries (Figures 22-10 to 22-12). Such images can be useful to guide the mapping or ablation catheter within the coronary cusp, particularly the left coronary cusp.

More recently, ICE has been used during catheter ablation procedures for ventricular arrhythmias associated with structural heart disease. ICE may provide excellent quality images of the left ventricle, both in longitudinal and cross-sectional planes. Such images can provide useful anatomic information such as myocardial thickness as well as real-time imaging of the catheter-tissue interface. This may allow assessment of catheter contact and perhaps also direct visualization of ablation lesion formation. Imaging of the papillary muscles could be important because an electroanatomic map may suggest that the catheter is not in contact with the endocardium (i.e., the point appears to be internal) when, in fact, the catheter is appropriately positioned on a papillary muscle in excellent contact (Figure 22-13).

ICE may be useful to evaluate regions of myocardial scarring. Identification of regions of myocardial scarring, particularly of scar border zones, may be very helpful in the guidance of such catheter ablation procedures. Figure 22-14 demonstrates a patient with a previous septal myocardial infarction who underwent catheter ablation for VT. The mapping or ablation catheter was manipulated by a remote magnetic navigation system. The VT was mapped to the scar border zone and successfully ablated.

Overall, the use of ICE during catheter ablation procedures is still a fairly new application for this technology. However, interventional electrophysiologists are already realizing the importance of the anatomic details available in real time with such imaging. As catheter ablation procedures become more reliant on substrate-based approaches, this demands a better understanding and visualization of cardiac anatomy and the relative positions of the EP catheters to the target ablation site and surrounding structures. ICE imaging is an important advance in imaging modalities

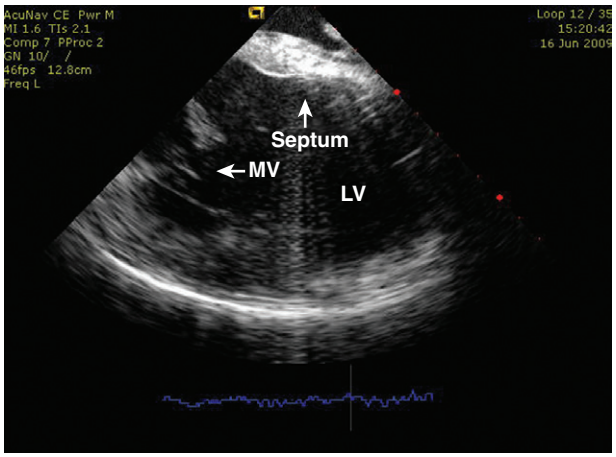

FIGURE 22-14 Intracardiac echocardiography image of the left ventricle (*LV*) in longitudinal view, demonstrating myocardial scar involving the mid to distal septum. *MV*, Mitral valve.

that meets many of these demands. More recent advances in ICE imaging technology are quite promising, such as three-dimensional imaging and integration with other imaging modalities such as CT or magnetic resonance imaging and electroanatomic systems.[25,26] Such developments, some of which are discussed below, will likely enhance the already important role of ICE imaging for catheter ablation procedures and provide the electrophysiologist with improved tools for better safety and efficacy of such procedures.

Image Integration or Intracardiac Echocardiography Fused with Electrophysiology Mapping

Three-dimensional imaging has become essential for orientation, mapping, and lesion delivery during complex EP procedures such as AF and VT ablation. Historically, three-dimensional electroanatomic mapping systems allowed real-time chamber reconstruction based on information acquired by mapping catheters as a part of the ablation procedure. Next, software was developed to allow three-dimensional CT reconstructions (usually acquired days before the procedure) to be imported into the mapping system and integrated with the real-time chamber reconstruction. This provided a more nuanced and detailed map of the chamber of interest but carried the disadvantage of temporal separation (and thus a hemodynamic or volume difference translating into possible anatomic differences) between the two images as well as increased exposure to intravenous contrast and ionizing radiation.

More recently, ICE-based three-dimensional reconstruction technology has been developed. Here, two-dimensional images are acquired in multiple planes with critical cardiac structures (e.g., left atrium, mitral valve, and left, right, superior, and inferior pulmonary veins) outlined and labeled in each plane. Imaging is usually performed from the right atrium, although one study showed a slightly lower integration error with imaging from the left atrium.[27] These labeled images are then combined to create a three-dimensional shell, which can then be merged with the shell created by an electroanatomic mapping system or three-dimensional CT reconstruction. The addition of the three-dimensional ICE reconstruction provides improved real-time, three-dimensional understanding of catheter and lesion placement and may obviate the need for CT imaging (and its attendant contrast exposure).

The next step in ICE imaging is the development of direct, real-time, three-dimensional imaging, eliminating the current need for the time required for three-dimensional ICE reconstruction (tracing structures, acquiring multiple planes of images).

Summary

As percutaneous intracardiac procedures increase in number and type, the applicability and usefulness of ICE grow, especially in cardiac EP. Future directions for ICE imaging include the development of real-time, three-dimensional ICE imaging as well as the combination of ICE imaging with EP interventional tools.

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CHAPTER 23

Principles and Techniques of Cardiac Catheter Mapping

Indrajit Choudhuri and Masood Akhtar

Introduction to Catheter Mapping

The cardiac electrophysiology mapping study is an invasive, stepwise, and logical exploration of tissue characteristics, associated stimulation and propagative responses, and activation characteristics of cardiac arrhythmia. In contemporary electrophysiology, it is *the* diagnostic methodology that guides ablation. While cardiac arrhythmia mapping was founded in the surgical theater in pursuit of accessory pathways and life-threatening ventricular tachycardia (VT) circuits, percutaneous catheter-based techniques have expanded the role of mapping and ablation to permit the evaluation and treatment of all manners of arrhythmias arising from endocardial, epicardial, and even perivascular sites for a variety of indications.

Mapping as Process

Intracardiac mapping refers to sampling of endocardial myocardial potentials for substrate analysis and arrhythmia diagnosis. Potentials are recorded by percutaneously introduced intracardiac electrode catheters, and their signal characteristics are evaluated in the context of the recording site and the underlying rhythm to deduce the putative arrhythmia mechanism and associated sites of involvement. Data may be collected using contact mapping in either a point-by-point and beat-by-beat manner, which requires both sustained arrhythmia and local contact between the recording electrode and myocardial surface, or through noncontact mapping that extrapolates global activation during isolated arrhythmia beats and do not require sustained arrhythmia or direct myocardial contact.

Contact catheter mapping techniques have been employed extensively for more than half a century and form the basis of all current mapping strategies. Mapping is often performed during the rhythm of interest—largely tachycardias of both supraventricular and ventricular origins. However, the arrhythmia cannot be directly evaluated in some because of hemodynamic intolerance or noninducibility or because the evaluation requires adjunctive data. In such cases, *substrate* mapping is performed during sinus rhythm or pacing to evaluate myocardial characteristics and to provide clues to the arrhythmia mechanism and critical sites of involvement. Substrate mapping for tachycardias of supraventricular origin, whether true paroxysmal supraventricular tachycardias (SVTs), atrial fibrillation (AF), or atrial flutters, has not been demonstrated to be routinely useful, though it continues to be investigated in conjunction with newer imaging techniques. Alternatively, substrate mapping is a mainstay of VT evaluation and is addressed separately.

Significance of the Local Electrogram

The single interpretive link between a tachycardia and the operator is the local electrogram (EGM). Proper interpretation of EGMs relies on simultaneous evaluation of signal morphology, timing, and location to identify sites of involvement and arrhythmia mechanism, which may then guide therapy, whether medical, electrical, or ablative. A comprehensive understanding of the significance and implications of the local EGM is therefore critical to the deductive process of catheter mapping.

The intracardiac EGM is a graphical representation of localized cardiac electrical activity occurring in the region of the recording electrodes. From a purely signal-processing perspective, the EGM is determined as the instantaneous difference between signals recorded from two electrodes, at least one being intracardiac, and the second either also intracardiac (*bipolar* configuration) or positioned more remotely (*unipolar* configuration), for example, in an intravascular position, or connected to the "Wilson" central terminal or system ground. The "local" myocardial region contributing to the EGM is relative, related to the distance between recording electrodes as well as the specific recording configuration. More closely spaced electrodes are generally insensitive to far-field components and improve the fidelity of the near-field signal but at the cost of signal amplitude; wider-spaced electrodes, however, will detect signal from a larger region and record a greater amplitude, but they may dilute the local signal detail with detected far-field elements (Figures 23-1 and 23-2).

By convention, electrodes within the heart are termed *exploring electrodes*, as they are "exploring" or detecting from the region of interest, whereas those placed remotely are termed *indifferent electrodes*, as their contribution is minimized, given that signal amplitude is inversely proportional to the square of the distance to the source. A unipolar signal, which is obtained when recording between an exploring electrode and an indifferent electrode, incorporates the features of both near-field and far-field signals detected from the myocardium spanning the distance between the electrodes. A bipolar signal is given by the *difference between unipolar signals* recorded from each of the two exploring electrodes, which usually are closely spaced, and so depicts only the near-field electrical activity, with little or no far-field contribution.

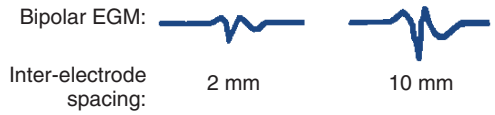

FIGURE 23-1 Effect of interelectrode spacing on bipolar electrogram *(EGM)* (filtering: high-pass >30 Hz, low-pass <500 Hz). With 2-mm interelectrode spacing, the local bipolar EGM (recorded from a septal location near the superior aspect of the tricuspid valve) has multiple "sharp" deflections of low amplitude compared with the same signal recorded with 10-mm interelectrode spacing, producing a larger amplitude signal, though with deflections that are more rounded.

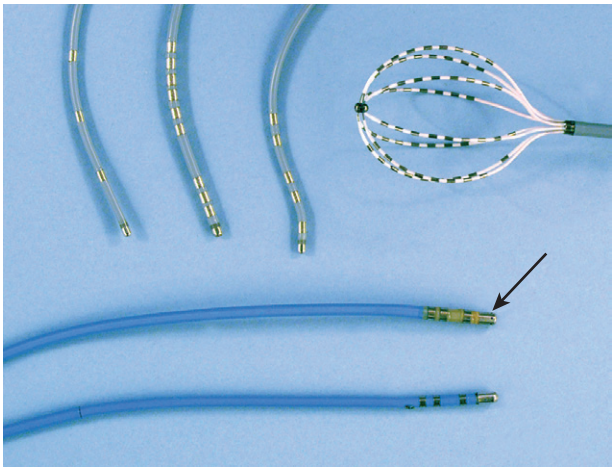

FIGURE 23-2 Examples of multi-electrode catheters used for intracardiac mapping. *Clockwise from top left*: Three diagnostic catheters with different interelectrode spacing and electrode distribution; multi-splined catheter with multiple closely spaced electrodes per spline; and two mapping catheters, each with a pair of bipoles in which the distal electrode has a larger surface area and may be used for delivering radiofrequency energy for the purpose of ablation. Note the upper of the two ablation catheters has small holes or ports (*arrow*) at the distal tip of the distal electrode, permitting irrigation during ablation.

Utility of the Unipolar Electrogram

The minimally filtered unipolar EGM manifests an initial positive deflection when a propagating signal approaches the exploring electrode and then a rapid negative deflection as the signal moves away from it, which results in an rS, or RS, morphology. When the exploring electrode is positioned at or beyond a nonconductive boundary (e.g., within scar), such that the signal can only move *toward* the recording electrode but then cannot continue to propagate past it, the unipolar EGM assumes an essentially upright R, or Rs, morphology. As the exploring electrode is moved within "range" or close to an arrhythmogenic focus, the amplitude and duration of the initial positive deflection decreases, and the negative deflection predominates. When the exploring pole is positioned *at* an arrhythmogenic focus (e.g., origin of focal atrial tachycardia [AT]), or close to a nonconductive boundary such that the signal can only propagate *away* from the electrode (e.g., VT exit site or accessory pathway insertion), a QS morphology

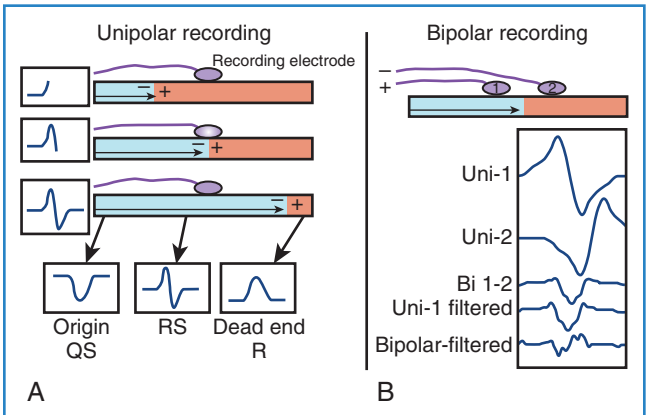

FIGURE 23-3 Generation of unipolar and bipolar electrograms (EGMs). **A,** The unipolar EGM consists of signal detected between two electrodes, of which only one electrode records cardiac signal and the other contributes little or no signal; the lack of contribution by the second electrode is achieved by placing it remote from the heart (i.e., extracardiac). With unipolar recording, a positive deflection is inscribed as a depolarizing wavefront approaches the recording electrode. The signal then returns to baseline when the wavefront reaches the electrode (as it can no longer "approach" the electrode), and subsequently a negative deflection is inscribed as the signal moves away from the recording electrode. If the electrode were positioned at an electrical dead end, such as next to unexcitable tissue, then the signal can only approach the electrode but not move past it and away from it; thus it inscribes only a positive deflection. If the electrode were positioned at a location such that the signal could only move away from the electrode, for example, at a depolarizing focus (e.g., origin of focal atrial tachycardia), then only a negative deflection is inscribed. **B,** The bipolar EGM consists of the difference signal generated by the two temporally disparate unipolar EGMs resulting when a depolarizing wavefront approaches the pair of electrodes contributing to the recording bipole. In bipolar recording configuration, the interelectrode distance is usually less than a few centimeters and may even be only a few millimeters, and the EGM consists of the difference between the two time-aligned unipolar EGMs recorded by each electrode comprising the recording bipole. As a depolarizing wavefront approaches a recording bipole, the unipolar signal recorded at the distal pole (*Uni-1*) is added to the inverted unipolar signal detected at the proximal electrode (*Uni-2*) by convention, resulting in a *difference* signal. Though both electrodes record the same signal, they do not record them at the same time because the electrode closer to the approaching wavefront will record a signal earlier in time than the other electrode, thereby introducing a temporal separation in the recorded signals such that the signals do not cancel. The far-field, low-frequency components of each unipolar electrogram are similar and essentially *do* cancel, but the high-frequency signals are preserved, and the resultant EGM contains multiple notches and deflections not seen in either of the two unipolar EGMs, representing the instantaneous differences in the signals. Hence the high-pass filtered unipolar EGM (*Uni-1 filtered*) resembles the unfiltered bipolar EGM. Further high-pass filtering of the bipolar EGM (*Bipolar-filtered*) removes more low-frequency components and enhances the high-frequency characteristics, resulting in a sharper, notched EGM. *(From Stevenson WG, Soejima K: Recording techniques for clinical electrophysiology,* J Cardiovasc Electrophysiol *16:1017–1022, 2005.)*

EGM results with a rapid initial downstroke (Figure 23-3, *A*; Figure 23-4). The maximum negative slope (intrinsic deflection) of the unipolar EGM coincides with depolarization of tissue directly beneath the recording electrode.[1] As such, the unipolar EGM may provide information on proximity to an arrhythmia

focus because of this sensitivity to far-field signals, and so may be iteratively evaluated to navigate toward and identify an arrhythmogenic focus or site of early activation. Although the unipolar EGM encodes whether the wavefront propagation is toward or away from the exploring electrode, it cannot further distinguish the specific direction of wavefront propagation.

While applicable for mapping focal tachycardias, unipolar recordings are somewhat limited in evaluating macro–re-entry when the circuit is entirely contained within a single chamber, as wavefronts arriving from all sites in the circuit would be expected to produce R waves.[2]

Utility of the Bipolar Electrogram

Bipolar EGMs are obtained from two exploring electrodes in relative proximity, each recording in unipolar configuration (see Figure 23-3, *B*). The lower-frequency components of the unipolar signals are contributed by essentially the same far-field signal and are canceled when their difference is obtained. However, the instantaneous local signals under each electrode differ, primarily in local activation time, voltage and frequency response, and propagation characteristics, generating a bipolar EGM with one or more rapid deflections (Figures 23-4 and 23-5).

Bipolar EGMs are particularly useful when mapping regions of abnormal and scarred tissue, as such sites tend to produce higher-frequency and lower-amplitude EGMs that may be otherwise obscured with unipolar mapping because of the contribution of the larger-amplitude far-field signal from surrounding healthier tissue. When effective ablation is delivered at a particular site, it is commonly observed that the bipolar EGM becomes smaller in amplitude or negative. This is related to loss of signal at the distal electrode (from which radiofrequency [RF] is delivered) with or without loss of signal at the proximal electrode (because of the dependence of the lesion radius on heat transfer and tissue necrosis), resulting in a diminished EGM and a negative EGM, respectively.

Unlike unipolar EGMs, the bipolar EGM does not exhibit a unique morphology when positioned at a tachycardia focus, though proximity may be estimated by its prematurity with respect to a timing reference such as the associated electrocardiography (ECG) wave of tachycardia beats (e.g., P or QRS). Nor can the morphology of the bipolar EGM provide information on the direction of wavefront propagation because of its insensitivity to far-field signals. However, the bipolar EGM *is* sensitive to the specific direction of wavefront propagation, as a wavefront propagating perpendicular to the orientation of the electrodes will simultaneously register nearly identical signals at both electrodes, which results in cancelation and complete absence of a recordable bipolar EGM when the difference is taken.

Utility of Simultaneous Unipolar and Bipolar Recordings in Focal Tachycardias

As stated, the amplitude and duration of the R wave of the unipolar EGM decrease with proximity to a tachycardia focus, and the intrinsic deflection of the unipolar EGM correlates well with local activation under the exploring electrode. A QS morphology of the unipolar EGM results when recording at the site of depolarization of a tachycardia origin. However, the timing of the maximal negative slope in the minimally filtered unipolar

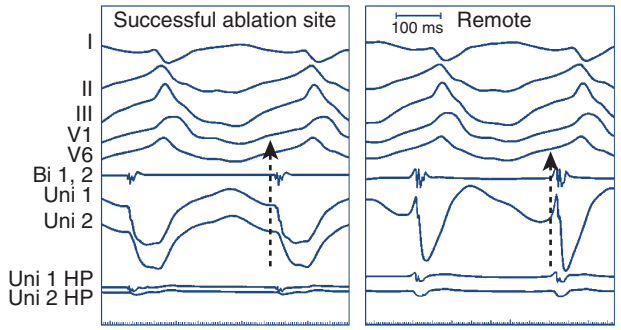

FIGURE 23-4 Comparison of unipolar and bipolar electrogram (EGM) characteristics. *Left,* At the origin of focal ventricular tachycardia, the two unipolar EGMs (*Uni 1*, *Uni 2*) exhibit nearly identical QS morphology with steep initial deflection. Note the minimal temporal difference between the onset of Uni 1 (*dashed arrow*) and Uni 2. *Right,* With the mapping catheter remote from the focus, the unipolar EGM exhibits an rS morphology. Note also that the bipolar EGMs exhibit a fractionated appearance at both locations; hence the local bipolar EGMs characteristics are not generally indicative of proximity to tachycardia focus. *(From Stevenson WG, Soejima K: Recording techniques for clinical electrophysiology,* J Cardiovasc Electrophysiol *16:1017–1022, 2005.)*

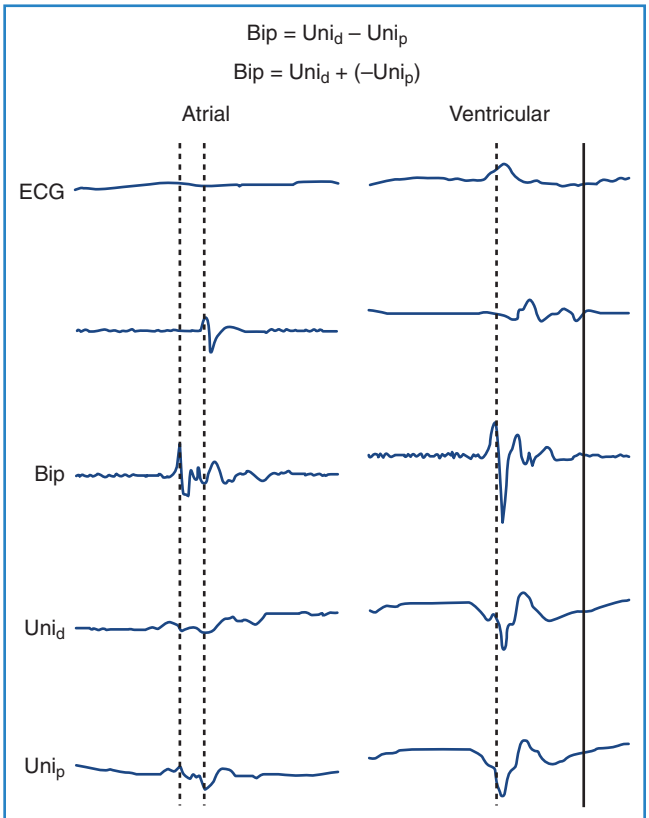

FIGURE 23-5 Examples of simultaneous unipolar and bipolar (*Bip*) electrograms (EGMs) obtained through a commercial graphic mapping system. Note that while both ventricular unipolar EGMs exhibit an initial QS pattern (*intersection identified by the dashed line*), the instantaneous signal at Uni_p appears more negative than on Uni_d, resulting in an instantaneous difference with a positive amplitude, hence the initial r wave in the bipolar ventricular EGM.

EGM is often difficult to gauge visually, and QS waves with lesser dV/dt may be seen a distance from a tachycardia focus.[2] The peak of the first deflection of the bipolar EGM also correlates well with local activation, and the prematurity of the bipolar EGM with respect to the surface ECG tachycardia beat may be used to identify a presumed tachycardia focus.[3] When the onset of the surface ECG wave is difficult to identify, assessing prematurity of the bipolar EGM may become unreliable, confounding the determination of proximity to a tachycardia focus. Instead, the unipolar EGM may be used to identify a tachycardia focus by identifying sites at which a QS morphology in the unipolar EGM coincides with the peak of the first deflection of the simultaneous bipolar EGM, as this obviates reliance on the surface ECG (Figure 23-6). The earliest sites obtained with bipolar mapping are associated with the shortest interval between the onset of the unipolar signal and the first peak of the bipolar signal, with successful ablation sites exhibiting intervals under 15 ms.[2]

Factors Affecting the Local Electrogram

Anisotropic Conduction and Electrocardiogram Morphology

Anisotropic conduction refers to preferential longitudinal conduction that is observed in adult cardiac myocytes.[4-6] In mature muscle cells, activation wavefronts may propagate across intercellular junctions both longitudinally and transversely. Because of the elongated configurations of ventricular myocytes, however, wavefronts propagating transversely encounter comparatively more intercellular junctions and, thus, travel more slowly than wavefronts moving an equal distance longitudinally. Therefore, normal myocardial conduction is described as uniformly anisotropic, with advancing wavefronts that are smooth in all directions but slower transversely than longitudinally, resulting in teardrop-shaped isochrones (Figure 23-7, *A*).

The "normal" ventricular EGM has been characterized during sinus rhythm in people with normal left ventricular function and without known structural heart disease. Normal bipolar EGMs obtained using multipolar catheters with 10-mm spacing are typically greater than 3 mV and of less than 70 ms duration without splitting, fractionation, or late components, though with somewhat lower amplitude and longer duration at the cardiac base.[7]

However, normal hearts do not exhibit "normal" EGMs and "normal" conduction patterns at all sites. Anisotropic conduction can become nonuniform in the absence of overt structural heart disease. Such anisotropy may be functional, related to anatomic and histologic barriers, borders, or alterations and varying orientations of overlapping myofibers. These histo-anatomic variances may predispose to local differences in signal characteristics, which, when detected in bipolar configuration, are then extracted and preserved, producing EGMs with multiple rapid deflections similar to those observed in patients with known structural heart disease.[8]

With advancing age, myocardial disease (e.g., myocardial infarction [MI]) and iatrogenic alterations in cellular architecture (e.g., prior ablation, maze procedure, external beam radiation), and associated deposition of connective tissue primarily along the longitudinal axis of cardiac fibers, lateral impulse propagation encounters greater resistance and becomes extremely slow and irregular (see Figure 23-7, *B*).[4-6] This remodeling of cellular interconnections and electrical uncoupling produces heterogeneous regions of anisotropic slow conduction with reduced voltage and frequency response to excitatory stimuli, resulting in low-amplitude, fractionated EGMs with prolonged duration (Figure 23-8).

Catheter Contact

Extrinsic factors also affect the timing and morphology of the local EGM. The main factor among these is stable catheter contact with myocardium. The recording electrode must be positioned with appropriate orientation that permits reliable and reproducible recordings, with adequate endocardial pressure to maintain catheter stability without injuring the heart wall. Often, the catheter and the myocardial wall will move synchronously, which suggests that the catheter tip is well seated against the endocardium. Unstable catheter position predisposes to alterations in EGM morphology and amplitude and even frank catheter dislodgment, which may escape notice and taint the information gleaned and mislead the operator.

Catheter Mapping: Integral Components

Conventional catheter arrhythmia mapping, usually referred to simply as *catheter mapping*, necessitates (1) a sustained tachycardia, (2) sampling of local EGMs through electrode catheters positioned in direct contact with the underlying myocardium, and (3) knowledge of the specific sites from which signals are recorded.

Sustained Arrhythmia

Inducibility of a sustained tachycardia in the diagnostic electrophysiology suite that replicates the clinical arrhythmia confirms a reproducible and functional physiologic mechanism. Catheter mapping is often performed during sustained tachycardia because it is only *during* tachycardia that sampled potentials convey the order of cardiac activation. Sustained tachycardia affords the opportunity to observe spontaneous behavior, evaluate activation characteristics, and introduce intentional perturbations, the response to which may further clarify the underlying mechanism. Finally, the inducibility of sustained tachycardia during diagnostic evaluation affords a direct assessment of acute procedural success, as noninducibility *after* ablation then becomes a relevant endpoint.

It is implicit that the tachycardia being mapped involves a single circuit or focus as identified by EGM morphology and the activation sequence that is identical from beat to beat. Varying activation sequences during sustained tachycardia, which suggest multiple mechanisms, circuits, or sites of involvement, generally are not amenable to catheter mapping alone.

Contact catheter mapping of nonsustained episodes or isolated tachycardia beats poses additional challenges, which prolong the process and may increase the potential for mapping errors as salvos and single beats may not be representative of the clinical tachycardia. Complete noninducibility precludes catheter mapping and halts the evaluation of the tachycardia in most cases, though anatomically directed ablation and substrate mapping may still be undertaken.

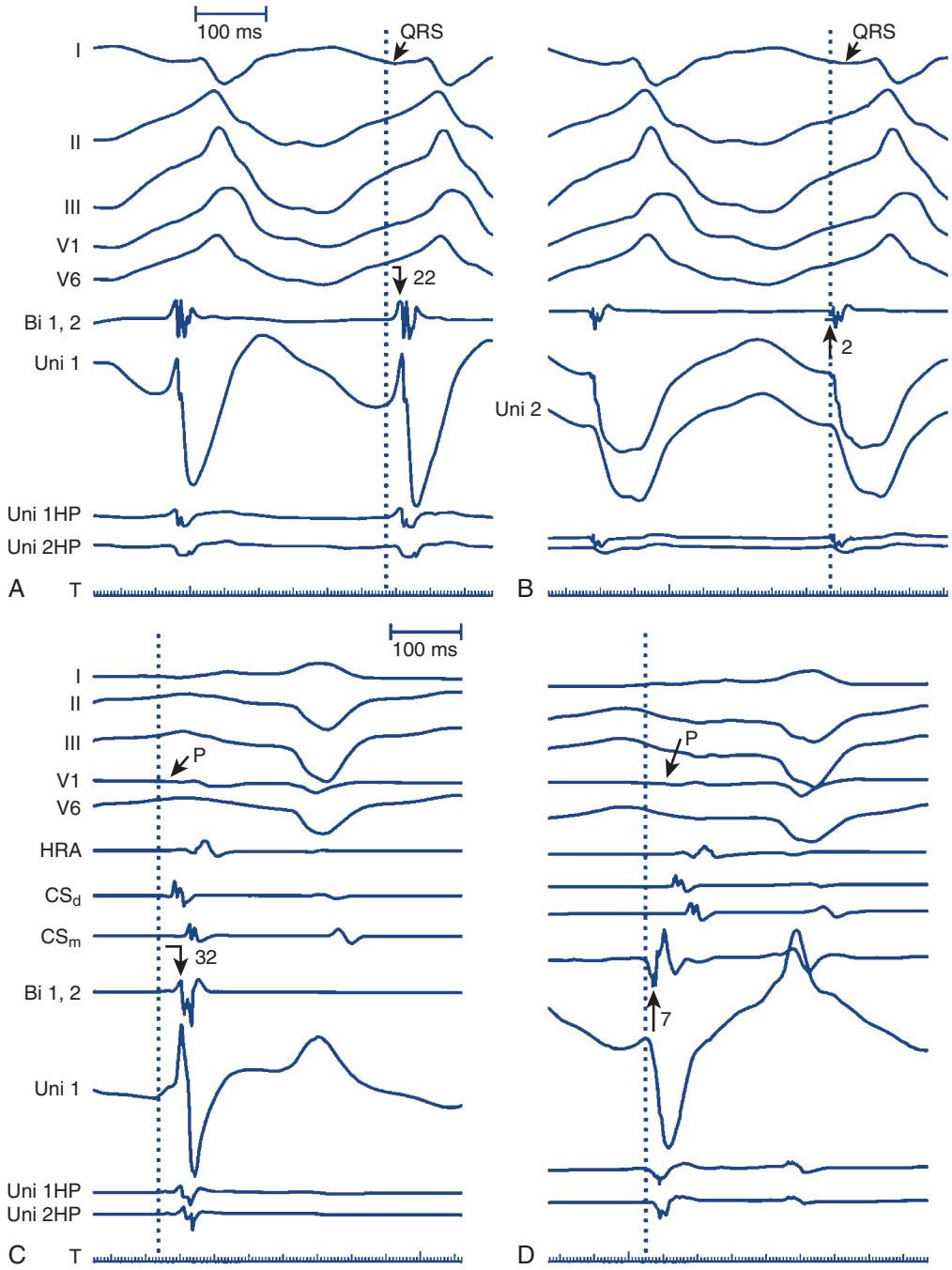

FIGURE 23-6 Utility of simultaneous unipolar (*Uni*) and bipolar (*Bi*) electrograms (EGMs). While the precocity of the detected EGMs is typically evaluated with respect to the onset of the electrocardiography (ECG) waveform of the tachycardia of interest (i.e., P wave for focal atrial tachycardia and QRS for focal ventricular tachycardia), the onset of the ECG deflection may be difficult to identify, particularly in real time and at increased sweep speeds. However, the high correlation of both the onset of the unipolar EGM (Uni_o) and first peak of the bipolar EGMs (Bip_p) with the onset of surface ECG waveform, implies that these two signals, which may be more easily compared with respect to timing, may be used together to determine proximity to a tachycardia focus. Specifically, minimizing the temporal difference between the onset of the unipolar EGM and the first peak of the bipolar EGM $(Uni_o - Bip_p)_{min}$ obtained from a standard multi-polar mapping catheter identifies the expected tachycardia origin. *Upper panels,* A focal ventricular tachycardia is being mapped. **A,** The onset of Uni_1 exhibits an initial R wave suggesting location remote from the focus, though proximity is difficult to determine as the onset of the QRS (*arrow*) is not easily identified. $Uni_o - Bip_p$ is 22 ms, and on close examination, the onset of the bipolar EGM (Bi1,2) is delayed with respect to the QRS. **B,** At the successful ablation site, Uni 1 exhibits a steep negative deflection at its onset with a QS morphology suggesting proximity to the tachycardia focus, though again, difficulty in identifying QRS onset (*black arrow*) poses a challenge to determining precocity at this location. The near-simultaneous onset of the bipolar EGM results in $Uni_o - Bip_p$ of 2 ms and identifies the earliest site of activation, and with close inspection, the onset of the bipolar EGM can be seen clearly preceding the onset of the surface QRS. Similarly, during focal atrial tachycardia (*lower panels*), $Uni_o - Bip_p$ is 32 ms at an unsuccessful ablation site (note the prominent R wave in Uni 1 and onset of Bi1,2 is delayed with respect to onset of the P wave), whereas at the successful ablation site, $Uni_o - Bip_p = 7$ ms (Uni 1 exhibits only an "embryonic" R wave and onset of the bipolar EGM precedes onset of the P wave). *(From Delacretaz Soejima K, Gottipaty VK, Brunckhorst CB, et al: Single catheter determination for local electrogram prematurity using simultaneous unipolar and bipolar recordings to replace the surface ECG as a timing reference,* Pacing Clin Electrophysiol *24:441–449, 2001.)*

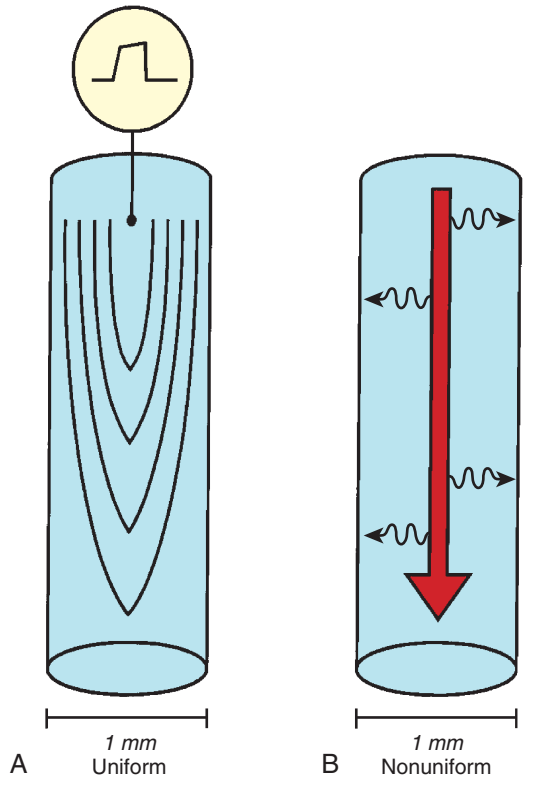

FIGURE 23-7 Anisotropic conduction in cardiac muscle. Schema depicts propagation characteristics for ventricular myocyte bundles with uniform (**A**) and nonuniform (**B**) anisotropic properties. Uniform anisotropic spread produces advancing wavefronts, depicted by isochrones in **A,** which spread smoothly in all directions, albeit more slowly transversely than longitudinally. The slow irregular spread of transverse excitation characteristic of nonuniform anisotropic conduction is depicted by the sawtooth curves in **B**.

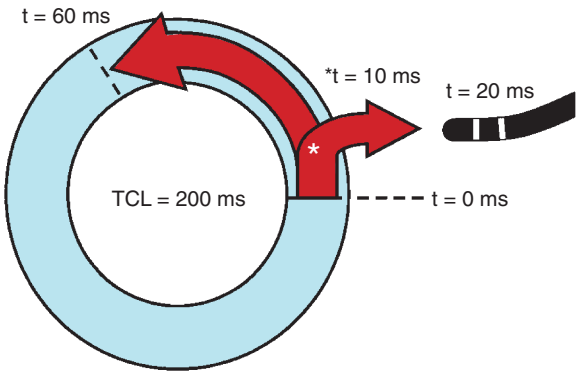

FIGURE 23-9 Schema of activation timing within a macro–re-entrant circuit and at bystander locations. With every revolution around a tachycardia circuit, wavefronts propagate within the circuit and leave the circuit to depolarize the adjacent myocardium (bystander sites). While activation at bystanders will always be activated later (t = 20 ms) than the nearest depolarized tissue from within the circuit (t = 10 ms), that same bystander may be activated earlier than other sites within the tachycardia circuit (t = 60 ms). Thus, local electrogram timing alone with respect to a timing reference is not indicative of whether a particular site is located within a macro–re-entrant circuit.
TCL, Tachycardia cycle length.

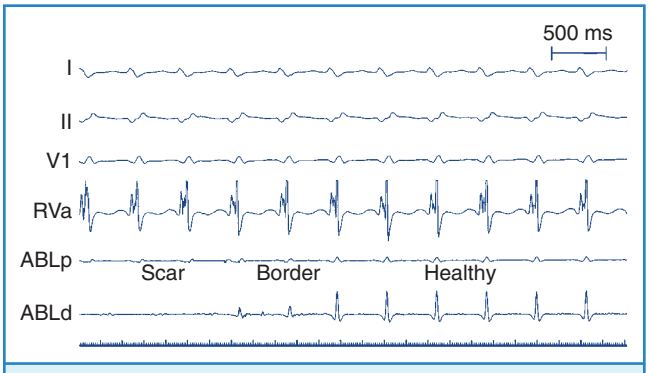

FIGURE 23-8 Comparison of normal and abnormal electrograms (EGMs) during ventricular tachycardia (VT) in a patient with prior myocardial infarction. During clinical VT, the mapping catheter is used to interrogate tissue characteristics of the VT circuit and the myocardium. With the mapping catheter positioned within a region of scar, low-amplitude, low-frequency local EGMs with prolonged duration are seen. As the mapping catheter is then dragged across the scar border zone and into an adjacent region with more healthy tissue, the higher frequency, larger amplitude signals are seen.

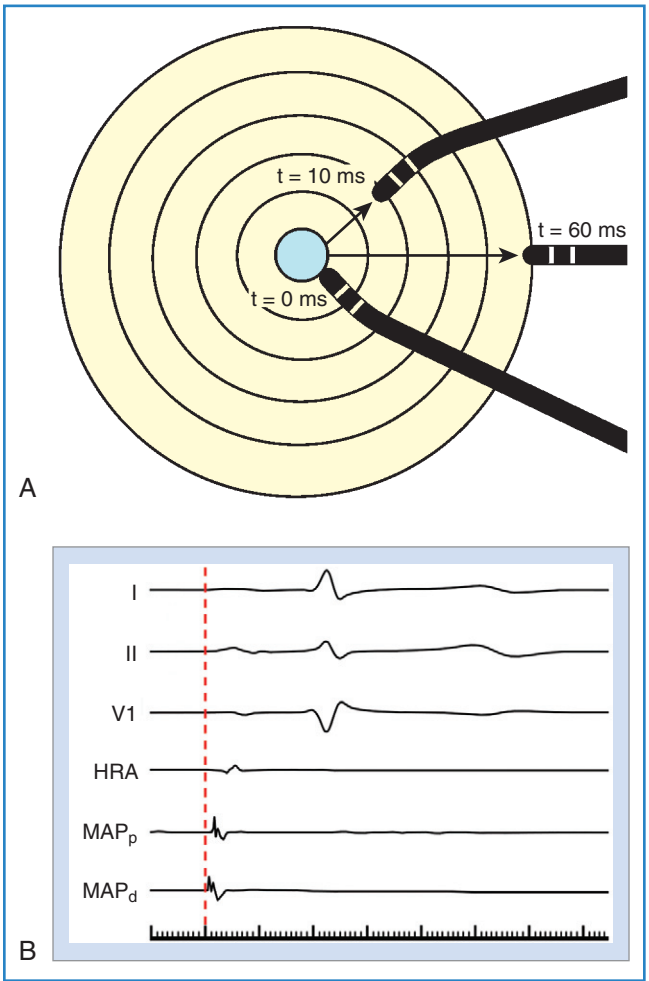

FIGURE 23-10 **A,** Schema of activation timing in a focal rhythm. Activation time increases as the tachycardia wavefront propagates away from the depolarizing focus. **B,** Mapping the sinus. While the typical location of the high right atrial (*HRA*) catheter is in proximity to the sinus node, mapping the activation identifies the earliest site approximately 27 ms earlier than the HRA catheter.

Use of Electrode Catheters

The recording of local activation signals during tachycardia is obtained through both *stationary* and *roving* electrode catheters. Standard diagnostic multipolar electrode catheters are introduced percutaneously, and the obtained signals—unipolar or bipolar EGMs—are displayed in real time on a digital recording system. Stationary electrode catheters may be positioned in any cardiac chamber and are typically maintained at a fixed site for the duration of the diagnostic evaluation. For safety and convenience, sites accessible transvenously via the right cardiac chambers are chosen, usually the high-lateral right atrium (approximating the site of sinus endocardial breakthrough), His bundle region (approximating the site of atrioventricular node [AVN] conduction), within the coronary sinus (CS) (approximating a posterior location and a right-left axis of activation of both the left atrium and the left ventricle), and the right ventricle (Figure 23-11). This "standard" catheter positioning approximates the normal conduction system axis and creates a skeleton of recording sites that defines the sequence and timing of activation from all four cardiac chambers, creating a fixed framework within which the tachycardia may be assessed. Other recording sites may be sampled as well to further enhance the diagnostic framework on the basis of the suspected arrhythmia.

Usually, a single roving mapping catheter is introduced to sequentially sample local potentials from cardiac chambers and sites pertinent to the tachycardia. The signal recorded by the mapping catheter is compared with the EGMs recorded by the stationary catheters as well as previously sampled sites to iteratively guide the operator to sites critical to the arrhythmia. Once such critical sites have been identified, further evaluation, such as pacing maneuvers, may be performed to confirm relevance to the tachycardia.

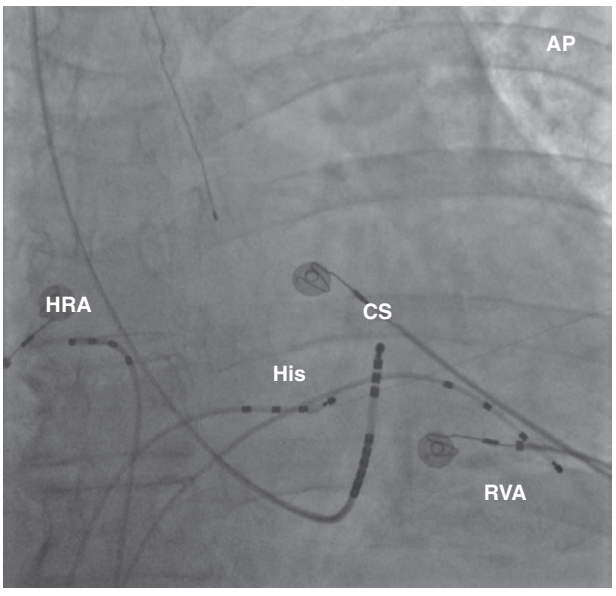

FIGURE 23-11 Anteroposterior (*AP*) fluoroscopic projection of "standard" intracardiac catheter locations. The high right atrial (*HRA*) catheter is positioned laterally in the right atrial appendage. The His catheter is positioned across the atrioventricular junction at the mid-to-superior septal aspect of the tricuspid valve. The right ventricular catheter is positioned in the apex (*RVA*). The coronary sinus (*CS*) catheter is positioned with the proximal electrode approximately 1 cm from the CS ostium.

Cardiac Anatomy and Implications for Mapping

Knowledge of recording sites is critical to guide mapping as EGMs are interpretable only when paired with location. Decisions regarding how to proceed with mapping, that is, where to map *next* or in which direction the sought target is expected, cannot be made without knowing the current catheter positions. Therefore, competent catheter mapping requires basic awareness of fluoroscopic anatomy for proper EGM interpretation. Conversely, fluoroscopy may belie the true location of catheters, given its inability to detect depth, but EGM evaluation may confirm catheter location, as specific anatomic sites are associated with distinguishing EGM patterns or morphologies such that the local anatomic region may be *inferred* from the recorded signals (Figure 23-12). Sites with distinctive bipolar EGM patterns include the valve annuli, atrial appendage, crista terminalis, His bundle, CS, and the junctions between the cardiac chambers and the vascular tree (Figure 23-13).

Standard electrophysiology mapping and catheter positioning are performed in the frontal anteroposterior (AP), and right anterior oblique (RAO) or left anterior oblique (LAO) projections, usually at 20 to 45 degrees of angulation. The frontal projection is particularly useful for advancing the catheter from the access site to the heart and allows good visualization of the right ventricular outflow tract (RVOT). In general, the oblique views may be used to distinguish anterior sites from posterior sites and to delineate the AV valve plane (RAO, Figure 23-14, *A*), to distinguish lateral sites from septal sites, and to assess the short axis of the heart (LAO caudal; Figure 23-14, *B*). The RAO view is often used to position the His bundle catheter, which is seen in profile at the superior margin of the tricuspid annulus. The LAO projection is used for mapping the mitral or tricuspid valve annuli and the septal, lateral, and basal parts of the left ventricle and can facilitate CS cannulation.

Approach to Catheter Mapping: Specific Techniques

The purest method of evaluating a tachycardia is performing the evaluation during the arrhythmia itself. Mapping and pacing techniques may then be applied to study the dynamics and physiology of the tachycardia and to introduce intentional perturbations, the response to which provides further clues to the tachycardia mechanism and essential sites of involvement. However, tachycardia may induce not only hemodynamic instability but also catheter instability caused by vigorous and rapid cardiac motion, which limits effective mapping. In such a case, pacing techniques may be employed during sinus rhythm to simulate or unmask some or all of the tachycardia physiology, thereby permitting evaluation of critical aspects without requiring induction of the clinical tachycardia.

Physiology of Arrhythmias Pertaining to Catheter Mapping

The paradigm of macro–re-entry is cavotricuspid isthmus–dependent atrial flutter, in which a well-defined circuit of

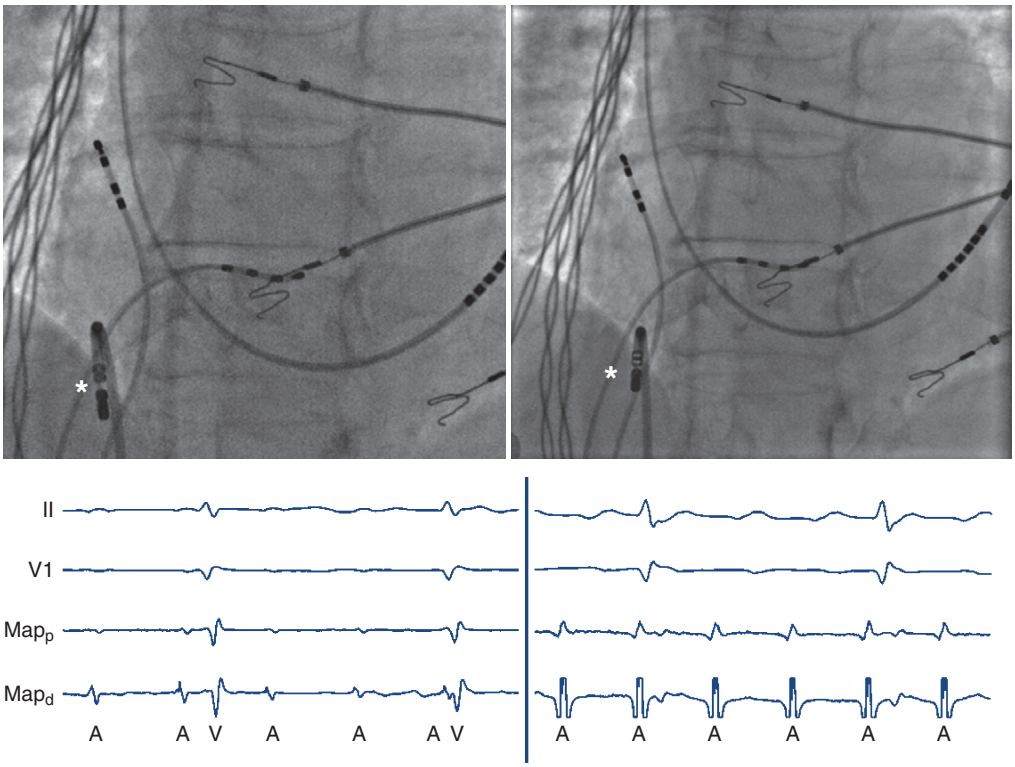

FIGURE 23-12 Utility of intracardiac electrograms (EGMs) in identifying relative catheter positions. *Left*, The mapping catheter is positioned just beyond the mid-cavotricuspid isthmus at the tricuspid annulus (30-degree left anterior oblique projection), identified by the appearance of both atrial and ventricular EGMs at the mapping catheter bipoles. Catheter withdrawal by less than a centimeter into the isthmus (*right*) is associated with minimal changes in the fluoroscopic appearance but is accompanied by obvious changes in EGM pattern, now exhibiting large atrial EGMs and only small, far-field ventricular EGMs.

tissue—comprising the subeustachian isthmus, inter-atrial septum, and the roof and lateral atrial wall anterior to the crista terminalis and superior vena cava—is continuously activated in sequence. During atrial flutter, the wavefront also propagates away from the circuit to other sites not critical to tachycardia maintenance, that is, bystander sites. If one considers the time to activate a bystander site and the time to activate a site within the tachycardia circuit, the bystander site will always be activated later than the nearest depolarized tissue within the tachycardia circuit in direct functional connection with the bystander site, though the bystander site may still be activated earlier than other sites within the tachycardia circuit (Figure 23-9). In other words, early and late activation in the setting of macro–re-entry is *relative* and, in isolation, not useful in characterizing a particular site within the circuit. Further, an *earliest* site of activation is never possible, as the tachycardia circuit is, by definition, a continuous path along which earlier sites of activation may always be identified.

The limit of a re-entrant circuit as the path length approaches zero is a tachycardia *focus*, which may harbor "micro–re-entry" or a truly focal firing mechanism. In either scenario, the tachycardia "circuit" comprises a relatively small, discrete, and localized mass of tissue, with all other sites considered bystander sites to which the wavefront propagates and activates later than the site at which the depolarization originates. Activation time to a particular site is a function of distance and factors affecting conduction away from the focus such that distant bystander sites are activated later than bystander sites closer to the tachycardia origin. In this case, *earliest* activation may be identified—*at* the tachycardia origin—and is a specific timing characteristic of focal rhythms (Figure 23-10, *A*).

As an example, sinus automaticity leads to spread of an excitation wave out of the sinus node and across the atrial muscle. The wavefront penetrates the atrial myocardial wall and may be detected endocardially as local depolarization. A diagnostic catheter in the superolateral right atrium (also referred to as *high right atrium* [HRA]) would be expected to be activated earlier than most other right atrial sites; however, it is unlikely to serendipitously coincide with the site of endocardial breakthrough and, therefore, would not be expected to be the earliest identifiable site of atrial activity. In fact, by scanning the right atrium with a mapping catheter, the earliest site of endocardial activity, representing the true site of sinus endocardial breakthrough, would be expected to precede activation at the diagnostic HRA catheter (see Figure 23-10, *B*).

Activation Sequence Mapping

The simplest and most direct method of studying a tachycardia is through activation sequence mapping, which requires an inducible, sustained, and stable tachycardia. On the basis of the position of stationary diagnostic catheters, the order of activation and sites and chambers involved may be inferred. A roving mapping catheter may be used to continuously scan the appropriate cardiac

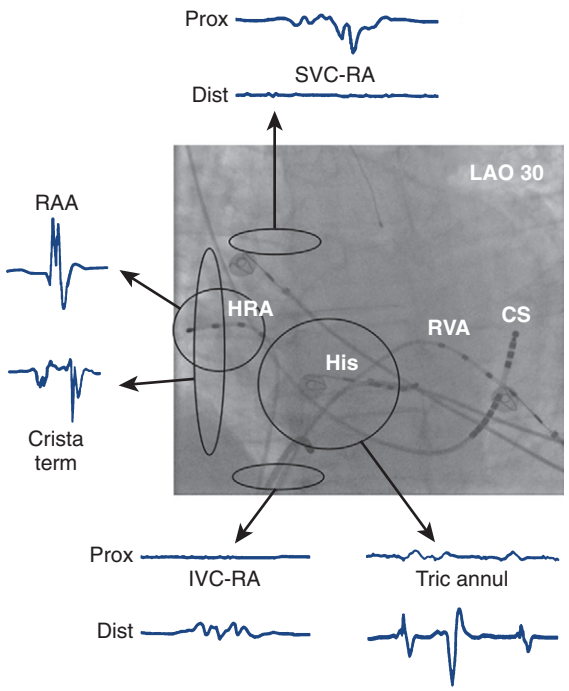

FIGURE 23-13 Left anterior oblique (*LAO*) fluoroscopic projection with characteristic electrograms (EGMs) recorded by a femorally inserted mapping catheter positioned at various sites with respect to fluoroscopic right atrial anatomy (*circles and ovals*) and standard catheter locations. *Counterclockwise from top:* Junction of the right atrium and superior vena cava (*SVC-RA*), with loss of signal on the distal bipole when situated within the SVC, and the proximal bipole, which remains intracardiac, still detects fractionated atrial EGMs; right atrial appendage (*RAA*), relatively large amplitude, sharp, "spiky" EGMs; crista terminalis (*Crista term*), demonstrating a "double potential" because of local conduction block across the crista but with detection of EGMs on either side of the crista ridge; junction of the right atrium and inferior vena cava (*IVC-RA*) demonstrating loss of signal on the proximal electrode when situated in the IVC but persistence of detected signal on the distal bipole that is still intracardiac; signal recorded from the tricuspid annulus (*Tric annul*) with the catheter more atrial than ventricular and therefore exhibiting large atrial EGMs and a smaller ventricular EGM between them on the distal bipole, as well as smaller far-field EGMs on the proximal bipole, which is not in contact with the myocardium. *CS,* Coronary sinus catheter; *HRA,* high right atrial catheter; *RVA,* right ventricular apical catheter.

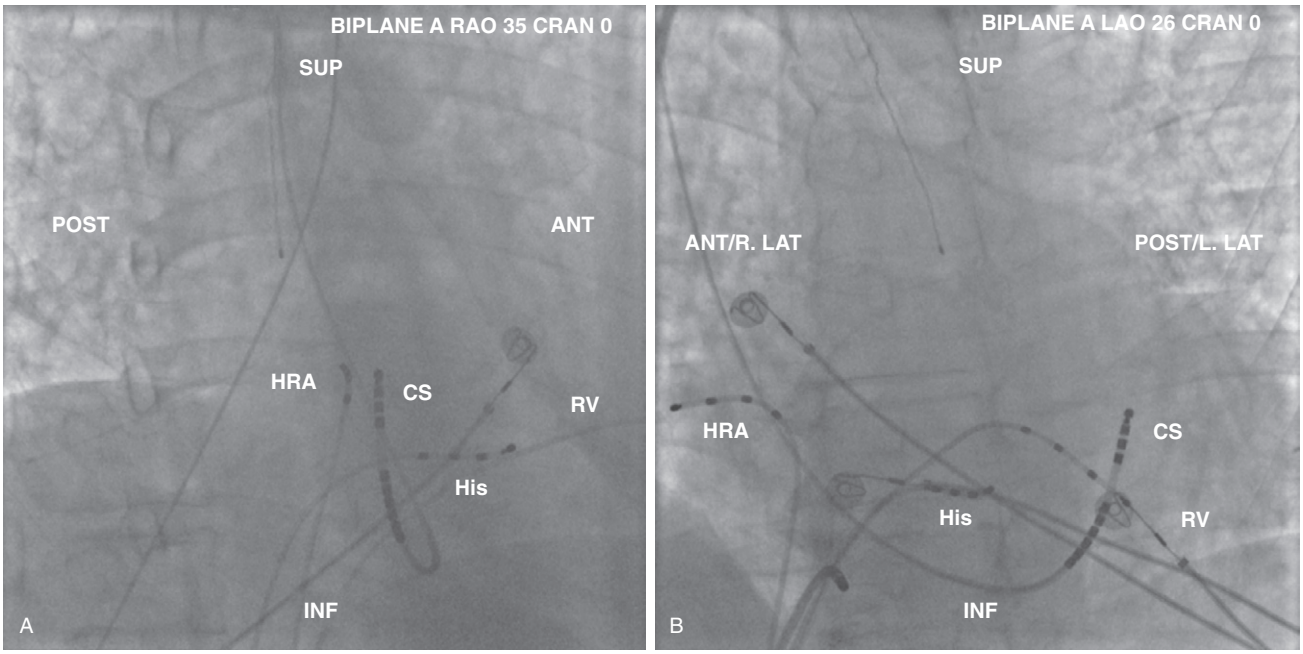

FIGURE 23-14 Utility of fluoroscopic projections to identify anatomic and catheter locations. **A,** A 35-degree right anterior oblique (*RAO*) projection. The coronary sinus (*CS*) catheter approximates the plane of the mitral annulus and allows discrimination of posterior (*POST*), and, therefore, atrial structures (e.g., high right atrial [*HRA*] catheter), from more anterior (*ANT*) right ventricular structures (the His catheter has crossed the atrioventricular valve plane, and the right ventricular (*RV*) catheter extends to the apex beyond the field of view). **B,** A 26-degree left anterior oblique (*LAO*) projection. The LAO projection opens the mitral annulus en face and allows septal and lateral (*LAT*) site to be distinguished. Note the CS catheter courses along the inferomedial, inferior, and lateral aspects of the mitral annulus. The HRA catheter is located laterally in the right atrial appendage, and the RV catheter courses out of plane, toward the observer. In both views, superior (*SUP*) is upward, and inferior (*INF*) is downward.

chamber(s) to determine the sites critical to the tachycardia and to apply the concept of "early" activation and determine proximity to the tachycardia circuit, whether macro–re-entrant or focal.

Mapping Focal Tachycardias

In the case of a focal rhythm, the signal obtained at a specific site is considered in comparison with a timing reference to deduce the site of origin and to determine the direction in which mapping would be fruitful; this is based on the concept that bystander sites are activated later than the tachycardia origin, that distant bystander sites are activated later than proximal bystander sites, and that the tachycardia origin will always be activated earliest compared with all other sites. The timing reference is usually the surface ECG or a signal originating from the chamber of interest, preferably close to the tachycardia focus. Sites activated earlier than the timing reference would be considered potential candidates of the true tachycardia origin. After detailed and extensive evaluation of all pertinent sites, the *earliest* detected site of activation should identify the tachycardia focus (see Figure 23-10, *B*).

Mapping Macro–Re-Entrant Circuits

Macro–re-entrant tachycardias do not have an earliest activated site. Rather, the tachycardia cycle length (TCL) identifies a time window during which each site along the circuit is activated once by the tachycardia wavefront because of a single revolution around the circuit. Compared with focal tachycardias, early activation and late activation, which are only *relative* terms, identify sites that are activated earlier or later than the reference but do not necessarily map the circuit pathway, as some bystander sites may be activated earlier than later-activated sites within the circuit. However, when sites activated late in the cycle length are very close to sites activated early in the cycle length, then this "early-meeting-late" site must identify a site along the plane of wavefront propagation that should transect the tachycardia circuit.

Again, considering typical right atrial flutter as the paradigm of macro–re-entry and using a proximal CS electrode positioned 1 to 2 cm beyond the CS ostium (os) as a timing reference, sites activated before the CS os could be considered early sites, whereas sites activated after the CS os could be considered late sites (Figure 23-15). With the mapping catheter positioned at the high septum, local activations occur later than the timing reference. As the catheter is advanced against the direction of revolution and inferiorly along the septum in proximity to the CS os, the mapping signal would fall earlier in the timing window and just precede the reference signal, as this site would be expected to be activated just before the reference. As the catheter is further advanced along the circuit, laterally across the cavotricuspid isthmus and then superoanteriorly to the crista terminalis, the mapping catheter signal would be recorded yet earlier with respect to the timing reference signal. Finally, on returning to the high septum, the mapping catheter would be activated even earlier but also could be considered as being "later" with respect to the reference signal associated with the previous tachycardia beat. Detecting the "early-meeting-late" sites, that is, early-activated sites adjacent to late-activated sites during a tachycardia, has physiologic significance in that it diagnoses macro–re-entry and sites that transect the tachycardia circuit, potentially providing a guide to ablation.

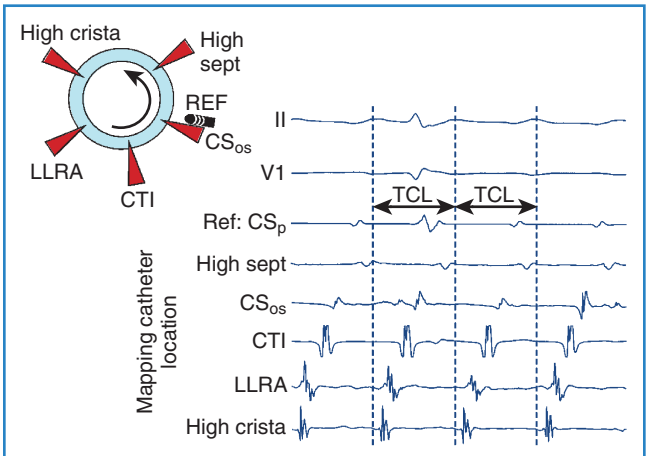

FIGURE 23-15 Timing of activation at various sites within the macro–re-entrant circuit of counterclockwise right atrial flutter and relation to timing reference. Electrocardiogram (ECG) lead II demonstrates the sawtooth appearance of typical atrial flutter with a gradual downstroke punctuated by a steeper negative deflection, followed by a more rapid upstroke and positive deflection, before the next gradual downstroke. ECG lead V1 demonstrates an initially isoelectric phase followed by positive deflection. A multi-electrode catheter is positioned within the coronary sinus with the proximal electrode (CS_p), serving as the timing reference (*REF*), positioned just beyond the ostium. Two adjacent windows of duration equal to the tachycardia cycle length (*TCL*) are shown with the onset of the window arbitrarily coincident with high crista activation, and thereby defining a single tachycardia revolution as from high crista to high crista. Consider the second or later window: With the mapping catheter located at the high right atrial septum (*High sept*), activation here occurs after the low septum and, therefore, later than the reference, and is very late within the timing window as this is the last area activated according to our arbitrarily defined cycle. With the mapping catheter moved against the direction of revolution to the coronary sinus ostium (CS_{os}), activation moves earlier in the timing window and occurs just before the reference, which is located just beyond the CS_{os}. As the mapping catheter is moved further along the circuit against the direction of revolution, local activation occurs progressively earlier within the timing window with each catheter position (cavotricuspid isthmus [*CTI*], low lateral right atrium [*LLRA*], high crista). Note also that the site activated *yet earlier* than the high crista location is the high septal location, but this activation extends beyond a single cycle and thus becomes *late* in the previous timing window, illustrating that with respect to macro–re-entrant rhythms, "early" and "late" are relative terms that have relevance only with respect to a specific timing reference and a single timing window of duration equal to one TCL.

However, mapping macro–re-entrant circuits in their entirety is a laborious process and usually not undertaken with catheter mapping techniques alone, as only a single site participating in a tachycardia circuit needs to be modified to interrupt re-entry and the tachycardia. Rather, the aim of the mapping study is primarily to confirm the mechanism as well as one site or a few critical sites of involvement. Therefore, an impression of the tachycardia mechanism and the expected location of critical components facilitate the mapping process and ablation.

One particular mapping characteristic of macro–re-entrant circuits is low-amplitude, prolonged, and fractionated potentials

preceding systolic activation of the tachycardia chamber. These *diastolic* potentials are felt to represent depolarization of a slowly conducting region during the diastolic phase of chamber activation, preceding systolic activation by potentially up to hundreds of milliseconds in the case of scar-mediated VT circuits (Figure 23-16). The finding of diastolic potentials should raise the suspicion that the recording site may be within a region of slow conduction, and, as slow conduction is one of the necessary elements in the accepted model of re-entry, it is important to recognize and evaluate it further for participation in the tachycardia circuit. Diastolic potentials are not sufficient evidence to prove participation, as bystander sites may also produce diastolic potentials, but the very finding of regions of slow conduction, as signified by diastolic potentials, suggests macro–re-entry as the tachycardia mechanism.

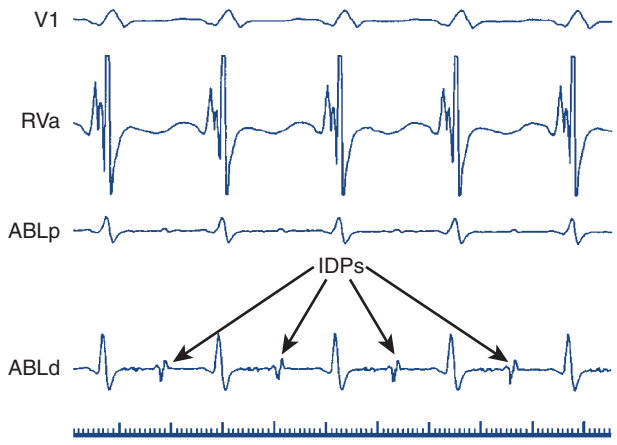

FIGURE 23-16 Mid-diastolic potentials. Catheter mapping during ventricular tachycardia reveals potentials separated from other intervening signals by an isoelectric phase during ventricular diastole—isolated diastolic potentials (*IDPs*). The relation between the IDPs and intervening ventricular electrograms is fixed, suggesting 1 : 1 activation. Identification of IDPs signifies regions of slow conduction that may participate in the re-entrant circuit.

Choice of Reference Signal

Relevant to the notion of early activation is the timing signal against which other signals are referenced. As a cardiac chamber is scanned, the mapping catheter recording can only be considered *early* (or late) in comparison with another signal, whether from the surface (ECG) or the endocardium (EGM). The choice of this *reference* signal is important as timing comparisons will be most useful if the reference is chosen appropriately. *Distant* references will be activated by the tachycardia wavefront only after propagating a distance to reach the reference, altering the relative timing of the mapping signals and making identification of true early and late sites ambiguous (Figure 23-17). Further, repetitive propagation to a remote reference may not always follow the same course or trajectory and varies the activation time at the reference, tainting the timing information. Therefore, some predetermination of the tachycardia mechanism and expected location aids in choosing an appropriate reference *in the vicinity* of the tachycardia, which results in more reliable mapping. A convenient reference that must, by definition, be in the vicinity of the tachycardia is the ECG wave (P or QRS) *during* tachycardia and is most useful in mapping focal tachycardias. Alternatively, in macro–re-entrant circuits, the ECG morphology of the P or QRS may represent an amalgamation of consecutive activation of different but contiguous myocardial regions throughout the TCL and does not necessarily identify any particular timing against which other signals may be referenced. The proximal electrode of the CS catheter is a particularly convenient reference signal because its position at the crux of the heart is fairly stable and in proximity to all four cardiac chambers.

Pacing Techniques to Facilitate Mapping

Entrainment

The seminal observations of Waldo in 1977, and others thereafter, on characteristic phenomena associated with re-entry form a cornerstone of electrophysiology mapping techniques. *Entrainment*

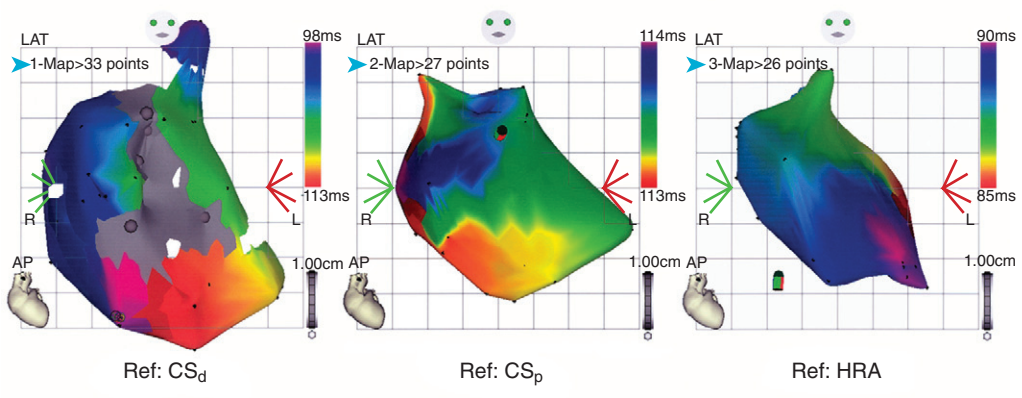

FIGURE 23-17 Impact of choice of timing reference on electroanatomic map. Macro–re-entrant atrial tachycardia in the same patient depicted using a three-dimensional graphic map of the activation sequence (anteroposterior [*AP*] projection, CARTO, Biosense Webster Inc., Diamond Bar, CA). Note that changing the timing reference alters the global activation timing, including location of the interpolated sites where early-activated and late-activated areas meet (*junction of red and violet colored regions*), signifying that activation mapping only attempts to depict the global activation sequence but does not identify a critical isthmus or region on which tachycardia maintenance depends. In all three maps, the direction of activation, from late to early (*violet to red*), as identified by the timing color bar, suggests counterclockwise revolution of the tachycardia.

may be defined as phase-locking of a self-sustaining oscillatory system to an external forced periodic driver.[9] In cardiac electrophysiology, entrainment is a response to pacing during tachycardia at a critical rate *faster* than tachycardia, which accomplishes penetration of the circuit and drives the tachycardia at the pacing rate and, by virtue of this, identifies an excitable gap of a putative re-entrant circuit.[10] Equally important, cessation of pacing or gradual reduction in pacing rate below that of tachycardia releases the circuit from the external driving influence of pacing and allows the tachycardia to resume at its original rate.[11]

From a practical perspective, entrainment is a tool for confirming re-entry and may be employed to clarify the mechanism of "unknown tachycardia." Entrainment is achieved by delivering an overdriving pacing train just faster than the tachycardia, usually 20 to 60 ms shorter than the TCL, depending on tachycardia origin, proximity of pacing to the circuit, and the presence of diseased myocardium. When the pacing train is asynchronously introduced, it may initially encounter tissue refractoriness, either locally or en route to or within the tachycardia circuit. In such a case, the noncapturing pacing train may be observed "overtaking" the tachycardia before myocardial capture occurs (Figure 23-18). Eventually, the paced impulse enters the circuit through the *excitable gap* and propagates in the direction of excitable tissue along the circuit path, which may be found both in the orthodromic and antidromic directions; therefore, each pacing stimulus spawns one antidromic wavefront and one orthodromic wavefront. The antidromic wavefront collides with the oncoming orthodromic wavefront of the previous tachycardia beat extinguishing the tachycardia, and a new orthodromic wavefront introduced by the pacing stimulus propagates around the circuit (Figure 23-19, *upper panel*).[11] With successful entrainment, no apparent termination of tachycardia is observed, as the tachycardia appears to continue at, or is "reset" to, the pacing rate; this is because each pacing wavefront continues to propagate orthodromically to produce a new "tachycardia" beat that is *not* the intrinsic tachycardia at all but, rather, the result of the pacing stimulus driving the tachycardia circuit orthodromically at the pacing cycle length.

ECG fusion is the evidence that the antidromic wavefront of each paced beat is colliding with and extinguishing the orthodromic wavefront of the previous beat. The degree of fusion is influenced primarily by the pacing site and rate and also by the time it takes to enter the tachycardia circuit, which is itself influenced by its proximity and conduction velocity to the circuit. When pacing at a set rate, the site of collision between an antidromic wavefront and previous paced beat's orthodromic wavefront is constant, so the degree of fusion is also constant (see Figure 23-19).

The specific degree of fusion and the resulting ECG morphology are determined by the timing and amount of myocardium activated by the pacing stimulus and the antidromic and orthodromic wavefronts. When pacing sites are remote to the circuit, myocardial capture by the pacing stimulus inscribes the ECG with morphology reflecting the pacing site, with minimal contribution from wavefronts propagating within the circuit (see Figure 23-18, *B*). When pacing sites are close to or within the tachycardia circuit, the pacing stimulus immediately engages the circuit and inscribes the ECG with morphology reflecting myocardial capture related to the orthodromic and antidromic wavefronts. When pacing at a rate just faster than tachycardia that does not terminate it, the antidromic wavefront may not propagate far into the circuit before colliding with the orthodromic wavefront of the previous beat, which has propagated nearly one complete revolution before encountering the antidromic wavefront. Both wavefronts will also have propagated out of the circuit, contributing to ECG inscription in proportion to the amount of myocardium activated. The orthodromic wavefront of the previous beat will also have spent the majority of the cycle length propagating to and activating the adjacent myocardium, whereas the antidromic wavefront with which it collides will have activated only the myocardium during the terminal portion of ECG inscription because of its late entrance into the tachycardia circuit and associated late myocardial breakout. The resulting ECG beat is a fusion of the two wavefronts that looks very similar to the intrinsic tachycardia beat, with only minimal ECG contribution by the antidromic wavefront and, therefore, minimal fusion.

If pacing entrains with fusion, when pacing at a faster rate that also does not terminate the tachycardia, the antidromic wavefront enters the tachycardia circuit earlier and penetrates deeper into it before encountering the orthodromic wavefront; this advances the site of collision antidromically and affords less time for the orthodromic wavefront to activate the myocardium and inscribe

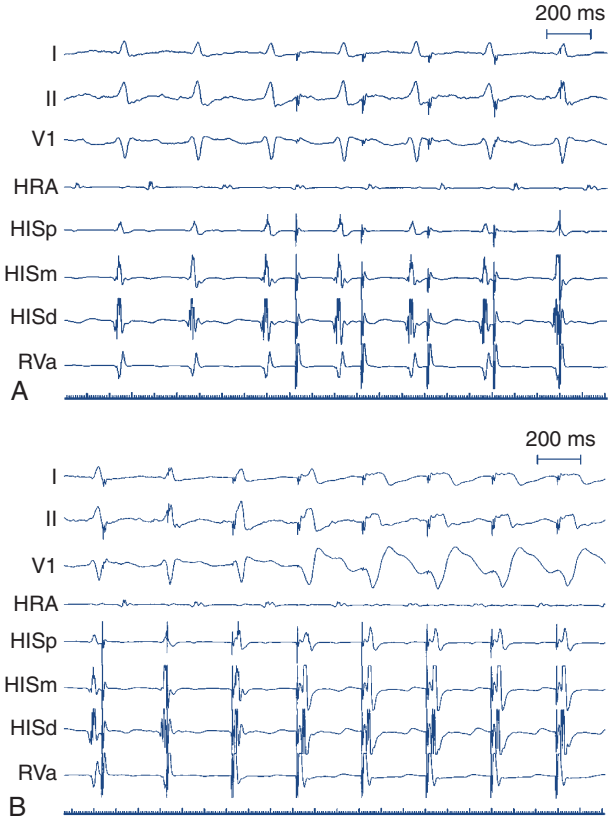

FIGURE 23-18 A, Initiation of pacing during tachycardia. Right ventricular pacing at 300 ms during tachycardia (324 ms) results in initial noncapture of the ventricular myocardium as the pacing stimuli "catch up" with the tachycardia. **B,** Pacing during tachycardia. Continued pacing results in the pacing stimulus overtaking the tachycardia, with eventual myocardial capture and fusion of the pacing stimulus with the tachycardia QRS. Note that at the left of the tracing on the RVa channel, during myocardial noncapture, the pacing stimulus is followed by a deflection related to polarization on the pacing electrode, whereas at the right of the tracing the pacing stimulus is followed by the electrogram of local myocardial capture.

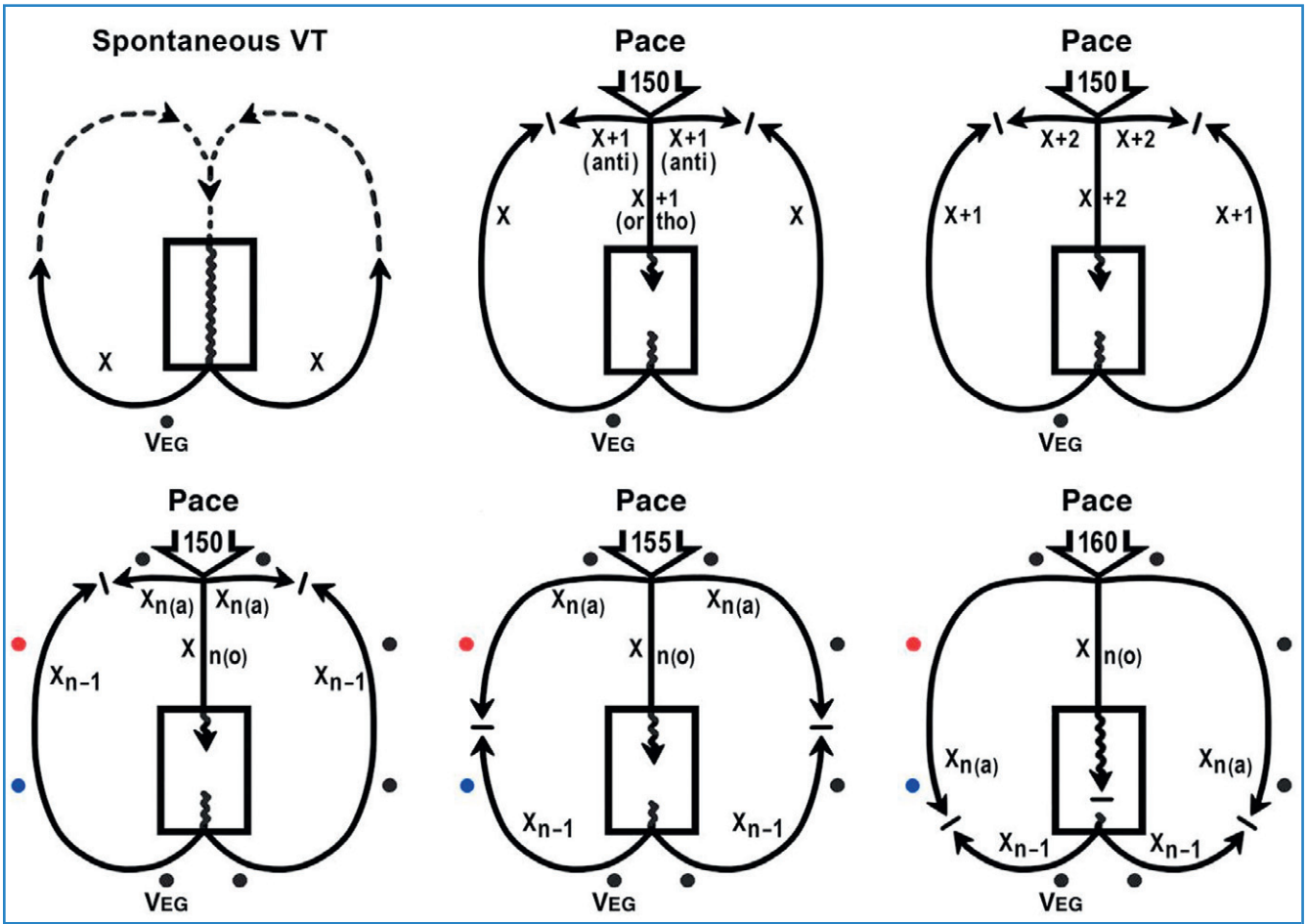

FIGURE 23-19 Demonstration of the first, second, and third criteria of entrainment. *Top row:* During ventricular tachycardia (*VT*) (*left*), the introduction of an overdrive pacing train at a rate just faster than tachycardia (*middle*) pre-empts the tachycardia wavefront (*X*), which travels orthodromically only, with a paced wavefront (*X+1*) that enters the tachycardia circuit and propagates both orthodromically and antidromically. Collision between the previous orthodromic (*ortho*) wavefront and the pre-empting antidromic (*anti*) wavefront (|) results in QRS fusion related to the site of collision. This collision terminates the tachycardia, but the X+1 orthodromic wavefront continues to propagate around the circuit and continues the tachycardia. Collision (*right*) between the X+1 orthodromic wavefront and the next antidromic wavefront (*X+2*) introduced by the next wavefront of the pacing train continually terminates and re-initiates the tachycardia, seemingly increasing the rate of the tachycardia to the pacing rate. If the pacing rate is maintained constant, the site of collision between the antidromic wavefront and previous orthodromic wavefront also remains constant, and thereby maintains a constant degree of fusion (criterion 1). *Bottom row:* With progressively faster pacing (*left:* 150 beats/min; *middle:* 155 beats/min; *right:* 160 beats/min), the site of collision is advanced antidromically along the circuit because of the deeper penetration of the antidromic wavefront, resulting in a greater degree of fusion between the paced QRS complex and the QRS complex associated with the previous orthodromic wavefront (criterion 2). With respect to a recording electrode located along the circuit (*red dot*), that site is activated by the orthodromic wavefront when pacing at 150 beats/min with the electrogram (EGM) and the activation time related to orthodromic activation. Pacing at 155 beats/min allows the antidromic wavefront to penetrate deeper along the circuit and past the recording site such that the site is now activated by the antidromic wavefront with the EGM and the activation time corresponding to antidromic activation (criterion 3). Similarly, pacing at 160 beats/min further advances the site of collision such that a recording electrode positioned more proximally along the circuit (*blue dot*), is activated by the antidromic wavefront with corresponding EGMs and activation times, whereas it was activated by the orthodromic wavefront during slower pacing rates. *(From Waldo AL: From bedside to bench: Entrainment and other stories,* Heart Rhythm *1:94–106, 2004.)*

the ECG. The antidromic wavefront contributes proportionally more to myocardial activation, which results in a greater degree of ECG fusion. The different degree of fusion in ECG waves at each pacing rate, which entrains but fails to interrupt tachycardia, is referred to as *progressive fusion* (see Figure 23-19).[11]

In conjunction with progressive fusion, pacing at two different rates faster than tachycardia that fails to terminate the tachycardia is also associated with a change of conduction time and EGM morphology at defined recording sites along the tachycardia circuit. Specifically, recording from a site along the tachycardia circuit *between* two sites of collision related to two different pacing rates is associated with a change in conduction time and EGM morphology at the recording site when pacing at one rate as compared with the other. Pacing at the slower rate results in more distal collision between the antidromic and orthodromic wavefronts, with the recording site activated by the orthodromic wavefront producing an EGM with specific morphology and activation time related to orthodromic propagation to the recording site. Pacing at the faster rate results in more proximal collision with the recording site, now activated by the antidromic

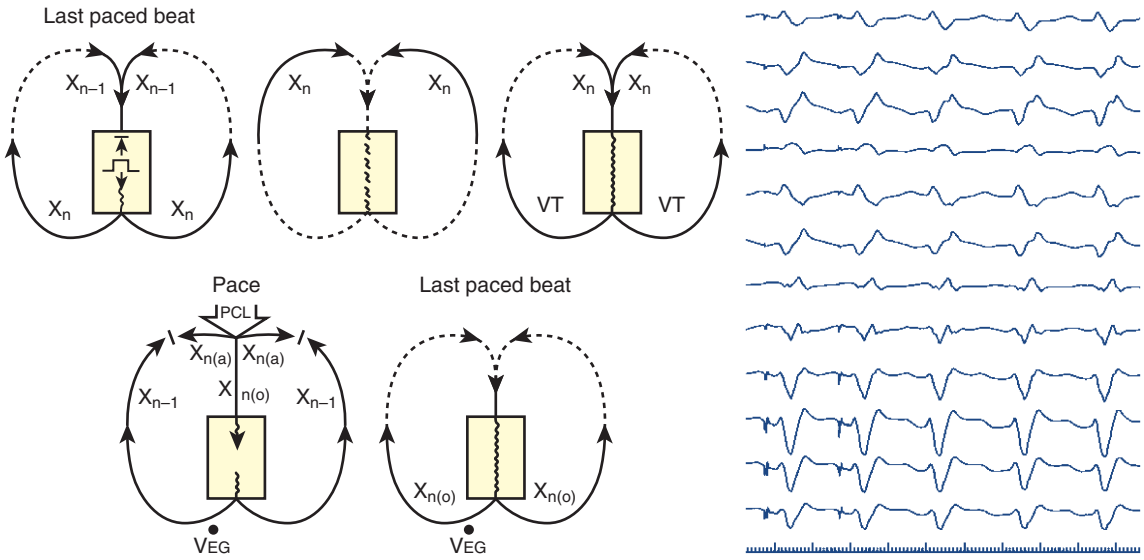

FIGURE 23-20 Demonstration of concealed entrainment (fourth criterion). *Left,* When pacing from a site that entrains the tachycardia with QRS morphology identical to the tachycardia, either by pacing from within the tachycardia circuit (*black rectangle*) or from a bystander site that is not associated with myocardial exit until after the wavefront enters the tachycardia circuit, concealed entrainment or concealed fusion is said to occur, as fusion between the antidromic and orthodromic wavefronts is not apparent and pacing does not alter the surface electrocardiographic morphology (*right*). The only electrogram manifestation of entrainment is acceleration of the QRS (and associated electrograms, not shown) to the pacing rate. With cessation of pacing, the last paced orthodromic wavefront propagates around the tachycardia circuit and now, not met by an antidromic wavefront, continues the tachycardia. The tachycardia continues at the intrinsic rate now no longer under the influence of overdrive pacing (*right*).

wavefront, producing a different EGM with specific morphology and activation time related to antidromic propagation to the recording site (see Figure 23-19).

Entrainment with fusion identifies a re-entrant mechanism, but the concept of *concealed* entrainment is of particular relevance; in this, overdrive pacing is *not* associated with an observable degree of manifest fusion, yet entrainment may be demonstrated and therefore re-entry may still be inferred. This occurs when two of the three potential sources of ECG fusion—the pacing stimulus and antidromic wavefronts—are unable to contribute to ECG inscription. Pacing either from within a tachycardia circuit or from a bystander site occurs such that the pacing stimulus cannot escape to the myocardium to contribute to ECG inscription; it also encounters local conduction block preventing antidromic propagation, *its* associated escape to the myocardium to impact ECG inscription, or both, and leaves only the orthodromic wavefront to contribute to ECG inscription. These circumstances may be encountered when pacing from within a scar that contains a slowly conducting region of a VT circuit. The pacing stimulus site cannot contribute to QRS inscription by virtue of pacing from within the scar, and the antidromic wavefront conducts only very slowly or blocks entirely and cannot escape to the surrounding healthy myocardium. Overdrive pacing results in only an orthodromic wavefront that is then entirely responsible for ECG inscription and therefore identical to tachycardia. It is important to recognize that concealed entrainment does not necessarily identify a site within the tachycardia circuit but, rather, identifies a site from which a pacing stimulus can penetrate the excitable gap of a re-entrant circuit and escape only to adjacent myocardium to affect ECG inscription by orthodromic propagation along the tachycardia circuit itself (Figure 23-20).

Similarly, the last paced impulse that entrains a tachycardia enters the tachycardia circuit and produces an orthodromic wavefront that does *not* encounter an antidromic wavefront because of cessation of pacing. This impulse inscribes an ECG wave that is contributed solely by the orthodromic wavefront and is *not* fused, and therefore it is identical to tachycardia. The orthodromic wavefront continues to engage the circuit now released from overdrive pacing, and the tachycardia resumes at its initial rate (see Figure 23-20).

Also, with cessation of pacing at the faster of two rates that entrain a tachycardia, the antidromic wavefront activates a recording site between the two sites of collision related to the two pacing rates and then collides with the orthodromic wavefront of the previous pacing stimulus. The recording site is then activated by the orthodromic wavefront of the last pacing stimulus, resulting in a change in the EGM morphology and activation time from that associated with the faster pacing rate to that of the slower pacing rate, which is identical to tachycardia.

Pacing at rates much faster than the tachycardia encroach on the refractory period of the tachycardia circuit such that the antidromic wavefront of the paced impulse collides with the previous orthodromic wavefront as expected, but the current orthodromic wavefront finds tissue ahead of it still unexcitable and also blocks, which results in localized, "complete" conduction block that prevents propagation along the circuit. The next paced beat may then propagate to a site within the tachycardia circuit, not necessarily along the path used during tachycardia, and that may have been, at least partially, functionally determined. Now, given the conduction characteristics of the fully recovered myocardium not otherwise influenced by functional characteristics imparted it by ongoing re-entry, the beat may propagate along a more direct

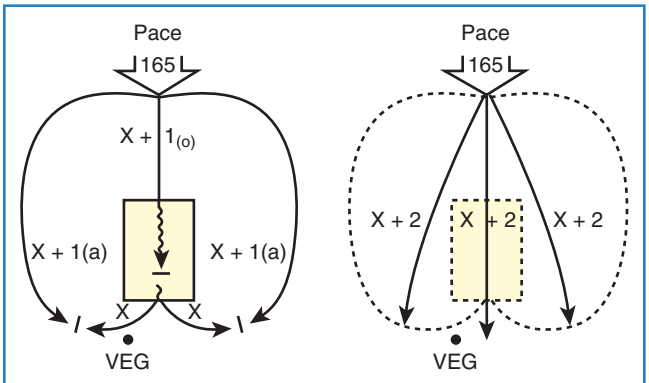

FIGURE 23-21 Overdrive pacing termination of tachycardia. Overdrive pacing at a rate much faster than tachycardia that terminates the tachycardia occurs because the antidromic wavefront and the previous orthodromic wavefront collide and extinguish the tachycardia, as occurs during entrainment. The next orthodromic wavefront finds the circuit still refractory impeding further conduction, thereby leaving the circuit unengaged by any wavefront and terminates the tachycardia. Subsequent wavefronts depolarize the sites along the circuit by propagating directly to those sites or under different functional influences during tachycardia, resulting in altered activation times and electrogram patterns.

trajectory and therefore with a shorter conduction time than during tachycardia and entrainment (Figure 23-21).[11]

Criteria of Entrainment

Criteria of entrainment during a tachycardia are as follows[11]:

1. When pacing at a constant rate that is faster than the rate of tachycardia and which fails to interrupt it, there is the *demonstration of constant fusion beats in the ECG, except for the last captured beat, which is not fused.*

2. When pacing at two or more constant rates that are faster than the rate of the tachycardia but which fail to interrupt it, there is the *demonstration of constant fusion beats in the ECG at each rate, but at different degrees.*

3. When pacing at a constant rate that is faster than the rate of tachycardia and which interrupts it, there is the *demonstration of localized conduction block to one or more sites for one beat, followed by activation of the site or sites by the next paced beat from a different direction and with a shorter conduction time.*

4. When pacing at two constant rates that are faster than the rate of tachycardia but which fail to interrupt it, there is the *demonstration of a change in conduction time to and EGM morphology at an electrode recording site—the EGM equivalent of the second criterion.*

Diagnostic Interpretation of the Response to Entrainment: The Postpacing Interval

While the preceding discussion on entrainment focused primarily on the specific physiology and various manifestations of phase-locking a tachycardia circuit to an overdriving pacing train, its diagnostic value lies primarily in the identification of macro–re-entry. However, the identification of macro–re-entry alone does not determine relevance of a particular pacing site to the re-entrant circuit. Distinguishing the sites near or within a tachycardia circuit from "bystanders" allows the identification of appropriate ablation targets. The evaluation of readily determinable parameters affords this practical and essential assessment without mapping the entire circuit.

The most fundamental assessment of the response to entrainment is the time for the last paced beat to propagate into and around the circuit and return to the pacing site—the postpacing interval (PPI). With cessation of pacing, the last paced impulse propagates into the circuit and generates both antidromic and orthodromic wavefronts. The antidromic wavefront is extinguished by the orthodromic wavefront of the previous pacing impulse, and the last orthodromic wavefront propagates through the entire circuit and, in addition to re-initiating the tachycardia, propagates out of the circuit. It is assumed that the conduction characteristics of the myocardium, which permit the engagement of the tachycardia circuit *from* the pacing site, functionally determine that the propagation trajectory and time for the wavefront to *return* to the pacing site are similar. Therefore, the PPI is the time for the pacing wavefront to propagate to the circuit, engage the circuit with a single revolution, and return to the pacing site. This is typically measured from the pacing stimulus artifact to the first return beat on the channel being paced. The conduction velocity during the movement around the tachycardia circuit is presumed to not be different from that during tachycardia, and therefore the duration to traverse the circuit once is the same as the TCL. The time difference between the PPI and the TCL is the time required to travel *to* and *back from* the circuit. The closer the pacing site to the tachycardia circuit, the shorter the total travel time. Therefore, with proximity to the tachycardia circuit, the PPI approximates the TCL, and the PPI-TCL *difference* approaches zero. When pacing from a site within a macro–re-entrant circuit, the PPI after entrainment equals the TCL (Figure 23-22, *A* and *B*).

Pacemapping

Pacemapping is a strategy in which pacing is performed during sinus rhythm in an attempt to match as closely as possible the paced and tachycardia-beat morphologies, with the site of closest match representing the presumed origin of the tachycardia. Paced sites are evaluated sequentially until the paced and tachycardia-beat morphologies match across all the leads of a standard ECG (Figure 23-23). Pacemapping may be applied as the primary mapping modality or as an adjunct and confirmatory strategy. The only requirement for pacemapping is that a clinical tachycardia recording be available for comparison. Pacemapping may be employed to map nearly any form of tachycardia in which at least one cardiac chamber is critically involved in tachycardia maintenance and the activation of that chamber is associated with a distinctive morphology that may be mapped. Hence, pacemapping is applicable to a broad range of tachycardias.

When a tachycardia produces a specific ECG beat morphology (P or QRS) that originates directly from a site critical to the clinical tachycardia, such as in a focal tachycardia, pacemapping may be used to guide ablation. Alternatively, tachycardias in which ECG beat inscription is related to an exit remote from the circuit (whether focal or macro–re-entrant) will not be successfully

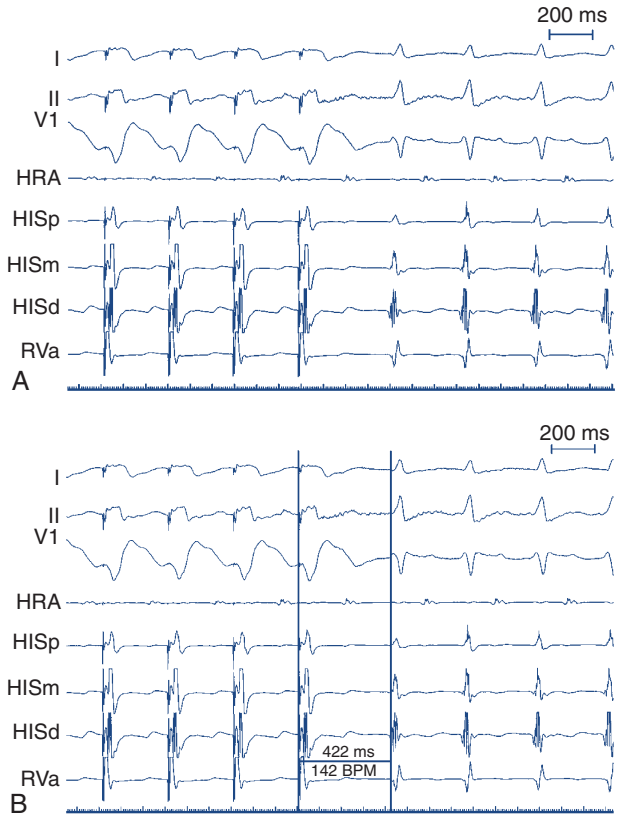

FIGURE 23-22 A, Termination of pacing during tachycardia. The tachycardia is accelerated to the pacing rate and, with cessation of pacing, the tachycardia resumes at its intrinsic cycle length, suggesting entrainment of the tachycardia. **B,** The postpacing interval. The interval between the last paced complex and the first return beat electrogram of the intrinsic tachycardia, known as the postpacing interval (PPI) when measured on the same channel as pacing, is greater than the tachycardia cycle length (TCL). In fact, with entrainment, the PPI can only be greater than or equal to the TCL but never less than the TCL on the pacing channel. In this case, the PPI (422 ms) exceeds TCL (340 ms) significantly (i.e., >40 ms), suggesting that the pacing site is remote to the tachycardia circuit.

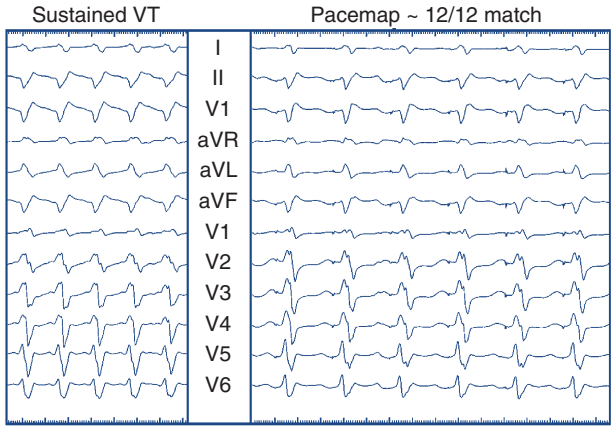

FIGURE 23-23 Pacemapping, in this case of ventricular tachycardia (*VT*) (*left*), is undertaken by pacing through the roving mapping catheter (*right*) from various candidate myocardial locations in an effort to reproduce the morphology of the clinical arrhythmia. True pacemap matches must reproduce not only the overall polarities of the QRS, but its smaller undulations, notches, and minor details. Note how the paced QRS complexes reproduce not only the primary vectors of the Q, R, and S waves of the clinical VT but also the more subtle features, and that these characteristics are reproduced in all 12 leads of the standard electrocardiogram, that is, a "12 out of 12" match.

guided by pacemapping, as the site of exit to the myocardium that is responsible for ECG inscription does not participate in the tachycardia (e.g., AVN re-entry tachycardia); therefore, sites that *do* reproduce the tachycardia ECG morphology are unlikely to represent successful ablation targets.

While macro–re-entrant circuits cannot, by definition, have a focal origin, sites of slow conduction, nonconductive tissue adjacent to healthier myocardium that is within the circuit itself, or both—as may be seen at accessory pathway insertions and exit sites in scar VT—produce a specific ECG morphology that is directly related to a site. This typical morphology *is* indicative of a site critical to the tachycardia and may be used to guide mapping and ablation.

In pacemapping, pacing is usually performed at the TCL to impart some of the functional characteristics of that rate to the local myocardium, thereby theoretically producing a paced ECG beat with morphology representative of tachycardia at that rate. Pacing at high stimulation currents may artificially broaden the immediate region of myocardium depolarized by the pacing stimulus and alter the paced morphology, potentially misleading the operator. Therefore, the general recommendation for pacemapping is to perform pacing at the TCL at twice the diastolic threshold to ensure reproducible and physiologic myocardial capture without augmenting the virtual electrode effect and imparting functional characteristics that are significantly different from those of tachycardia.

These recommendations, however, have been investigated. An assessment of atrial conduction times from various pacing sites at various pacing rates has demonstrated that the myocardial milieu of conduction is not significantly affected by the pacing rate and that the virtual electrode effect is not significant when pacing at maximum output compared with twice the diastolic threshold, with bipolar configuration using electrode catheters with 2-mm spacing. Therefore, in atrial bipolar stimulation using closely spaced electrodes, P-wave morphology appears to be relatively insensitive to stimulation rate and output.[12]

The electrical configuration of pacing impacts the morphology of the paced complex and, therefore, pacemapping. The spatial resolution of unipolar pacemapping was evaluated in the right atrium and CS by Man et al[13] and found to be not less than 17 mm, suggesting that mapping techniques that rely on discrimination of ECG P-wave morphology, such as atrial pacemapping and concealed entrainment in the atrium, are unlikely to be precise.

When comparing unipolar ventricular pacemapping with bipolar ventricular pacemapping, only minor differences in QRS morphologies are occasionally noted with 5-mm electrode spacing, though increased spacing (10 mm) increases the frequency of minor differences. While major morphologic differences between unipolar and bipolar pacemapping are uncommon, a larger number of morphologic differences may occur at 10 mA compared with pacing at threshold or twice threshold. As a result,

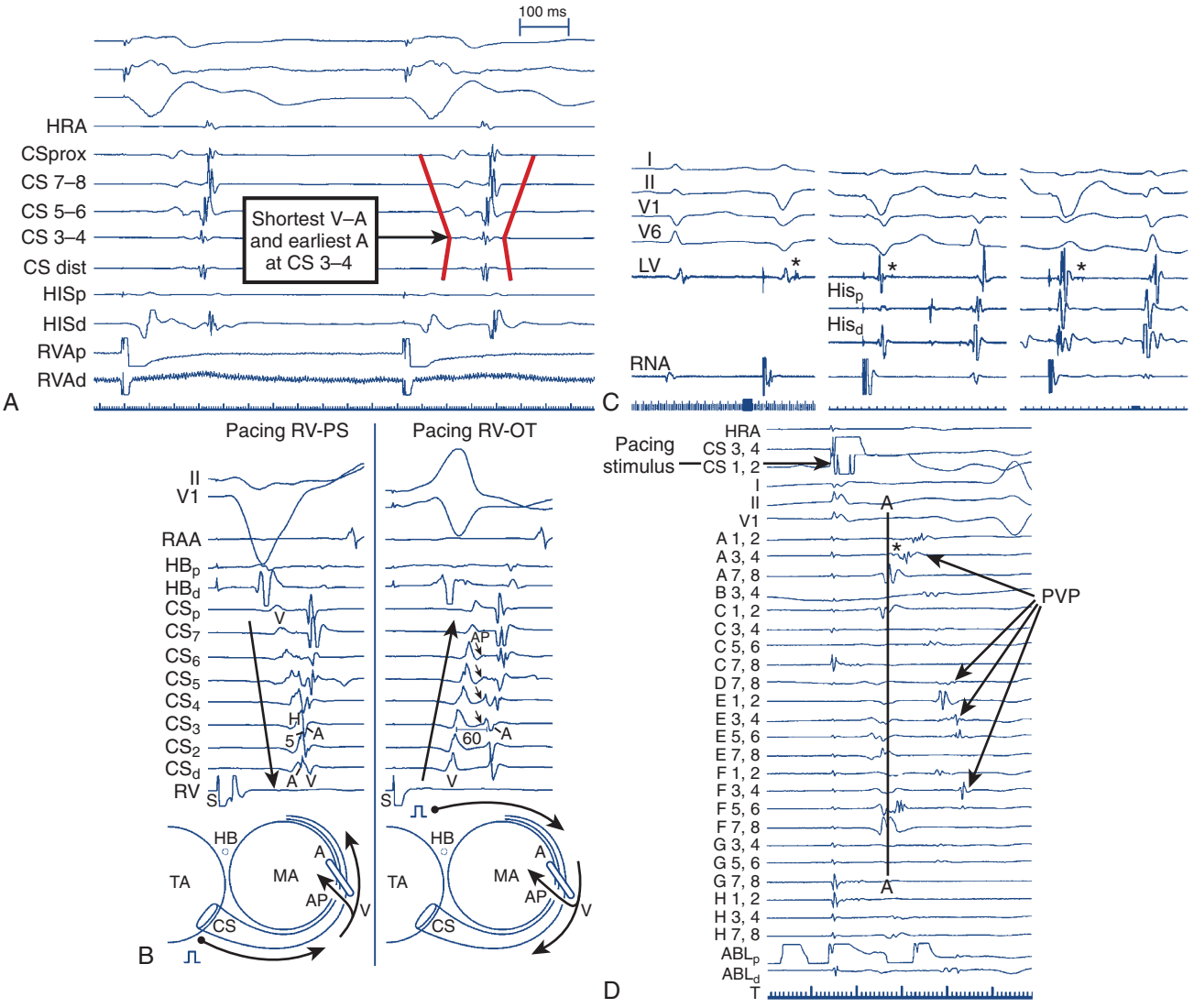

FIGURE 23-24 A, Pacing during sinus rhythm (*SR*) to simulate tachycardia physiology and unmask bypass tract insertion. This patient has a manifest accessory pathway with electrocardiogram delta-wave pattern suggestive of left free wall location (*not shown*). During SR, antegrade conduction over the bypass tract suggested earliest ventricular activation at or beyond coronary sinus (CS) distal, but ventricular pacing with retrograde conduction over the accessory pathway identified earliest atrial activation and shortest local V-A at CS 3-4. **B,** Pacing during SR to simulate tachycardia physiology and to unmask bypass tract insertion site. As the large majority of bypass tracts have oblique trajectories and therefore disparate ventricular and atrial insertions, the atrial activation sequence will have a directionality as determined by the CS activation, in left-sided pathways. Ventricular pacing from the right ventricular (*RV*) posterior septum/apex (**A**) activates both the basal left ventricular *and* the accessory pathway in a septal-to-lateral direction, resulting in bypass tract activation *in parallel* to the basal left ventricle, with overlap of associated ventricular and atrial electrograms. Right ventricular outflow tract (*RVOT*) pacing (**B**) results in lateral-to-septal activation of the basal left ventricle, countercurrent to atrial activation over the accessory pathway. Ventricular activation becomes separated from the septal-to-lateral atrial activation over the bypass tract, in this case exposing a pathway potential. **C,** Ventricular pacing to identify isolated diastolic potentials (IDPs) not otherwise appreciated during SR. Examples of ventricular myocardial mapping to identify components of ventricular tachycardia circuits demonstrates that ventricular pacing allows identification of IDP (*asterisks*) not detected at the same location when the ventricle is activated in SR (*adjacent beat in each panel*). This is explained by SR activation of the left ventricle through the His–Purkinje system that activates multiple myocardial regions nearly simultaneously with resultant wavefront collision preventing unimpeded propagation through the slowly conducting channels. Right ventricular pacing slows the activation of the left ventricle and provides a degree of unidirectionality that permits engagement and propagation through the slowly conducting channels without collision of multiple wavefronts, thereby permitting detection of the IDP. **D,** Identification of pulmonary vein (PV) potentials with a 64-pole multi-spline multi-electrode catheter placed in a left PV during SR distal CS pacing. The atrial potentials are shown (**A**), and the second potentials identify conduction into the PV. Note that in addition to identifying conduction to multiple sites in the vein, the site of entrance is identified by the earliest PV potential. Ablation at the earliest PV potential blocks passive conduction to other sites, thereby avoiding ablation at secondarily activated sites. SR without distal CS pacing leads to multiple left atrial wavefronts that may engage the PV simultaneously, thereby masking true entrance sites with far-field signals from multiple nearby activated sites. (***A*** *and* ***B,*** *From Otomo K, Gonzalez MD, Beckman KJ, et al: Reversing the direction of paced ventricular and atrial wavefronts reveals an oblique course in accessory AV pathways and improves localization for catheter ablation,* Circulation *104(5):550–556, 2001;* ***C,*** *From Arenal A, Glez-Torrecilla E, Ortiz M, et al: Ablation of electrograms with an isolated, delayed component as treatment of unmappable monomorphic ventricular tachycardias in patients with structural heart disease,* J Am Coll Cardiol *41:81–92, 2003.)*

the authors concluded that unipolar and bipolar ventricular pacing from the same catheter location can result in QRS complexes that differ, incriminating anodal capture during bipolar pacing, which is directly related to interelectrode distance and stimulus intensity. Further, because the virtual electrode effect of anodal capture is variable and can variably alter the QRS configuration during pacing, bipolar pacemapping may have less spatial resolution than unipolar pacemapping, making it more difficult to localize sites of VT origin.[14]

Various algorithms have been devised to predict the origin site for atrial and ventricular tachycardias. These will be covered in more depth in other chapters in this text. In general, tachycardias arising from leftward sites propagate away from leads aVL and I, whereas tachycardias arising from more rightward sites propagate toward those leads. Inferior and posterior sites result in propagation away from leads II, III, and F, whereas sites located more anteriorly result in propagation toward them. Finally, tachycardias originating from basal sites propagate toward leads V5 and V6, whereas tachycardias originating from apical sites propagate away from V5 and V6. An awareness of the anticipated site of origin facilitates the mapping process by reducing the extent of myocardial territory explored.

Pacing to Modify Activation

In specific situations, particularly when activation sequence mapping is not feasible, pacing may be used to alter the activation sequence and direction of wavefront propagation in an effort to unmask critical aspects of the tachycardia physiology that may not be apparent during sinus rhythm.

Atrial pacing and ventricular pacing are commonly employed to identify accessory pathway insertions by mapping the earliest site of ventricular and atrial activation, as well as the shortest A-V and V-A interval (Figure 23-24, *A*), respectively. Further, Jackman et al demonstrated that accessory pathway potentials may be unmasked by introducing pacing that activates the accessory pathway "countercurrently," that is, pacing from a site opposite to the accessory pathway obliquity such that the pacing wavefront engages the pathway from a site lateral to the medial insertion, or medial to the lateral insertion, resulting in prolonged A-V and V-A conduction intervals and thus exposing the accessory pathway potential that may be otherwise masked by overlapping signals during sinus rhythm and when pacing from more traditional sites (Figure 23-24, *B*).[15]

Arenal et al demonstrated that right ventricular pacing may be used to identify EGMs with isolated diastolic components that may not be otherwise identifiable in sinus rhythm (Figure 23-24, *C*).[16] For ablation of AF, pacing from the distal CS electrode facilitates left pulmonary vein isolation by separating pulmonary vein potentials from far-field left atrial signals and identifies the sites of entrance into the left pulmonary veins that are difficult to appreciate in sinus rhythm because of overlapping signals (Figure 23-24, *D*).[17]

Conclusion

The theory and practice of catheter mapping of arrhythmia requires an awareness of available techniques as well as an appreciation of their clinical significance and applicability to various clinical scenarios. Catheter mapping is fundamental to the practice of electrophysiology, and its contribution to elucidating arrhythmia mechanisms will continue to grow in parallel with the current understanding of cardiac excitation.

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CHAPTER 24

Electrophysiological Evaluation of Supraventricular Tachycardia

Thorsten Lewalter, Samuel Levy, Shih-Ann Chen, and Sanjeev Saksena

Paroxysmal supraventricular tachycardia (PSVT) is a common condition that affects a wide range of age groups. The clinical syndrome of PSVT and its presentation and management are discussed in detail in Chapter 41. Electrophysiologic study (EPS) of PSVT is routinely performed in clinical laboratories as a component of the diagnostic and therapeutic approach to management of this condition. The clinical presentation of a patient with PSVT includes a variety of tachyarrhythmias, as detailed in Chapter 41 and summarized in Table 24-1. The purpose of EPS is to differentiate the mechanisms of PSVT in an individual patient and help guide appropriate therapy for patient management. These therapeutic approaches can include catheter ablation procedures (see Chapter 93), drug therapy (see Chapters 79 and 80) and, rarely, device therapy (see Chapter 41). For special consideration of drug therapy or ablation in pediatric or pregnant patients, see Chapters 72, 74, and 75, respectively. The focus of this chapter is to delineate the diagnostic information elicited at clinical EPS in two common forms of PSVT—namely, atrioventricular (AV) nodal reentrant tachycardia (AVNRT) and AV reentrant tachycardia (AVRT). EPS of atrial tachycardia (AT) is examined in Chapter 29.

Diagnostic Approach to the Patient with Supraventricular Tachycardia

The initial diagnostic approach to the patient with PSVT, as mentioned in Chapter 41, is documentation of the arrhythmia by electrocardiogram (ECG).

Differential Diagnosis of Supraventricular Tachycardia from the Electrocardiogram

ECG documentation of the tachycardia is essential for the proper diagnosis and management of SVT. SVT may sometimes present with wide QRS complexes, and a clinical EPS is helpful in determining if the cause is bundle branch block (BBB) or aberrant conduction. Differentiating PSVT from ventricular tachycardia (VT), particularly when pre-excitation is present, is definitively accomplished at EPS.

Electrophysiological Study of Supraventricular Tachycardia

An EPS is used for diagnostic and therapeutic purposes. During these procedures the underlying atrial and ventricular substrate is assessed. PSVT initiation during these procedures allows ECG documentation of the underlying symptoms of the tachycardia, such as evanescent palpitations, if it has not been previously recorded; definition of the mechanism of the tachycardia and the critical components of the circuit; evaluation of symptoms and hemodynamics during the arrhythmia; and, if indicated, performance of radiofrequency ablation or evaluation of the efficacy of antiarrhythmic therapy.

Atrioventricular Re-entrant Tachycardia and Atrioventricular Node Re-entrant Tachycardia

The methods of catheter placement and programmed electrical stimulation are discussed in detail in Chapter 20 and are not revisited here in detail. In brief, multipolar electrode catheters are placed in the right atrium, His bundle region, coronary sinus, and right ventricle. Recordings are obtained from these regions as well as the right and left AV ring for bypass tract mapping or more detailed septal pathway localization. Programmed atrial stimulation is usually performed from the high right atrium, coronary sinus, right ventricular apex, and the atrial or ventricular insertion site of a bypass tract as needed. In some instances, alternate pacing sites can include the left atrium, right ventricular outflow tract, right ventricular septum, or left ventricle. For the study of propagation and induction of tachycardia, the extrastimulus technique is widely used, although burst pacing is an alternative. These techniques are discussed in Chapter 20. Facilitiation of induction may require the administration of pharmacologic agents such as isoproterenol or atropine (see Chapter 72). Other pharmacologic agents such as adenosine may be used for diagnostic purposes to evaluate the presence of accessory pathway conduction or termination of PSVT involving the AV node (see Chapter 72).

Most SVTs are caused by a re-entrant mechanism and may be induced in the laboratory by using programmed electrical stimulation. In A-V junctional tachycardias, electrophysiological study permits induction of tachycardia in more than 90% of patients with AVRT or AVNRT. In patients with AVNRT, premature atrial stimulation can demonstrate dual AV nodal conduction and induce the tachycardia to determine its mechanism. The arrhythmias associated with WPW syndrome include reciprocating or circus movement tachycardias and atrial arrhythmias. In some instances of AVNRT, concomitant pre-excited QRS complexes may exist because of passive conduction over an accessory pathway that may serve as a passive bystander. Tachycardias related to Mahaim fibers have a particular electrocardiographic presentation with LBBB and left-axis deviation. The ECG in sinus rhythm shows the features of WPW syndrome (Figure 24-1). The

Table 24-1 Paroxysmal Supraventricular Tachycardias with Narrow and Wide QRS Complexes

SINUS NODE DISORDERS
Paroxysmal sinus tachycardia
Nonparoxysmal sinoatrial tachycardia
AV NODAL RE-ENTRANT TACHYCARDIAS
Slow-fast
Fast-slow
Slow-slow
RE-ENTRANT AND ECTOPIC ATRIAL TACHYCARDIAS
Intra-atrial re-entrant tachycardia
Automatic atrial tachycardia (unifocal or multifocal)
PRE-EXCITATION SYNDROME: WOLFF-PARKINSON-WHITE SYNDROME
Orthodromic atrioventricular re-entry
Permanent junctional reciprocating tachycardia
Antidromic atrioventricular re-entry
Atrial tachycardia, atrial flutter, or atrial fibrillation with or without accessory pathway conduction
OTHER PRE-EXCITATION SYNDROMES: MAHAIM CONDUCTION
Nodoventricular and nodofascicular re-entry
Atrial tachycardia, AV nodal re-entry, or atrial fibrillation with nodoventricular or nodofascicular bystander conduction
Atrial tachycardia, atrial flutter, or atrial fibrillation with enhanced AV nodal conduction
AUTOMATIC AV JUNCTIONAL TACHYCARDIAS

AV, Atrioventricular.

electrophysiological study often demonstrates decremental conduction over the accessory pathway.

Atrioventricular Nodal Re-Entrant Tachycardia

Dual Atrioventricular Nodal Pathway

During electrophysiological evaluation, typical AVNRT manifests antegrade conduction via a "slow" pathway and retrograde conduction via a "fast" pathway.[1-10] The electrophysiological characteristic is the presence of dual AV nodal pathway physiology demonstrated by a discontinuous AV node functional curve. Discontinuous AV nodal conduction is defined as a sudden increment of 50 ms or greater in the A-H or H-A interval ("jump"), with a decrement in prematurity of the extrastimulus by 10 to 20 ms. In some patients, a jump (>50 ms) of any consecutive A-H intervals during incremental atrial pacing is found, which might be a manifestation of dual AV nodal pathways. Typically, the jump phenomenon is followed by induction of a slow-fast AVNRT (Figure 24-2). During tachycardia in typical slow-fast AVNRT, a long A-H interval with a short V-A interval can be documented (Figure 24-3). When performing endocardial mapping, the earliest atrial activation during tachycardia can be detected at the slow pathway area around the coronary sinus ostium. In contrast, atypical AVNRT has antegrade conduction through a "fast" or "slow" pathway and retrograde conduction through a "slow" pathway.[2,3]

To differentiate AVNRT from AVRT, the following maneuvers can be used[4-6]:

- V-A interval timing during tachycardia: V-A interval during slow-fast AVNRT is mainly shorter than 50 ms, whereas V-A intervals exceed 50 ms during orthodromic AVRT

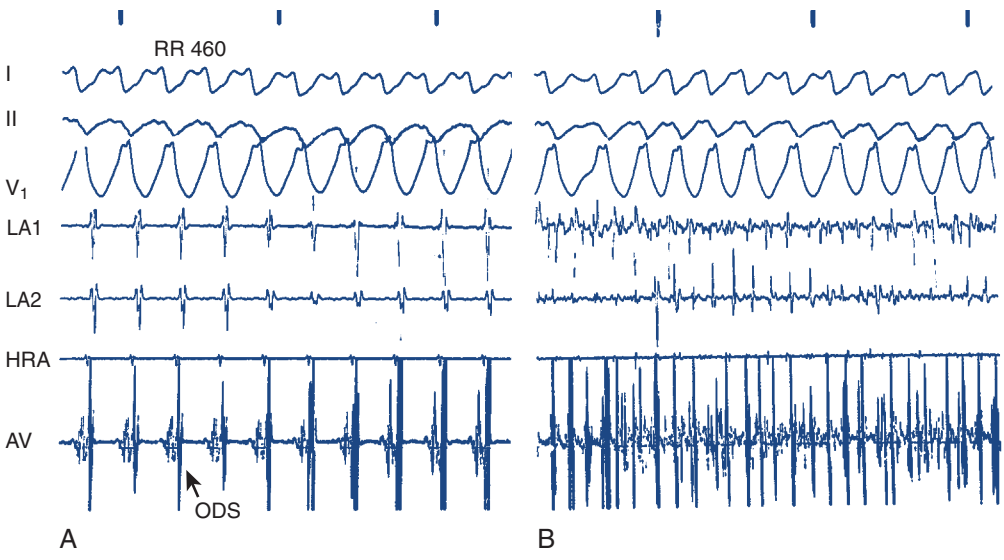

FIGURE 24-1 Tachycardias with pre-excited QRS complexes. *Top to bottom,* Electrocardiogram leads I, II, and V1; high right atrium (*HRA*); and left atrium (*LA1* and *LA2*). **A,** Consistent with an antidromic reciprocating tachycardia. **B,** Atrial fibrillation conducted over a left-sided accessory atrioventricular (*AV*) pathway termination of supraventricular tachycardia with vagal maneuvers.

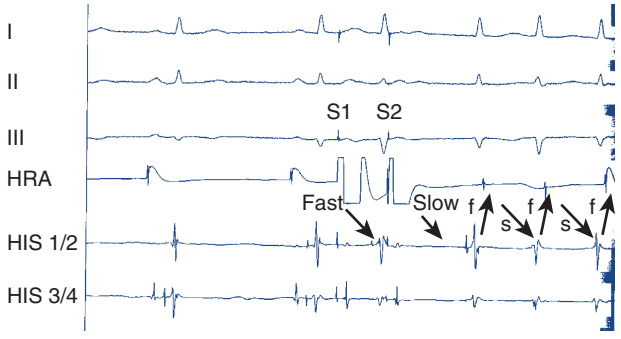

FIGURE 24-2 Induction atrioventricular nodal re-entrant tachycardia (AVNRT). Atrial extra stimulus pacing with an A-H jump and induction of typical slow-fast AVNRT. *HRA,* High right atrium.

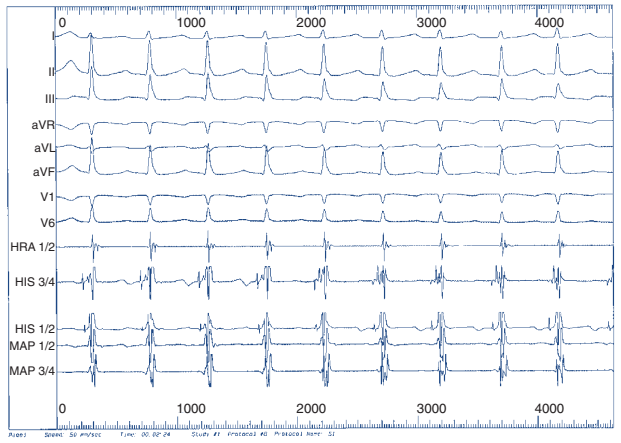

FIGURE 24-3 Typical slow-fast atrioventricular nodal re-entrant tachycardia with a short V-A interval.

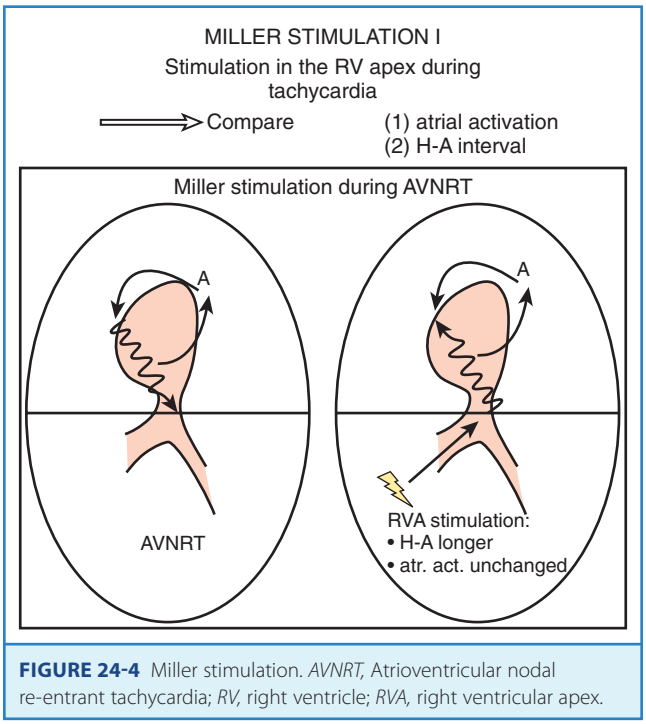

FIGURE 24-4 Miller stimulation. *AVNRT,* Atrioventricular nodal re-entrant tachycardia; *RV,* right ventricle; *RVA,* right ventricular apex.

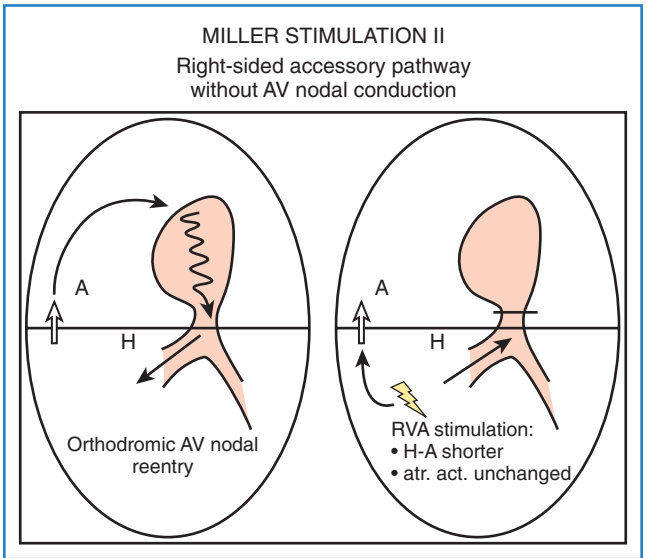

FIGURE 24-5 Miller stimulation. *AV,* Atrioventricular; *RVA,* right ventricular apex.

- Miller stimulation (Figures 24-4 and 24-5)
- Para-Hisian stimulation at the summit of the ventricular septum
- Programmed extrastimulation maneuvers (Figures 24-6 and 24-7)

Two important concepts of dual AV nodal pathways have been further clarified by provocative pharmacologic testing and catheter ablation in patients with AVNRT. One major question has been whether dual AV nodal pathways are fully intranodal and caused by longitudinal dissociation of AV nodal tissue or extranodal, involving separate atrial inputs into the AV node. From clinical studies of slow pathway potentials, LH (low followed by high) frequency potentials are observed during asynchronous activation of muscle bundles above and below the coronary sinus orifice. HL (high followed by low) frequency potentials are caused by asynchronous activation of atrial cells and a band of nodal-type cells that may represent the substrate of the slow pathway.[7-10] Thus the slow and fast pathways are likely to be atrionodal approaches or connections rather than discrete intranodal pathways. The results of catheter ablation indicate that the fast and slow pathways have their origins outside the limits of the compact AV node and that the tissues targeted during successful ablation are

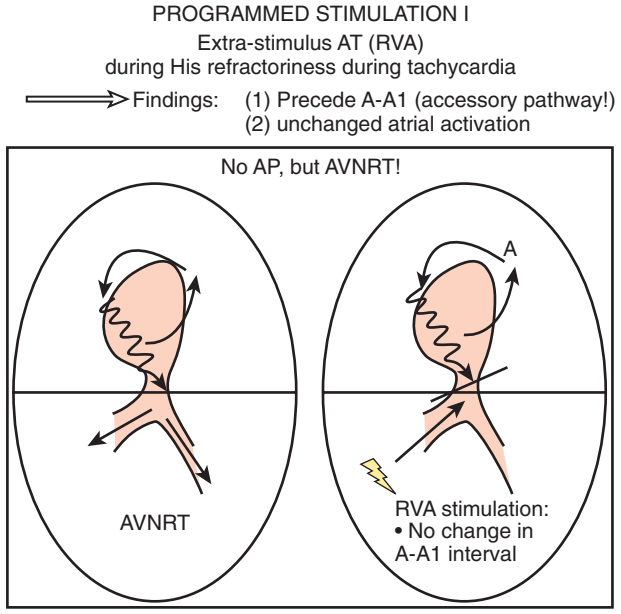

FIGURE 24-6 Programmed stimulation. *AP,* Accessory pathway; *AVNRT,* atrioventricular nodal re-entrant tachycardia; *RVA,* right ventricular apex.

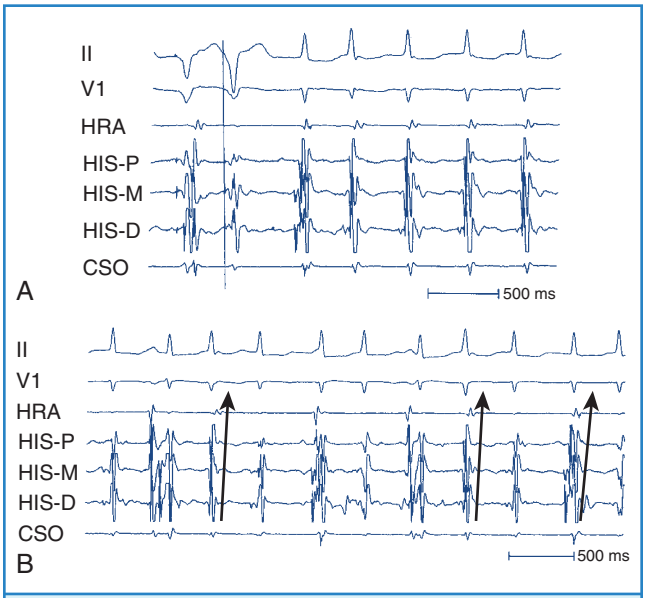

FIGURE 24-8 A, Right ventricular stimulus induces atrioventricular nodal re-entrant tachycardia (AVNRT). Although the last pacing beat (*vertical line*) does not conduct to the atrium, AVNRT still occurs. **B,** AVNRT with occasional retrograde conduction to the atrium (*arrows*). *HRA,* High right atrium; *HIS-P,* proximal portion of the His bundle; *HIS-M,* medial portion of the His bundle; *HIS-D,* distal portion of the His bundle; *CSO,* coronary sinus ostium.

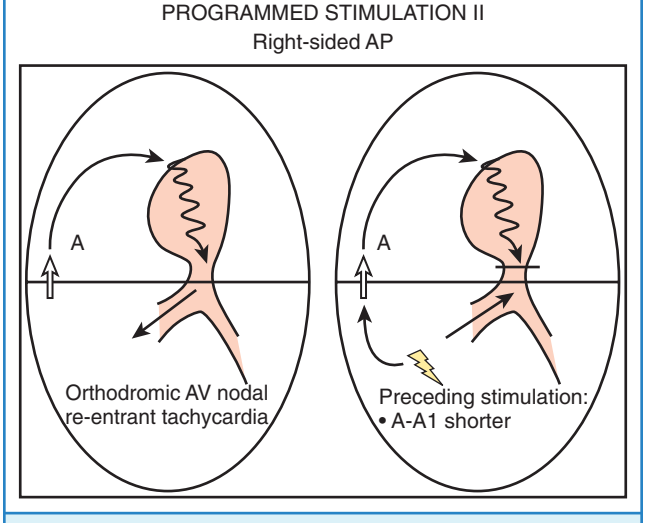

FIGURE 24-7 Programmed stimulation. *AP,* Accessory pathway; *AV,* Atrioventricular.

composed of ordinary working atrial myocardium surrounding the AV node itself.[11-14] Furthermore, AV or VA conduction block during AVNRT favors the concept that atrial and ventricular tissues are not involved in the maintenance of this tachycardia (Figures 24-8 and 24-9).[15,16]

Unusual Physiology of Dual Atrioventricular Nodal Pathways

Some patients with AVNRT have multiple antegrade and retrograde AV nodal pathways with multiple discontinuities in the AV node function curve or dual AV nodal pathways with a continuous curve during programmed electrical stimulation.[13,17] Furthermore, variant forms (slow-slow, slow-intermediate, fast-intermediate) of AVNRT have been noted (Figures 24-10 and 24-11).[11-13] Whether multiple antegrade and retrograde AV nodal pathways originate from anatomically different pathways or represent anisotropic conduction–induced functional pathways is still being debated. Several investigators have demonstrated the marked heterogeneity of the transitional cells surrounding the compact AV nodal pathway. The non-uniform properties of the AV node can produce anisotropic conduction and suggest that the antegrade and retrograde fast pathways are anatomically distant from the multiple "antegrade slow" and "retrograde slow" or intermediate pathways, respectively. Clinical studies have demonstrated that successful ablation or modification of retrograde slow and intermediate pathways occurs at different sites from the antegrade fast or slow pathway, and the possibility of anatomically different antegrade or retrograde multiple pathways should be considered. Furthermore, in the patients who have successful ablation of multiple antegrade slow pathways or retrograde slow and intermediate pathways at a single site, anisotropic conduction over the low septal area of the right atrium is a possible explanation for the presence of multiple antegrade and retrograde AV nodal pathways.[11-13,17]

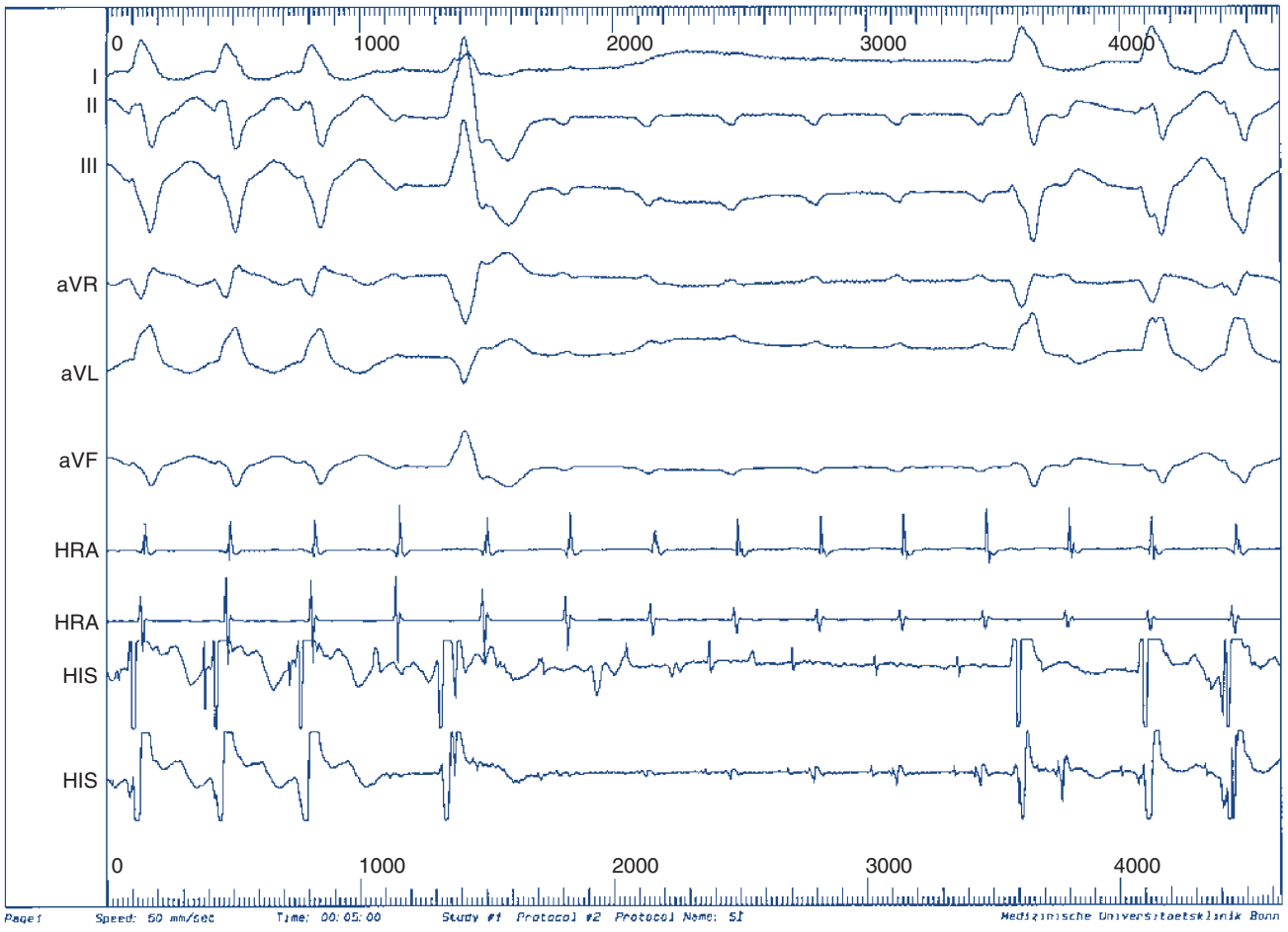

FIGURE 24-9 Infra-His block during typical slow-fast atrioventricular nodal re-entrant tachycardia. *HIS*, Quadrupolar catheter in His position; *HRA*, quadrupolar catheter in high right atrium.

Patients with AVNRT can have continuous AV node conduction curves. These patients do not exhibit an A-H jump with two extrastimuli and two drive cycle lengths during atrial pacing from the high right atrium and the coronary sinus ostium. The possible mechanisms of the continuous AV node function curves in AVNRT include the following: (1) the functional refractory period of the atrium limits the prematurity with which atrial premature depolarization will encounter the refractoriness in the AV node, which, in turn, produces inability to dissociate the fast and slow AV node pathways; and (2) fast and slow AV nodal pathways have similar refractory periods and conduction times.[17]

Atrioventricular Re-entrant Tachycardia

Anatomy and Electrophysiology of Accessory Pathways

The oblique orientation of most accessory pathways has been demonstrated by detailed endocardial and epicardial mapping techniques.[18-20] The locations of atrial and ventricular insertion sites of accessory pathways can differ by up to 2 cm; furthermore, some accessory pathways have antegrade and retrograde conduction fibers at different locations. This finding has been proven by different ablation sites for antegrade as well as retrograde conduction.[21] Thus the anatomic and functional dissociation of the accessory pathway into atrial and ventricular insertions and antegrade and retrograde components is possible. Approximately 90% of AV accessory pathways have fast conduction properties, and the other accessory pathways (including Mahaim fibers) show decremental conduction properties during atrial or ventricular stimuli with shorter coupling intervals.[22-25] These pathways with decremental conduction may be sensitive to several antiarrhythmic drugs, including verapamil and adenosine. Accessory pathways in the right free wall and posteroseptal areas have a higher incidence of decremental conduction properties. When decremental conduction is present, the possibility of Mahaim fibers, such as atriofascicular or nodoventricular pathways, must be considered. Several studies have demonstrated that most of the ventricular insertion sites of these particular bypass tracts are close to the right bundle branch and that the

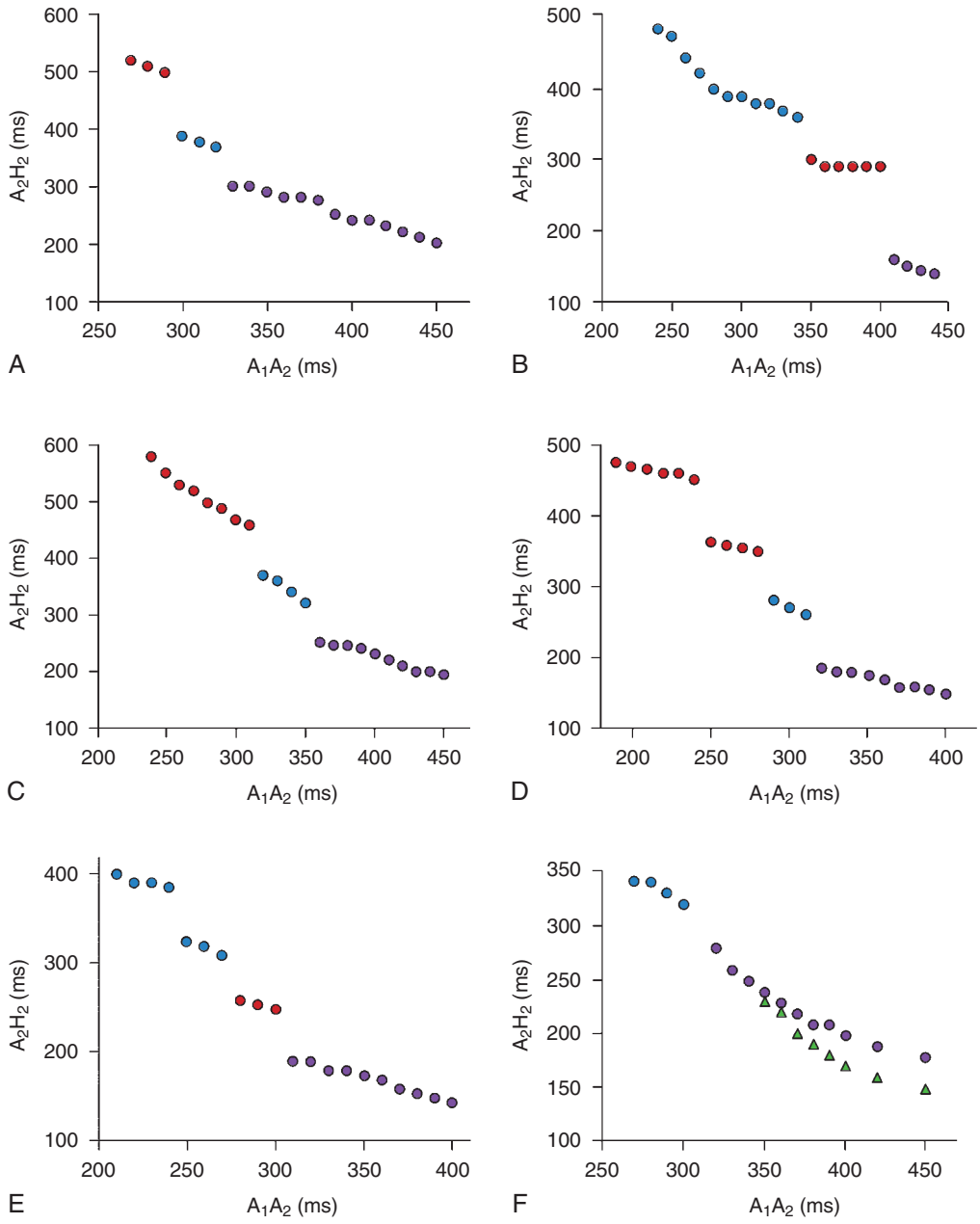

FIGURE 24-10 **A** to **D,** Atrioventricular (AV) nodal conduction curve with multiple jumps. Five patterns of tachycardia (slow-fast form) induction demonstrated by AV node conduction curves (A_2H_2 vs. A_1A_2). A_2H_2, atrio–His bundle conduction interval in response to atrial extra stimulus; A_1A_2, coupling interval of atrial extra stimulus. *Purple circles* indicate fast pathway conduction; *blue circles* indicate slow pathway conduction without initiation or maintenance of sustained tachycardia; *red circles* indicate slow pathway conduction with initiation and maintenance of sustained tachycardia. **A,** Only the first slow pathway is used for induction and maintenance of sustained tachycardia (pattern 1). **B,** Only the second slow pathway is used for induction and maintenance of sustained tachycardia (pattern 2). **C,** The first slow pathway is used during sustained tachycardia; either the first or the second slow pathway is used for initiation of tachycardia (pattern 3). **D,** The first slow pathway is used during sustained tachycardia; any of the three slow pathways is used for initiation of tachycardia (pattern 4). **E,** The third slow pathway is used during sustained tachycardia; either the second or third slow pathway is used for initiation of tachycardia (pattern 5). **F,** AV nodal conduction curve without AH jump. Curve relating A_2H_2 interval to prematurity of atrial extra stimuli (A_1A_2). Before ablation, a smooth curve without evidence of dual AV nodal pathway is present (s). After critical AH delay, tachycardia also is induced (*green triangles*). Ablation in the slow pathway zone eliminates the "tail" of the curve. *(E, From Tai CT, Chen SA, Chiang CE, et al: Multiple anterograde atrioventricular node pathways in patients with atrioventricular node reentrant tachycardia,* J Am Coll Cardiol *28:725–731, 1996. F, From Tai CT, Chen SA, Chiang CE, et al: Complex electrophysiological characteristics in atrioventricular nodal reentrant tachycardia with continuous atrioventricular node function curves,* Circulation *95:2541–2547, 1997.)*

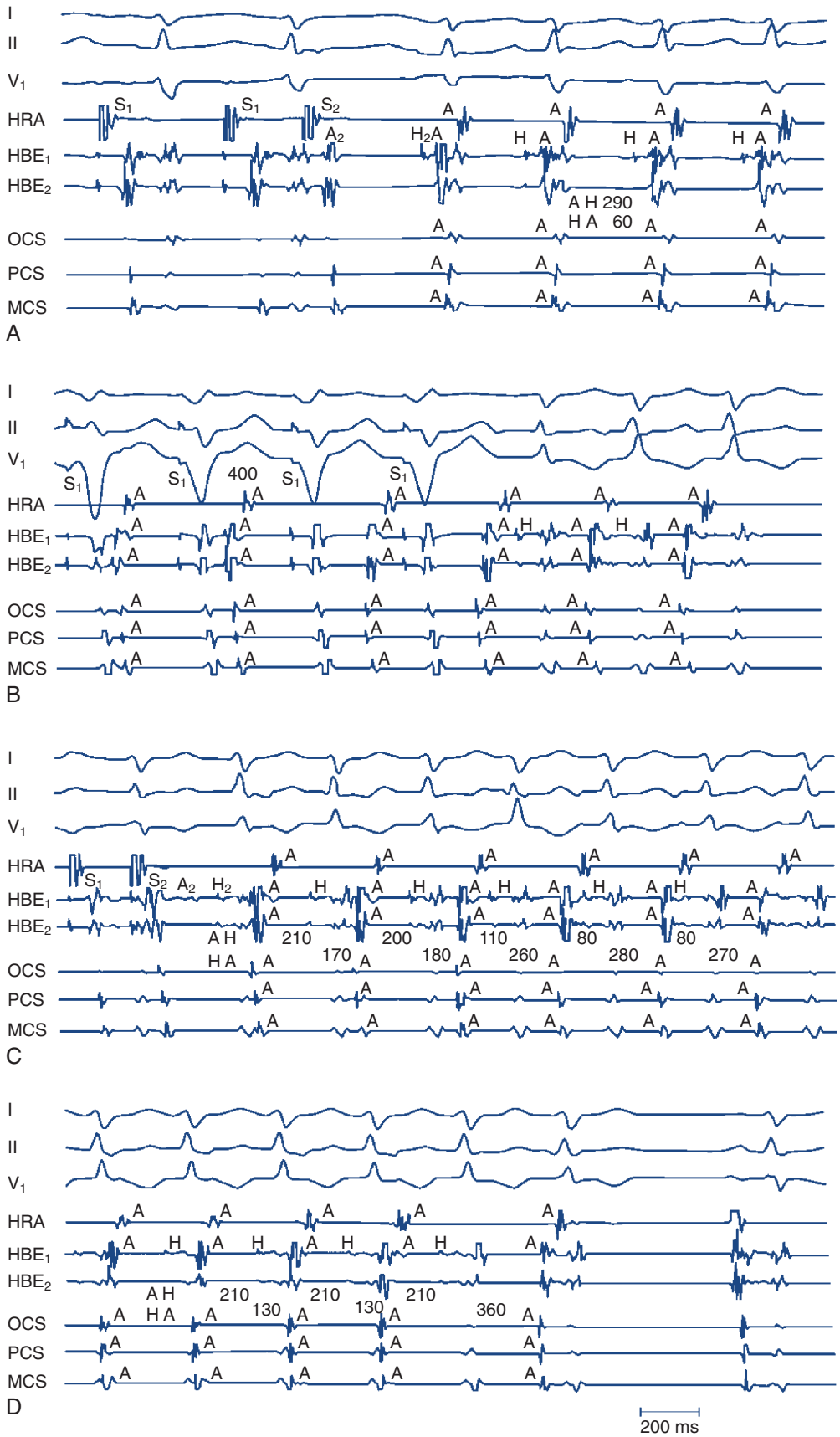

FIGURE 24-11 Recordings show four types of atrioventricular nodal re-entrant tachycardia (AVNRT) and echo. **A** and **B,** The baseline state. **C** and **D,** Intravenous infusion of isoproterenol. **A,** Induction of slow-fast form of AVNRT by atrial extra stimulus, with the earliest atrial activation at the ostium of the coronary sinus (*OCS*). **D,** A slow-slow form AVNR echo before termination of slow-intermediate form of AVNRT. A_2 and H_2, Atrial and His bundle response to the atrial extra-stimulus (S_2), respectively; *HRA,* high right atrium; HBE_1, distal bundle of His area; HBE_2, proximal bundle of His area; *PCS,* proximal coronary sinus; *MCS*, middle coronary sinus; S_1, basic paced beats; S_2, extra stimulus. *(From Tai CT, Chen SA, Chiang CE, et al: Electrophysiologic characteristics and radiofrequency catheter ablation in patients with multiple atrioventricular nodal reentry tachycardias,* Am J Cardiol *77:52–58, 1996.)*

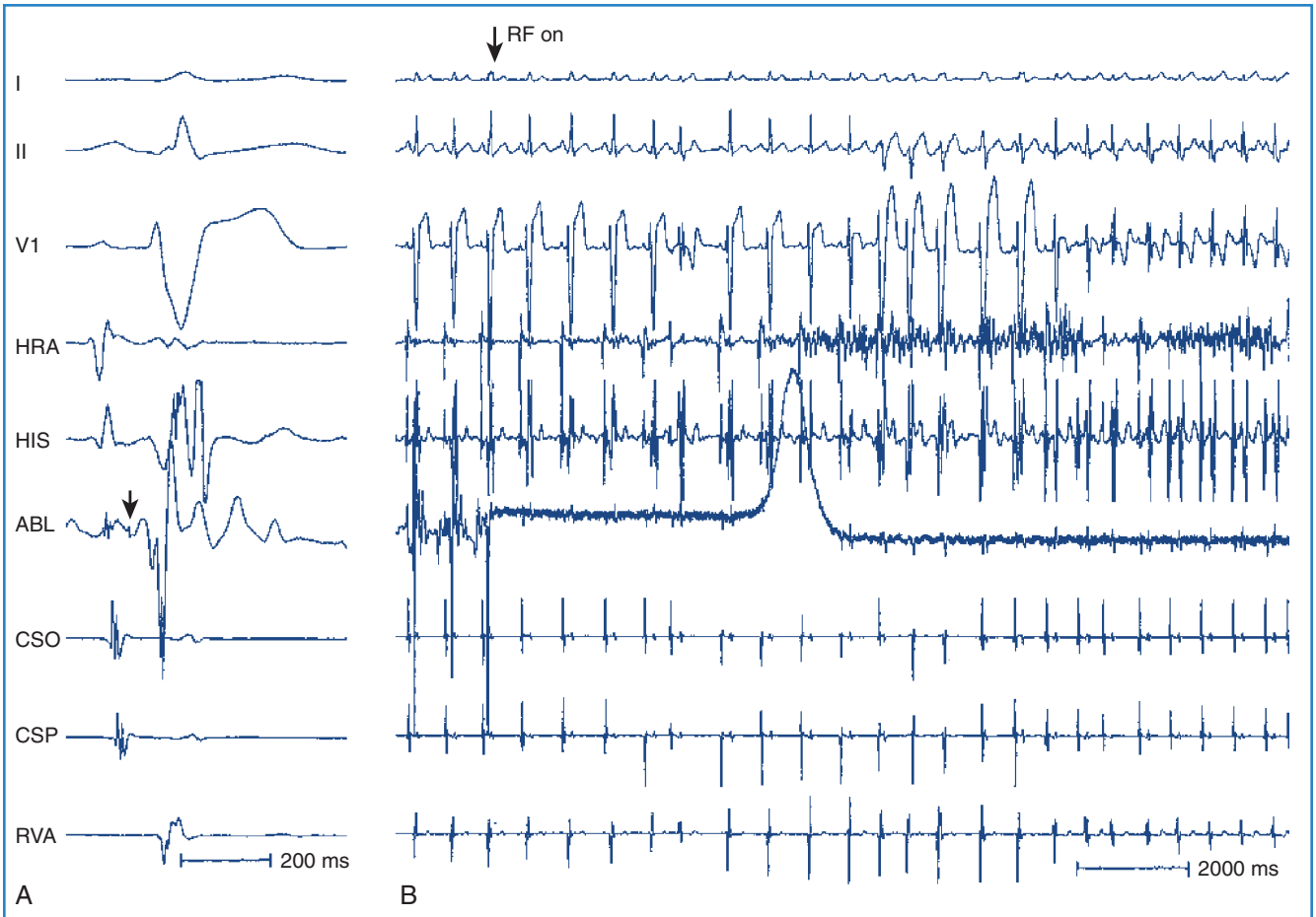

FIGURE 24-12 A, A mapping catheter along the posterolateral aspect of tricuspid annulus records the Mahaim fiber potential (*arrow*). **B,** Application of radiofrequency (*RF*) energy on this point (*arrow*) eliminates Mahaim fiber conduction with disappearance of ventricular pre-excitation. *HRA,* High right atrium; *ABL,* ablation; *CSO,* coronary sinus ostium; *CSP,* proximal coronary sinus; *RVA,* right ventricular apex.

typical Mahaim fiber potential can be recorded along the tricuspid annulus in patients with the atriofascicular pathways (Figure 24-12).[26-29]

Electrophysiological Findings in Atrioventricular Re-entry Tachycardia

The manifest accessory pathway can be diagnosed from the 12-lead surface ECG with a typical δ wave and is confirmed by a reduced, absent, or negative H-V interval. During the electrophysiological study, recordings should be obtained from the tricuspid annulus and the mitral annulus directly or indirectly from the coronary sinus as well as the normal AV nodal–His conduction system. Atrial and ventricular pacing and extrastimulation, isoproterenol provocation, and induction of atrial fibrillation (AF) to assess antegrade conduction over an accessory pathway are essential elements of the electrophysiological study. Ventricular pacing and extrastimulation can define retrograde conduction properties such as refractoriness and conduction time and the location of the pathway. Switching of conduction between the accessory pathway and the AV nodal–His axis can be demonstrated on reaching the effective refractoriness of one or the other conduction pathway. Atrial pacing or extrastimulation can accentuate antegrade pre-excitation up to the refractoriness of the pathway. Tachycardia induction requires unidirectional block in one of the AV conduction pathways (AV node–His axis or accessory pathway) coupled with critical conduction delay in the circuit.

For the diagnosis of accessory pathway–mediated AVRT, a premature ventricular depolarization can be delivered during the tachycardia when the bundle of His is refractory and the impulse still conducts to the atrium; this indicates that retrograde propagation conducts to the atrium over a pathway other than the normal AV conduction system. The definition of AVRT involves

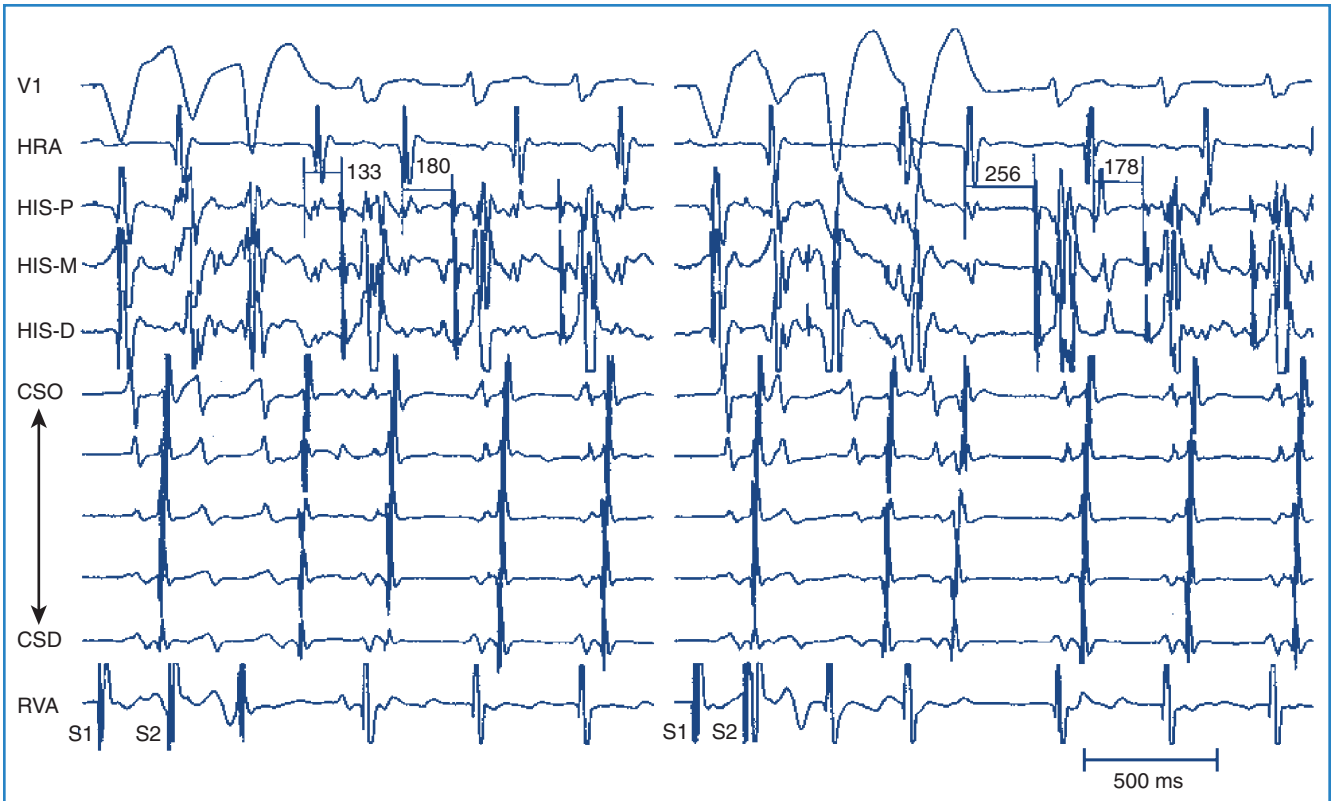

FIGURE 24-13 Right ventricular extrastimulus (S_1S_2) with V3 phenomenon induces atrioventricular (AV) re-entry tachycardia with retrograde conduction through the left lateral accessory pathway. *Left,* The first and second tachycardia beats show antegrade conduction time (A-H interval) of 133 and 180 ms, respectively. *Right,* The S_1S_2 coupling interval is shorter than that on the left, and the antegrade conduction time is much longer in the first tachycardia beat than the second tachycardia beat (256 vs. 178 ms), with the difference larger than 50 ms suggesting the possibility of antegrade conduction through the slow pathway in the first tachycardia beat. *HRA,* High right atrium; *HIS-P,* proximal portion of the His bundle; *HIS-M,* medial portion of the His bundle; *HIS-D,* distal portion of the His bundle; *CSO,* coronary sinus ostium; *CSD,* distal portion of the coronary sinus; *RVA,* right ventricular apex.

re-entry over one or more AV accessory pathways and the AV node, and the classic classification of AVRT includes orthodromic and antidromic tachycardias.[29-31] For the initiation of orthodromic tachycardia, a critical degree of delay in the A-V or V-A interval, which can be in the AV node or His-Purkinje system, is usually necessary. However, dual AV nodal pathway physiology, with or without AVNRT, can be noted in some patients (Figure 24-13). Ventricular pacing from different sites can provide valuable information about retrograde conduction through the AV node or via a septal pathway (Figure 24-14). The incidence of antidromic AVRT is much lower than orthodromic AVRT. Comparison with sinus rhythm shows a fully pre-excited QRS complex. Rapid conduction in retrograde AV nodal–His axis is necessary for the initiation and maintenance of antidromic tachycardia. The atrial premature beat usually can advance the next pre-excited ventricular complex through the antegrade accessory pathway, or it can terminate the AVRT through collision with the previous retrograde wavefront (Figure 24-15). The incidence of multiple accessory pathways is approximately 5% to 20%, and antidromic tachycardia is common in this situation.

The most difficult situation for the differential diagnosis of AVRT is the so-called *Mahaim tachycardia*, which includes atriofascicular or nodofascicular (or nodoventricular) re-entry tachycardia and AVNRT with an "innocent bystander" bypass tract. These arrhythmias often appear as wide-complex tachycardias with LBBB and left-axis deviation. However, the presence of ventriculoatrial dissociation favors nodofascicular tachycardia. Sternick et al recently described a simple parameter to distinguish between decremental or rapidly conducting pathways during pre-excited tachycardia: An AV interval of more than 150 ms during pre-excited tachycardia is reliable for detecting a decrementally conducting accessory pathway.[32]

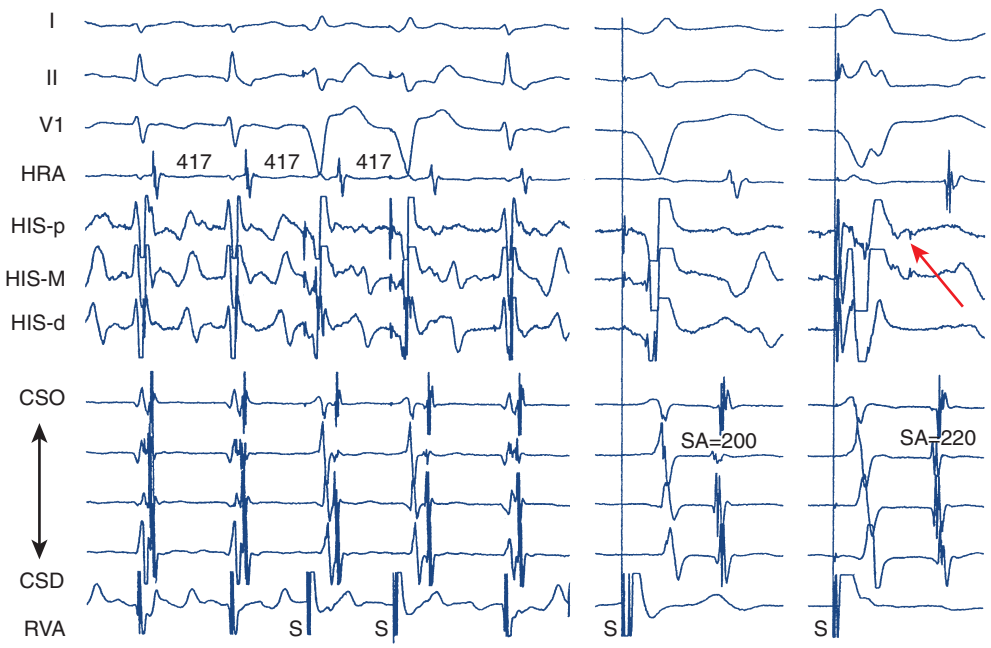

FIGURE 24-14 *Left,* Delivery of two right ventricular apex stimuli during tachycardia without changing the tachycardia cycle length (417 ms) or atrial cycle length. The earliest atrial activation is on the proximal part of the coronary sinus. *Middle,* Ventricular stimuli from the right ventricular apex with the same pacing cycle length as tachycardia cycle length, and the interval from stimulus to atrial activation on the coronary sinus is 220 ms. *Right*, Ventricular stimuli from the basal part of the right ventricle with the same pacing cycle length as tachycardia cycle length. The interval from stimulus to atrial activation on the CS is 220 ms. The retrograde bundle of His potential is found before atrial activation. The stimulus to the A interval (220 ms) is much longer than the QRS-A interval during tachycardia. These findings suggest atrioventricular nodal re-entrant tachycardia with demonstration of a lower common pathway during ventricular pacing and exclude the possibility of retrograde accessory pathway in the posteroseptal area.

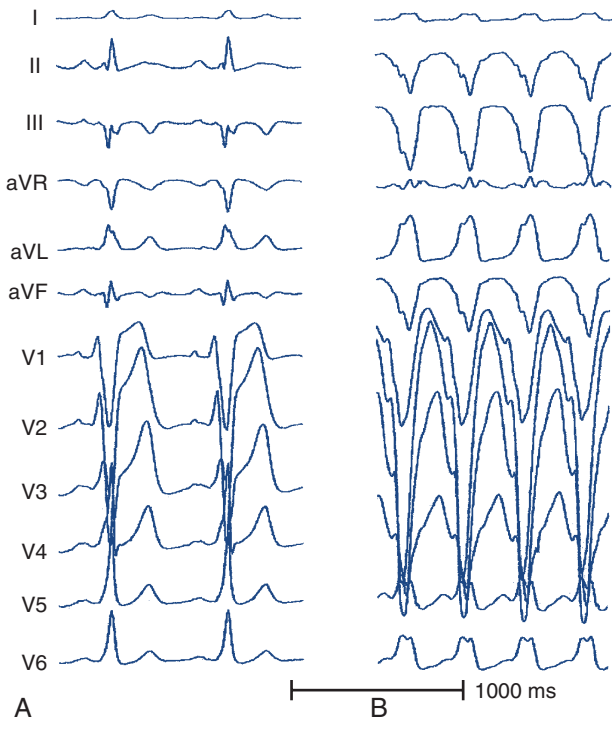

FIGURE 24-15 A, A 12-lead electrocardiogram (ECG) during sinus rhythm. **B,** Surface 12-lead ECG of antidromic tachycardia.

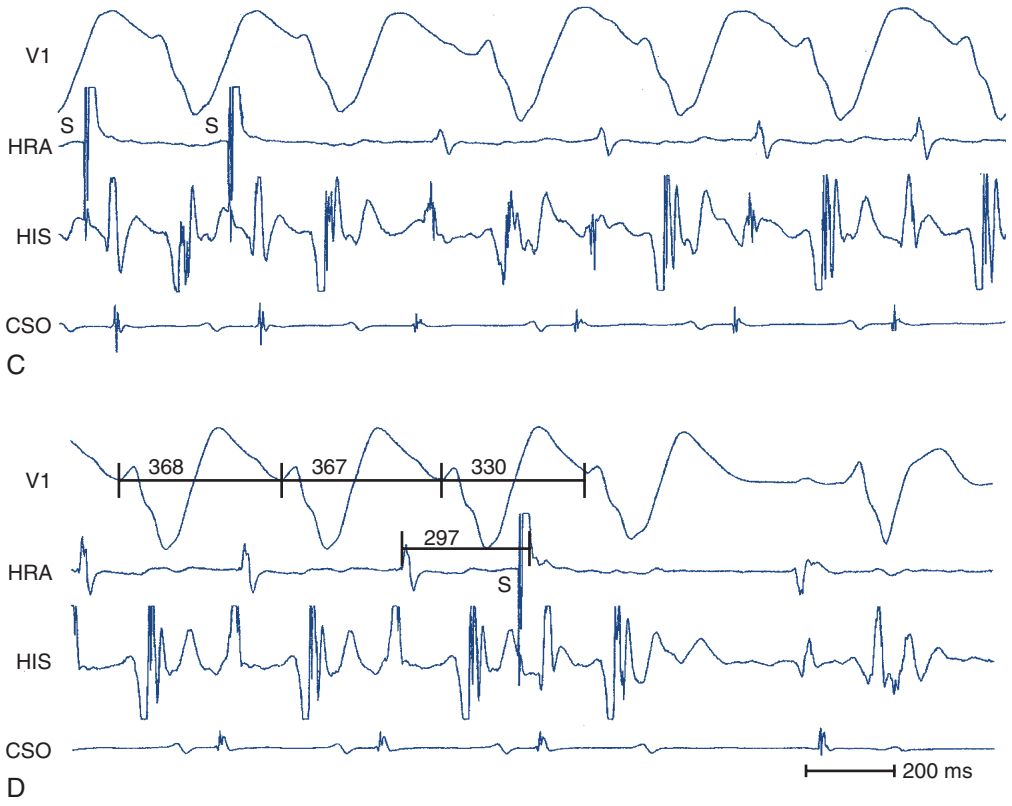

FIGURE 24-15, cont'd C, Rapid atrial pacing (*S*) induces antidromic atrioventricular (AV) re-entry tachycardia with antegrade conduction through right free wall accessory pathway and retrograde conduction through slow AV nodal pathway (earliest retrograde atrial activation in the coronary sinus ostium [*CSO*]). **D,** One atrial premature beat pre-excites the ventricle through the accessory pathway; however, this atrial premature beat (*S*) also collides with retrograde atrial activation, and AV re-entry tachycardia is terminated. *HRA,* High right atrium.

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CHAPTER 25

Electrophysiological Evaluation of Ventricular Fibrillation

Matthew Wright, Frederic Sacher, and Michel Haïssaguerre

Introduction

Sudden cardiac arrest accounts for between 300,000 and 400,000 deaths in the United States alone each year. Although the underlying pathophysiology for the majority of these deaths is coronary artery disease (CAD), in autopsy studies, evidence of recent occlusive coronary thrombus is present in only up to 64% of patients.[1] Thus up to one third of all cases of unexplained sudden cardiac arrest may be primarily caused by cardiac arrhythmias, with ventricular fibrillation (VF) being the culprit arrhythmia in the majority of patients. Although secondary and primary prevention trials have demonstrated the superiority of implantable cardioverter defibrillators (ICDs) compared with antiarrhythmic drugs (AADs) in preventing death, which represents ICD therapy as the gold standard treatment for this condition, current methods of risk stratification are primarily based on the assessment of left ventricular ejection fraction (LVEF).[2,3]

Moreover, approximately 10% of all deaths are unaccounted for, with autopsies revealing structurally normally hearts. Even with postmortem genetic testing, specifically for long QT syndrome (LQTS), 96% of young males who died from sudden cardiac death (SCD) had no attributable cause. Although a number of genetic syndromes that can result in VF, such as Brugada syndrome and arrhythmogenic right ventricular cardiomyopathy (ARVC), have been identified, a large population of young, otherwise healthy patients still die from idiopathic VF, which is difficult to diagnose. This chapter explores the diagnostic modalities available to the electrophysiologist to identify and risk stratify patients at risk of SCD.

Programmed Ventricular Stimulation

The use of invasive electrophysiological study (EPS) to risk stratify patients goes back almost 40 years to the observation by Wellens et al that in patients with prior myocardial infarction (MI) and ventricular tachycardia (VT), programmed ventricular stimulation could be used to induce the same VT (Figure 25-1).[4] Although the sensitivity of programmed ventricular stimulation has been refined since its original description, a nonclinical ventricular arrhythmia is induced in approximately one third of patients.[5] Although protocols vary among institutions, stimulation is normally performed from both the right ventricular apex and the right ventricular outflow tract (RVOT). Initially, single, double, and then triple extrastimuli are applied to a sensed ventricular beat, reducing the last extra stimulus by 20 ms each time until the effective refractory period (ERP) is reached. An eight-beat drive train is then followed by a single extrastimulus, then two and finally three extrastimuli, with the coupling interval of the last extrastimulus being decreased by 10 or 20 ms until the ERP is reached for the first extrastimulus. Typically, 600-ms and 400-ms drive trains are used. Most operators stop extrastimuli at a coupling interval of 180 to 200 ms because with shorter coupling intervals, the specificity of the test is reduced and polymorphic VT and VF occur more frequently.[6] However, recent work suggests that patients with VT of a cycle length 200 to 250 ms are at high risk of a subsequent event and that this should not be taken as a nonsignificant event in patients with ischemic cardiomyopathy (Table 25-1).[7]

Ischemic Heart Disease

The Multicenter Unsustained Tachycardia Trial (MUSTT) was a multi-center prospective study that enrolled 2202 patients with significant CAD, reduced LVEF (<40%), and nonsustained VT and subjected patients to programmed ventricular stimulation.[8] VT was induced in just over one third of patients. These patients were then randomized to either no AAD therapy or AAD therapy guided by repeated stimulation. If VT remained inducible despite AAD therapy, an ICD was implanted. Patients in whom sustained monomorphic VT was induced were monitored by a registry. Although this study confirmed that patients with inducible VT off AADs had a higher rate of arrhythmic events over the following 5 years compared with those without inducible VT (36% vs. 24%; $P = .005$), the event rate in patients without inducible VT at the time of invasive EPS was not insignificant (Figure 25-2).[9]

As just stated, it is not uncommon to induce polymorphic VT and VF at shorter extrastimulus coupling intervals and with multiple extrastimuli. In the MUSTT trial, induction of polymorphic VT or VF was considered positive only if this occurred with up to two extrastimuli. In a retrospective analysis of the Multicentre Automatic Defibrillator Trial II (MADIT-II), for which patients had to have an LVEF less than 30% and a prior MI, programmed ventricular stimulation was prognostic only when a positive result was taken—that is, not when polymorphic VT or VF had been induced with aggressive pacing.[9,10] Although many studies were performed on acute arrhythmia suppression with AADs, the long-term use of AADs to prevent VT and VF has been disappointing, and it is now common to implant ICDs in patients at risk. However, this is mainly based on the patient's LVEF, not on invasive testing.[8,9,11,12]

Current guidance for the use of programmed ventricular stimulation is based largely on the MADIT-I and MADIT-II trials and the results of the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT).[11-13] In the United Kingdom, the National Institute for Health and Clinical Excellence updated the guidelines for ICD implantation, which are used in other health care systems

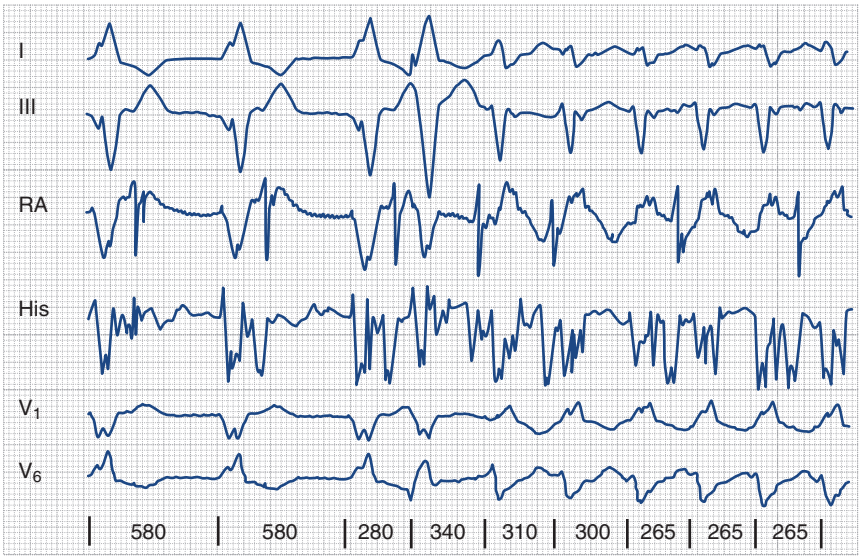


FIGURE 25-1 The initial description of induction of ventricular tachycardia with programmed ventricular stimulation. Initiation of a tachycardia by a single right ventricular premature beat (premature beat interval of 280 ms) during regular driving of the right ventricle (basic cycle length of 580 ms). No bundle of His electrogram precedes the ventricular complex. As shown in the right atrial lead, the first ventricular complex during the tachycardia is followed by retrograde atrial activation; thereafter 2:1 ventriculoatrial conduction is present during the tachycardia. The QRS complex configuration during the tachycardia suggests a left ventricular origin. *(From Wellens HJ, Schuilenburg RM, Durrer D: Electrical stimulation of the heart in patients with ventricular tachycardia,* Circulation *46:216–226, 1972.)*

Table 25-1 Popular Programmed Ventricular Stimulation Protocols

REFERENCE	DRIVE TRAIN (S1), CL	STIMULATION SITES	BURST PACING	S2	S3	S4
Wellens et al[4]	8 beats, not specified	RV		X		
Josephson[53]	SR, 600 ms, 400 ms	RVA, RVOT ± LV	To 220 beats/ms or loss of 1:1 capture	X	X	X
Kumar et al[14]	8 beats, 400 ms	RVA		X	X	X
MUSTT[5]	8 beats, 600 ms, 400 ms	RVA, RVOT	350 to 250 beats/ms for 15 beats	X	X	

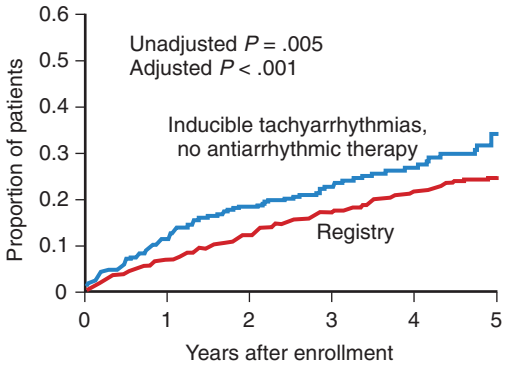
S2-S4 are progressively brought down in 10- to 20-ms increments to the effective refractory period.
Stimulation at twice diastolic threshold, in 2-ms rectangular pulses.
SR, *Sinus rhythm;* RV, *right ventricular;* RVA, *right ventricular apex;* RVOT, *right ventricular outflow tract;* MUSTT, *Multicenter Unsustained Tachycardia Trial.*

throughout the world. These evidence-based guidelines suggest that the role of programmed ventricular stimulation in the decision to implant an ICD is restricted to patients with a previous MI (>6 weeks), an LVEF of 30% to 35%, a lack of New York Heart Association (NYHA) class IV symptoms, and nonsustained VT on monitoring. These criteria were derived from the enrollment criteria to the MADIT-I study. Patients who were enrolled in the MADIT-II study with an LVEF less than 30% did not need to undergo invasive EPS. Although it appears that programmed ventricular stimulation has quite a narrow indication in the decision of when to implant an ICD, it still remains a useful tool. The absolute benefit from ICD implantation in the MADIT trial was 12% per year in which patients had to have a "positive" test result compared with a more modest absolute benefit of approximately 3% and 1.5% per year, respectively, in the MADIT-II and SCD-HeFT populations, in whom programmed ventricular stimulation was not used to determine ICD implantation.

On the basis of the MUSTT trial results, patients with clinically significant CAD and an LVEF of 30% to 40% and nonsustained VT would also benefit from ICDs if they had a positive programmed ventricular stimulation test result.[8,9] Again, a large absolute benefit was demonstrated in this patient population, although for most patients the clinically significant CAD was a prior MI.

A recent study has shown that performing programmed ventricular stimulation may be beneficial when patients presented within the first few weeks after an MI and with an LVEF of less than 40% (Figure 25-3).[14] ICD implantation is not routinely considered in these patients as a result of the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT), which demonstrated that patients with an ICD implanted within the first month of an MI with an LVEF of less than 35% and depressed autonomic function, as assessed by heart rate variability, actually had a worse outcome.[15] Although fewer patients died of arrhythmic events, the rate of nonarrhythmic death was substantially high. These data, as well as those from the Immediate Risk Stratification Improves Survival (IRIS) trial, which also investigated early implantation of an ICD in high-risk patients (as assessed by reduced LVEF <40%, depressed autonomic function, or nonsustained VT on Holter monitoring), demonstrated no absolute mortality benefit from implantation.[14] This has led to the current situation in which high-risk patients do not receive ICDs after an MI.[16,17]

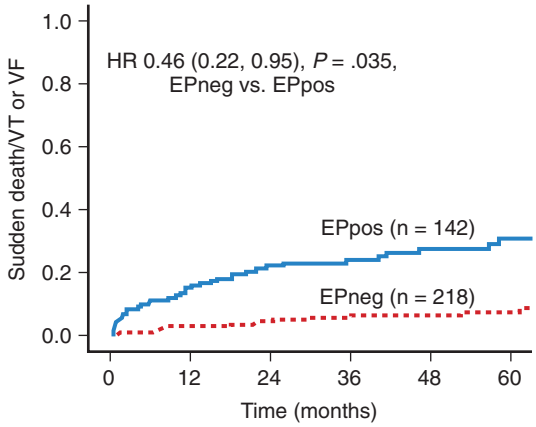
In the latest study, however, programmed ventricular stimulation has been used to risk stratify patients, in contrast to the noninvasive measures in the IRIS and DINAMIT studies. In the study by Kumar et al, patients with previous MI and an LVEF less than 40% had programmed ventricular stimulation at an average



No. at risk

Inducible tachyarrhythmias, no antiarrhythmic therapy	353	290	242	178	118	67
Registry	1397	1212	1074	787	530	308

FIGURE 25-2 The role of invasive electrophysiological testing in patients with ischemic cardiomyopathy from the Multicenter Unsustained Tachycardia Trial (MUSTT). Shown are Kaplan-Meier estimates of the rates of cardiac arrest or death from arrhythmia in the registry patients and the patients with inducible ventricular tachyarrhythmias who were not assigned to antiarrhythmic therapy. *(From 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 *342:1937–1945, 2000.)*



Number at risk

EPneg	218	206	180	119	92	65
EPpos	142	115	95	68	52	43

FIGURE 25-3 The role of invasive electrophysiological study after myocardial infarction. Shown are Kaplan-Meier curves for sudden death or ventricular tachycardia or ventricular fibrillation (*VT or VF*) stratified by those with inducible VT or VF at invasive electrophysiological (*EP*) study 9 days after successful revascularization. *HR*, Hazard ratio. *(From Kumar S, Sivagangabalan G, Zaman S, et al: Electrophysiology-guided defibrillator implantation early after ST-elevation myocardial infarction,* Heart Rhythm *7:1589–1597, 2010.)*

of 9 days after the acute event. An ICD was implanted in patients in whom VT could be induced with a cycle length greater than 200 ms with up to four extrastimuli. In this study, patients with a positive test result were at a substantially higher risk (hazard ratio [HR], 14.3) compared with those who had a negative test result, and implantation of an ICD seemed to confer benefit in this patient population. An important distinction in this study compared with the earlier DINAMIT and IRIS trials was that patients had to have been successfully revascularized before enrollment.

The results of MUSTT, taken together with the more recent work on early programmed ventricular stimulation after successful revascularization, suggest that programmed ventricular stimulation is a useful tool in risk stratifying patients with a reduced ejection fraction after MI (Table 25-2). Compared with signal-averaged electrocardiograms (ECGs) and LVEF, programmed ventricular stimulation is the best predictor of spontaneous ventricular arrhythmia late after MI in patients with reduced ejection fraction.[18,19]

Idiopathic Dilated Cardiomyopathy

The role of programmed ventricular stimulation in the risk assessment of patients with idiopathic dilated cardiomyopathy (IDCM) is not well studied. Approximately 50% of patients with IDCM will have SCD caused by ventricular arrhythmia as opposed to progressive heart failure.[20] Impairment of left ventricular function alone does not appear to be a specific marker for risk.[11,21,22] In the Cardiomyopathy Trial (CAT), 104 patients with IDCM and an LVEF less than 30% were randomized to either medical or ICD therapy.[23] This trial had a very low rate of β-blocker use, which makes interpretation more difficult in the contemporary era. Despite this, overall mortality was very low, and the trial was stopped early because of futility.

In the Amiodarone Versus Implantable Cardioverter-Defibrillator: Randomized Trial in Patients With Nonischemic Dilated Cardiomyopathy and Asymptomatic Nonsustained Ventricular Tachycardia (AMIOVIRT), 103 patients were enrolled, but this trial was also stopped early after just over 2 years because of a failure to show any benefit of an ICD. Again, there was a relatively low mortality rate of 12%.[21] Although the use of β-blockers was better, only 53% of patients were taking them at the time of the study. Invasive EPS was again not used to risk stratify patients. In the Defibrillators in Non-Ischaemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial, a much larger number of patients were enrolled compared with either CAT or AMIOVIRT, with similar inclusion criteria.[22] In addition, a greater population was on optimal medical therapy, with 84% of the population on β-blockers and 86% on angiotensin-converting enzyme (ACE) inhibitors, although spironolactone was not then part of the standard therapy. However, patients were excluded if they had undergone invasive EPS within 3 months. Although implantation of an ICD led to a significant reduction in the rate of SCD (HR, 0.2), it did not lead to an overall reduction in death from any cause.

A smaller study did investigate the use of programmed ventricular stimulation in this patient population as well as the presence of nonsustained VT on ambulatory monitoring.[24] Although more than 80% of patients enrolled in the study were taking β-blockers, fewer than one fourth of patients were taking β-blockers at the start of the study. With a stimulation protocol of a six-beat drive train with two or three extrastimuli from a single site, monomorphic VT was inducible in 7% of patients. The addition of the third extrastimulus increased overall inducibility, but this was caused by the induction of polymorphic VT,

Table 25-2 Use of Invasive Electrophysiological Testing after Myocardial Infarction

TRIAL	PATIENTS	LVEF (%)	EPS PROTOCOL	TREATMENT	TIME POST-MI	MEAN FOLLOW-UP (MO)	OUTCOME
MADIT[1]	196	≤35	RVA, RVOT, 2 drive cycle lengths, up to S4[2]	ICD or medical therapy	3 weeks (75% >6 mo)	27	ICD better
MUSTT[3]	704	≤40	See Table 25-1	ICD or medical therapy	40% <1 year	39 (median)	ICD better
CARISMA[4]	312	≤40	RVA, RVOT, 2 drive cycle lengths, up to S4		6 weeks	24	PES predictive of arrhythmic events
Kumar et al[5]	360	≤40	See Table 25-1	ICD or medical therapy	9 days	49	ICD guided by PES favorable
Bourke et al[6]	502	Not randomized to EF	RVA up to S4[7]		11 days	1 year	Poorer prognosis if inducible arrhythmia
Roy et al[8]	150	46	RVA and RVOT up to S3		12	10	No difference according to PES

LVEF, *Left ventricular ejection fraction;* ICD, *implantable cardioverter defibrillator;* PES, *programmed electrical stimulation;* RVA, *right ventricular apex;* RVOT, *right ventricular outflow tract.*

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4. Huikuri HV, Raatikainen MJ, Moerch-Joergensen R, 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 *30:689–698, 2009.*

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8. Roy D, Marchand E, Theroux IP, et al: Programmed ventricular stimulation in survivors of acute myocardial infarction, Circulation *72:487–494, 1985.*

ventricular flutter, and VF. During a mean follow-up of just over 2 years, the positive predictive value (PPV) was poor at 29%. Although the negative predictive value (NPV) of programmed ventricular stimulation was high, there was a very low event rate in the overall study population.

A more recent study looked at inducibility of ventricular tachyarrhythmias and subsequent therapy from an ICD implanted for secondary prevention.[25] By using a different stimulation protocol from the previous study, with four basic drive train cycle lengths, up to two ventricular stimulation sites, and up to three extrastimuli, the investigators found that induction of polymorphic VT or VF was more predictive of subsequent fast VT or VF events than if sustained monomorphic VT was induced. They also found that these patients had a worse overall mortality rate despite having a similar left ventricular systolic function.[26] However, this was a retrospective study, and the data collection took place over a long period, from 1994 to 2007, limiting the clinical application of this study.

In conclusion, programmed ventricular stimulation is of limited value for risk assessment in patients with IDCM and has no randomized controlled trial data to support its use.

Hypertrophic Cardiomyopathy

Although patients with hypertrophic cardiomyopathy (HCM) are at high risk for ventricular arrhythmia, programmed ventricular stimulation is rarely performed in this patient population. Compared with ischemic cardiomyopathy, in which the substrate for ventricular arrhythmia is defined and relatively fixed, the substrate in HCM is more diffuse, and the mechanism underlying arrhythmic death may be modified by abnormal vascular responses or preceding the ischemia.[27] Although a study using programmed ventricular stimulation in a high-risk group of patients did induce sustained ventricular arrhythmia in 43% of patients, sustained monomorphic VT was only induced in 10% of patients.[28] However, programmed ventricular stimulation has poor PPV and NPV in the risk stratification of patients with HCM. Other markers of risk, namely a history of syncope, nonsustained VT on Holter monitoring, family history, and left ventricular wall thickness, are used in the decision-making process relating to the need to implant an ICD.[3] Cardiac magnetic resonance imaging (MRI) to assess myocardial fibrosis, with late gadolinium enhancement to risk stratify these patients, has created some interest, but this is not routine clinical practice.[29,30]

Congenital Heart Disease

Although patients with corrected congenital heart disease most frequently die from ventricular arrhythmia, the overall incidence is low.[31,32] This leads to the diagnostic dilemma of how to risk stratify patients. Although programmed ventricular stimulation has been used in various studies in an attempt to identify high-risk individuals, most studies have focused on patients with repaired tetralogy of Fallot. In a retrospective, multi-center study

of 252 patients with repaired tetralogy of Fallot, the PPV of inducible ventricular arrhythmia with programmed ventricular stimulation was 55%, and the presence of sustained monomorphic or polymorphic VT was a strong predictor of future ventricular arrhythmia or SCD (HR, 5.0, $P = .0002$ vs. HR, 12.9, $P < .0001$, respectively).[33] Unfortunately, the clinical use of programmed ventricular stimulation is limited because of a poor NPV.[33,34]

Arrhythmogenic Right Ventricular Cardiomyopathy

In ARVC, the myocardium in the right ventricle, and sometimes in the left ventricle, is replaced by fibro-fatty tissue; this substrate can give rise to ventricular arrhythmias, leading to death.[35,36] Although it is generally agreed that patients who present after having survived an episode of VF or VT should be implanted with an ICD, the treatment of asymptomatic patients with arrhythmogenic right ventricular dysplasia (ARVD) is more difficult.[3,37] Although programmed ventricular stimulation has been used in this population of patients to aid risk stratification, a recent multicenter study has clearly shown that no benefit exists.[38,39] In this multi-center study, 106 patients with ARVC were implanted with ICDs on the basis of the presence of a single risk factor for SCD, including programmed stimulation. Although only 67 patients underwent invasive EPS (the reasons that patients did not undergo programmed ventricular stimulation were not discussed), the PPV of the test was only 35% for VF or VT and the NPV was 74%.[39] These data do not support the use of programmed ventricular stimulation in the risk assessment of patients with ARVD.

Brugada Syndrome

The use of programmed ventricular stimulation in Brugada syndrome is vigorously debated between groups that strongly believe in its role in risk stratification and those that do not.[40-47] Although sustained ventricular arrhythmia is easier to induce in patients with Brugada syndrome than in healthy control subjects and is reproducible within the same patient, its prognostic value is debated, with the Brugada researchers strongly supporting its use in risk stratification.[48] This is based on a large prospective multicenter trial that enrolled 408 asymptomatic patients, with inducibility at EPS being the strongest predictor of subsequent SCD or resuscitated VF.[41] The same group also reported that provocative stimulation was useful in a mixed population of symptomatic and asymptomatic patients, with inducible VF being more frequent in symptomatic patients.[42,49] More recently, a combination approach in which inducibility of VF at EPS is one of a number of risk factors taken into account, suggests at least some role for programmed stimulation.[50] The highest risk patients had a type 1 ECG at baseline, syncope, a family history of SCD, and a positive EPS result. In patients with only one of three criteria—family history of SCD, syncope, or a positive EPS—no events were noted (Figure 25-4).

However, these conclusions have been contested by a number of groups and studies. In a study in which 86 patients underwent provocative testing were compared with 114 who did not, prior syncope and a Brugada type 1 ECG predicted future events but programmed ventricular stimulation did not.[46] Similar results were found in a further study, with inducible VF being more frequent in symptomatic patients than in asymptomatic patients. However, programmed stimulation had no clinical use in asymptomatic patients, who had a very low event rate over the duration of the trial.[51] Although the mean follow-up was 40 months, this relatively young group of patients could be expected to live for many years, so a longer follow-up period is required.

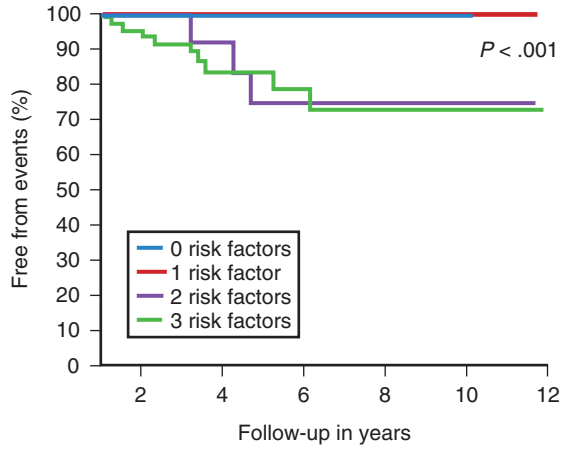

FIGURE 25-4 Risk stratification in Brugada syndrome: a multi-factorial approach. Shown are Kaplan-Meier survival curves in the entire population of 245 patients who underwent electrophysiological study (EPS). Risk factors considered were family history of sudden cardiac death, syncope, and positive EPS result. Curves are plotted according to the presence of 0, 1, 2, or 3 risk factors (family history of sudden cardiac death, syncope, and positive EPS result). *(Modified from Delise P, Allocca G, Marras E, et al: Risk stratification in individuals with the Brugada type 1 ECG pattern without previous cardiac arrest: Usefulness of a combined clinical and electrophysiologic approach,* Eur Heart J *32:169–176, 2011.)*

A large meta-analysis of the use of programmed stimulation that included 15 studies did not support a role for invasive EPS in Brugada syndrome.[52] However, the contentious nature of this issue is reflected in the consensus guidelines for sudden cardiac arrest, with an overall conclusion that the role of programmed ventricular stimulation in Brugada syndrome will be resolved only when a large prospective study is performed.[52] Until then, however, the guidelines limit the role of invasive testing to patients with spontaneous ST elevation and assign it as only level C evidence.

Conclusion

Although programmed ventricular stimulation is being performed less often now than in the past, it still has a role in the risk stratification of patients, particularly in those with ischemic cardiomyopathy. Although clinical presentation, underlying pathology, and ejection fraction clearly form the basis of most guidelines for implantation of ICDs, programmed ventricular stimulation can stratify very high-risk patients who have been successfully revascularized. The role of invasive EPS in primary electrical diseases such as LQTS and Brugada syndrome is debatable, but it seems that it has little, if any, role in this population.

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All references cited in this chapter are available online at expertconsult.com.

CHAPTER 26

Electrophysiological Evaluation of Recurrent Ventricular Tachycardia

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Introduction

Ventricular tachycardia (VT) is typically an ominous sign in the setting of structural heart disease. Its evolution to ventricular fibrillation (VF) and sudden cardiac death (SCD) has become increasingly recognized. Patients at particularly high risk are those with chronic coronary artery disease (CAD) with prior myocardial infarction (MI) and marked left ventricular (LV) systolic dysfunction.[1] In the post-thrombolytic era, the incidence of sustained VT after MI is still approximately 2% to 4% in the first 48 hours and then stabilizes to about 0.5% per year thereafter. As many as 5% to 10% of the patients will experience VF or SCD that is usually preceded by sustained VT.[2,3] An estimated 40% of individuals who have an implantable cardioverter defibrillator (ICD) placed for an index event of sustained VT will have recurrent VT.[4,5] However, all VTs are not equal by nature; some can occur in the absence of structural heart disease and have a very benign prognosis. The disease states associated with VT and the management of VT will be addressed in greater length in other chapters of this text. This chapter will delineate the approach to the electrophysiological evaluation of recurrent VT.

Mechanisms

Understanding the underlying mechanism behind a patient's VT is essential before proceeding with additional evaluation and with acute and long-term management. The major categories are briefly reviewed.

Abnormal Automaticity

Normal automaticity refers to reliable depolarization and impulse formation of pacemaker cells. Such cells in the ventricle normally provide escape rhythms of less than 50 beats/min. VT caused by *abnormal automaticity* may occur when ventricular myocytes generate impulse formation at an accelerated rate compared with the normal rate because of an altered threshold for sodium (Na^+) influx into the cells. This mechanism is thought to underlie accelerated idioventricular rhythms in the setting of acute hypokalemia, hypomagnesemia, cocaine intoxication, focal inflammation, acute myocarditis, or ischemia.[5] In the absence of such derangements, VTs of this type typically are seen in children or young adults.

Triggered Activity

Action potentials may occasionally propagate afterdepolarizations caused by oscillations in the membrane potential. Such triggered activity may either occur as early afterdepolarizations (EADs) or delayed afterdepolarizations (DADs). EADs occur during phase II or III of the action potential, are more likely to occur during bradycardia, and are implicated in torsades de pointes induced by drugs or electrolyte abnormalities and in some variants of congenital long QT syndrome (LQTS). DADs occur during phase IV of the action potential, are more tachycardia dependent, and are believed to be responsible for ventricular arrhythmias occurring in digitalis intoxication and outflow tract VTs.[5] The mechanism may also play a role in VT in the setting of acute MI.[5]

Re-entry

Re-entry is, by far, the most common mechanism of VT associated with structural heart disease. Clinical characteristics include spontaneous induction by premature ventricular complexes with usually abrupt initiation and termination. It requires tissue that can conduct unidirectionally with either fixed or functional block as well as a region of relatively slow conduction that permits recovery of previously depolarized tissue and a circus rhythm to propagate. The mechanism underlying most VTs in the setting of structural heart disease is re-entry caused by a scar. Although a myocardial scar or functional block caused by a nonischemic insult can serve as the pathophysiological substrate, chronic CAD with prior infarct, particularly in the setting of compromised LV function, is the most common underlying pathology.[1]

Noninvasive Assessment

Much information can be gleaned noninvasively in the evaluation of recurrent sustained VT. Efforts should thus be initially directed toward optimizing the use of available tools.

Surface Electrocardiogram

As in the face of any wide-complex tachycardia, a supraventricular etiology, with intrinsic bundle branch block, aberrancy, or antegrade accessory pathway conduction, should first be ruled out. The baseline electrocardiogram (ECG) can be very helpful in the initial

assessment of presumed VT.[5] The presence of a bundle branch block or manifest pre-excitation at baseline that is identical to that seen during clinical tachycardia speaks against VT as a diagnosis. Importantly, even minor differences in the wide QRS complex tachycardia compared with the sinus rhythm recording suggest a ventricular origin. The presence of Q waves in contiguous leads or ST elevations in the absence of acute MI suggests prior MI and aneurysm with a scar, respectively, and strongly suggests VT, especially if the infarct site is consistent with the presumed VT exit (see below). The presence of a widened QRS at baseline, which is a marker of His-Purkinje disease, suggests a predisposition for bundle branch re-entrant or fascicular VT. If a 12-lead ECG of the clinical arrhythmia is available, the presence of ventriculoatrial dissociation or capture or fusion beats is diagnostic for VT. Additional axis and morphology characteristics may also be present that may point toward VT as the diagnosis.[3,6]

In the absence of a 12-lead ECG during presumed VT, the sinus rhythm ECG may still be helpful. A completely normal ECG typically reflects a structurally normal heart. Outflow tract VTs frequently occur in this setting and should be strongly considered in the presence of a strong suspicion for VT. A long or short Q-T interval or characteristic ST-segment elevation features in leads V1 and V2 might suggest an inherited arrhythmia substrate such as LQTS, short QT syndrome (SQTS), or Brugada syndrome, respectively. These arrhythmia syndromes are more likely to present with polymorphic VT.

If a 12-lead ECG has been obtained during VT, much additional information may be gleaned from it. First, the "clinical" VT will be apparent, which will be of great assistance during electrophysiological study prior to ablation. Pacemapping strategies will be greatly assisted by this in the setting of poorly hemodynamically tolerated or noninducible VTs and substrate-based ablation (discussed in later chapters). Knowing which of many potentially inducible VTs during electrophysiological study are pertinent also will ensure that those VTs are targeted during the ablation procedure. Finally, a likely "site of origin," or at least close approximation of the VT exit from a larger macro–re-entrant circuit, can often be determined.[7]

A general strategy should begin with determining the bundle branch morphology. A left bundle branch block (LBBB) pattern, defined by presence of a terminal S wave in the QRS complex in lead V1, indicates either a right ventricular (RV) origin or a septal LV origin. A right bundle branch block (RBBB) pattern, defined by the presence of a terminal R in V1 almost uniformly indicates an LV origin. The frontal plane axis should then be examined. In the inferior leads, a positive QRS axis will indicate a superior (thus inferiorly directed) VT exit, and a negative axis will indicate an inferior one. Transition in the precordial leads, defined by the first precordial lead where the R is greater than S, indicates how basal (transition ≤ lead V2) or apical (negative throughout precordium) is the VT circuit exit or focus.[7] This strategy, coupled with intracardiac mapping (described below) works well in almost all cases except for VT occurring in the presence of a large apical infarction, in which septal versus lateral exits are difficult to distinguish.[8] Assessing the timing of the surface QRS onset to the RV apical intracardiac recording during VT suggests a lateral origin if the time exceeds 100 ms.[8]

The above localization strategy was developed in patients with re-entrant VT caused by chronic CAD and prior infarction but can be applied to other forms of VT as well. Here, clinical history and pattern recognition can be additionally helpful. In a young patient with no known heart disease or evidence for CAD, VT with LBBB and tall, monomorphic R waves in leads II, II, and aVF strongly suggest an outflow tract origin and idiopathic VT. A young, athletic person with several premature ventricular contractions (PVCs) or VT morphologies localized to the RV should raise suspicion of arrythmogenic right ventricular cardiomyopathy (ARVC), particularly in the presence of ε-waves or T-wave inversions in the early precordial leads, V1 to V3, or other surface ECG clues during sinus rhythm. It is important to note, however, that re-entrant VT associated with nonischemic cardiomyopathy typically originates near the peripulmonic, aortic, superior or all of these mitral valves and can mimic right ventricular outflow tract/left ventricular outflow tract (RVOT/LVOT) morphology.[5]

Imaging

Noninvasive imaging is often much more sensitive than the surface ECG in assessing for presence of structural heart disease and, in particular, for a scar or ischemia. This can usually be easily accomplished by traditional methods of echocardiography or nuclear scintigraphy. Magnetic resonance imaging (MRI) is a generally less accessible but often more sensitive tool for detecting both LV and RV abnormalities.[9] The presence of an ICD or pacemaker has long been viewed as a contraindication for performing an MRI, but experiences at several centers, including those of the authors of this chapter, have shown that it can be done safely.[10] The presence of a sessile intracardiac thrombus should be ruled out before any invasive evaluation or intervention is attempted in the presence of significant structural heart disease, given the high risk for thromboembolism and stroke.

Electrogram Information from the Implanted Cardioverter Defibrillator

For patients with an ICD, the VT information stored on the device should be carefully reviewed. The number of events, both nonsustained ones and those resulting in therapy, reflects the arrhythmia burden and should determine the urgency with which subsequent medical care is executed. This includes initiation of antiarrhythmic therapy and catheter ablation.[1] Device-recorded intracardiac electrograms (EGMs) may be especially helpful in determining if catheter ablative therapy may be required; if it is, EGMs will help target the ablation site if a surface 12-lead ECG of the clinical VT is not available. Events predominated by polymorphic VT without clear monomorphic PVC trigger, for instance, may be less amenable to ablation unless a reproducible trigger is evident. Depending on the stability of the patient's condition, noninvasive programmed stimulation (NIPS) testing through the device could be considered to find out if the intracardiac EGM of any induced VT resembles those stored from spontaneous clinical events so that the occurrence of clinical VT may be identified on 12-lead ECG.

Invasive Assessment of Ventricular Tachycardia

Additional Preparation

Before pursuing more invasive evaluation with electrophysiological study and possible ablation, it is important to perform an evaluation of the presence and status of CAD and to determine LV function and reserve, either noninvasively, as described above,

or via cardiac catheterization. Deaths related to the procedure are often attributable to underestimation of the importance of the ischemic burden before the procedure and the volume overload during the procedure. Documentation of the anticoagulation status and, as indicated, exclusion of an unstable LV thrombus are important. Identification of vascular access problems before the procedure ensures its safety and success. Severe arterial disease or the presence of aortic stenosis will require a trans-septal approach. Details of present and past antiarrhythmic therapy must be considered. Ideally, discontinuation of any ongoing therapy for at least five half-lives should occur before electrophysiological study and ablation; because of the unstable nature of many patients' conditions, this is often not possible. Many patients will have been treated with amiodarone. Its long half-life and storage in body fat will mean that amiodarone will be present even if stopped several days before the procedure. The results of programmed stimulation and subsequent ablation should be interpreted with this knowledge.

Initiating Ventricular Tachycardia

A hallmark of re-entrant VT is the ability to induce it and terminate it by ventricular programmed electric stimulation (PES) in the electrophysiological laboratory. Because of changes in refractory periods and tissue conduction velocities, along with variations in heart rates, re-entry is favored by fast heart rates and sudden changes in rate. A critical basic pacing rate in PES, therefore, is often needed to initiate a re-entrant tachycardia in a given patient, and several different basic pacing drive cycle lengths with extrastimuli should be used to try to induce it.[7] Notably, triggered VTs also can be occasionally initiated with ventricular PES; thus, induction with PES does not exclude the latter as a mechanism for VT.[7] In inducing VT with PES, it is important to attempt stimulation from additional ventricular sites other than the RV apex. Additional stimulation from sites such as the RVOT or the LV may be required to initiate a monomorphic, sustained VT in 10% to 20% of patients in whom stimulation from the RV apex is ineffective.[7] Frequently, VT with a RBBB pattern will best be initiated by stimulating from the lateral LV.

Methods for PES vary significantly. Pacing for eight beats with basic drive cycle lengths of 600 and 400 ms followed by the introduction of one to four extrastimuli is generally the most accepted protocol. The ability to induce sustained monomorphic VT (MMVT) increases successively with the number of extrastimuli, up to three. MMVT can be induced in 96% of those with sustained clinical VT and in 75% of those who have survived sudden arrhythmic cardiac death.[7] Beyond three extrastimuli, additional yield is minimal; sensitivity and inducibility increase marginally, but with a significant decrease in specificity as less stable and more nonclinical VTs, polymorphic VTs (PMVTs), or both are induced.[7] In the majority (80% to 85%) of patients, clinical VT can be induced in this fashion; however, occasionally, induction is more effective when the basic "drive" is provided by sinus rhythm, with extrastimuli introduced via pacing. If a specific VT is identified, the introduction of additional extrastimuli may be used for induction, recognizing the potential for the induction of less clinically relevant arrhythmias. On occasion a short-long-short stimulation sequence may be advantageous. This stimulation has been described for the induction of bundle branch re-entry but can be used for the induction of other VTs associated with structural heart disease that are not induced with a more standard stimulation protocol.[7]

Induction of VT with burst pacing or sympathetic stimulation, for instance, with isoproterenol infusion or stress testing, is much more likely to occur with triggered arrhythmias. Interestingly, atrial burst pacing is somewhat more likely to induce outflow tract tachycardias compared with ventricular burst pacing.[3]

VT caused by abnormal automaticity is not affected by PES, either in terms of initiation or termination; the inability to induce clinical VT with PES, as described above, suggests automaticity as a mechanism. These VTs are affected by basic heart rate and are typically elicited during bradycardia.[7] Some are enhanced by the infusion of isoproterenol.

Certainly, the goal of these procedures is to reproducibly initiate VT and to perform maneuvers that lend support to its underlying mechanism. If the diagnosis of VT is not certain, confirming it in the electrophysiological laboratory is fairly straightforward. The diagnosis of VT can be established with the mode of arrhythmia induction and the presence of atrial and ventricular dissociation at the onset of VT elicited with pacing maneuvers. Atrial stimulation can be used during a wide complex tachycardia that is suspected of being antidromic SVT over a bypass tract when the His atrial activity is refractory to confirm atrial participation in the circuit. As alluded to earlier, re-entrant VT can be initiated and terminated by ventricular PES. Its other hallmarks are (1) an inverse relationship between the coupling interval of the ventricular extrastimulus and the return cycle length of the tachycardia; (2) the ability to entrain the VT with progressive fusion with shorter pacing cycle lengths; and (3) the ability to demonstrate entrainment with concealed fusion at isthmus sites.[3]

Given the relative predominance of re-entrant VT versus other types of VT, the following discussion on mapping strategies will focus on those used for re-entrant VT. More detailed discussion regarding mapping and ablation of other VT subtypes appears later in this chapter.

Mapping Strategies: Hemodynamically Stable, Re-entrant Ventricular Tachycardia

Hemodynamically stable, relatively slow VT that is easily inducible and stable in response to pacing comprises a small minority of re-entrant VTs, especially in the setting of ischemic heart disease. However, when re-entrant VT is present, detailed activation and entrainment mapping can be performed. The goal of both is to identify the critical elements of the re-entrant circuit that are protected by anatomic or functional boundaries (a dense scar or valvular structures) and which would therefore be easiest to successfully target with ablation. The surface ECG recording of VT typically represents the wavefront as it exits the scarred area and begins to depolarize the healthy myocardium. The "exit" is frequently at the end of the most critical portion (isthmus) of the circuit and is located at the border of a scar. However, it is possible for the isthmus to be quite far from the edge of the scar and the wavefront to activate the diseased myocardium for several centimeters before engaging the normal myocardium. Once the wavefront encounters the normal myocardium, it then propagates away from this site to depolarize the rest of the ventricles as well as to complete the depolarization of other portions of the circuit, including the outer scar border (outer loop) and the "entrance" to the isthmus region (Figure 26-1, *A*). Occasionally, the wavefront may propagate through a path within the scar or area of functional block (inner loop) that is not critical to the maintenance of the circuit.[11]

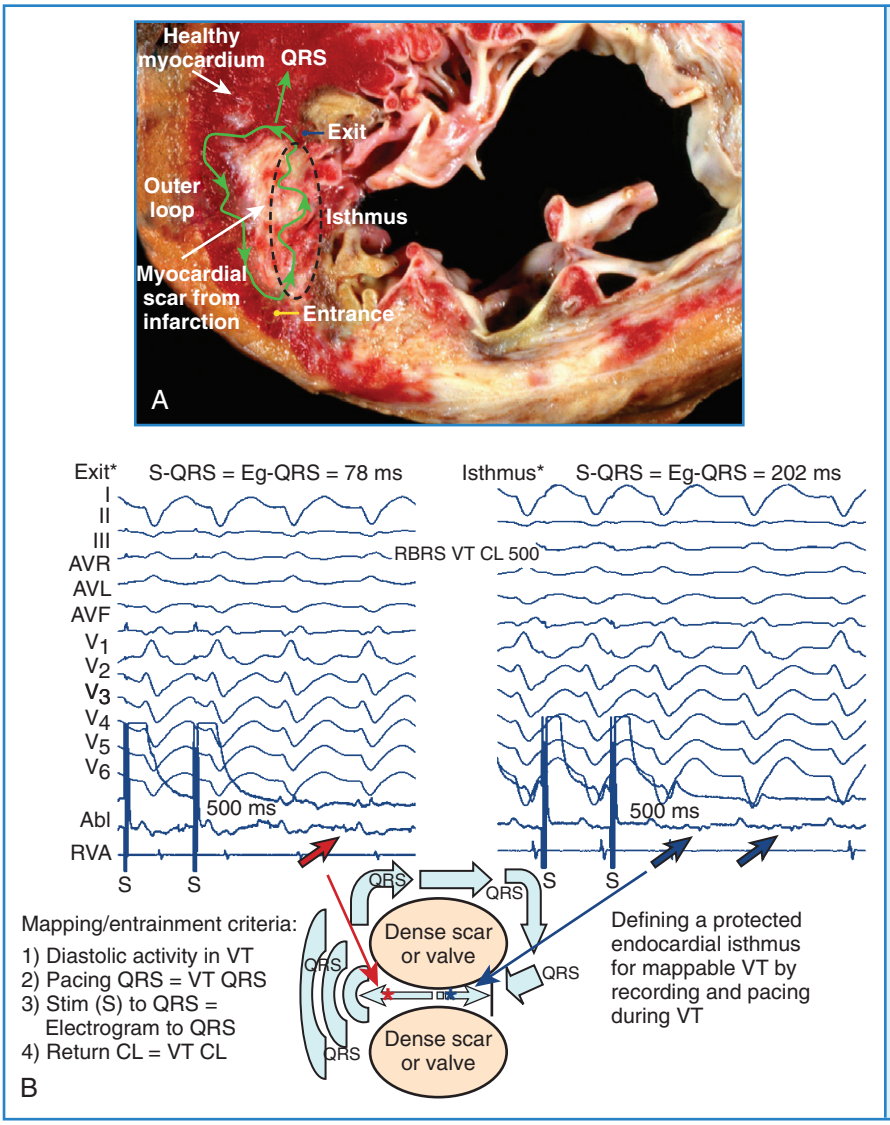

FIGURE 26-1 A, A theoretical re-entrant ventricular tachycardia (*VT*) circuit and components in a patient with prior myocardial infarction. A functional conduction barrier caused by a scar houses the critical isthmus for the re-entrant circuit; the wavefront enters the proximal end and exits from the distal end of the isthmus. Its course through the broader area of the healthy myocardium marks the outer loop of the re-entrant circuit. **B,** Activation and entrainment mapping to identify components of VT circuit and appropriate site for focal ablation (*Abl*). The exit site within the VT circuit (*red arrow*) will have the same QRS as the VT with pacing from the site during VT, a short stimulus to QRS interval that matches the electrogram (EGM) to QRS interval and the return cycle length (*CL*) when pacing is stopped equal to the VT CL. Moving further into the protected isthmus, the EGM is recorded in mid-diastole during VT (*long arrow*), the longer stimulus to QRS interval during pacing equals the EGM-to-QRS interval, and the return cycle to the site of stimulation when pacing is stopped will still equal the VT CL. (***A,*** *Courtesy Dr. William Stevenson.)*

During activation mapping, isolated potentials, or abnormal, low-amplitude signals recorded during electrical diastole based on surface ECG analysis, are identified. These recordings are felt to represent depolarization of the aforementioned important portions of the re-entrant circuit, including the most critical (isthmus).[8,12,13] Isolated potentials have been found to be present in about half the isthmus sites and represent areas at which radiofrequency (RF) energy application may be most effective in terminating VT.[12] However, the isthmus width can range from 6 to 26 mm, and the presence of a broad isthmus may make activation data more difficult to interpret.[13] Importantly, isolated diastolic potentials also have been found to be present at bystander sites that are close to, but not participating in, the VT circuit or can even represent far-field activation of tissue remote from the mapping site. Identifying sites critical to the re-entrant circuit can sometimes be better characterized with entrainment mapping (described below) or with pacing from a remote site to dissociate the potential from the VT. The presence of bystander sites as well as the presence of multiple loops of re-entry can often confound analysis.

Entrainment mapping can be performed in hemodynamically tolerated VT that remains stable in response to pacing. Pacing slightly faster than the VT will cause continuous resetting of the re-entry circuit. Sites within the circuit will have a postpacing interval (PPI), or time to return to the site of pacing, within 30 ms of the tachycardia cycle length (TCL). It then follows that the farther away from the circuit that entrainment is attempted, the larger will be the difference between the PPI and the TCL as the time to and from the circuit will need to be added. It should be ensured that the EGM selected for PPI measurement represents local depolarization. The EGM of interest can be very difficult to identify when multiple fractionated signals are present, as is common in the presence of a scar, or when local potentials directly depolarized by pacing are obscured by the pacing artifact. Other major assumptions when interpreting the response to entrainment include the following: (1) Pacing does not alter the path of the circuit or initiate another VT; and (2) conduction time through the circuit is unchanged with entrainment compared with VT. Care should therefore be taken to pace only slightly faster than the TCL, as faster pacing has been shown to alter the

VT circuit. Additionally, the presence of antiarrhythmic medications may further decrease conduction velocities during pacing and can potentially confound analysis, particularly when pacing at even modestly faster rates.[11]

Assuming the conditions described above are met, entrainment mapping can be very helpful in identifying the re-entrant circuit components. Entrainment from all isthmus sites will demonstrate concealed fusion with entrainment or demonstrate capture with pacing, but without a change in QRS morphology of the paced beats compared with VT. At isthmus exit sites, the pacing stimulus to the QRS interval (S-QRS), which represents the conduction time from the pacing site to the re-entry circuit, should be short, or less than 30% of the TCL. At central isthmus sites, the S-QRS should be intermediate, or 31% to 50% of the TCL. At isthmus entrance sites, the S-QRS will be longer, or 51% to 70% of the TCL. At all of these sites, additionally, the S-QRS time should also equal the EGM-to-QRS time during the VT (see Figure 26-1, *B*). Termination with catheter pressure can occur when mapping in this region suggests a narrow isthmus predisposed to block with the slightest of pertubations.[11] The presence of inner-loop or adjacent bystander sites can be confusing, as entrainment also will demonstrate concealed fusion when stimulation is performed at these sights. The S-QRS for the former will be very long (usually >70% of TCL); for the latter, the PPI will not be similar to the TCL, and the S-QRS and the EGM-QRS time will not be equal. At outer loop sites, QRS fusion with entrainment will be manifest because of the propagation of stimulated antidromic wavefronts away from the scar border in addition to within the VT circuit. Evidence that the site is within the VT circuit is that the PPI will approximate the TCL. If the scar border along this portion of the circuit is in continuity with healthier myocardium, the width of this circuit portion may be quite broad; termination with either focal ablation or catheter trauma is thus often less successful (<10%) at these sites.

Even after detailed mapping is performed, it may not be possible to delineate the entire circuit, as parts of the re-entry circuit may not be confined to the endocardium but also may course through the mid-myocardium or the epicardium.

Mapping Strategies: Hemodynamically Unstable Ventricular Tachycardia

The vast majority of clinical VTs will not be hemodynamically tolerated, will be difficult to induce at the time of electrophysiological study, or it will be difficult to completely characterize it using the strategies outline above. Sinus rhythm substrate characterization is now incorporated as part of the routine procedure for all of those being considered for VT ablation. Other specifics to ablation approaches for VT will be discussed in detail in later chapters.

Sinus Rhythm Voltage Map

A detailed substrate and voltage map should be created, with efforts initially focused on areas of known infarction or scarring on the basis of prior imaging. The endocardial extent of the anatomic abnormality has been well characterized using bipolar voltage criteria of 1.5 to 2.0 mV; this helps identify normal signal amplitude recorded from the LV endocardium using a commercially available electroanatomic mapping system (CARTO, Biosense Webster, Inc., Diamond Bar, CA) with a 4-mm electrode tip mapping catheter.[8] Low-voltage areas of the endocardium typically serve as the arrhythmia substrate for most patients with sustained VT. Thus, a color range corresponding to endocardial bipolar voltages of 0.5 to 1.5 mV will highlight areas of densely scarred myocardium or aneurysm (<0.5 mV), border zone of a scar (0.5 to <1.5mV), and healthy myocardium (>1.5 mV). It is important to note that the extent of an endocardial scar identified on voltage mapping often will exceed that observed on thallium imaging in patients with extensive septal involvement. This phenomenon may be caused by lower sensitivity of the thallium imaging in identifying subendocardial versus transmural infarction (Figure 26-2).

Late Potential Mapping and Ablation

Frequently, double potentials, late potentials, or both during sinus rhythm can be observed on bipolar recordings within or at the borders of a scar that has been delineated by voltage mapping. Late potentials are defined as distinct bipolar EGMs that are inscribed after the end of the surface QRS complex and separated from the major initial component of the local ventricular EGM by an isoelectric interval. They are felt to represent delayed activation within the diseased myocardium and have often been found at critical sites within re-entrant VT circuits.[13] Investigators have shown that these potentials are found within 89% of isthmus sites, 57% of entrance, and 20% of exit sites (Figure 26-3).[13] This strategy, combined with voltage mapping, identifies appropriate ablation targets and provides a more refined substrate-based approach for VT ablation.

Pacemapping

In conjunction with a detailed voltage map and available VT morphologies from 12-lead surface ECGs or from ICD electrograms, pacemapping is used to approximate the VT exit site for VT that cannot be characterized by activation or entrainment mapping because of hemodynamic instability.[8,13] The procedure involves pacing at different ventricular sites along the border of the scar during sinus rhythm to identify site(s) at which the paced QRS morphology mimics that observed during VT. When using pacemapping to localize the VT exit site, certain important limitations must be recognized. The paced QRS morphology may not accurately reflect the site of origin of the VT and may not identify an appropriate site for VT ablation. Bidirectional conduction from the pacing site may not mimic the unidirectional wavefront of activation associated with the VT circuit. Furthermore, the output used to capture with pacing, especially if high, can influence the pattern of ventricular activation and produce a different QRS morphology in sinus rhythm because of an increase in the size of the virtual electrode; this will differ from that during VT even when pacing within a critical site of the VT circuit. Nevertheless, pacemapping can approximate the exit site of the VT circuit in most patients and is a generally accepted method for mapping when more detailed options are limited because of poor hemodynamic intolerance or noninducibility of VT.

Conducting Channels

Many slower, more mappable VTs demonstrate conduction through densely infarcted myocardium (<0.5 mV). In these cases, viable channels of the conducting myocardium may be identified by decreasing the color range such that narrow channels of larger voltage surrounded by areas of extremely low voltage can be

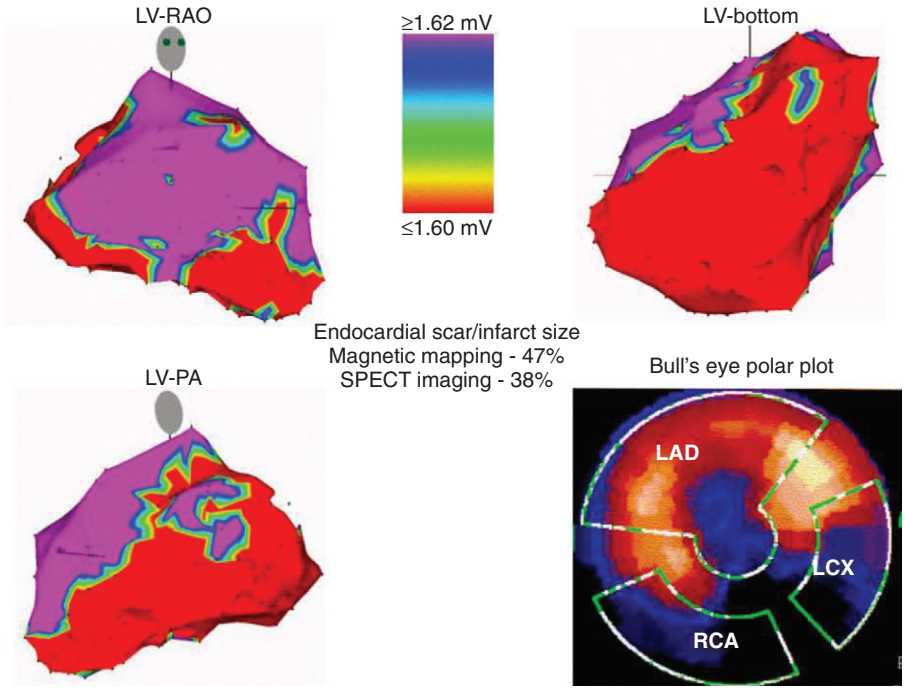

FIGURE 26-2 Sinus rhythm voltage map and perfusion imaging correlate in a patient with prior inferior myocardial infarction. The color range for the voltage maps is between 1.62 mV and 1.60 mV to emphasize the difference between normal (*purple*) and abnormal (*red*) or scarred endocardial myocardium. In the perfusion scan, the nonviable scar was defined as areas with less than 50% tracer uptake compared with maximal pixel uptake and is displayed as a "bull's-eye" polar map (*bottom right*). In patients with ventricular tachycardia, the extent of abnormality identified as involving the septum is typically underestimated by the perfusion scan consistent with the subendocardial extension of the scar, which serves as the typical substrate for ventricular tachycardia.

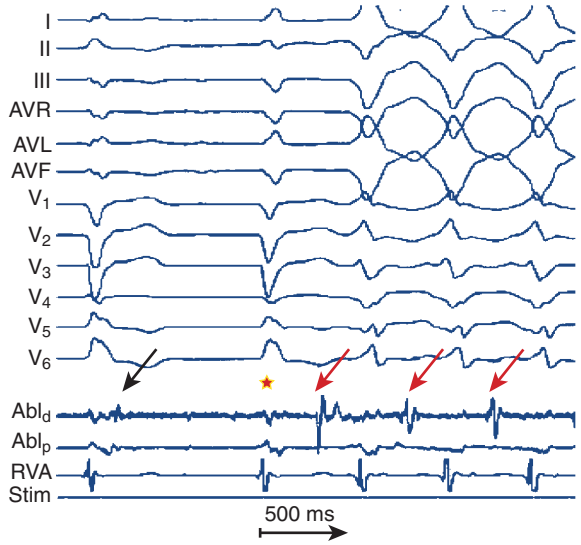

FIGURE 26-3 Late potentials (LPs) as a surrogate marker for identification of ventricular tachycardia (VT) circuit. At the isthmus site, LPs are present in sinus rhythm (*black arrow*). Spontaneous initiation of monomorphic VT is preceded by sudden loss of LPs (*star*), followed by the emergence of mid-diastolic potentials during VT (*red arrows*). The late potentials in sinus rhythm are a marker for mid-diastolic potential in sinus rhythm.

visualized.[13] Such channels also can be identified during RV pacing in the absence of ongoing VT.[8] Fractionated EGMs, with isolated delayed components, multiple components, or both are often seen at isthmus sites; however, these low-amplitude signals may be obscured in sinus rhythm because of depolarization of the surrounding larger mass of the more normal myocardium. Changing the direction of depolarization, for instance, with pacing, has been observed to better elucidate these signals and potential channels of conduction. RV apical pacing has been used for this purpose. While the identification of conducting channels in conjunction with other methods can be useful, it is often not specific enough to be the sole mapping guide.[8]

Noncontact Mapping

A final approach to mapping poorly tolerated or otherwise unmappable VT is via noncontact mapping using a multielectrode system. The currently available system is a woven braid of 64 wires 0.003 inches in diameter mounted on a 7.6-mL balloon on a 9-Fr catheter. Each wire has a 0.025-inch break in insulation, producing noncontact unipolar electrodes. It allows display of more than 3300 mathematically derived unipolar EGMs via inverse solution to Laplace's equation.[14] Good correlation has been observed between EGMs computed using the noncontact balloon and those obtained simultaneously by direct catheter contact, with reasonable results reported in limited clinical experiences to date.[14] However, the system is currently somewhat

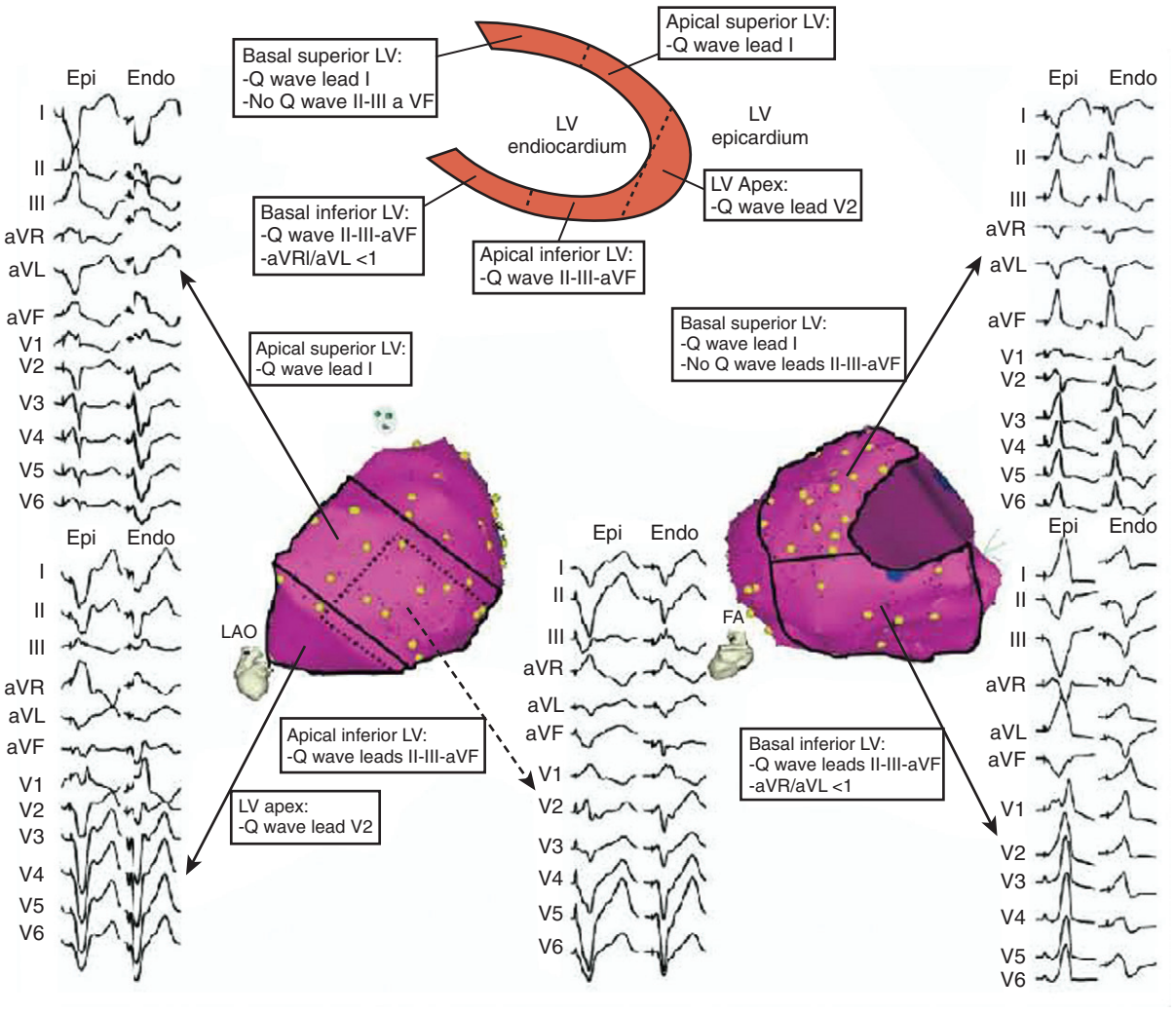

FIGURE 26-4 Surface 12-lead electrocardiogram morphologic characteristics suggestive of an epicardial ventricular tachycardia origin. *(Modified from Bazan V, Gerstenfeld EP, Garcia F, et al: Site-specific twelve-lead ECG features to identify an epicardial origin for left ventricular tachycardia in the absence of myocardial infarction,* Heart Rhythm *4:1403–1410, 2007.)*

cumbersome to use, as it requires a customized amplifier system and a Silicon Graphics workstation to run the software. Other limitations include (1) potential need for contact mapping in areas that are inaccessible by the balloon system because of low-amplitude signals or excessive (>34 mm) distance from the balloon to the endocardial surface and (2) easy loss of position of the balloon in patients with normal LV function in the setting of recommended retrograde aortic positioning.

Epicardial Ventricular Tachycardia Mapping

Features that may indicate the need for epicardial mapping and ablation can be apparent on the surface 12-lead ECG recorded during VT.[15,16] These include the presence of a particularly wide-QRS VT with a slurred initial aspect of the QRS complex. A Q wave in lead I is a particularly sensitive characteristic for identifying an epicardial VT site of origin in patients with nonischemic cardiomyopathy. If it is present and if Q waves are absent in the inferior leads, a basal and superolateral epicardial focus is suggested (Figure 26-4). The details of epicardial mapping and ablation are discussed in later chapters.

Unique Considerations for Assessment in Specific Types of Ventricular Tachycardia

Ventricular Tachycardia with Nonischemic Left Ventricular Disease

Patients with VT in the setting of nonischemic LV cardiomyopathy typically have, in addition to depressed LV function, low-voltage areas consistent with the scar frequently in perivalvular distribution, and often with epicardial involvement (Figure 26-5). The mechanism of VT in this disease substrate is usually re-entry.[8] Intracardiac EGMs in scarred regions frequently are abnormal and fractionated, and the overall surface, signal-averaged ECG is abnormal.[3] Mapping and ablation strategies are as outlined above for typical re-entrant VT caused by ischemic heart disease.

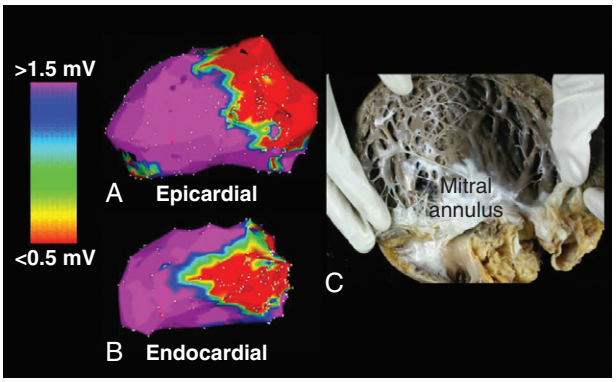

FIGURE 26-5 Example of bipolar low-voltage abnormality and scar distribution in a patient with nonischemic cardiomyopathy and ventricular tachycardia. **A** and **B,** Left lateral views of epicardial and endocardial voltage maps, respectively, demonstrating basal lateral low-voltage areas consistent with the scar. To distinguish the scar from fat, these low-voltage areas also show multicomponent fractionated and late electrograms. **C,** The endocardium from a transplanted heart from a patient with nonischemic cardiomyopathy and ventricular tachycardia identifying the endocardial scar adjacent to the mitral annulus.

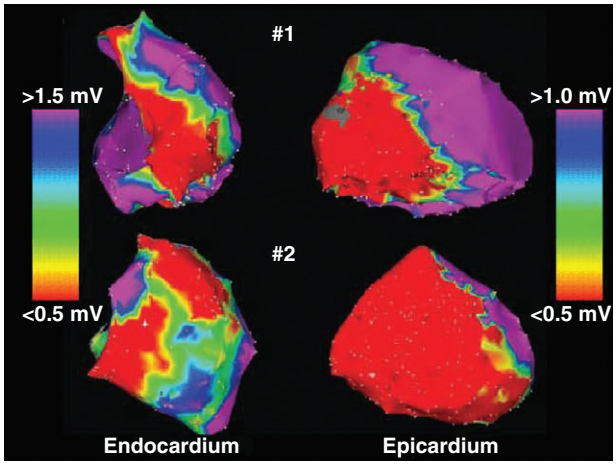

FIGURE 26-6 Bipolar voltage maps showing periannular and more extensive epicardial versus endocardial areas of low voltage consistent with the scar in two patients with arrythmogenic right ventricular cardiomyopathy or dysplasia and ventricular tachycardia. Epicardial electrograms also were fractionated and show late potentials.

Arrhythmogenic Right Ventricular Cardiomyopathy or Dysplasia

Patients with arrhythmogenic right ventricular cardiomyopathy or dysplasia (ARVC/D) have a progressive disorder with autosomal-dominant inheritance that is marked by fibro-fatty infiltration of the normal myocardium. This process primarily involves the RV but may also involve the LV. It can begin with localized dysplasia, which is recognized only on postmortem examination in patients with documented VT. In a pathologic condition, the process appears to first affect the epicardium, spreading gradually inward through the myocardium. The most commonly affected areas are the RV infundibulum, the inferoposterior subtricuspid region, and, less commonly, the RV apex marked by aneurysm formation. Of note, the location of most abnormal EGMs and the source of VT is perivalvular (pulmonic, tricuspid, or both). The prevalence is estimated to be 1:5000 to 1:10,000 in the general population, and it accounts for 5% of SCD events in adults younger than 35 years and 22% of SCD in athletes. The clinical course is marked by progressive RV dysfunction that may predispose to VT, VF, or both, and RV heart failure. Possible infectious and immunologic causes have been postulated as triggering mechanisms acting on a genetically defined desmosomal protein abnormality, given that as many as 80% of hearts affected by ARVC/D at autopsy have inflammatory infiltrates. When ventricular arrhythmias occur, they usually are re-entrant and of multiple LBBB morphologies, reflecting a diffusely affected right ventricle.[16] VT with an epicardial site of origin is suggested by 12-lead ECG characteristics of a Q or a QS in the inferior leads for inferiorly exiting sites or in lead V2 for VTs exiting from the anterior RV.[16] Successful ablation of epicardial VT enhances the overall success of VT ablation in this setting (Figure 26-6).[16] Ablative therapy should be considered before the administration of amiodarone in this young patient population and to treat patients who experience ICD shocks.[16]

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is an autosomal-dominant inherited disorder of sarcomeres, with variable penetrance and expression, which leads to myocyte hypertrophy and disarray and varying degrees of usually asymmetric LV septal hypertrophy. The risk of SCD in this population has long been recognized, and ICD implantation for primary and secondary prevention has increased in the last several years. High-risk characteristics that justify ICD implantation in either setting include prior cardiac arrest; familial sudden death; massive left ventricular hypertrophy (LVH), or maximum LV wall thickness 30 mm or greater; syncope; multiple episodes of recurrent nonsustained VT; hypotension during exercise stress testing; end-stage disease, marked by systolic dysfunction often with LV remodeling and dilation; presence of LV apical aneurysm; and prior alcohol septal ablation.[17] The last two subgroups have become increasingly recognized for their higher risk of repetitive episodes of MMVT. Patients with HCM and apical aneurysm comprise about 2% of an HCM cohort. Their higher incidence of MMVT is thought to be caused by focal myocardial scarring of the distal LV, which arises from chronically abnormal strain at the junction of the apical aneurysm and the rest of the myocardium. The mechanism of VT is re-entry, and VT ablation that targets the apical endocardial and epicardial circuits has proven successful.[17] Residual scar from alcohol septal ablation can be substantial, occupying about 10% of the total LV mass, and it has also been shown to be arrhythmogenic in some HCM patients. Some series have reported a fourfold increased risk of appropriate ICD shocks in these patients, compared with those who underwent surgical myomectomy for the treatment of outflow obstruction.[17]

Idiopathic Ventricular Tachycardia

Idiopathic VT occurs in otherwise normal hearts, has a very benign prognosis, and accounts for about 10% to 15% of clinical VTs.[18] The most common type generally originates from the

RVOT and has also been known as *repetitive monomorphic VT*. Its mechanism is believed to be triggered, and the typical clinical presentation is with salvos of nonsustained MMVT in the setting of caffeine, emotional stress, or exercise.[5] In the electrophysiological laboratory, the arrhythmia can often be provoked with catecholamine infusion or with burst pacing in the atrium or ventricle and can often be terminated with adenosine infusion.[3] The typical pattern of the VT observed on the 12-lead ECG is LBBB with large, monophasic R waves in the inferior leads. Most of these VTs arise from the septal-anterior aspect of the RVOT from a narrow segment just under the pulmonic valve. Less frequently, they may originate from the free wall or posterior-septal aspect of the superior RVOT or the LV.

A mapping scheme based on 12-lead ECG characteristics has been developed to assist with localization in the RVOT before ablation (Figure 26-7, *A*).[19] Septal RVOT VTs will tend to have taller and narrower inferior, monophasic R waves and a slightly earlier precordial transition compared with corresponding

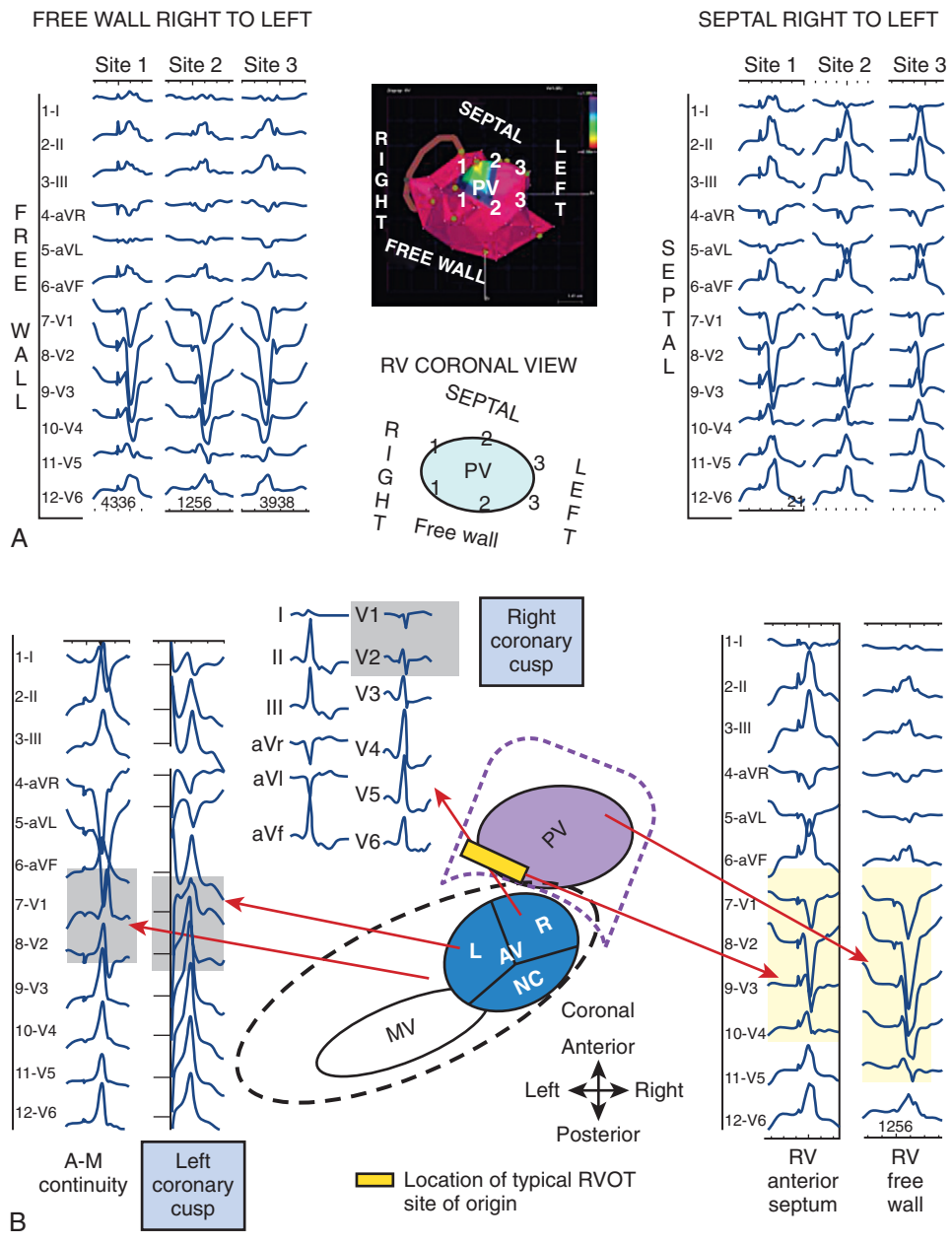

FIGURE 26-7 Electrocardiogram (ECG) characteristics of outflow tract ventricular tachycardias. **A,** Comparison of free wall versus septal right ventricular outflow tract (*RVOT*) origin defined by pacemapping. Note the progressive negativity in lead I with more anterior and leftward site of origin (from site 1 to 3). Compared with septal sites, free-wall characteristics include later precordial QRS transition, increased QRS duration, QRS notching in the inferior leads, and relatively smaller amplitude QRS in leads II, III, and aVF. **B,** ECG patterns associated with selected outflow tract locations. Note the relation of aortic valve cusps to the anatomy of the RVOT and mitral valve, and associated ECG changes corresponding to various sites of origin. Later QRS precordial transition of RVOT free wall versus septal sites is highlighted in *yellow*. Progressive increase in R wave and earlier precordial transition from right coronary cusp, left coronary cusp, and aorto-mitral (*A-M*) continuity is highlighted in *gray*.

free-wall RVOT VTs; free-wall VTs often will have notched R waves in the inferior leads. To distinguish between anterior RVOT sites and posterior RVOT sites, the most discriminating lead to assess is lead I. Anterior RVOT VTs will often have a predominantly negative QRS complex (qs) in lead I, whereas posteriorly originating VTs will be more positive, with a small *r*. VTs originating between the two will accordingly have a more intermediate or biphasic to multi-phasic complex (qr/rs pattern) in lead I with net isoelectric polarity.

Occasionally, idiopathic VT can originate from sites above the pulmonic valve and in the LVOT and surrounding areas, including the AV cusps.[20] ECG criteria have also been developed to distinguish VTs originating in the LVOT from those originating in the RVOT. Surface ECG clues that indicate an LVOT versus RVOT site of origin include (1) RBBB and tall, monophasic inferior R waves with a dominant R wave in V1 and lack of precordial transition, with or without a late-appearing S wave in lead V6; or (2) LBBB and inferiorly directed axis with an earlier precordial R-wave transition than would be expected in RVOT VT (usually by V2) (see Figure 26-7, *B*). Additional criteria to localize VTs within the basal LV region include (1) QRS duration and (2) R-wave in V1, both of which help distinguish between medial versus lateral sites.[20]

Finally, there are surface ECG clues that have been developed to further elucidate the VT site of origin from the aortic valve cusps as opposed to the RVOT.[20] The majority of these VTs originate from the left coronary cusp (LCC), especially the junction between the right and left cusps. In lead V1, a multi-phasic M or W pattern may be observed for VT arising from the LCC or a distinctive qr pattern if originating from the anterior mitral cusp (AMC); overall, the R-wave duration and the R- or S-wave amplitude observed in cusp VT compared with RVOT VT are greater. In lead I, often a terminal S is present for VT originating from the LCC or AMC. The precordial transition is earlier overall than in the RVOT.

Infrequently (about 9% to 13% of idiopathic VT), outflow tract VT can arise from epicardial locations. These tachycardias often originate from or close to the proximal coronary veins. An epicardial origin can be suggested by (1) delay in the activation in the initial portion of the QRS as reflected in the precordial leads, (2) marked increase in R-wave amplitude in the inferior leads, (3) an S wave in lead I, as part of an rs or qs pattern, (4) aVL/aVR Q-wave ratio greater than 1.4, or (5) all of these.

If VT occurs spontaneously in the electrophysiological lab, activation and pacemapping are performed to target the area of earliest activation and best pacemapping. Prelab provocation with exercise testing is suggested to document the 12-lead ECG pattern associated with the VT.

Idiopathic fascicular VT is another major subset of idiopathic VT. It typically originates from the left posterior fascicle and involves the LV inferior septum from the base to the apex, with a superficial endocardial Purkinje network participating in what largely is felt to be a re-entrant circuit, although some debate exists as to whether mechanism is triggered or abnormal automaticity in selected patients.[18] The arrhythmia tends to be uniquely verapamil sensitive, and, in the electrophysiological laboratory, can be induced with PES and occasionally with rapid atrial or ventricular burst pacing. The VT is not typically induced with isoproterenol infusion, but the drug may potentiate initiation with programmed stimulation. The morphology of the VT is typically RBBB with left-superior axis deviation (consistent with a posterior fascicular origin). Mapping during VT is preferable, for the purposes of confirming the diagnosis and ablation. Areas where the earliest pre-QRS Purkinje potential is seen have been targeted for ablation with successful elimination of the arrhythmia. Even when sustained VT cannot be induced, a mapping strategy in sinus rhythm, based on the assumption of a sizable macro–re-entrant circuit along the septum, can be undertaken. The area along the mid-septal LV endocardium can be mapped to identify Purkinje potentials. An ablation line is then drawn from the inferior margin to the mid-septum.[18]

Summary

Comprehensive electrophysiological evaluation of recurrent VT should incorporate details from the patient's clinical history and noninvasive data to tailor the appropriate approach for more invasive study and potential ablation. In addition to the patient history, surface 12-lead ECGs of the VT and cardiac imaging studies often provide insight related to the VT mechanism and site of origin. Most VTs can be initiated with programmed stimulation, which allows for confirmation of the ECG diagnosis and further evaluation. The majority of VTs in the setting of structural heart disease is attributable to re-entry. Effective mapping and ablation strategies for both hemodynamically tolerated VTs and nontolerated VTs, which allow for VT elimination or control in patients with and without structural heart disease, have been developed.

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CHAPTER 27

Electrophysiological Evaluation of Atrial Tachycardia and Atrial Flutter

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Atrial Tachycardia

Focal atrial tachycardia (AT) is the least common type of supraventricular tachycardia (SVT), comprising approximately 10% to 15% of patients referred for electrophysiological evaluation of SVT.[1] Possible mechanisms include triggered activity, enhanced automaticity, or micro–re-entry. AT has been defined as rhythmic atrial activation spreading centrifugally from a focal area less than 2 cm.[2] Although no difference in prevalence exists between genders and any age group may be affected, some evidence suggests that older patients are more likely to have multiple foci from the right atrium that have a nonautomatic mechanism and are recurrent after catheter ablation.[3]

It is well recognized that focal ATs are not randomly distributed but, rather, congregate around defined anatomic locations. In the right atrium, the most common site is along the crista terminalis (CT), with foci also clustering around the tricuspid annulus, coronary sinus os, right atrial appendage, perinodal region, and inter-atrial septum.[4-7] In the left atrium, the pulmonary veins provide the majority of foci, with the mitral annulus, left septum, left atrial appendage, and noncoronary aortic cusp being other potential locations.[8-12] Knowledge of this clustering is of great assistance to the electrophysiologist while attempting to localize the likely site of origin during an electrophysiology study.

Indications for Referral to the Electrophysiology Laboratory

Although focal atrial ectopy is common, it is rarely symptomatic. In contrast, frequent ectopy and sustained tachycardia are often symptomatic and prompt patients to present to the clinician for assessment. Incessant AT may also induce left ventricular dysfunction, which can resolve after curative ablation[3] Focal AT tends to respond poorly to pharmacologic therapy, making catheter ablation an increasingly used procedure. The American College of Cardiology, the American Heart Association Task Force on Practice Guidelines, and the European Society of Cardiology Committee (ACC/AHA/ESC) consensus guidelines published in 2003 provide a class I recommendation for catheter ablation of focal AT in patients with incessant tachycardia or recurrent symptoms.[1]

Importance of Surface Electrocardiogram and P-Wave Morphology

The surface electrocardiogram (ECG) can be a useful guide to the likely anatomic site of origin for focal AT. This information can then be used by the clinician during intracardiac electrophysiological mapping to target specific areas. Kistler et al published an algorithm for the localization of atrial tachycardias based on the surface ECG P-wave morphology (PWM) that was able to identify the correct anatomic location with an accuracy of 93%.[13] PWM is typically described as positive, negative, isoelectric, bifid, or biphasic (positive-negative or negative-positive). When analyzing PWM, it is important to ensure that the preceding T wave is not superimposed. Spontaneous ventricular ectopic beats, programmed ventricular extrastimuli, or vagal maneuvers such as the Valsalva maneuver or carotid sinus massage may assist with separation of the T wave and P wave. Distinguishing left and right atrial foci is of importance when planning a procedure, as trans-septal access may be anticipated on the basis of PWM. A left-sided focus is suggested by a positive P wave in V1 and a negative P wave in I and aVL.

Specific anatomic sites have characteristic PWMs. Examples of right atrial foci PWMs are shown in Figure 27-1. Foci from the crista terminalis account for two thirds of right atrial foci.[4] The characteristic PWM is similar to the sinus rhythm being positive-negative in V1, positive in I and II, and negative in aVR.[13] Foci from the tricuspid annulus (TA) tend to have a negative P wave in V1 and V2, with superior locations displaying positive PWM in II, III, and aVF and inferior locations displaying negative PWM in the inferior leads. Right atrial appendage locations have indistinguishable PWM to superior TA locations. Focal ATs from the coronary sinus (CS) ostium are characterized by deeply negative PWM in the inferior leads, positive in aVL and aVR, and isoelectric-positive or negative-positive in V1. Septal locations may have variable PWM.

In the left atrium, pulmonary veins are the most common sources of foci. Representative left atrial PWMs are shown in Figure 27-2. V1 is typically positive across the chest leads, aVR is negative, and aVL is isoelectric or negative.[13] Right and left superior pulmonary veins (PVs) tend to have positive PWM in the inferior leads; conversely, right and left inferior PVs have low-amplitude or inverted P waves inferiorly. Left-sided veins exhibit a broader notched P wave in V1 and in the inferior leads, compared with right-sided veins. The left atrial appendage (LAA) foci have a PWM similar to that of the left superior PV, although a deeply negative P wave in lead I, particularly in the setting of incessant tachycardia, is a strong clue that this may be an LAA focus.[11] Mitral annular locations near the aorto-mitral continuity tend to have biphasic negative-positive PWM in V1 and isoelectric or negative PWM in aVL. More recently, focal AT from the noncoronary cusp of the aortic valve has been described, with a PWM similar to the mitral annular location.[9] A positive P wave in leads I and aVL may help differentiate this site from the mitral annular location.

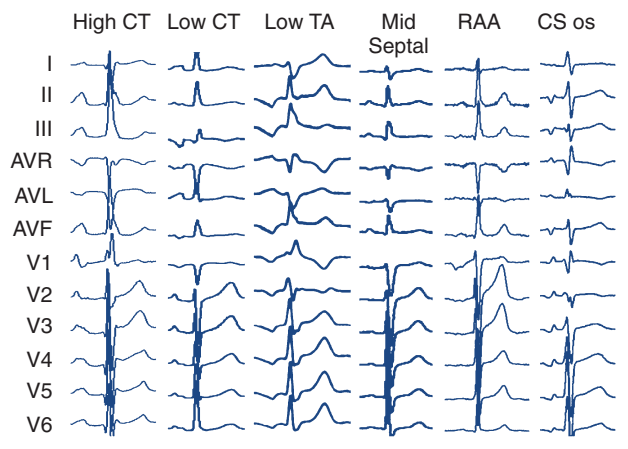

FIGURE 27-1 Representative examples of P-wave morphology for selected right atrial sites. *CT*, Crista terminalis; *TA*, tricuspid annulus; *RAA*, right atrial appendage; *CS*, coronary sinus.

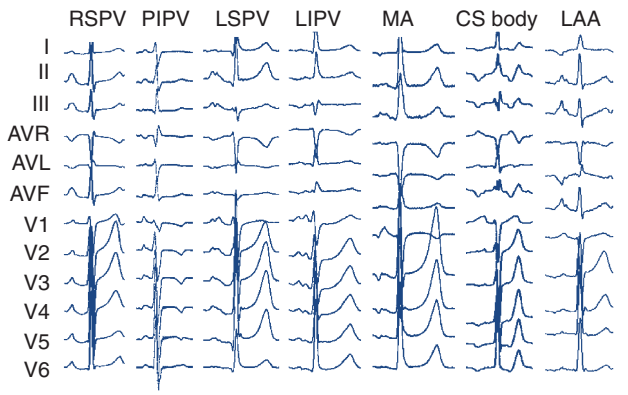

FIGURE 27-2 Representative examples of P-wave morphology for selected left atrial sites. *RSPV*, right superior pulmonary vein; *RIPV*, right inferior pulmonary vein; *LSPV*, left superior pulmonary vein; *LIPV*, left inferior pulmonary vein; *MA*, mitral annulus; *CS*, coronary sinus; *LAA*, left atrial appendage.

Confirming the Diagnosis

The diagnosis of focal AT can usually be made on the surface ECG. Important differential diagnoses include sinus tachycardia (ST), atrioventricular node re-entry tachycardia (AVNRT), atrioventricular reciprocating tachycardia (AVRT), and macro–re-entrant AT. On the surface ECG, AT typically manifests with a long R-P interval. However, at rapid rates, decremental AV nodal conduction may result in an apparent short R-P tachycardia. While both typical AVNRT and AVRT characteristically present with a short R-P interval, this relationship is fixed or "hooked." In focal AT, a variable or unhooked R-P relationship may be present. When clearly not of sinus origin, PWM can be used to distinguish AT from ST. However, AT arising from the superior crista terminalis may have a morphology indistinguishable from that of ST. Indeed, these tachycardias were previously termed "sinus node re-entry." The presence of a "warm-up" over three to four beats at onset and "cool-down" over three to four beats at termination supports a diagnosis of AT over ST, which typically accelerates and decelerates over more than 30 seconds.[14] Macro–re-entrant AT generally manifests with an undulating baseline and no clear isoelectric segment (which is usually seen in focal AT). It is important to note that focal tachycardias at very short cycle lengths may show no isoelectric baseline and mimic macro–re-entry. Similarly, focal tachycardia in atria with scarring and slowed conduction may also show an undulating baseline because of circuitous propagation away from the focus.

Once a provisional diagnosis has been made on the surface ECG, more detailed information and confirmation of the mechanism and site are obtained by intracardiac recordings at electrophysiology study.

Confirming the Diagnosis Using Intracardiac Recordings and Pacing Maneuvers

By far, the most common reason for the inability to map and perform ablation on AT is noninducibility. Infusion of isoproterenol may induce tachycardia in automatic AT. Burst atrial pacing and atrial extrastimulation may induce tachycardia, particularly in AT, because of micro–re-entrant or triggered mechanisms. Beyond these simple induction techniques, no detailed attempts are usually made to classify a focal AT by mechanism, as mapping is targeted to the focal site of origin in any case.

Although the surface ECG may have provided a likely diagnosis, intracardiac recordings and pacing maneuvers during tachycardia are often required to exclude alternative diagnoses. On examination of the intracardiac recordings, the relationship between the ventricular and atrial electrograms (VA relationship) is seen to be fixed or "hooked" in AVNRT and AVRT but variable in AT. Various pacing maneuvers may facilitate the observation of VA unhooking. Following termination of the atrial overdrive pacing at a cycle length that is just below the tachycardia cycle length, the VA relationship remains fixed in both AVNRT and AVRT; however, VA unhooking is observed when the mechanism is focal AT.[15] The response after entrainment of the tachycardia by ventricular pacing (confirmed by acceleration of the atrial rate to the pacing rate) is also helpful. A "V-A-V" response is characteristic of AVRT or AVNRT, and a "V-A-A-V" response is observed in AT. In addition, AT may be excluded if termination of the tachycardia occurred without atrial depolarization during burst ventricular pacing at a 200- to 250-ms cycle length for three to six beats. Demonstration of entrainment from "within the circuit" (Post-pacing interval—Tachycardia cycle length [PPI — TCL] <20 ms) from two sites more than 2 cm apart or the ability to record activity throughout the entire tachycardia cycle length are both definitive for macro–re-entrant AT.[1]

Conventional Mapping

The hallmark of focal AT is the identification of a focal site of early activation with centrifugal spread on endocardial mapping. A local activation time of more than 20 to 30 ms before the surface ECG P-wave onset indicates a potential site for successful ablation.[16] Attempts to define the clear P-wave onset (using pacing maneuvers or adenosine if it cannot be seen) are important. The P-wave onset can then be referenced to a stable intracardiac reference point such as the proximal CS bipole.

Multipolar catheters (20-pole TA or CT) may act as a guide to the focal origin and may also be helpful to rapidly recognize any change in the mechanism or the site of origin of the tachycardia. Pace mapping may also be used to complement activation sequence mapping. The endocardial activation sequence during pacing from various sites that has been mapped by using a

catheter can be compared with the spontaneous activation sequence seen during tachycardia.[17]

Determining whether a focus originates in the right atrium or the left atrium is a critical first step in identifying the site of origin. In general, when the earliest activation in the right atrium occurs over a relatively large region on the septal aspect, a left atrial focus is suspected. Usually, when a focus originates in the left atrium, the earliest activation timing with respect to P-wave onset will not be less than −10 ms at the right atrial septal sites. When uncertainty exists (e.g., presumed perinodal focus), it is necessary to perform left atrial mapping.

Electrogram Characteristics of Successful Sites

Several groups have reported on the presence of electrogram fractionation recorded from ablation catheters at the sites of successful ablation. However, this finding is not universal and may be specific to certain anatomic regions only (e.g., electrograms for focal AT arising from the CT commonly show fractionation, but those at the tricuspid and mitral annulus usually do not).[16] It is hypothesized that these fractionated signals represent underlying slow conduction caused by impaired intercellular coupling, which results in the potential for micro–re-entry.

Many electrophysiological laboratories use the unipolar electrogram at the ablation catheter tip to identify the characteristic QS pattern of a successful ablation site.[18]

The termination of sustained tachycardia with pressure from an intracardiac catheter has been reported to improve on the specificity and positive predictive value of identifying an AT focus.[19] In practice, if ablation is performed at a site of termination by catheter pressure, it may be uncertain whether ablation has been successful or if mechanical pressure has simply caused transient stunning of the focus. In the experience of the authors, ablation at the site of mechanical termination carries a relatively high risk of recurrence.

Atrial pacing during tachycardia at a rate just below the tachycardia cycle length has been used to identify the site of focal origin.[20] In theory, at the site of origin the PPI-TCL should equal 0 ms. In a recent study, the postpacing interval minus the tachycardia cycle length was 11 ± 8 ms at sites of successful ablation.

Three-Dimensional Electroanatomic Mapping Systems

The development of three-dimensional mapping systems has significantly improved the ability of clinicians to successfully locate and ablate foci. Both the CARTO (Biosense Webster, Johnson & Johnson, Diamond Bar, CA) and NavX (Diag Corporation, Minnetonka, MN) systems use complex algorithms for the registration of a mapping/ablation catheter position in three-dimensional space relative to a fiducial point. This allows the construction of three-dimensional chamber geometry with activation sequence mapping (traditionally color coded). In addition, these data can be superimposed onto images of the atrium taken by either computed tomography or magnetic resonance imaging (MRI) scans allowing detailed and accurate correlation of the atrial anatomy with intracardiac electrograms (for an example, see Figure 27-3). Several groups have verified the usefulness of these systems in locating and ablating AT foci.[16] Despite these advantages and the potential for a reduction in radiation exposure because of lower fluoroscopy times, these mapping systems still require frequent ectopy or sustained tachycardia for effective mapping.

Ablation

Standard radiofrequency ablation catheters may be used in the vast majority of cases; irrigated tip catheters may be useful in areas of the atrium with slow blood flow, such as trabeculated areas and within the CS. Cryoablation is an alternative energy source with the advantage of reversibility at −30° C. Moreover,

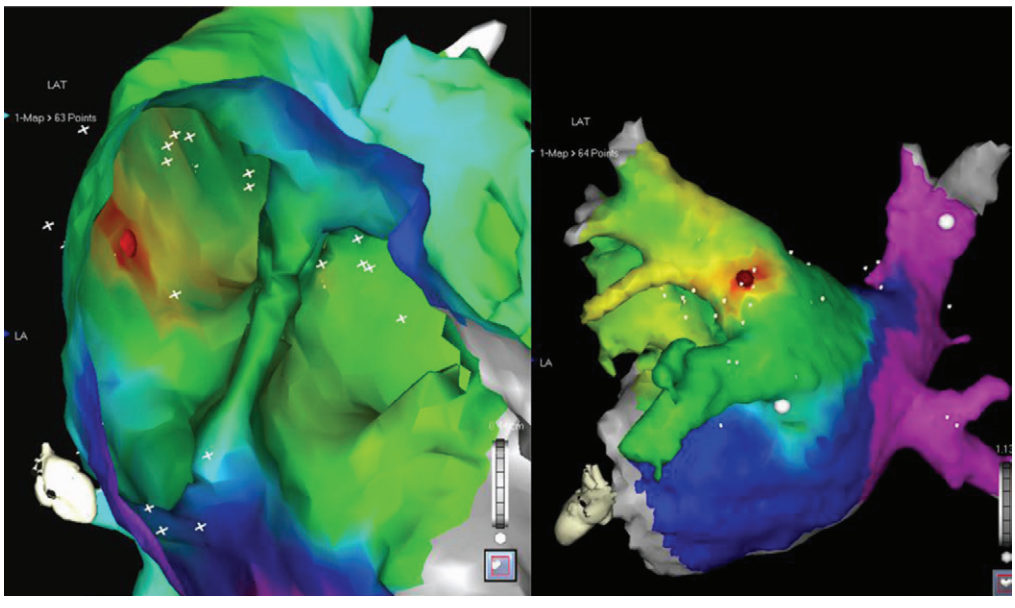

FIGURE 27-3 Example of activation map of focal atrial tachycardia arising from left superior pulmonary vein using CARTO three-dimensional mapping system integrated with computed tomography scan. *Left panel* shows the internal "cut-out" view. *Right panel* shows the view of the posterior atrium. Activation timing is color coded, with early sites in *red* and late sites in *purple*. Centrifugal activation is seen from the left superior pulmonary vein; ablation was successful at this site (*red dot*).

once applied at this temperature, the catheter remains firmly adherent to the underlying tissue, providing excellent catheter stability. These attributes make this energy source an ideal choice for perinodal foci, where permanent AV-nodal block can be avoided by assessing for block with a reversible lesion before applying a full lesion at −80° C (−112° F).[21] Long vascular sheaths may assist with catheter direction, contact, and stability.

The desired endpoint for the procedure will depend on the inducibility of the focus during mapping. Incessant tachycardia has the most definitive endpoint of noninducibility; the endpoint for infrequent ectopy is obviously much more difficult to assess. Testing after ablation with isoproterenol infusion and burst pacing may help uncover unsuccessful ablation attempts. Characteristic acceleration ("speeding") of the tachycardia prior to abrupt termination may be seen at sites of successful ablation.

Overall, the success rates for catheter ablation are excellent; reported series cite cure rates between 69% and 100%.[16] On the basis of pooled data, recurrence was predicted to be approximately 7%.[3] Factors predicting recurrence in this analysis included male gender, multiple foci, older age, and coexisting cardiac pathology. Right atrial foci were predicted to have higher success rates.

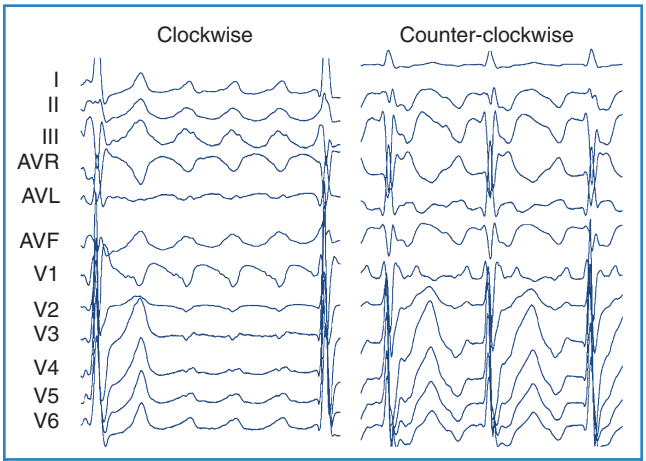

FIGURE 27-4 Twelve-lead ECG of typical counter-clockwise (*right panel*) and clockwise (*left panel*) flutter. Note the isoelectric-positive P wave in V1 and negative P-wave morphology in the inferior leads for typical flutter, compared with a negative P wave in V1 and upright inferior lead P waves in clockwise flutter.

Macro–Re-entrant Atrial Tachycardia

Definitions

Macro–re-entrant AT is a broad term that encompasses both typical (cavo-tricuspid isthmus [CTI])–dependent) atrial flutter and atypical (non–CTI-dependent) atrial flutter (or macro–re-entrant tachycardias). They have in common the classic requirements for re-entry: obstacles which create areas of anatomic or functional conduction block around which two pathways may conduct; unidirectional block in one pathway; and areas of slow conduction creating an excitable gap. Classic entrainment identifies areas "within" the circuit and should be demonstrable by pacing from at least two sites more than 2 cm apart and finding a postpacing interval minus tachycardia cycle length of 20 ms or less. Identification of a critical isthmus by demonstration of concealment (whether on the surface or by intracardiac recordings) is fraught with problems and is of limited practical utility in the atrium.[2]

Typical Atrial Flutter

Typical atrial flutter is the most common form of macro–re-entrant AT and typically has a cycle length of approximately 200 ms. This may be considerably longer (ranging up to 300 ms) in the presence of atrial disease with atrial enlargement and conduction slowing, particularly in the presence of antiarrhythmic agents which slow conduction. Its prevalence is estimated at 5 per 100,000 in those younger than 50 years and increases with age to almost 600 per 100,000 among those older than 80 years.[22] Men are affected 2.5 times more frequently than are women.[22] The anatomic boundaries of this circuit are well known and are described elsewhere in this text (see Chapter 44).

The diagnosis is strongly suggested by the presence of the characteristic flutter wave morphology and endocardial activation pattern and is confirmed by entrainment within the CTI.

The more common direction of wavefront propagation is counter-clockwise (CCW) around the tricuspid annulus (TA); descending direction in the anterolateral walls and ascending in the posteroseptal walls, although clockwise rotation (reverse typical or clockwise flutter) is also seen.

Atypical flutter may be defined as a flutter circuit that is not dependent on the CTI. Lower loop re-entry is a particular case, which is described below.

The surface ECG of typical CCW flutter is characterized by isoelectric-positive P waves in V1 transitioning to negative across the precordium (Figure 27-4). Flutter waves in the inferior leads are generally deeply inverted and have a variable secondary upright component timing with activation of the atrial free wall from superior to inferior. When this secondary component is prominent, it may be difficult to determine whether the flutter wave is predominantly "up" or "down." The ECG appearance of clockwise typical CTI-dependent flutter is more variable. Commonly, V1 is broad and negative with notching, transitioning to positive across the precordium; the inferior leads are usually broad and positive with notching (see Figure 27-4).[23] Other macro–re-entrant circuits have variable ECG characteristics and, as such, detailed intracardiac electrophysiological studies are required for accurate anatomic localization.

Indications for Catheter Ablation

In general, pharmacologic therapy for atrial flutter is either targeted at ventricular rate control using AV-nodal blocking agents (such as β-blockers and cardiac-selective calcium channel blockers) or maintenance of sinus rhythm with class I and III antiarrhythmic drugs. Both these approaches have limitations; the overall maintenance of sinus rhythm on antiarrhythmic drugs is between 36% and 73%.[1] Evidence from a randomized prospective study of catheter ablation versus medical therapy demonstrated sinus rhythm at 21 ± 11 months in 80% of patients with catheter ablation, compared with 36% for those on antiarrhythmic drugs.[24] In addition, the ablation group had significantly fewer hospital admissions and episodes of atrial fibrillation (AF). For patients with coexisting AF, in whom flutter is the dominant rhythm, catheter ablation has been shown to reduce the burden of flutter and assist pharmacologic control of AF.[1] The ACC/AHA/ESC

consensus guidelines provide a class I recommendation for catheter ablation of atrial flutter if it is recurrent, is poorly tolerated, or re-emerges after class I antiarrhythmic or amiodarone therapy.[1] A class IIa recommendation is given for atypical flutter after failure of antiarrhythmic medications.

Anatomy of the Cavo-Tricuspid Isthmus

The anatomy of the CTI has been described as a quadrilateral structure bounded anteriorly by the TA and posteriorly by the eustachian ridge. It is limited laterally by the terminal insertion of the crista terminalis and medially by the CS ostium and the thebesian valve. Trabeculae within the CTI are formed by pectinate extensions of the crista terminalis and intervening connective tissue.[25-27] The thicknesses of CTI trabeculae and the eustachian ridge vary markedly, being largely fibrous tissue with sparse muscle fibers in some patients and deeply trabeculated with thick muscle bundles and intervening pouches or recesses in others.[28] It is this variability in anatomy that determines the ease or difficulty of ablation. The CTI tends to be wider more laterally than in the middle or septal regions. The septal aspect of the CTI lies close to the posterior extensions of the AV node and to the middle cardiac vein.[28] The smooth vestibular component around the tricuspid valve orifice lies immediately over the right coronary artery.[25]

Ablation Techniques

For CTI-dependent flutter, the ablation endpoint is demonstration of complete bi-directional conduction block within the isthmus. Different catheter configurations have been used, but a classic approach would include catheters positioned in the His-bundle, coronary-sinus, and tricuspid-annular locations (see Figure 27-7). Ablation may be performed during atrial flutter or sinus rhythm. Patients in sinus rhythm usually have ablation performed during pacing from the proximal coronary sinus to facilitate the identification of a change in activation sequence on the TA catheter signifying slowing of CTI conduction or block. The usual approach is anatomically guided and commences with ablation at the TA with either continuous pullback or focal point-by-point ablation across the CTI to the right atrium–inferior vena cava (RA–IVC) junction (eustachian ridge). At each point, the adequacy of the lesion is confirmed by the diminution of the local electrogram signal (Figure 27-5) and the emergence of local double potentials on the ablation catheter.

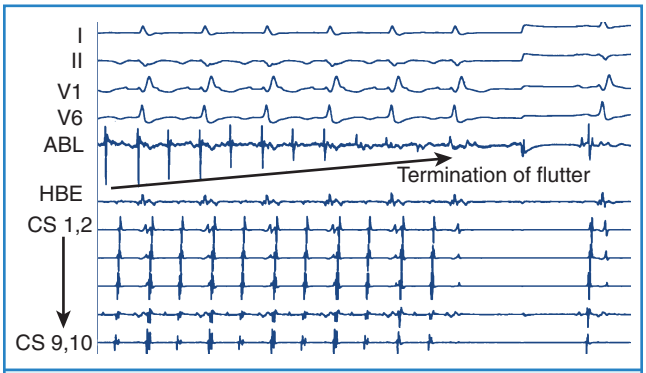

FIGURE 27-5 Progressive diminution of electrogram on ablation catheter (*ABL*) results in adequate lesion creation confirmed by termination of flutter. *HBE*, His bundle electrogram; *CS*, coronary sinus.

Even though the anatomic approach is the more widely used one, an alternative technique sequentially targets areas of high bipolar voltage along the CTI in descending order until block is achieved.[29] In this small series, the authors demonstrated successful blockade in all patients, with recurrence at 8 months in 1 of 18 patients. The ability to produce complete blockade without a contiguous lesion set is in keeping with the anatomic description of the CTI being composed of discrete muscle bundles.

Endpoints for Ablation

Initial reports on the technique for ablation of the CTI focused on the termination of flutter during ablation and noninducibility.[30] Since then, the importance of demonstrating complete bi-directional block across the CTI has been highlighted by greatly improved success rates of between 90% and 100%.[1] Block from the septal aspect to the lateral aspect of the isthmus is readily appreciated by a sudden change in activation sequence on the TA catheter when pacing at the proximal CS (Figure 27-6). Activation after block is seen to descend down the lateral wall of the RA.[30] Bi-directional block (i.e., lateral to septal) is confirmed by pacing from a site lateral to the CTI line. Activation should ascend along the lateral wall and descend at the septum, activating the atrium adjacent to the His-bundle catheter before the CS catheter (Figure 27-7).[30] The mapping of locally split atrial double potentials (DPs) along the line of ablation can also assist in demonstrating complete block and distinguishing block from conduction slowing.[31] If the spacing between DPs is less than 90 ms, a local gap should be suspected; mapping for areas with closely spaced DPs can assist when ablation has not yet produced complete block.[32,33] A gap in the ablation line may also be identified by fractionated electrograms (Figure 27-8). Conversely, widely split local DPs more than 110 ms are associated with complete block.[32,33] An increase in splitting of more than 50 ms from baseline is also indicative of block.[34] If it is uncertain whether block is complete, based on local DPs, pacing from differential sites distant from the CTI on the septal and anterior walls can be helpful. When pacing further from the line of conduction block, the separation of local DPs decreases when block is complete.[35,36] The trans-isthmus conduction interval, which can also be measured, is defined as the time between the pacing stimulus (either septal or lateral to the isthmus) and the local atrial electrogram on the contralateral side of the ablation line. An increase in the trans-isthmus conduction interval (interval between the pacing stimulus, either septal or lateral to the line of ablation, and the atrial electrogram on the other side of the CTI) of more than 50% from the baseline is highly predictive of complete isthmus block (see Figure 27-6).[34] When evaluating the presence of complete block, it is important to pace and record immediately adjacent to either side of the line of block to avoid an "apparent" block (see example in Figure 27-9).

Occasionally, it may appear that block is incomplete due to pseudo-conduction. This occurs when conduction across the crista terminalis allows collision of wavefronts on the anterior right atrial wall mimicking trans-isthmus conduction. Pacing from the mapping catheter within the CTI immediately medial to the line of ablation and recording on the TA catheter immediately lateral can clarify this.[35] Transient CTI block occurs and will usually demonstrate recovery of conduction within 20 to 30 minutes of ablation. Where practical, this should be the waiting period after block is seen to ensure the recovery does not occur.[37]

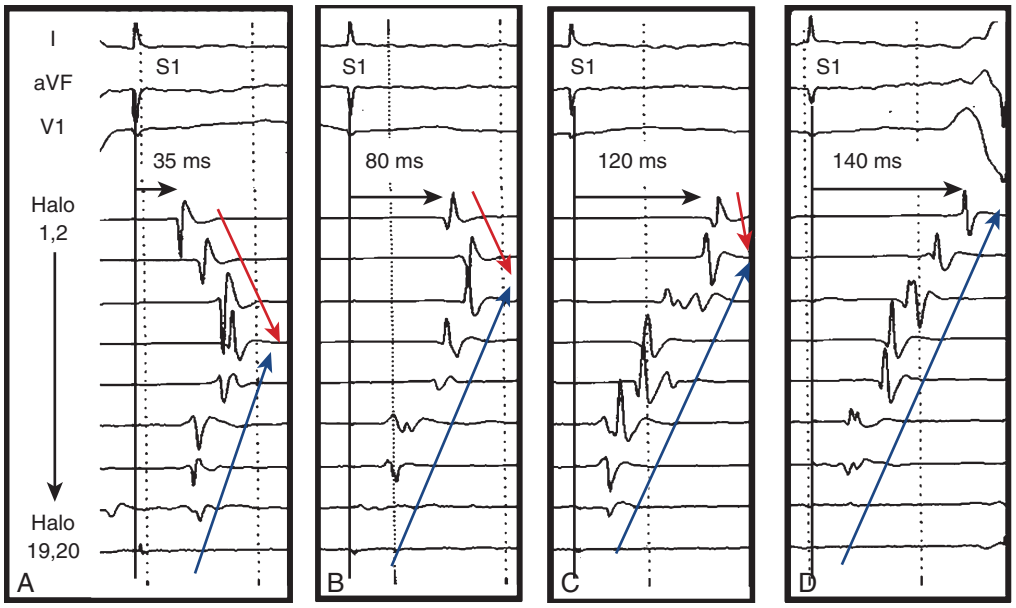

FIGURE 27-6 **A** to **D,** Progressive increase in trans-isthmus conduction interval pacing from the proximal coronary sinus ("septal" to the isthmus line) as isthmus block is achieved. In **D,** note (i) long trans-isthmus conduction time, and (ii) change in activation sequence on the 20-pole catheter across the tricuspid annulus (*Halo*), where the distal bipole (*Halo 1,2*), located lateral to the isthmus, is activated last.

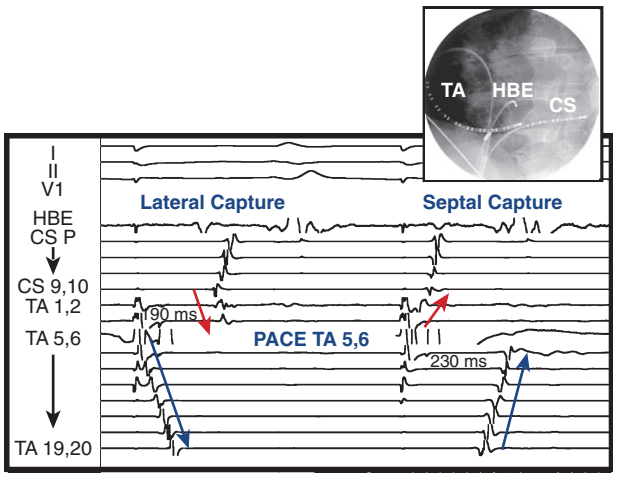

FIGURE 27-7 With tricuspid annulus (TA) catheter positioned across both septal and lateral portions of cavo-tricuspid isthmus (CTI), bi-directional block can be demonstrated when pacing TA 5,6 with alternating lateral and septal capture during respiration.

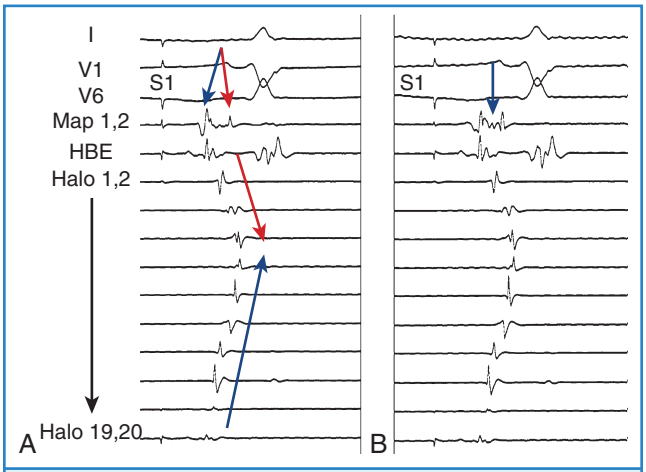

FIGURE 27-8 Electrocardiogram (ECG) and intracardiac electrograms from cavo-tricuspid isthmus ablation. **A** shows incomplete block despite locally split double-potential signal (*red and blue arrows*) on ablation catheter (*Map 1,2*), suggesting that the ablation line gap lies elsewhere. **B,** Further mapping along the cavo-tricuspid isthmus ablation line identifies a gap signified by fractionated signal on ablation catheter (*blue arrow*). *Map 1,2*, Distal ablation catheter; *HBE*, His-bundle electrocardiogram; *Halo*, deflectable 20-pole catheter positioned around tricuspid annulus; *S1*, pacing stimulus.

Radiofrequency remains the energy source of choice for ablation of typical atrial flutter. Studies have demonstrated that 8-mm tip catheters are superior to 4-mm tip catheters in terms of procedural duration and success.[38] The use of irrigated tip catheters is also superior to standard 4-mm tip catheters.[39] A recent comparison between irrigated 4-mm tip catheters and nonirrigated 8-mm tip catheters yielded equivalent results.[40] The use of electroanatomic mapping produces results similar to those of conventional mapping in terms of procedure time and radiofrequency duration but reduces fluoroscopy time.[41] Cryoablation has been used effectively and has the advantages of catheter stability and absence of pain.

As previously described, anatomic variations can cause difficulty achieving successful ablation.[28] A prominent sub-eustachian pouch may result in inadequate power delivery when a nonirrigated catheter is used. Prominent pectinate muscles may pose difficulties with catheter stability and lesion depth creation. A

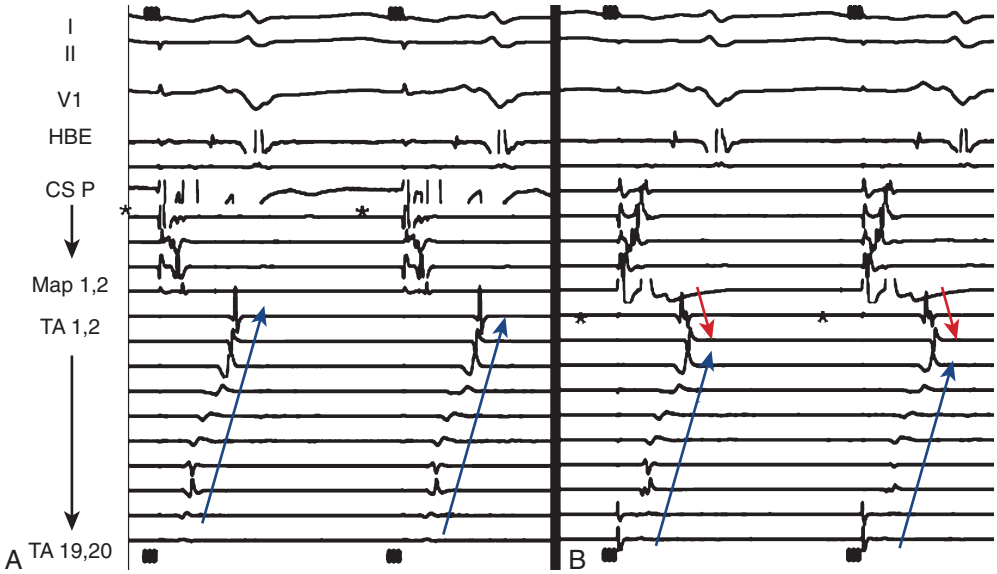

FIGURE 27-9 A, Pacing from proximal coronary sinus (*CS P, **), isthmus block appears complete on the tricuspid annulus catheter (*TA*). **B,** Pacing at the medial isthmus from the ablation catheter (*Map 1,2, **) shows that isthmus block is incomplete. *HBE*, His bundle electrocardiogram.

more medial approach will help avoid the thicker musculature and the deep recesses between trabeculations. The use of linear phased-array intracardiac ultrasonography can assist in defining difficult anatomy.[42]

Procedural Efficacy

In a worldwide pooled analysis of ablation for CTI-dependent flutter, including more than 7000 patients, the long-term success was 97% with an incidence of major complications of 0.4%.[43] Repeat procedures were, however, needed in 4%. The late occurrence of AF after ablation for CTI-dependent flutter is well recognized. It has been previously described that up to 70% of patients with a history of flutter ablation subsequently develop AF, even with no antecedent history of AF.[44] More recently, another group demonstrated that 50% of patients with no history of AF subsequently develop this arrhythmia after successful ablation of flutter. The majority of these (almost 70%) developed AF within 1 year of the flutter ablation.[45] The incidence of AF following ablation was similar when compared with that in a group of historical controls receiving pharmacologic management of flutter. In the majority of patients with atrial flutter, the arrhythmia commences via a transitional period of atrial fibrillation, which may be necessary for the development of a line of a functional block in the intercaval region of the right atrium.[46] Despite the high late incidence of atrial fibrillation, ablation of CTI-dependent flutter provides good symptomatic relief with a reduced requirement for antiarrhythmic drugs and cardioversion for refractory arrhythmias and can facilitate management of AF.[1,45,46]

Lower Loop Re-entry

Lower loop re-entry is an uncommon variant of typical flutter manifesting as CCW activation around the IVC involving the CTI and the low posterior RA with conduction across the terminal crest. The turnaround point is thus lower than in typical flutter, and the cycle length is appropriately shorter.[47] Despite these differences, ablation of the CTI is successful for treating this arrhythmia.

Atypical, or Non-CTI–Dependent Atrial Flutter

The term *atypical atrial flutter* encompasses a range of macro–re-entrant ATs that are not solely dependent on the CTI and whose surface ECG is not that of typical CCW or clockwise flutter. These atypical circuits can occur in the macroscopically normal heart or may be associated with previous cardiac surgery, congenital heart disease, and, as shown more recently, after ablation of atrial flutter. In patients with congenital heart disease, a thorough understanding of the underlying abnormality and the nature of corrective surgery, including surgical access, is essential. Macro–re-entry can exist in both left and right atria, and often multiple circuits can coexist. Dual-loop re-entry has been frequently described, and one circuit may involve the CTI. Indeed, even when the CTI is not involved in a circuit, it is important to also perform CTI ablation in this population, as otherwise there will be a high late incidence of CTI-dependent flutter. In one series, in which three-dimensional electroanatomic mapping was used, the CTI was involved in "incisional" flutter in 92%, with 27% being treated with CTI ablation alone. A line of DPs along the right atrial free wall was associated with dual loops in all instances.[48] In patients with the substrate for macro–re-entry, "focal" sources with early activation and centrifugal spread may coexist.[48,49]

Mapping techniques generally involve a combination of multipolar activation mapping, entrainment mapping, and creation of detailed three-dimensional activation maps (CARTO or NavX). Multipolar and entrainment mapping can provide a rapid guide to the anatomic region of the tachycardia circuit. It must be recognized that entrainment in patients with atypical flutter in the presence of significant atrial scarring can have potential drawbacks. Entrainment may terminate a circuit or result in one flutter

changing to a different circuit. When marked conduction slowing is present, entrainment can result in decrement, prolonging the post-pacing interval even when in the circuit. These problems notwithstanding, entrainment is a highly effective technique to rapidly localize a tachycardia region.

Multipolar activation mapping is most useful for right atrial circuits, as it indicates rapidly whether wavefronts in the anterior and posterior right atrial free wall and in the septum are ascending or descending.

Nevertheless, three-dimensional mapping remains the cornerstone of ablation of these often complex circuits. High-density activation maps registered to critical anatomic structures provide a detailed understanding of the tachycardia sequence. Just as important is the anatomic information provided by voltage mapping that demonstrates regions of low voltage and scar, which are the potential anatomic obstacles and the substrate for re-entrant circuits. Lines of DPs and regions of fractionated electrograms can be annotated and may also be critical to the mechanism of tachycardia. Circuits may have a critical channel where focal ablation can terminate a macro–re-entrant circuit.[50] Alternatively, some circuits are broad activation wavefronts without a critical channel. In these cases, ablation lines are created between scars or to anatomic obstacles such as the mitral or tricuspid annulus or the inferior or superior caval veins. In addition, these maps can be superimposed on detailed imaging by CT or MRI, thus allowing the correlation of the electrical substrate with anatomic structures.

Interpretation of three-dimensional maps should be made with caution. In patients with extensive scarring and conduction slowing, it is possible to record the complete tachycardia cycle length with a "head meets tail" (i.e., early meets late) in a region that is actually far from the tachycardia circuit. It is therefore the approach of the authors of this chapter to always initially identify sites involved in the tachycardia mechanism with entrainment. Another approach is to include in the map only those sites where PPI-TCL is less than 40 ms.

When broad circuits are identified, linear ablation between two anatomically defined structures is necessary for termination of tachycardia. The most commonly used endpoint in reported series is termination of tachycardia with ablation and inability of the tachycardia to reinitiate (noninducibility). However, for the majority of sites where linear ablation is performed, whether in the right atrium or in the left atrium, the definitive endpoint should be the use of mapping techniques to confirm conduction block.

Right Atrial Macro–Re-entry

Right atrial circuits independent of the CTI are an uncommon cause of right atrial macro–re-entry, accounting for 4% of cases, as reported by one series.[51] The anatomic substrate for re-entry in this group appears to be spontaneous scarring in the free wall of the RA and is marked by the presence of DPs, areas of low voltage, and electrical silence.[49,51] The high incidence of coexisting sinus node dysfunction highlights the global pathology of the right atrium in this population.[49] The approach in this group invariably also involves ablation of the CTI, described previously as typical CCW flutter, which is nearly always also inducible. Ablation from the lower portion of the scar to the IVC is usually the narrowest part of the circuit, although the superior vena cava and the TA are alternative anatomic anchors.[49,51] Channels within scars may also be seen, and ablation within these areas can also result in termination of the circuit.[49] Ablation in this area may be painful, and potential phrenic nerve damage should be avoided by pacing at high output to exclude phrenic nerve capture before ablation.[52] Acute success defined by termination and noninducibility is high in these patients, in excess of 90%.[49,51]

Upper Loop and Figure-of-8 Re-entry

Another type of atypical right atrial flutter involving the upper right atrial free wall has been termed *upper loop re-entry*.[51,53] Non-contact mapping studies demonstrated this to comprise CCW (descending activation of free wall anterior to the CT) or clockwise (ascending activation of free wall anterior to the CT) activation involving the crista terminalis, an area of a functional block, and the superior vena cava.[54] The lower turnaround point for these circuits is by conduction through a gap in functional block in the crista terminalis. Ablation in this conduction gap to complete the line of block is successful in treating this arrhythmia.[54] This circuit may be seen in isolation as a single loop or be involved in dual-loop (figure-of-8) re-entry with lower-loop (type I figure-of-8 re-entry) or free-wall (type II figure-of-8 re-entry) circuits.[55] In these cases, ablation of the free-wall channel (type II) and/or conduction gap in the crista terminalis (type I) is effective.[55]

"Incisional" Re-entry

Right atrial macro–re-entrant circuits resulting from previous atriotomy incisions for correction of congenital heart disease are well recognized and have been termed *incisional* or *scar-mediated flutter*.[56]

In patients with repair of atrial septal defect, atypical flutter most usually involves the atriotomy scar in the atrial free wall (Figure 27-10). Circuits involving the septal patch have rarely been reported. In patients with Mustard or Senning repair for dextro-transposition of the great arteries (D-TGA), the majority of circuits will involve the remnant of the CTI, which is now located in the pulmonary venous atrium.[57] Access to this chamber is difficult and requires either a circuitous retrograde approach or puncture across a thick/prosthetic baffle; this is the limiting factor in ablation (Figure 27-11). Circuits in variants of Fontan repair are unique in that they infrequently involve the CTI in patients who often have tricuspid atresia. Circuits are most commonly found in the free wall and can involve the crista terminalis, the inferior or superior vena cavae, or the base of the conduit. Often these Fontan right atria are severely enlarged showing extensive regions of low voltage and scarring with multiple circuits. Patients with repair of tetralogy of Fallot may also develop atrial arrhythmias, as surgery frequently involves a trans-atrial approach resulting in a long free-wall scar.

Reported success rates for ablation of scar-mediated re-entry in patients with surgically corrected congenital heart disease have varied widely, particularly with the underlying condition, although acute success has been achieved in excess of 80%.[48,56] Early recurrences may be as high as 59%, although long-term freedom from arrhythmias can be achieved in the majority of patients after multiple procedures.[48]

Left Atrial Macro–Re-entry

Left atrial flutter circuits typically involve re-entry around anatomic structures such as the mitral annulus, the pulmonary vein ostia, and regions of electrical silence or scar. The majority of

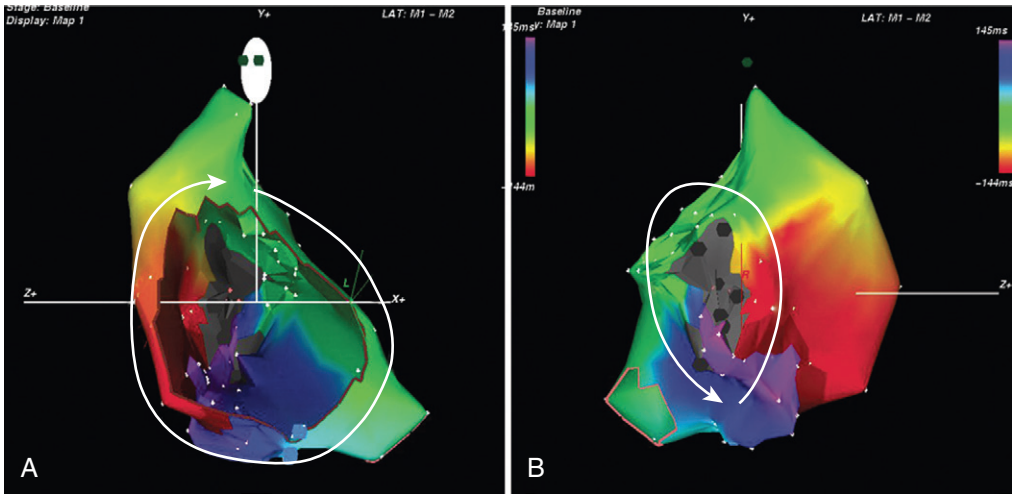

FIGURE 27-10 Color-coded activation map from a case of "incisional" right atrial re-entry after atriotomy with dual-loop circuits. Early activation is marked in *red* and late in *purple*. **A** Demonstrates clockwise atrial flutter around the tricuspid annulus in a left anterior oblique projection. **B** Demonstrates simultaneous "dual-loop" counter-clockwise activation around the free-wall atriotomy scar (*gray area*).

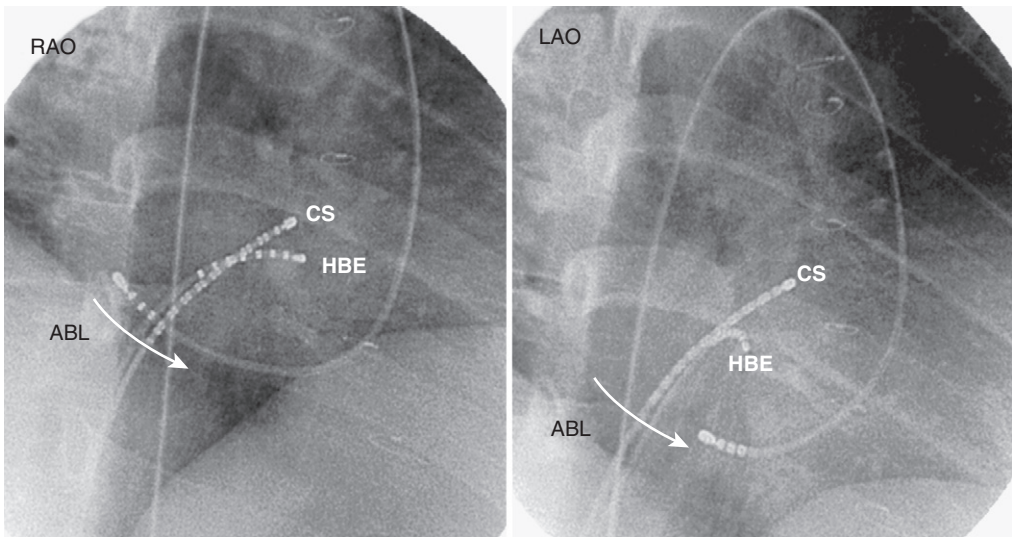

FIGURE 27-11 Right anterior oblique (*RAO*) and left anterior oblique (*LAO*) projections of a retrograde aortic approach for ablation of the cavo-tricuspid isthmus remnant in a patient with a previous Mustard surgical repair. *ABL*, Ablation catheter; *CS*, coronary sinus; *HBE*, His bundle electrogram.

these patients have significant structural heart disease such as cardiac failure, mitral valve disease, and left atrial enlargement.[58] Areas of electrical silence demonstrated by voltage mapping most frequently occur in the posterior left atrium and the left atrial roof. Many of these circuits demonstrate broad activation wavefronts and dual-loop re-entry, and multiple circuits frequently occur. Perimitral re-entry, whether clockwise or CCW, is the most frequently observed circuit. Linear ablation is performed between the lateral mitral annulus and the left inferior pulmonary vein (through the "mitral isthmus") with confirmation of a bi-directional conduction block using the CS catheter for recording conduction discontinuity and the mapping catheter for pacing (Figure 27-12). Ablation within the CS is often required to complete this line. Alternatively, ablation may be performed between two electrically silent anatomic obstacles (e.g., the mitral annulus and areas of left atrial scar) (see Figure 27-12). Circuits around the right-sided or left-sided veins can be successfully ablated with a "roof line" of ablation between the left and right superior pulmonary veins. For both the roof line and the mitral line, it may be necessary to perform circumferential ablation to isolate the pulmonary vein to "anchor" the roof or mitral line to a region of a conduction block. In some cases, scarring around the base of the pulmonary vein will obviate the need for circumferential isolation. Other circuits may be smaller and involve regions of scarring in the posterior atrium or in the roof.[58] Circuits around silent areas can be ablated by joining these areas to one of the pulmonary veins or to another silent area.[58] The acute success rates of approximately 70% for left atrial macro–re-entry are less than those of typical CTI-dependent flutter, with a significant proportion requiring multiple procedures.[58] Left atrial

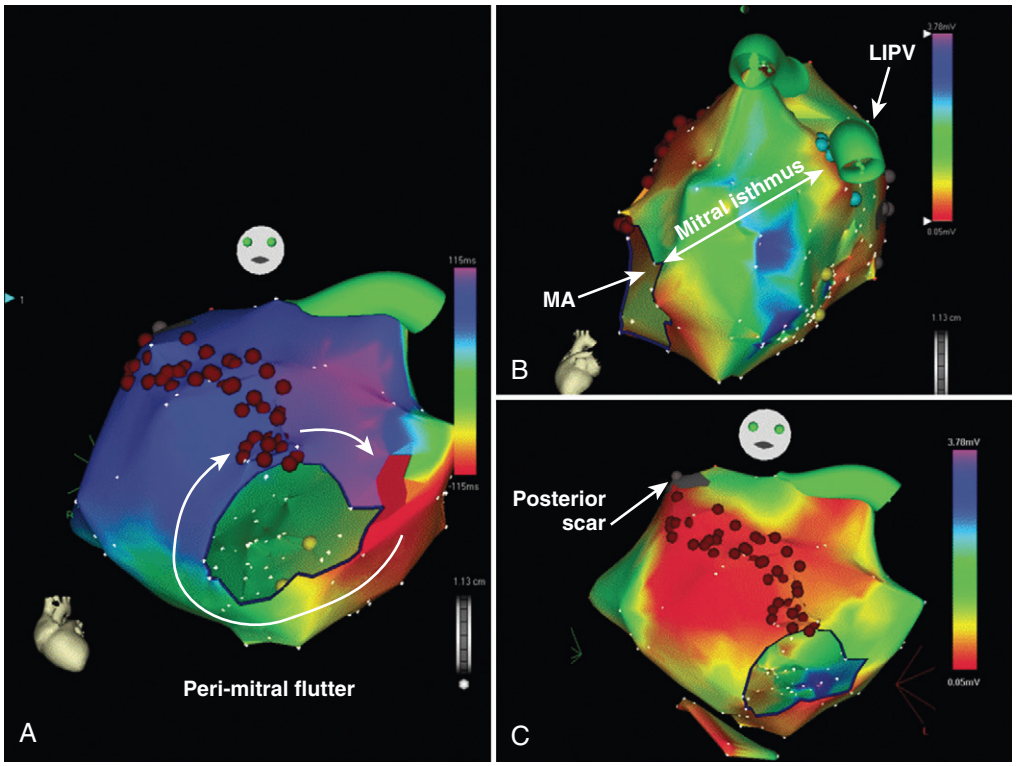

FIGURE 27-12 Electroanatomic map of peri-mitral flutter ablation. **A,** Color-coded activation map (*red = early, purple = late*) in left anterior oblique (LAO) projection demonstrates clockwise circuit around the mitral annulus (*white arrows*). **B,** Voltage map in left lateral projection demonstrates high voltage in the mitral isthmus between the mitral annulus and the left inferior pulmonary vein. **C,** LAO projection voltage map (*red = low voltage*). Due to high voltages in the mitral isthmus region, ablation line (*red dots*) performed through the low-voltage zone from the mitral annulus to the posterior scar (*gray*). *MA*, mitral annulus; *LIPV*, left inferior pulmonary vein.

macro–re-entry involving the CS musculature has also been reported and can be managed by circumferential ablation around the CS.[59]

Atrial Tachycardias After Catheter Ablation of Atrial Fibrillation

With the rapidly increasing number of patients undergoing ablation for atrial flutter, the incidence of AT as a byproduct of this procedure is also increasing. The reported incidence of AT after pulmonary vein isolation ranges from 4.7% to 25%, which reflects the wide variation in patient populations and in the initial ablation approaches.[60-62] In general, initial conservative management with pharmacologic therapy and elective cardioversion is appropriate, as many of these circuits will settle spontaneously after the early postablation period.[63] Of those with AT during the initial procedure, almost half experience spontaneous resolution.[60] Of those with AT during short-term follow-up, approximately 30% experience spontaneous resolution.[60] However, when the flutter persists beyond the first 3 months from the index ablation procedure for atrial flutter, it is probable that a further ablation procedure will be required.

The nature of the tachycardia is, in large part, determined by the type of ablation performed at the initial procedure and also by the presence of abnormal left atrial substrate, more frequently observed in patients with long-lasting persistent AF.

In patients who have undergone only circumferential pulmonary vein isolation for paroxysmal AF without any additional substrate modification (linear or fractionated electrogram ablation), many tachycardias will be focal and related to pulmonary vein sources with reconnection of the pulmonary vein to the left atrium.[64] Occasional non-PV foci will be involved. Simple pulmonary vein reisolation will be sufficient to cure the problem in the majority of cases. Macro–re-entrant circuits are not common in this population. The surface ECG PWM may be highly variable in these patients as previous ablation alters propagation patterns and hence the P-wave appearance.

In contrast, in patients who have undergone linear ablation for persistent AF, the most common mechanism of AT will be macro–re-entry related to gaps in previous ablation lines.[60-62] The incidence of gap-related flutter will also depend on whether a bi-directional block across ablation lines was confirmed during the index procedure.[63]

In patients who have had extensive ablation of fractionated electrograms, small re-entrant circuits have been described.[65] For some of these circuits, broad fractionated electrograms recorded on adjacent bipoles may cover the entire tachycardia cycle length.[65-67]

Recently, Jais et al described a deductive mapping strategy for atrial tachycardias following AF ablation based on three steps: (1) cycle length regularity, (2) search for macro–re-entry (entrainment involving >2 separate atrial segments), and (3) if macro–reentry excluded, search for focal origin giving a centrifugal

activation of the atria.[65] This strategy has proved to be highly effective. In addition, mapping of the RA and entrainment of the CTI should be performed prior to left atrial access, as previous ablation can alter the appearance of a typical CCW flutter.[63]

Reported success rates for ablation of AT following previous AF ablation have generally been high ranging from 77% to 93%.[60-62] However, it should be recognized that when extensive atrial ablation is performed in patients with an abnormal atrial substrate, the potential for multiple different re-entrant circuits may develop.

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CHAPTER 28

Electrophysiological Evaluation of Atrial Fibrillation

Sanjeev Saksena and Nicholas D. Skadsberg

Introduction

Atrial fibrillation (AF), one of the earliest arrhythmias described, is the most common cardiac arrhythmia in humans and is particularly common in older adults. The Framingham Heart Study noted that the incidence of AF in individuals age 60 years was 4% and as high as 15% in those older than 70 years.[1] Effective evaluation and management of AF will have substantial clinical and public health impact in an aging population. The mechanisms of AF have been widely debated and are often extrapolated from experimental data. These are discussed in Chapter 4. Human studies have reported data regarding clinical mechanisms that are at significant variance with some experimental concepts. Clinical investigations have centered on the relative role of triggers and substrate, focal automaticity and organized versus random re-entry, and the applicability of experimental and mathematical models to human AF. The clinical electrophysiological study (EPS) remains the gold standard for the investigation and evaluation of human AF.

The major objectives in a clinical EPS of a patient with AF are presented in Box 28-1.

Electrocardiographic Definition and Clinical Classification

AF is characterized by the absence of P waves and the presence of small, irregular oscillations (fibrillatory, or f, waves) on electrocardiographic recordings. *Fibrillation* has been defined as either fine or coarse, based on the ability to discern well-defined f waves, without evidence of organized activity in the surface electrocardiogram (ECG). More recently, organized tachycardias have been documented at the onset of AF events, in intracardiac recordings at surgery, or during clinical EPSs performed in patients with AF.[2-4] Recent reports that used advanced mapping techniques have documented multiple organized atrial tachyarrhythmias in a given patient with AF.[5] Careful evaluation of ECGs with high gain or body surface mapping reveals evidence of varying f-wave morphology and periods of atrial flutter or atrial tachycardia (AT). (Figure 28-1, *A*).[6,7]

The current clinical classification of AF defines new-onset AF (first episode) or recurrent AF (≥2 episodes) with three types of presentation.[8,9] *Paroxysmal AF* is defined as recurrent AF that terminates spontaneously within 7 days, whereas *persistent AF* is AF that is sustained beyond 7 days, or lasts fewer than 7 days but requires pharmacologic or electrical cardioversion (see Figure 28-1, *B*). The difference between the two clinical AF presentations may lie in the probability of AF termination within a defined period, which, in turn, may be based on the complexity of the AF mechanisms initiating or maintaining AF. When cardioversion fails or is not attempted, the patient has been defined as having *permanent AF*. More recently, aggressive cardioversion with high-energy, repeated shocks or intracardiac shocks has demonstrated effective termination of even permanent AF, leading to decreasing use of this term. Thus, it is more appropriate to define persistent AF as being new-onset or established (duration ≥1 year) persistent AF. A particular patient may have AF episodes that fall into one or more of these categories. The relationship of clinical classes of AF to EPS findings in each class is examined later.

Patients with AF generally have ECG and EPS evidence of delays in intra-atrial conduction. This manifests on the surface ECG as prolonged P-wave duration or notched P waves in sinus rhythm. In extreme examples, virtual segmentation of the P wave can occur with three levels of intra-atrial conduction block based on P-wave morphology. Increasing P-wave duration is associated with more advanced forms of AF such as persistent or permanent AF and frequent relapses after therapy. Prolongation of P-wave duration may be related to temporal dissociation of right atrial and left atrial activation, slowing of conduction, or fragmentation of atrial potentials often seen as late potentials on a P-wave signal-averaged ECG. It is recommended that EPS evaluation of AF commence with a high-gain 12-lead ECG at higher paper speeds (50 to 100 mm/s) to accurately assess P-wave duration and morphology. Correlation of the P wave with intracardiac signals is valuable and should be systematically performed. Periods of organized f waves can often be correlated with organized tachyarrhythmias on intracardiac recordings, as discussed later in this chapter.

Intracardiac Electrophysiological Studies for the Evaluation of Atrial Fibrillation

Early Electrophysiological Observations in Atrial Fibrillation

Early EPSs in patients with AF used limited recording and stimulation methods. The focus of the studies was largely on measurement of atrial electrophysiological properties, assessment of atrial conduction in the right atrium (RA) and the left atrium (LA), and the atrioventricular (AV) propagation of paced atrial beats or spontaneous or induced AF or other concomitant tachyarrhythmias. Two or three multi-polar catheters were typically positioned in the high RA and the mid-RA, His bundle region, and the coronary sinus.[10] Abbreviation of atrial effective and functional refractory periods during programmed atrial stimulation is

Box 28-1 Goals for Electrophysiological Evaluation of Atrial Fibrillation

1. Define the triggering arrhythmias that initiate and maintain AF.
2. Delineate the anatomic substrate and its electrophysiological properties.
3. Evaluate potential comorbidities: sinus node function and atrioventricular conduction.
4. Correlate electrocardiographic classification and electrophysiological properties to establish the stage of AF progression in the individual patient.
5. Find a reliable method for AF induction, preferably by promoting a spontaneous AF event.
6. Map the potential regional locations of the triggers and the atrial substrate involved in its genesis.
7. Determine the potential benefits of different therapies, including preventative, suppressive, reversion, and ablative approaches.

AF, *Atrial fibrillation.*

seen in patients with AF, with concomitant loss of rate adaptation atrial refractoriness. In addition, an increase in the dispersion of atrial refractoriness in the atria occurs in these patients compared with control subjects.[11] Intra-atrial conduction times in humans show increased conduction delay in the RA, manifest as increased P-A intervals, and prolonged inter-atrial conduction time measured as P–distal coronary sinus interval. These delays account for the prolonged global P-wave duration seen on the ECG (Figure 28-2). More recently, other markers of conduction delay during sinus rhythm have been identified, including fragmented or multi-phasic intracardiac atrial potentials and late potentials on P-wave signal-averaged ECG recordings. Regional intracardiac atrial electrogram recordings show a propensity for split potentials in certain locations (e.g., crista terminalis, coronary sinus, eustachian ridge at the cavo-tricuspid isthmus, posterior LA), suggesting that anatomic structure can alter atrial electrical propagation patterns. Attuel emphasized the importance of increased dispersion of atrial refractoriness in these patients and its relationship to inducible AF.[11,12]

In addition, patients with AF can have electrical comorbidities. Ventricular activation patterns should be evaluated, especially when they show concomitant wide QRS patterns. These can be related to either aberrant conduction over the normal or diseased His-Purkinje axis or accessory pathway conduction. Sinus node dysfunction and AV block can coexist with AF. Bradycardia-tachycardia syndrome is a common manifestation of both AF and sick sinus syndrome in older adults. Formal sinus node and AV conduction testing in this population may show a substantial proportion of patients with abnormal EPS findings; these methods are discussed elsewhere in this text. This should be incorporated in the clinical electrophysiological evaluation of the patient with AF.

Programmed Stimulation for Induction of Atrial Fibrillation

Programmed atrial stimulation was first introduced in patients with AF by Haft more than 30 years ago.[13] Single-paced atrial premature beats during atrial pacing or sinus rhythm–induced episodes of AF or flutter in these patients. This was accepted as a marker of atrial vulnerability to AF. Subsequently, Bauernfeind et al studied patients with Wolff-Parkinson-White (WPW) syndrome and AF and performed tests to select an effective drug therapy.[14] Effectiveness in these studies was defined by prolongation of atrial refractoriness, abolition of accessory pathway conduction, and suppression of inducible AF. A standardized protocol for programmed stimulation in AF was first proposed by our group in 1999 and is described in detail later in the chapter.[15]

Atrial Fibrillation Mapping and Anatomic-Physiological Correlations

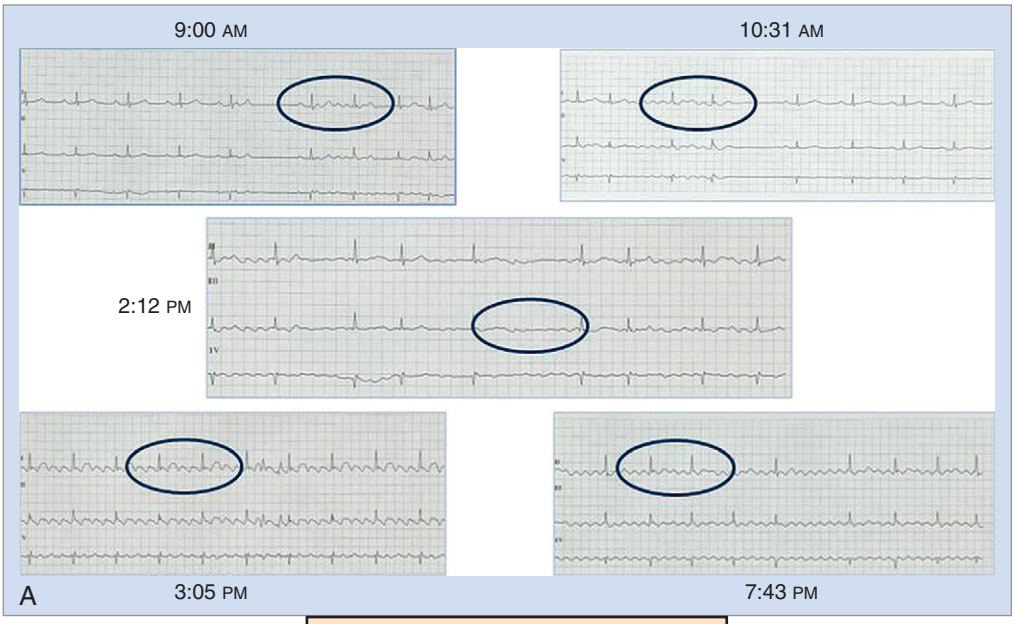
More recently, the focus of electrophysiological evaluation has shifted to mapping of either induced or spontaneous AF, detailed activation mapping of the RA and LA for triggers, organized tachycardias, identification of an abnormal atrial substrate, or all of these findings. All of these are demonstrable with atrial tissue voltage mapping or atrial electrogram morphologic abnormalities in sinus rhythm or AF (Figure 28-3). Such mapping is accomplished by placement of multiple electrode catheters in the RA and LA and is complemented by three-dimensional contact mapping or noncontact mapping (NCM) of the atrium. In this chapter, the multi-electrode catheter approach is discussed first. Three-dimensional mapping techniques are discussed in detail elsewhere. We have combined these two methods in a single procedure designed to achieve a complete electrophysiological evaluation, with simultaneous bi-atrial mapping complemented by high-resolution NCM mapping of the atrium of interest. This approach permits beat-to-beat real-time activation mapping of AF from onset to termination.

Clinical Electrophysiological Techniques for the Evaluation of Atrial Fibrillation

Contact Electrode Catheter Techniques

Clinical EPS in a patient with AF should consist of a systematic approach to the analysis of arrhythmias by recording and measuring a variety of electrophysiological parameters and events with the patient in sinus rhythm, AF, or both and by evaluating his or her response to programmed electrical stimulation. The study includes the measurement of conduction intervals (if necessary after cardioversion), the use of programmed atrial stimulation, and responses to a variety of interventions. Electrograms are recorded at paper speeds of 100 to 200 mm/s. At a minimum, multi-electrode catheters are placed in the high lateral RA, across the bundle of His, and in the coronary sinus to record left atrial electrograms and activation. Right atrial recordings can be obtained from the free wall, the septum, and the tricuspid isthmus for regional right atrial activation patterns (Figure 28-4). A duodecapolar catheter is widely used for this purpose. This catheter is typically placed with its distal electrode in the low lateral right atrial free wall with the proximal set lying along the inter-atrial septum (see Figure 28-4, *C*). This allows simultaneous recordings of the anterior free wall of the RA and the inter-atrial septum.

Left atrial recordings can be indirectly obtained epicardially from the left pulmonary artery or directly endocardially after a trans-septal puncture. In the former, a decapolar catheter is placed in the left lower pulmonary artery in a branch typically encircling the left atrial appendage (LAA) (see Figure 28-4, *C*). In this fashion, recordings from the left atrial lateral wall, left superior pulmonary vein (PV), roof of the LA and PVs, and right superior PV can be indirectly obtained to evaluate conduction in



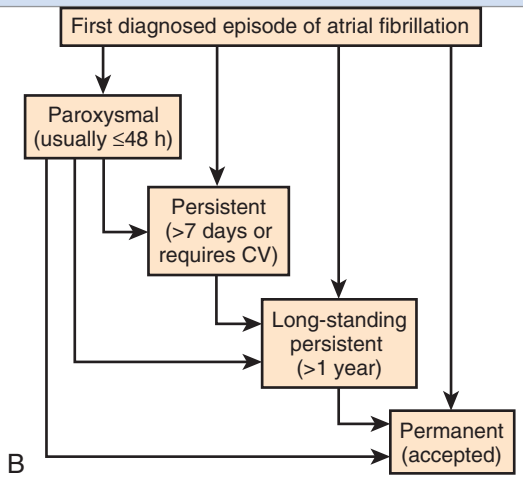


FIGURE 28-1 A, Electrocardiographic rhythm strips of recurrent paroxysms of atrial fibrillation (AF) in a single patient during the course of a single day demonstrating varying fibrillation (f)-wave morphology. *Top panel, left,* Onset of spontaneous AF episode at 9 AM triggered by premature beats with large atrial signals consistent with an ectopic focus, typically seen with focal initiation of pulmonary vein tachycardia. *Right,* Termination of the episode at 10:31 AM showing reorganization of fine fibrillation seen on the first two beats into coarse larger f waves before termination. *Middle panel,* Periods of coarse and fine fibrillatory activity with and without clearly discernible f waves during a sustained AF episode. *Bottom left,* Organized atrial activity consistent with typical atrial flutter with a rate of 250 beats/min during a subsequent event. *Right,* Organized atrial tachyarrhythmia with a faster cycle length consistent with atypical atrial flutter with a rate of 300 beats/min later in the same day. **B,** Clinical classification of atrial fibrillation episodes. *CV,* Cardioversion. *(Modified from European Heart Rhythm Association; European Association for Cardio-Thoracic Surgery, Camm AJ, Kirchhof P, Lip GY, 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 *31[19]:2369–2429, 2010.)*

the superior LA. Trans-septal left atrial mapping requires interatrial septal puncture at the fossa ovalis by using a Brockenborough needle mounted within a trans-septal sheath and dilator assembly, usually guided by intracardiac echocardiography. Although detailed technical steps in this procedure are beyond the scope of this chapter, the important elements are illustrated in Videos 28-1 through 28-6 on the Expert Consult web site that accompanies this textbook. With the trans-septal approach, the distal electrode can be placed in the left superior PV, across the left atrial roof and the fossa ovalis. The catheter can also be manipulated into each of the PVs for mapping (Figure 28-5; see Videos 28-7 to 28-10). Note the proximity of the left pulmonary artery electrode catheter to the trans-septal electrode catheter along the superior LA (see Figure 28-5, *B*).

Alternatively, preformed electrode catheters can be used to map the atrium or PVs. A circular preformed multi-electrode catheter (e.g., Lasso catheter, Biosense Webster, Diamond Bar, CA) or small linear catheters (e.g., Cardima Pathfinder, Cardima Inc., Fremont, CA) can also be used for mapping within tubular structures—such as the PVs, the superior vena cava (SVC) or the inferior vena cava (IVC), the coronary sinus, or atrial appendages—or at their ostia in the atrium. The Lasso catheter comes in

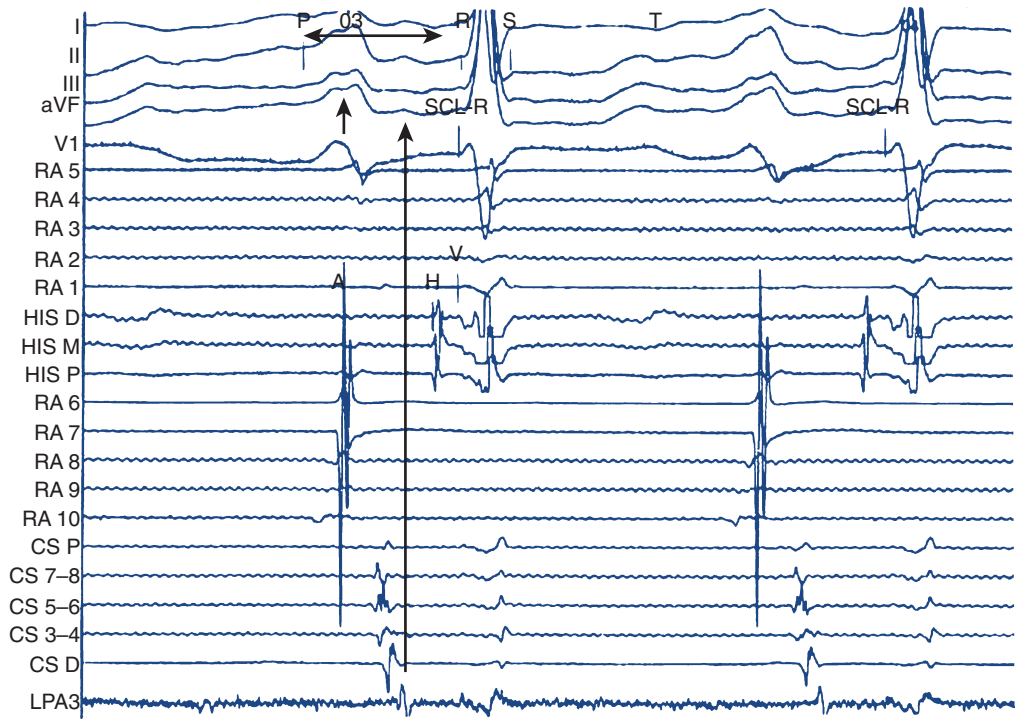


FIGURE 28-2 Genesis of an abnormally prolonged P wave is shown. Surface electrocardiographic leads I, II, III, aVF, and V1 are displayed with intracardiac channels. RA 1 to 5 recordings represent sequential electrograms from the superior to inferior right atrial free wall, RA 6 to 10 are sequential recordings from superior to inferior inter-atrial septum. *CSP to CSD* represents sequential recordings from the proximal to distal coronary sinus, and *LPA* are indirect epicardial recordings from the superior left atrium. This recording in a patient with persistent atrial fibrillation demonstrates prolonged inter-atrial conduction time from the high right atrium to the CSD and LPA recordings in the left atrium, resulting in a prolonged P-wave duration of 220 ms. *CS*, Coronary sinus electrogram; *CSD*, distal coronary sinus; *CSP*, proximal coronary sinus; *H*, His bundle; *HIS*, His bundle electrogram; *LPA*, left pulmonary artery; *RA*, right atrium; *SCL*, R-RR interval; *V*, ventricle.

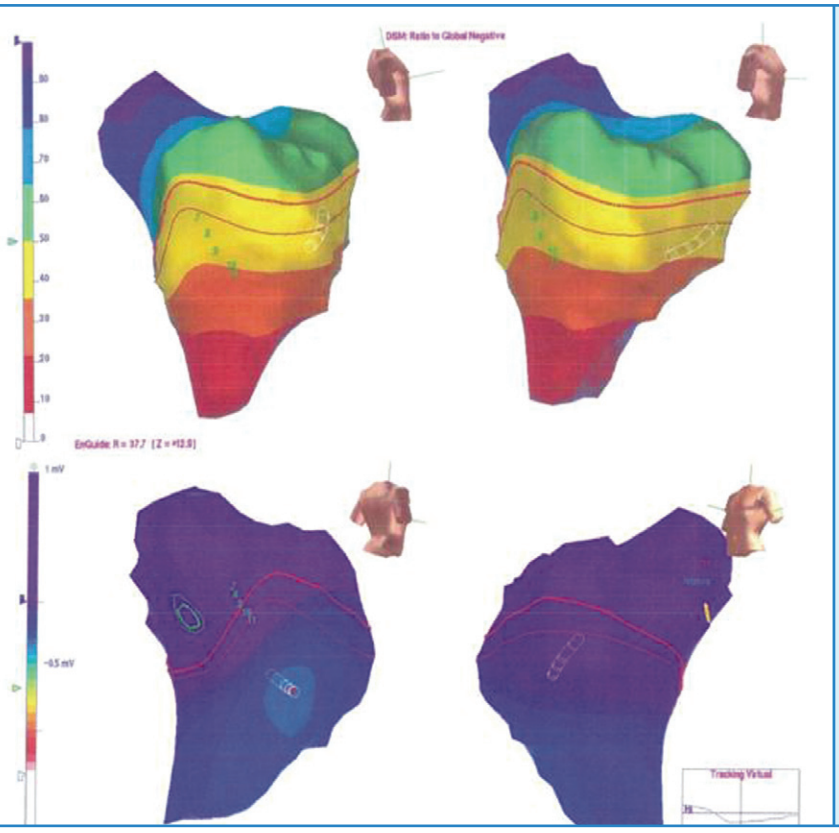


FIGURE 28-3 Illustrations of activation and voltage maps to characterize the atrial substrate and its functionality. Isochronal maps (*top*) show activation wavefront propagation in the right atrium with corresponding voltage maps of the right atrium (*bottom*).

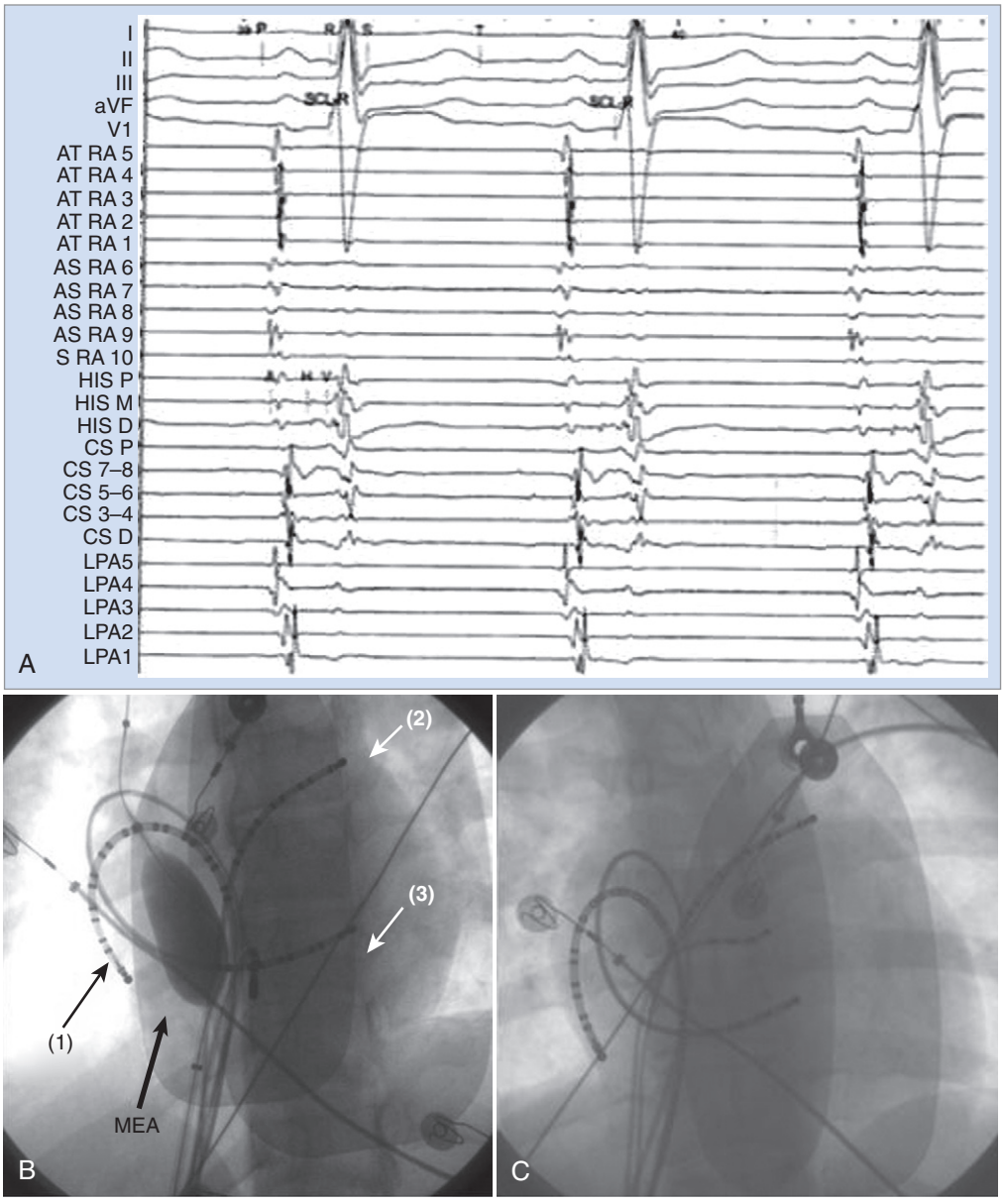


FIGURE 28-4 Bi-atrial catheter mapping recordings (**A**) with electrode catheter placement shown fluoroscopically in the left anterior oblique projection. Labels show individual electrode duo-decapolar catheter placement for right atrial recordings (**B**). **C,** Decapolar catheter placement for left atrial recordings from the left pulmonary artery. *MEA*, Multi-electrode balloon array for noncontact mapping with dye-filled balloon.

different configurations (10 or 20 electrode poles) and variable spacing (8 mm, 2-6-2 mm) and curve diameters (see Figure 28-5, *D*). It allows circular mapping at the PV ostia, which can have varying anatomic configurations, and within the veins for segmental mapping. The Pathfinder catheter permits placement well inside the vein and its branches. Because ablation within the PV is being undertaken with decreasing frequency, this is most useful in careful assessment of gaps in isolation lines. Activation within the veins during sinus rhythm, paced atrial stimuli, and spontaneous premature atrial beats can be recorded and localized. Figure 28-6 shows recordings during atrial pacing in a patient with persistent AF. The ablation catheter records a delayed potential within the left superior PV, and a spontaneous atrial premature beat originates from this site with electrogram sequence reversal confirming the PV potential (PVP) as the second component of the local electrogram.

A multi-electrode basket catheter has been designed for global right atrial and left atrial mapping.[16] Recently, the use of the High Density Mesh Mapper–Ablator catheter (Bard Electrophysiology, Lowell, MA) was described.[17] It allows multiple simultaneous recordings along vertical splines in a circumferential array when the basket or mesh catheter is opened to achieve contact with the endocardium in the atrium of interest (Figure 28-7). A computer contour of atrial activation is developed on the basis of electrogram timing. Severe atrial dilation or anatomic abnormalities may impede complete recording sequences. One prospective study of PV isolation in patients with AF who have this device demonstrated that the method was safe and yielded good primary

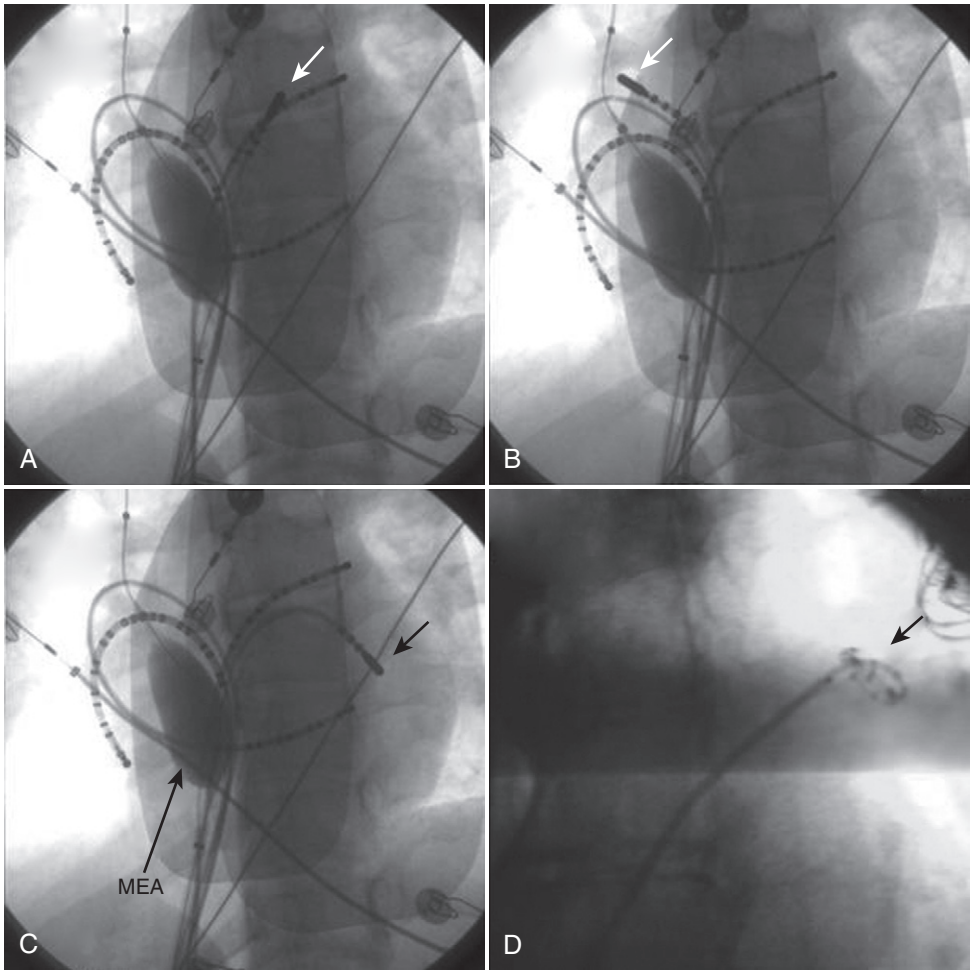


FIGURE 28-5 Fluoroscopic views of mapping procedure for individual pulmonary veins with ablation catheter tip electrode shown at tip of *arrow*. **A,** Left superior pulmonary vein. **B,** Right superior pulmonary vein. **C,** Left inferior pulmonary vein. **D,** Lasso catheter with circular electrode array being delivered to the ostium of the left superior pulmonary vein. *MEA,* Multi-electrode balloon array.

success rates and a favorable clinical outcome at 6 months.[17] A more recent report showed a substantially higher AF recurrence rate at 18 months.[18]

Pacing Techniques During Electrophysiological Evaluation

Programmed atrial stimulation, which is used to assess electrophysiological properties, performs provocative testing in the patient with AF. Incremental pacing and the introduction of programmed single or multiple extrastimuli are used to:

1. Characterize the physiological properties of the sinus node, AV conduction system, atria, and ventricles.
2. Induce AF, atrial flutter, or AT and permit analyses of the mechanisms of AF in a given patient.
3. Evaluate the effects of drugs and electrical interventions on the function of the AV conduction system, the atrium, and the ventricle and determine the efficacy of these drugs in the treatment of AF.

One standard programmed stimulation protocol based on prior studies conducted by our group is to use one to three atrial extrastimuli using two drive trains.[15] At a minimum, two stimulation sites, that is, the high RA and the coronary sinus ostium, are used. Additional stimulation sites can include the distal coronary sinus, the LA, or PVs. The definition used for inducible sustained AF is a tachyarrhythmia longer than 30 seconds. The sensitivity for induction of AF with this protocol was 89% and the specificity was 92% (Figure 28-8).

Figure 28-9, *A*, shows a typical programmed electrical stimulation protocol in a patient with AF. Note the induction of right atrial flutter with a clockwise activation pattern and a cycle length of 240 ms. Induction of organized tachyarrhythmias in patients with AF should alert the operator to the existence of such tachycardias in the initiation or maintenance of AF in that patient. Often, more than one such tachyarrhythmia will be elicited, especially in patients with persistent AF. Spontaneous AF episodes can also be recorded and the evolution of AF examined (see Figure 28-9, *B*). Note the conversion of an organized tachyarrhythmia seen as coarse AF on the ECG in this patient to a more complex arrhythmia with the evolution of fine AF and the appearance of

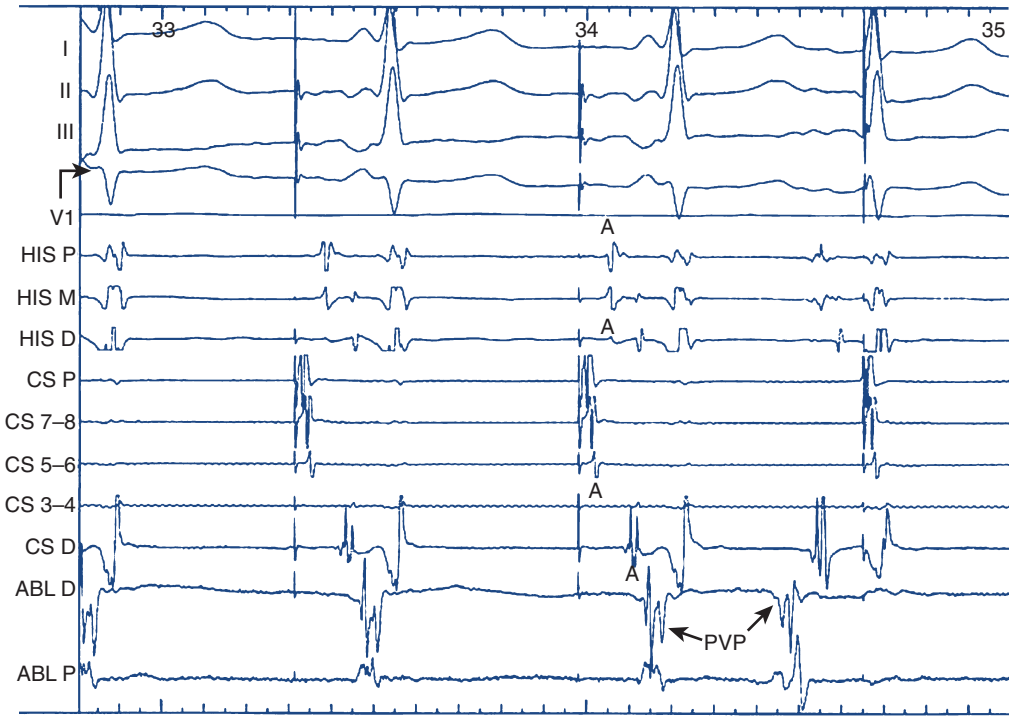


FIGURE 28-6 Pulmonary vein potential shown by arrow during atrial pacing as a second deflection after atrial electrogram and as trigger of atrial premature beat preceding the surface P wave and atrial electrograms in the coronary sinus and bundle of His regions. See legend to Figure 28-1 for abbreviations.

fragmented electrical activity, initially in the coronary sinus electrograms and later in the septal electrograms. This continuous fractionated electrical activity is often referred to as *complex fractionated atrial electrogram* (CFAE) mapping and is used as a target for substrate ablation. In addition, pacing can be performed in specific atrial regions to assess conduction across anatomic obstacles (e.g., the cavo-tricuspid isthmus). Rapid atrial pacing can be used for entrainment and termination of organized tachycardias (discussed in more detail elsewhere in this text). Burst pacing is often unsuccessful in the termination of rapid tachycardias (see Figure 28-9, *C*). Giorgberidze et al reported modest success with high-frequency atrial pacing during organized tachycardias seen in patients with AF.[19] Pacing within and immediately outside PVs can be performed for entrance and exit block before and after an intervention (see Figure 28-9, *D*).

Interventions During Electrophysiological Studies in Atrial Fibrillation

A variety of interventions can be used during electrophysiological studies in patients with AF. Most commonly, these are used to initiate spontaneous AF or to terminate an arrhythmia event. Spontaneous AF events may fail to occur during EPS. Isoproterenol is commonly used to elicit such events by increasing trigger activity, particularly from PVs. Isoproterenol has been used at moderate to high doses (4 to 15 μg/min) to initiate spontaneous AF. Consideration of concomitant comorbid conditions such as ischemia or heart failure should guide its use. Hemodynamic monitoring is desirable in this instance. Rare instances of adenosine or vagomimetic drugs to induce AF have been reported. Adenosine, methacholine, and even alcohol infusions have been used to elicit AF in the laboratory. Alternatively, the authors have found that cardioversion of sustained AF can allow emergence of spontaneous atrial premature beats (APBs) and AF events after cardioversion. Figure 28-10 shows early recurrence of triggering APBs with short salvoes of AT, followed by spontaneous onset of an AF episode. The onset tachycardia is a type 1 counterclockwise atrial flutter, which rapidly induces a left atrial tachyarrhythmia from the superior LA, probably arising in PVs. Early recurrences of AF have, in our experience, been similar to spontaneous AF events in origin and propagation.

Choice of Mapping Techniques

Until now, catheter mapping of human AF has been limited to electrogram recordings in specific regions of interest (e.g., PVs), and regional mapping has been limited to intraoperative studies.[20] Several techniques have been reported for the regional catheter mapping of discrete focal sources of AF in specific atrial regions.[21] For example, a Lasso catheter can be used for the focal mapping of PVs, where rapidly firing foci play an important role in the initiation and maintenance of AF.[3] However, a major limitation of the regional catheter method has been infrequent and sporadic recordings of spontaneous AF, necessitating repetitious stable rhythms.

In an effort to overcome such limitations, several elegant, high-resolution catheter mapping systems have been developed, allowing three-dimensional anatomic assessment coupled with electrophysiological recordings to create an accurate picture of the heart's electrical sequence (Figures 28-11 and 28-12). The CARTO mapping system (Biosense Webster) uses ultra-low

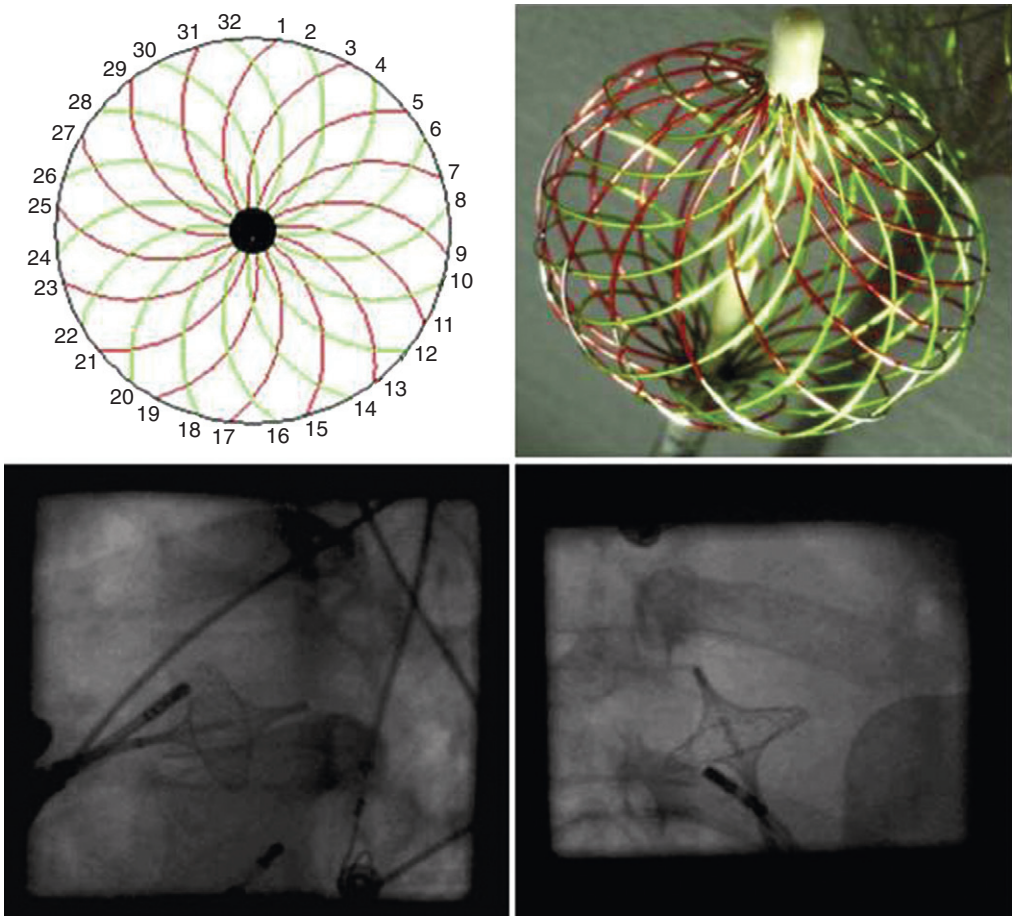


FIGURE 28-7 Multi-electrode catheter for recording and mapping (Mesh Mapper–Ablator, Bard Electrophysiology). The *upper panels* show electrode array (*top left*), fully expanded to allow contact with the atrial endocardium (*top right*). The *lower panels* show fluoroscopic images (*lower left,* right anterior oblique view; *lower right,* left anterior oblique view) with the catheter array deployed in the left atrium and expanded fully to make circular contact with the atrial wall. *(From Meissner A, van Bracht M, Schrage MO, et al: Segmental pulmonary vein isolation in atrial fibrillation: New insights from the high density mesh mapper technique in an electrophysiologically guided approach,* J Interv Cardiol Electrophysiol *25[3]:183–192, 2009.)*

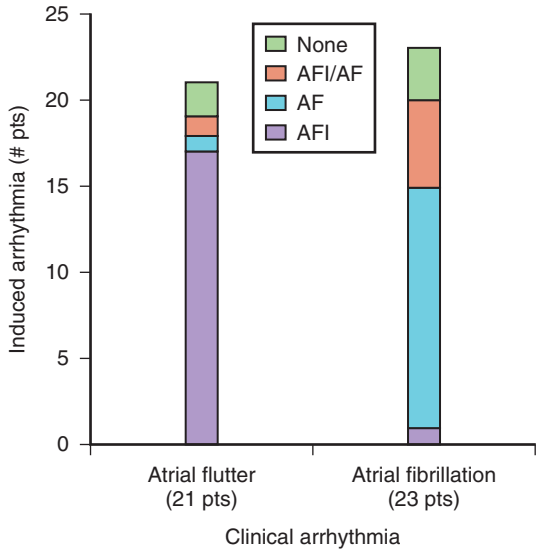


FIGURE 28-8 Comparison of spontaneous and induced atrial fibrillation (*AF*) in patients (*pts*) with a standardized programmed stimulation protocol using up to three extrastimuli from two atrial stimulation sites in patients with spontaneous atrial flutter (*AFl*) (*left*) and spontaneous atrial fibrillation (*right*). Note that there is a high sensitivity for induction of the spontaneous arrhythmia in both patient groups. However, additional arrhythmias that had not been previously recorded spontaneously can be induced. *(Modified from Krol RB, Saksena S, Prakash A, et al: Prospective clinical evaluation of a programmed atrial stimulation protocol for induction of sustained atrial fibrillation and flutter,* J Interv Cardiol Electrophysiol *3:19–25, 1999.)*

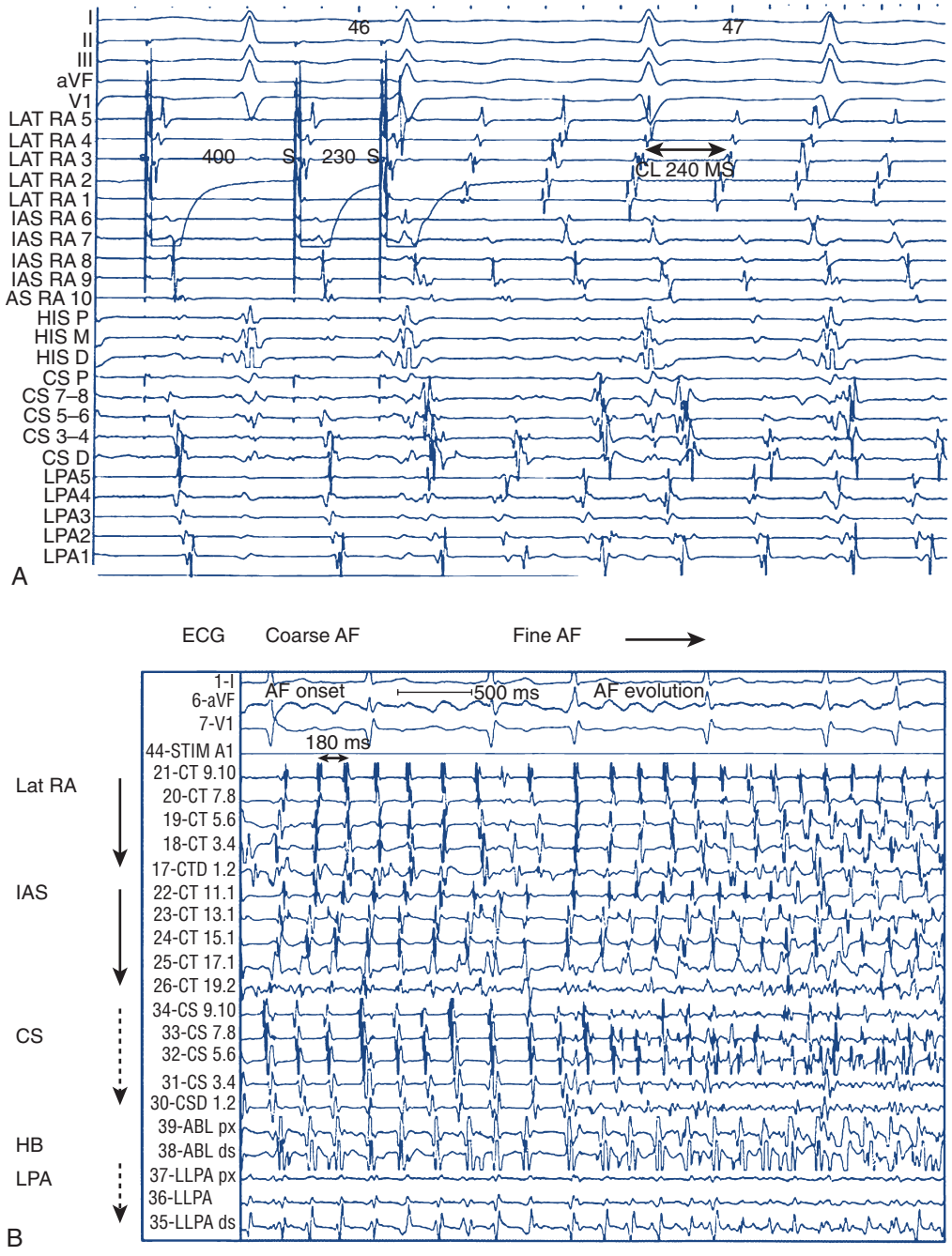


FIGURE 28-9 A, Induction of typical atrial flutter at electrophysiological study with single atrial extrastimulus in a patient with atrial fibrillation (*AF*). **B,** Transition from onset of coarse AF with an isoelectric period to fine sustained AF on the electrocardiogram. Note the organized atrial tachyarrhythmia on the left and the subsequent appearance of fibrillatory activity in the intracardiac recordings. (***B,*** *From Saksena S, Skadsberg ND, Rao HB, Filipecki A: Biatrial and three-dimensional mapping of spontaneous atrial arrhythmias in patients with refractory atrial fibrillation,* J Cardiovasc Electrophysiol *16[5]:494–504, 2005.)*

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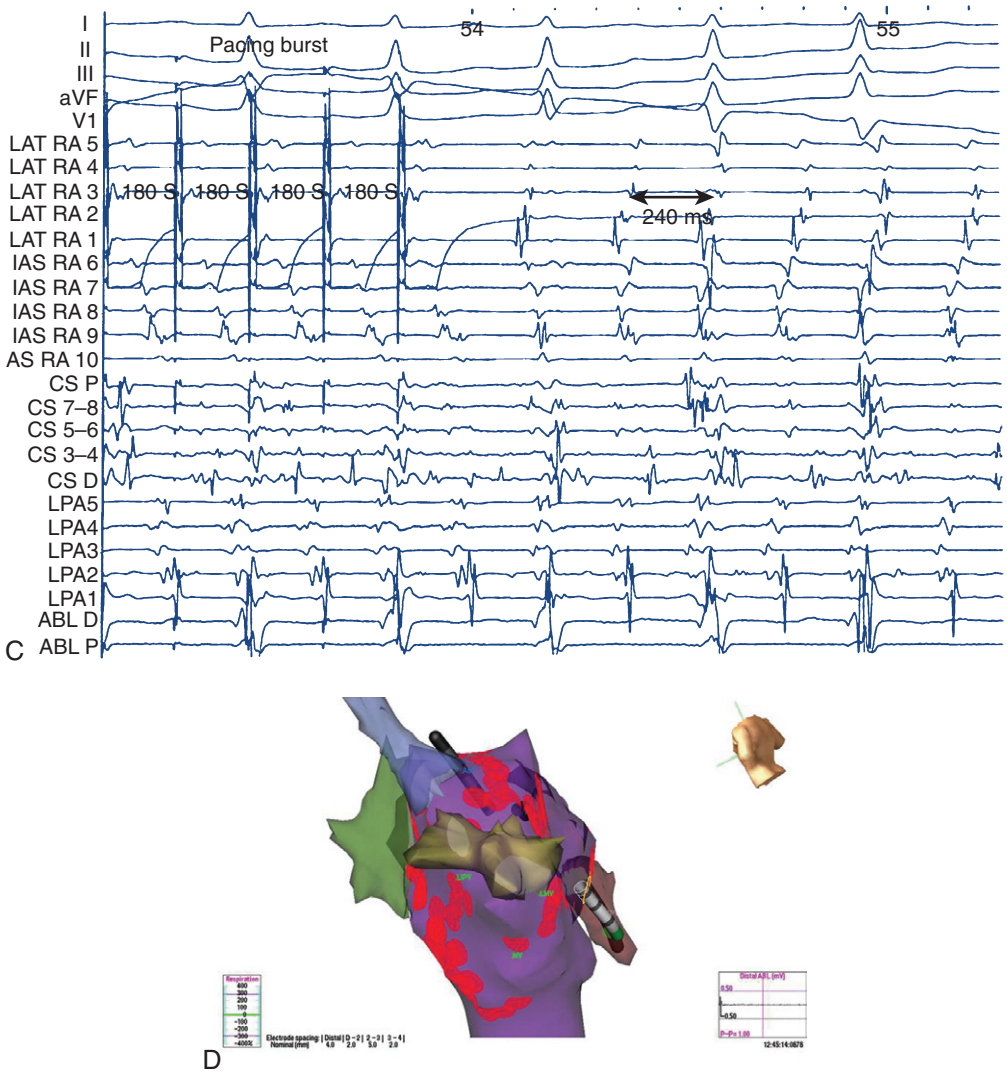

FIGURE 28-9, cont'd C, Failure of rapid atrial pacing during AF despite evidence of resetting and possible entrainment of right atrial tachyarrhythmia but failure to interrupt AF because of inability to terminate right atrial tachyarrhythmia and pacing had no effect on left atrial tachyarrhythmia. **D,** Three-dimensional map of the left atrium using the Nav-X system (left posterolateral view; St. Jude Medical) with electrode catheter placement in the right inferior pulmonary vein after pulmonary vein antral isolation. Note that the pulmonary vein antra are encircled with ablation lesions. The catheter is advanced into the right inferior pulmonary vein with gradual disappearance of electrogram recordings seen on the display from the distal electrode, demonstrating complete vein isolation (*arrow*). See Figure 28-1 for abbreviations.

magnetic field technology to reconstruct three-dimensional maps and activation sequences. The Nav-X system (St. Jude Medical, St Paul, MN) uses similar principles to create static anatomic maps. The EnSite system (St Jude Medical) uses a multi-electrode mapping balloon catheter to create maps and define the location of the mapping and ablation catheter. The detailed function of these systems is discussed in Chapter 92. All these systems represent a paradigm shift in the way that AF can be mapped and AF ablations are performed. Recent tools allow integration of real-time catheter-based mapping with imported scans from magnetic resonance imaging (MRI) or computed tomography (CT).[22] Coupled with the identification of CFAEs, such mapping systems facilitate ablation procedures in patients with persistent or permanent AF.

Bi-atrial Contact and Noncontact Mapping Techniques

Recently, our group has integrated simultaneous bi-atrial catheter mapping with high-resolution, three-dimensional noncontact mapping to provide a rapid and reliable method to map both induced and spontaneous AF.[5,23,24] The major advance with this technique is to permit beat-to-beat simultaneous bi-atrial mapping that greatly shortens the mapping procedure. Triggers and tachycardias can be mapped in single cardiac cycles. In brief, four to six multi-polar electrode catheters are placed in the RA at the lateral RA, the bundle of His, the inter-atrial septum, the coronary sinus, the LA (via a patent foramen ovale), or the left pulmonary artery (under local anesthesia). When ablation is planned, a transseptal puncture may be substituted for indirect recordings from a pulmonary artery. An endocardial balloon electrode (EnSite) can

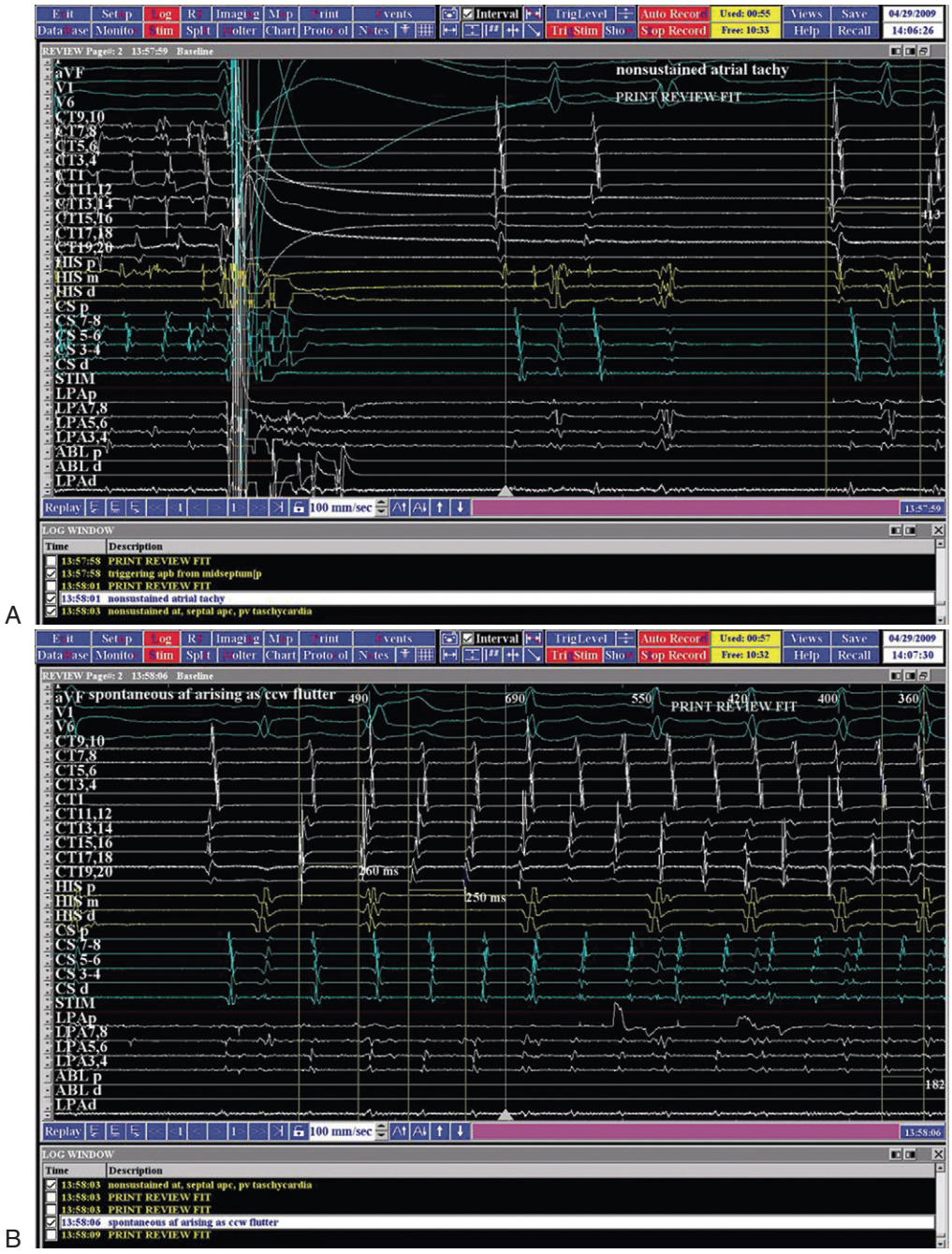

FIGURE 28-10 Bi-atrial contact catheter electrode mapping in a patient with persistent atrial fibrillation (AF). **A,** Sustained AF is seen on the left of the recording, which is terminated by a cardioversion shock (*yellow*). Sinus rhythm with frequent spontaneous atrial premature beats (APBs) is restored. The site of APB origin (*white arrowheads*) is reproducible. **B,** This recording shows onset of spontaneous AF in the same patient with an organized type 1 counterclockwise right atrial flutter followed by the onset of a superior left atrial tachycardia, probably arising from pulmonary veins.

be introduced into the atrium of interest (see Figures 28-4 and 28-5, *C*). On occasion, the balloon can be placed in the LA and later relocated to the RA for bi-atrial high-resolution mapping (see Figure 28-10). Three-dimensional mapping of AF in the RA or LA is then combined with the contact catheter map.

A three-dimensional contour in the RA or LA can be developed with the array and is comparable with the chamber contours seen with electroanatomic systems (see Figure 28-11). On occasion, the two contours can be integrated (see Figure 28-12). The electrode catheter recordings and locations can be anatomically located on the contour. We use identifiable landmarks in the lateral RA, such as the orifices of the great veins, the entire ring of the tricuspid annulus, the coronary sinus ostium, the tricuspid valve–IVC isthmus sites, the lateral RA from superior to inferior locations, and the inter-atrial septum at multiple sites along a cranio-caudal axis.

Beat-to-beat mapping is feasible. Figure 28-13, *A,* shows a static image with combined contact electrode locations on the

three-dimensional contour. Figure 28-13, *B*, shows simultaneous display of contact electrograms and virtual recordings from the balloon array. The activation wavefront can be seen in multiple frames in a single cycle; also, the isochrones map of this cycle is seen in the lower left corner. This can also be viewed online as a continuous loop (see Videos 28-11 and 28-12). This integrated display is now ready for the acquisition and analysis of different rhythms. Sinus rhythm propagation, extrastimulus behavior, and induced or spontaneous arrhythmia initiation can be studied with these recordings. Beat-to-beat imaging and analysis are feasible in real time. During sustained tachyarrhythmias, whether induced or spontaneous, arrhythmia circuits can be correlated with their anatomic locations. For example, Video 28-11 shows a noncontact map of the RA at the onset of a spontaneous AF event, starting as an organized type 1 counterclockwise right atrial flutter that is succeeded by a left atrial tachyarrhythmia with bystander right atrial activation on the noncontact map. AF or other associated tachyarrhythmias may occur spontaneously during the study. Alternatively, they may have to be induced for analysis. Induced AF may differ in some features from spontaneous AF or may evolve into patterns similar to spontaneous AF.

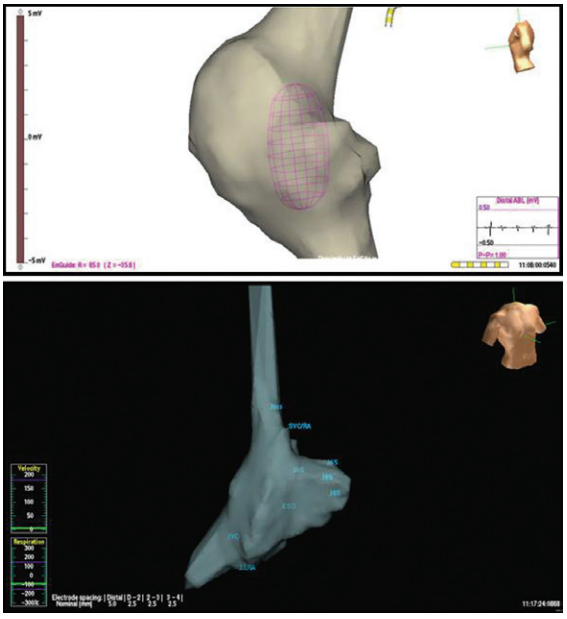

FIGURE 28-11 Right atrial contour maps developed using the magnetic navigation method with the Nav-X system (*lower panel;* St. Jude Medical) and the virtual contour using the noncontact mapping approach with EnSite balloon array (*top panel;* St. Jude Medical). Note the similarity of anatomic structural details with display of electrograms from the catheter electrode tip with both systems. In addition, the balloon array permits global atrial activation recordings on a beat-to-beat basis (see Figure 28-13).

Clinical Electrophysiological Findings in Atrial Fibrillation

Normal Atrial Electrophysiology

Intra-atrial conduction in the RA is determined from the P-A interval, is commonly found between the middle and distal coronary sinus leads, and should not exceed 130 ms. The routes of inter-atrial conduction are complex and have been studied by using detailed atrial mapping with noncontact and contact approaches. Rossi noted that the atrial septum was contributed to by both RA and LA fiber bundles, which wrapped along the coronary sinus.[25] Physiological studies have suggested that inter-atrial conduction occurs over Bachmann's bundle in the inter-atrial groove. It was also noted that ostial coronary sinus stimulation propagated along the mitral valve ring first before the rest of the LA was activated, suggesting an inferior inter-atrial connection.[26] Lemery and colleagues performed right atrial and left atrial noncontact mapping during sinus rhythm and atrial pacing and demonstrated inter-atrial conduction over two distinct regions via Bachmann's bundle and the coronary sinus.[27] Regional atrial conduction shows splitting of wavefronts along the crista terminalis anteriorly and posteriorly and preferential

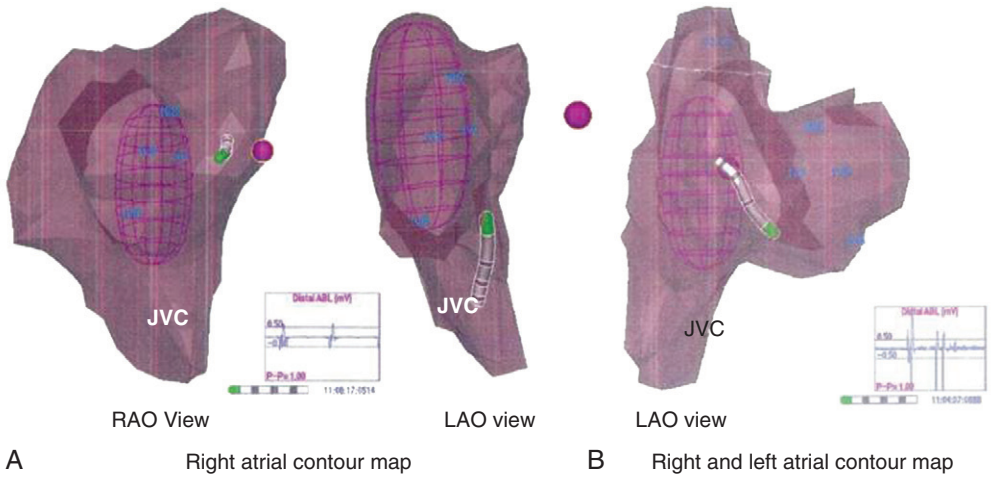

FIGURE 28-12 A, Noncontact mapping showing the three-dimensional contour of the right atrium. **B,** Noncontact mapping with three-dimensional contour of the right and left atria. The left atrium is seen posterior to the right atrium. *RAO*, Right anterior oblique projection; *LAO*, left anterior oblique projection.

propagation along the superior and inferior LA. Left atrial activation may be indirectly recorded as a far-field signal in the PV.

Atrial Electrophysiology in Disease States

Observed abnormalities of diseased human atria in experimental studies include elevation of the resting membrane potential, depression of the maximal amplitude of the potential, and decreased upstroke velocity of the action potential. Such abnormalities have been related to a patient's history of atrial tachyarrhythmia and the presence of a dilated atrium.[28,29] In patients with sick sinus syndrome and lone AF or a history of primary atrial tachyarrhythmia, inter-atrial and intra-atrial conduction times were found to be increased.[30,31] Furthermore, induction of atrial tachyarrhythmias by atrial extrastimulation was highly correlated with increases in the inter-atrial or intra-atrial conduction times. Three-dimensional noncontact mapping can show slowly propagating atrial activation in the diseased atrial substrate, with low-voltage electrograms, fragmentation and split potentials, and areas of conduction block (see Figure 28-3). These can be more obvious during spontaneous or induced AF. Bi-atrial reductions in electrogram voltage during three-dimensional mapping of patients with lone AF have been documented.[32] Regional variability in alterations in conduction velocity and regional changes in atrial refractoriness were noted. In 20 patients undergoing bi-atrial high-density contact mapping, spectral analysis demonstrated greater fractionation and higher dominant frequencies in patients with persistent AF and in the LA during AF compared with patients with paroxysmal AF.[33]

Regional Atrial Electrophysiology

Animal models and studies in humans have demonstrated the important role atrial fibrosis plays in the development and maintenance of AF.[34,35] Marcus et al reported significant regional variability in left atrial voltage as assessed by electroanatomic mapping in patients with atrial arrhythmias and in patients with AF who exhibited significantly more low-voltage areas in the septum and posterior walls.[36] Although voltage is only a potential surrogate for fibrosis, these findings align with a histologic study in patients with AF and mitral valve disease in whom a disproportionate amount of fibrosis was located in the septum and posterior wall of the LA.[37] Additionally, the investigators found that left atrial electrogram amplitude decreased with age. Aging was found to be associated with regional conduction slowing, anatomically determined conduction delay at the crista, and structural changes that include areas of low voltage in the RA.[38] This electrical and structural remodeling may explain the increased propensity to AF with aging. In patients with symptomatic congestive heart failure (CHF), electroanatomic maps demonstrated lower mean voltage and greater heterogeneity in voltage compared with those in 21 controls undergoing radiofrequency (RF) ablation for AV nodal re-entrant tachycardia.[39] Electroanatomic and conventional mapping techniques provided evidence of significantly impaired atrial conduction throughout the RA as well as anatomically determined functional conduction delay at the crista and indirect evidence of conduction slowing across the LA and Bachmann's bundle. Fractionated electrograms in the atrial substrate are now being targeted for ablation, particularly in patients with persistent AF.[35] Figure 28-9, *B*, shows the appearance of fractionation in coronary sinus electrograms, low septal electrograms, ablation electrograms, and posterosuperior left atrial recordings. The mechanism of these electrograms remains under investigation.

Pulmonary Vein Electrophysiology

PVs play an important role both in the onset and in the maintenance of AF. Early observations by Haïssaguerre et al demonstrated that AF initiation is often caused by focal electrical discharges predominantly located within PVs.[3] PV electrograms can be mapped as described earlier. All four veins are mapped, and electrical activity resulting in premature beats or an atrial

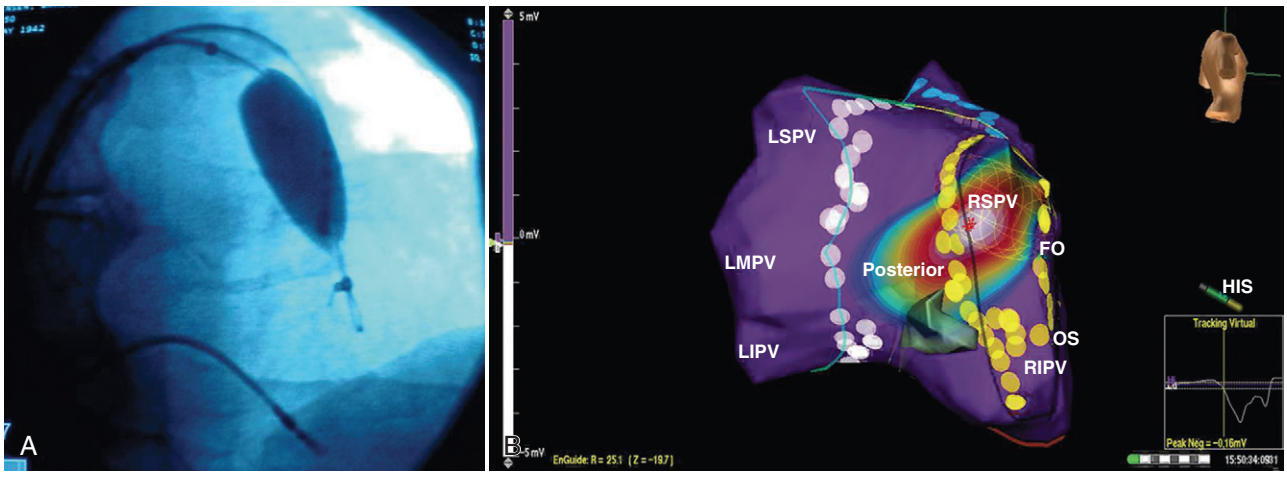

FIGURE 28-13 A, Fluoroscopic image of the EnSite balloon (St. Jude Medical) array placement in the left atrium in the anteroposterior projection. Note that the balloon is stabilized with the distal pigtail loop in the mitral valve. A double trans-septal approach is needed to place the ablation catheter seen posterior to the balloon electrode. **B,** Atrial premature beat arising from the right superior pulmonary vein (*RSPV*) and emerging into the left atrium; the propagation can be tracked on the noncontact map of the left atrium. *LSPV,* Left superior pulmonary vein; *LMPV,* left mid pulmonary vein; *LIPV,* left inferior pulmonary vein; *FO,* foramen ovale.

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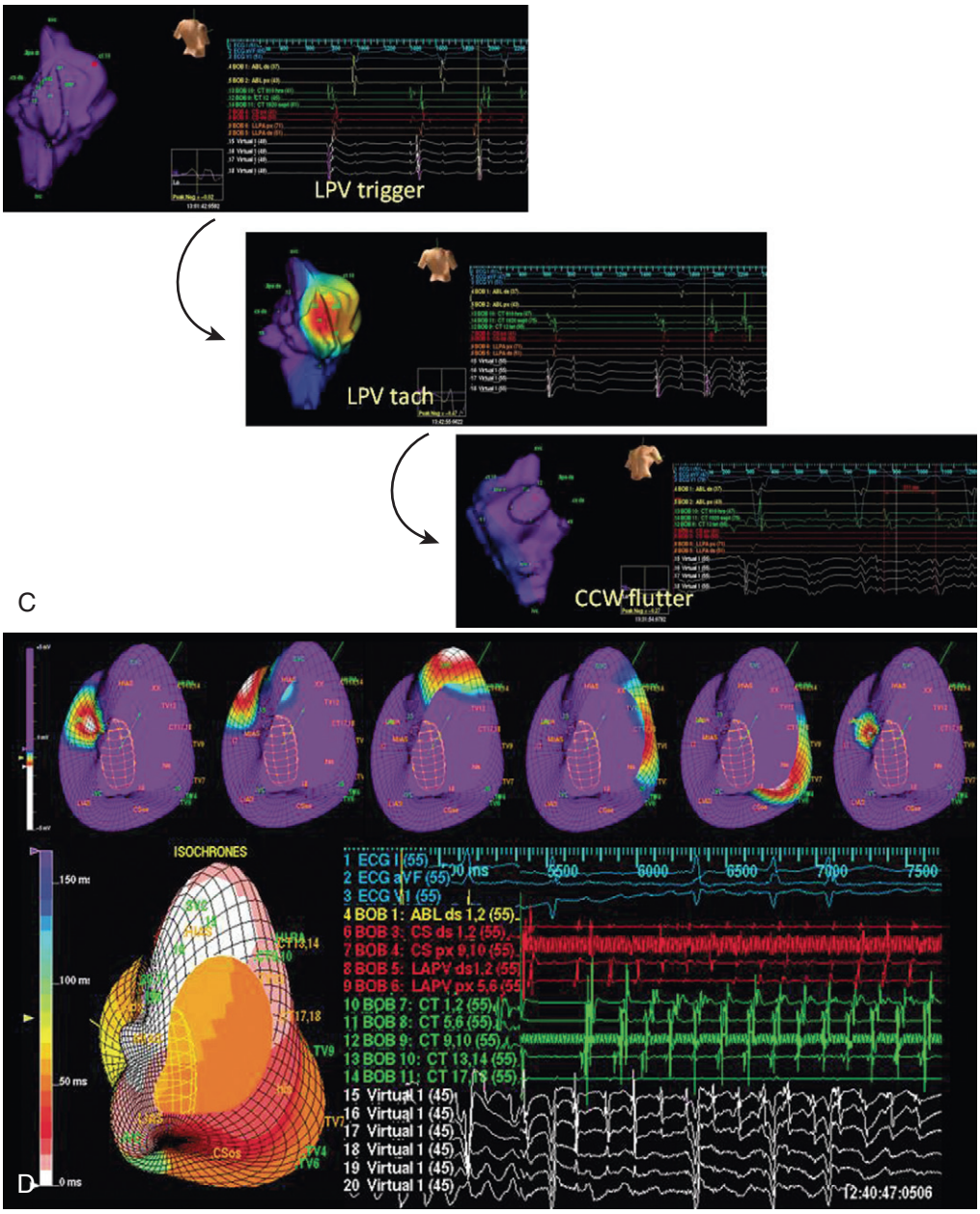

FIGURE 28-13, cont'd C, Right atrial noncontact mapping and bi-atrial catheter mapping of the two atria. Spontaneous atrial flutter in the right atrium is seen on the intracardiac recordings despite surface electrocardiographic recording of atrial fibrillation (AF). The noncontact map confirms the circulating right atrial wavefront frame by frame demonstrating a macro–re-entrant pathway (*top panel*). The lower left isochronal map shows the complete activation cycle. The bi-atrial catheter map shows the organized tachycardia in this patient with established persistent AF. **D,** Bi-atrial noncontact mapping of a spontaneous AF episode on a beat-to-beat sequence showing a triggering atrial premature beat from the superior left atrium (*top recording*) initiating a left atrial tachycardia arising in the superior left atrium in the vicinity of the pulmonary veins with breakthrough into the bystander right atrium (*middle recording*). This is followed by a counterclockwise right atrial flutter, which is tracked through the entire macro–re-entrant pathway on the noncontact map. (***D*** *Modified from Saksena S, Skadsberg ND, Rao HB, Filipecki A: Biatrial and three-dimensional mapping of spontaneous atrial arrhythmias in patients with refractory atrial fibrillation*, J Cardiovasc Electrophysiol *16[5]:494–504, 2005.)*

tachycardia can occur spontaneously or be induced by electrical stimulation or pharmacologic agents or even cardioversion shocks. In patients with AF, pulmonary venous effective refractory periods (ERPs) were significantly shorter than left atrial ERPs and significantly shorter than the PV ERPs of patients without AF.[40] The PV potential functional refractory periods (FRPs) of patients with AF were also significantly shorter than those of controls, whereas the FRPs of the PV-LA junction and the left atrial ERPs were comparable, demonstrating that the main difference between patients with AF and those without AF is observed in PVs rather than at the junction with the LA or in the LA itself. In association with the more pronounced decremental conduction times in PVs, these short ERPs and FRPs provide a very favorable milieu for arrhythmogenicity, particularly re-entry in or

around the veins, which may perpetuate arrhythmia and thus act as a substrate for AF maintenance.

Similar electrophysiological properties of PVs and atria have been reported when exposed to short-term AF induced by rapid atrial burst pacing, which suggests electrical remodeling as a potential mechanism.[41] However, as the disease progresses from paroxysmal AF to permanent, long-term AF, other processes occur in the atria leading to contractile and structural remodeling.[42]

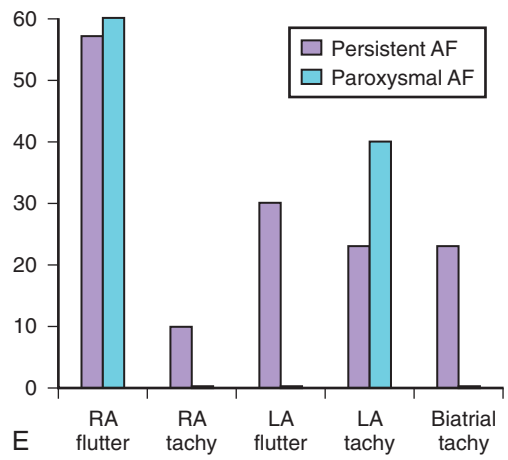

FIGURE 28-13, cont'd E, Spontaneous atrial tachyarrhythmias recorded with bi-atrial noncontact mapping in spontaneous paroxysmal and persistent AF events during electrophysiological procedures. Note the bi-atrial distribution of atrial tachycardias in both conditions, but a wider spectrum of atrial tachycardias is seen in persistent AF. *RA,* Right atrium; *LA,* left atrium; *tachy,* tachycardia. (***E,*** *Modified from Saksena S, Skadsberg ND, Rao HB, Filipecki A: Biatrial and three-dimensional mapping of spontaneous atrial arrhythmias in patients with refractory atrial fibrillation*, J Cardiovasc Electrophysiol *16[5]:494–504, 2005.)*

Insights into Atrial Fibrillation Mechanisms from Bi-atrial and Three-Dimensional Mapping

Studies we have conducted in patients with paroxysmal and persistent AF with combined contact bi-atrial and noncontact three-dimensional mapping have allowed analysis of the regional origin of APBs and atrial tachyarrhythmias during spontaneous AF. Evolution into sustained AF and its maintenance have been examined. APBs are most often multi-focal and often bi-atrial in origin in both paroxysmal and persistent AF. One or more APBs can trigger spontaneous AF events in a given patient (Figure 28-14). APBs triggering spontaneous AF demonstrate a wider distribution of origin in persistent AF, with the highest frequency arising from the superior LA and the septum. The onset AT may commence at a location distant from the APB origin (e.g., type 1 flutter) or in proximity to the trigger (e.g., PV trigger initiating re-entrant tachycardia in the posterior left atrium) (see Figure 28-14). Organized atrial tachyarrhythmias are seen in both paroxysmal and persistent AF. At least two atrial tachyarrhythmias, most commonly PV tachycardia and common right atrial flutter, are seen in paroxysmal AF (see Figure 28-14; Videos 28-11 and 28-12), A wider spectrum of atrial tachyarrhythmias can be seen, particularly in persistent AF. This includes focal PV tachycardia; left atrial flutter with macro–re-entry, including mitral isthmus flutter; type 1 isthmus-dependent or type 2 non–isthmus-dependent right atrial flutter; and upper or lower loop flutter of focal AT (see Figure 28-14). Organized atrial tachyarrhythmia distribution in persistent AF (right or left atrial flutter) or tachycardia has demonstrated a wider bi-atrial origin compared with paroxysmal AF. Further, mitral

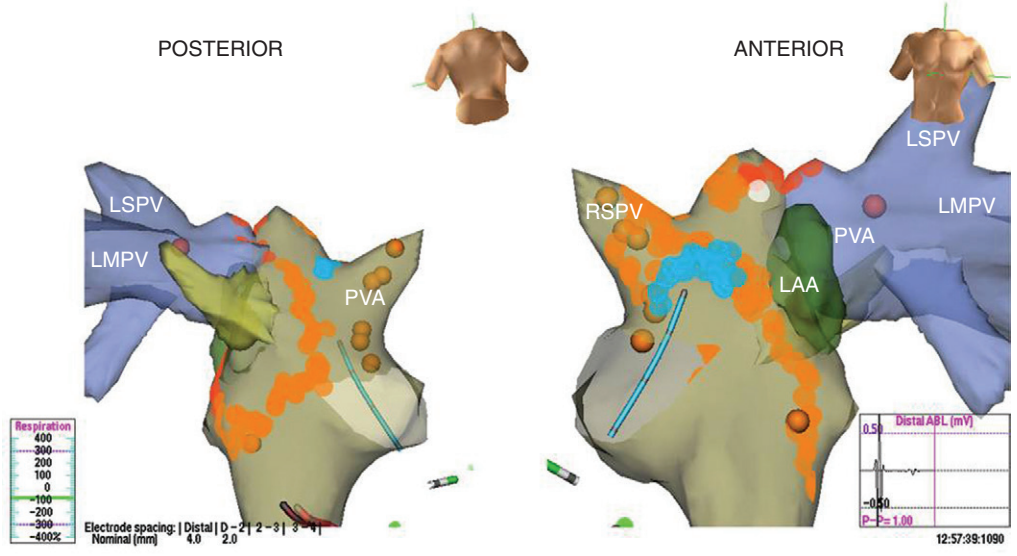

FIGURE 28-14 Three-dimensional map of the left atrium and pulmonary veins showing anatomic variants with a very large left pulmonary antrum with superior, middle, and inferior veins and secondary branches. Wide area circumferential ablation lesions are shown as circular markers. Left atrial compartmentalization is in progress, with isolation of the antral regions and roof and mitral isthmus linear lesions. *LAA*, Left atrial appendage; *LSPV*, left superior pulmonary vein; *LIPV*, left inferior pulmonary vein; *RSPV*, right superior pulmonary vein; *PVA*, pulmonary vein antrum.

isthmus–dependent left atrial flutter was more prevalent in patients with persistent AF, whereas isthmus-dependent or non–isthmus dependent right atrial flutter was comparable in prevalence in both types of AF. Therefore, AF progression is most likely related to the development of a bi-atrial substrate for the arrhythmia and proliferation of these atrial tachyarrhythmias that result in the persistence of an individual event. These findings bridge the divide between observations obtained with regional catheter recordings and intraoperative findings in humans.

Role of Electrophysiological Evaluation in Therapies for Atrial Fibrillation

Preablation and Ablation Lesion Mapping

Mapping is performed at electrophysiological evaluation in patients with AF to guide ablative therapies. PV triggers and tachycardia have been targeted by focal, segmental, and isolation procedures. Atrial tachyarrhythmias in either atrium are ablated with linear or focal lesions, and linear lesions are used to compartmentalize the atria. In addition to PV isolation and linear ablation of re-entrant tachycardias detected during electrophysiological testing, more recent mapping and ablation procedures for persistent AF incorporate the ablation of CFAEs as a substrate modification strategy in the catheter ablation of AF.[35,43] CFAE regions are targeted with the belief that atrial fractionated potentials indicate areas of nonuniform wavelet propagation and slowed conduction, thus being partly responsible for the perpetuation of AF. Despite early reports of excellent clinical outcomes associated with CFAE-guided left atrial ablation, the clinical outcomes of CFAE ablation have varied widely in other reports, with sinus rhythm maintenance rates ranging between 54% and 74%.[44,45] Investigation of the efficacy of CFAE as a stand-alone treatment under three-dimensional mapping system guidance in patients with persistent AF demonstrated that only 9% (2 of 23) of patients who received CFAE ablation were in sinus rhythm after a single ablation procedure without antiarrhythmic medication compared with 41% (22 of 54) of patients with CFAE plus PV isolation ablation procedures.[46] The CFAE region has been found to play an important role in the perpetuation of AF as demonstrated by a higher number of focal discharges, frequency of wave breaks and wave fusions, and slower conduction than in non-CFAE regions.[47] Several recent technical solutions have been used to allow automatic detection and characterization of CFAEs, ranging from virtual unipolar signals (EnSite) to the fast Fourier transformation (Bard Electrophysiology) of signals from the tip of the ablation catheter up to tiny electrodes on a specialized multi-polar catheter (PentaRay, Biosense Webster). Finally, ablation lesion location and contiguity can be indicated on contour maps (see Video 28-13 and Figures 28-14 and 28-15).

Postablation Mapping

Electrophysiological mapping is performed after catheter ablation to assess the adequacy of the ablation. Focal ablation of PV triggers is assessed by the elimination of PV potentials (see Figure 28-9, *D*), whereas isolation procedures require demonstration of entrance and exit blocks in the PV. Entrance block evaluation requires coronary sinus or atrial pacing with PV recordings. Exit block evaluation requires PV stimulation with left atrial recordings from the sites on the opposing aspect of the isolation lesions to demonstrate linear lesion integrity (see Videos 28-14 through 30-16 and Figure 28-16).

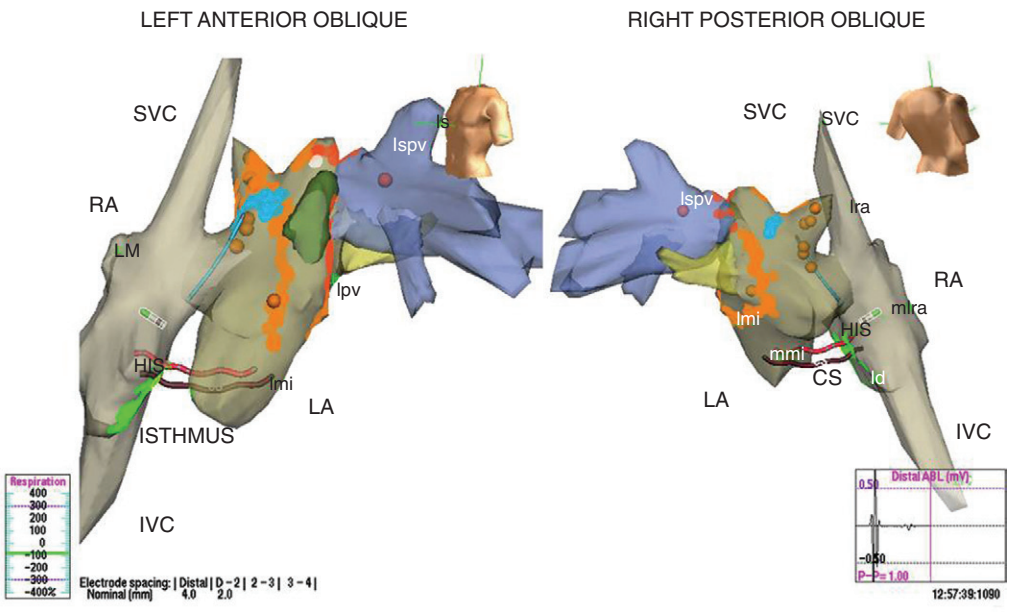

FIGURE 28-15 Three-dimensional map of the right and left atria and pulmonary veins showing venae cavae draining into the right atrium (*RA*) in addition to the features shown in Figure 28-14 in the same patient. A cavo-tricuspid isthmus linear ablation line is seen in the RA. The coronary sinus is marked by the electrode catheter shown in *red*. *LA*, Left atrium; *CS*, coronary sinus; *Isthmus*, cavo-tricuspid isthmus; *SVC*, superior vena cava; *lspv*, left superor pulmonary vein; *lpv*, left pulmonary vein; *RA*, right atrium; IVC, inferior vena cava.

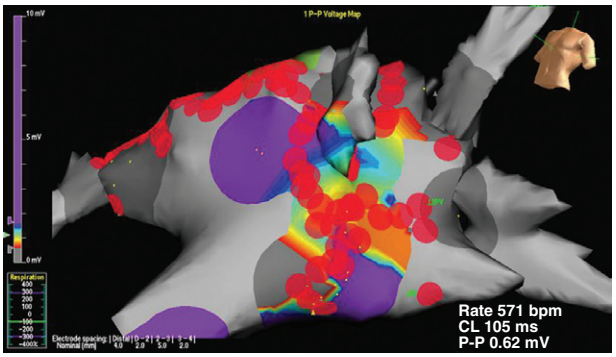

FIGURE 28-16 Three-dimensional map of the roof of the left atrium and pulmonary veins showing a voltage map after a linear roof ablation line has been created to compartmentalize the left atrium. The voltage map shows low electrogram voltage at the lesion site and relatively normal voltages on either side of the line. Gaps in the linear lesion can be identified by preserved tissue voltage and absence of activation delays on an activation map.

Electrophysiological Assessment of Interventions: Drugs, Pacing, and Cardioversion Therapy

Drug testing for antiarrhythmic drug efficacy is rarely performed at this time. The feasibility of drug testing in electrophysiological procedures, which use suppression of spontaneous or reproducibly induced AF as an endpoint, has been sporadically demonstrated but has not been widely used. Recent therapeutic focus has been directed at the interaction of pacing modes with arrhythmogenic mechanisms in AF. The effects of pacing can influence the electrical properties of the triggers and the substrate in AF. Acute testing at EPS can demonstrate the impact of these pacing methods. Overdrive atrial pacing can suppress triggers, and multiple-site atrial pacing can result in a reduction in conduction delay with P-wave abbreviation and in the dispersion of atrial refractoriness.[48,49] Single-site nonconventional permanent atrial stimulation (e.g., at Bachmann's bundle) can pre-excite the LA via preferential inter-atrial conduction and shorten the total atrial activation time.[50,51] Short-term studies have shown that multiple-site atrial pacing results in modification of the electrophysiological properties of the arrhythmogenic atrial substrate and has been shown to reduce AF induction at EPS.[52] Dual-site atrial pacing, in which the high RA and the coronary sinus ostium are used, pre-excites the LA via the posteroinferior atrial connections at this level. It has been shown echocardiographically to reduce P-wave duration by 20% to 30%, advance left atrial activation, and improve left ventricular filling.[53,54] Bi-atrial pacing using a left atrial pacing site in combination with standard right atrial pacing has effects similar to those of dual-site right atrial pacing.

The efficacy of internal cardioversion shocks and determination of atrial defibrillation thresholds have both been performed successfully during electrophysiological procedures. These are discussed in more detail in Chapter 90.

Conclusion

Electrophysiological evaluation of AF permits understanding of AF mechanisms and comorbidities, helps identify targets for interventions such as ablation, and provides the basis for developing a therapeutic strategy for the management of AF.

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CHAPTER 29

Electrophysiological Evaluation of Syncope

Hugh Calkins

Introduction

This chapter reviews the role of electrophysiology (EP) testing and tilt-table (TT) testing in the evaluation of patients with syncope. A broader view of the differential diagnosis of syncope and the overall diagnostic and therapeutic approaches to syncope are discussed in a separate chapter. This chapter focuses on the value and limitations of EP testing and TT testing when evaluating a patient with syncope.

Electrophysiology Testing

Indications

EP testing can provide important diagnostic information in patients presenting with syncope. The results of EP testing can be useful in establishing a diagnosis of sick sinus syndrome, carotid sinus hypersensitivity, heart block, supraventricular tachycardia (SVT), and ventricular tachycardia (VT). The indications for EP testing in the evaluation of patients with syncope are outlined in detail in the European Society of Cardiology (ESC) Guidelines on Management of Syncope (Table 29-1).[1] It is generally accepted that EP testing should be performed in patients when the initial evaluation suggests an arrhythmic cause of syncope (class 1). This group of patients includes those with an abnormal electrocardiogram (ECG), structural heart disease, or both. Patients whose clinical history suggests an arrhythmic cause of syncope and those with a family history of sudden death are also included in this group. It is also generally accepted that EP testing should not be performed in patients with a normal ECG and no heart disease and in whom the clinical history does not suggest an arrhythmic cause of syncope (class 3). Class 2 indications for performing an EP study are shown in Table 31-1. These indications suggest that EP testing is appropriate when the results may affect treatment and in patients with "high-risk" occupations, in which case every effort should be expended to determine the probable cause of syncope.

Electrophysiology Testing Protocol

When EP testing is undertaken in a patient with syncope, a comprehensive EP evaluation should be performed. This should include an evaluation of sinus node function by measuring the sinus node recovery time (SNRT) and an evaluation of atrioventricular (AV) conduction by measurement of the H-V interval (His bundle to ventricle conduction time) at baseline, with atrial pacing, and following pharmacologic challenge with intravenous procainamide. In addition, programmed electrical stimulation using standard techniques should be performed to evaluate the inducibility of ventricular and supraventricular arrhythmias. The minimal suggested EP protocol recommended by the ESC is provided in Table 29-2. Although the minimal suggested EP protocol recommended by the ESC includes only double extrastimuli and two basic drive train cycle lengths, it is common practice in the United States to include triple extrastimuli and three basic drive train cycle lengths. It is also common practice to limit the shortest coupling interval to 200 ms. In select patients, when a ventricular arrhythmia is highly suspected, EP testing with atrial and ventricular programmed stimulation may be repeated after an infusion of isoproterenol. In my experience, this is of particular importance in the presence of suspicion of a supraventricular arrhythmia such as AV nodal re-entrant tachycardia or orthodromic AV reciprocating tachycardia as the cause of syncope.

Assessment of Sinus Node Function

Sinus node function is evaluated during EP testing primarily by determining the SNRT, which is determined by pacing the right atrium at cycle lengths between 600 and 350 ms for 30 to 60 seconds. The SNRT is defined as the interval between the last paced atrial depolarization and the first spontaneous atrial depolarization resulting from activation of the sinus node. The SNRT is corrected for the underlying sinus cycle length (SCL) and expressed as the corrected SNRT (CSNRT = SNRT − SCL). An SNRT longer than 1.6 seconds or a corrected SNRT greater than 525 ms is generally considered abnormal. A secondary pause is defined as an inappropriately long pause between the beats that follow the first sinus recovery beat after atrial overdrive pacing. Evaluation of secondary pauses increases the sensitivity of the SNRT in the detection of sinus node dysfunction. Identification of sinus node dysfunction as the cause of syncope is uncommon during EP tests (<5%). The sensitivity of an abnormal SNRT or CSNRT is approximately 50% to 80%. The specificity of an abnormal SNRT or CSNRT is greater than 95%.[2] The prognostic value of an abnormal CSNRT or SNRT has not been well defined. Gann and colleagues demonstrated a relationship between an abnormal SNRT and the effect of pacemaker placement on symptoms.[3] Another study reported that patients with a markedly prolonged CSNRT (>800 ms) had a risk of syncope eight times higher than that with CSNRTs less than 800 ms.[4] It is important to note that the absence of evidence of sinus node dysfunction during EP testing does not exclude a bradyarrhythmia as the cause of syncope.[5]

Table 29-1 Indications for Electrophysiology Testing in the Evaluation of Patients with Syncope

CLASS 1
When the initial evaluation of syncope suggests an arrhythmic cause of syncope
In patients with abnormal electrocardiography, structural heart disease, or both
In patients with syncope associated with palpitations or a family history of sudden death
CLASS 2
To evaluate the exact nature or mechanism of an arrhythmia that has been identified as the cause of syncope
In patients with cardiac disorders in which arrhythmia induction has a bearing on the selection of therapy
In patients with syncope who are in a high-risk occupation and in whom every effort to exclude a cardiac cause of syncope is warranted
CLASS 3
In patients with normal electrocardiograms and no heart disease and no palpitations

Table 29-2 Minimal Suggested Protocol for Electrophysiology Testing for the Diagnosis of Syncope

Measurement of sinus node recovery time and corrected sinus node recovery time by repeated 30- to 60-second sequences of atrial pacing at 10 to 20 beats/min higher than the sinus rate and at two faster pacing rates.
Measurement of the H-V interval (His bundle to ventricle) during sinus rhythm and with incremental atrial pacing. If the baseline study is inconclusive, pharmacologic provocation with an infusion of procainamide (10 mg/kg IV) is recommended.
To evaluate the exact nature or mechanism of an arrhythmia that has been identified as the cause of syncope.
Programmed electrical stimulation in the ventricle to assess ventricular inducibility.
Programmed stimulation should be performed at the apex and outflow tract and at two basic drive cycle lengths with up to two extrastimuli.
Programmed electrical stimulation to evaluate the substrate for inducibility of supraventricular arrhythmias.

Table 29-3 Diagnostic Findings of Electrophysiology Testing for Syncope

Class 1	A normal EP study cannot completely exclude a tachyarrhythmia or a bradyarrhythmia as the cause of syncope. When an arrhythmia is believed to be the likely cause of syncope, further evaluation, perhaps with a loop recorder, is recommended. An abnormal finding on EP testing may not be diagnostic of the cause of syncope. An EP study is considered to be diagnostic of the cause of syncope in the following situations: Sinus bradycardia and a markedly prolonged CSNRT Bi-fasicular block and a baseline H-V interval (His bundle to ventricle) of >100 ms or second- or third-degree His-Purkinje block with incremental atrial pacing High-degree His-Purkinje block provoked with IV procainamide Induction of sustained monomorphic VT Induction of rapid SVT that reproduces the patient's symptoms or results in hypotension
Class 2	The diagnostic value of an EP study is less well established: When the H-V interval is >70 ms but <100 ms With induction of PMVT or VF in patients with Brugada syndrome, ARVD, and those resuscitated from cardiac arrest
Class 3	The induction of PMVT or VF has a low predictive value in patients with an ischemic or dilated cardiomyopathy.

EP, *Electrophysiology;* CSNRT, *corrected sinus node recovery time;* IV, *intravenous;* VT, *ventricular tachycardia;* SVT, *supravenricular tachycardia;* VF, *ventricular fibrillation;* ARVD, *arrhythmogenic right ventricular dysplasia;* PMVT, *pacemaker-modulated VT.*

Assessment of Atrioventricular Conduction

During EP testing, AV conduction is assessed by measuring the A-H interval (AV node to His bundle conduction time) and the H-V interval by determining the response of AV conduction to incremental atrial pacing and atrial premature stimuli. If the results of an initial assessment of AV conduction in the baseline state are inconclusive, procainamide (10 mg/kg) may be administered intravenously and atrial pacing and programmed stimulation repeated. According to the 2004 ESC Guidelines on Management of Syncope, the findings at EP study that establish heart block as the probable cause of syncope are bi-fasicular block and a baseline HV interval longer than 100 ms or demonstration of second- or third-degree His-Purkinje block during incremental atrial pacing or when provoked by an infusion of procainamide (Table 29-3).[1] According to these guidelines, the finding of an H-V interval between 70 and 100 ms is of less certain diagnostic value. Among studies that have reported the results of EP testing in evaluating patients with syncope, AV block was identified as the probable cause of syncope in approximately 10% to 15% of patients. Donateo and colleagues reported the results of a systematic evaluation of patients with syncope in the setting of a bundle branch block on their baseline ECG.[6] Of 347 patients referred for evaluation of syncope, 55 had a baseline bundle branch block pattern. Systematic evaluation of these patients, including EP testing, resulted in a diagnosis of cardiac syncope in 25 patients (45%): AV block in 20 (36%), sick sinus syndrome in 2 (3.6%), VT in 1 (1.8%), and aortic stenosis in 2 (3.6%). Neurally mediated syncope was diagnosed in 22 patients (40%) and syncope remained unexplained in 8 (15%).

The role of EP testing in the assessment of AV conduction and as a predictor of AV block in patients with syncope has been derived from a large number of studies. Scheinman et al evaluated the prognostic value of the HV interval.[7] The rate of progression to AV block at 4 years was 4%, 2%, and 12%, respectively, for patients with H-V intervals less than 55 ms, 55 to 69 ms, and greater than 70 ms, respectively. The risk of progression to AV block was 24% among those with an H-V interval greater than 100 ms. Other studies have investigated the prognostic value of development of intra-His block or infra-His block with incremental atrial pacing. These studies demonstrated that the presence of

these blocks in response to incremental atrial pacing is a specific but insensitive parameter. Dini et al, for example, demonstrated that pacing-induced AV block was observed in 7% of 85 patients who were evaluated.[8] Complete AV block developed within 2 years in 30% of these patients. The diagnostic value of acute intravenous pharmacologic stress testing has been performed with ajmaline, procainamide, and disopyramide. High-degree AV block is seen in approximately 15% of these studies.[8-10] During 24 to 63 months of follow-up, 43% to 100% of these patients develop spontaneous AV block. It has therefore been concluded that induction of AV block during pharmacologic stress testing of AV conduction is highly predictive of development of AV block. It is important to note, however, that a negative EP assessment of AV conduction does not eliminate AV block as the cause of syncope, nor does it exclude that AV block may develop over time. Link et al reported that at 30 months of follow-up, permanent AV block occurred in 18% of patients with syncope who had a negative EP test.[11] Similarly, Gaggioli reported that 19% of patients with syncope and a negative EP evaluation developed permanent AV block within 62 months of follow-up.[12]

Programmed Electrical Stimulation to Evaluate Supraventricular Arrhythmias as the Cause of Syncope

Although it is uncommon for an SVT to result in syncope, this is an important diagnosis to establish as most types of supraventricular arrhythmias can be cured with catheter ablation. Therefore the identification of an SVT as the probable cause of syncope is important because it represents one of the most easily treatable causes of syncope. The usual setting in which an SVT may result in syncope is when a patient with underlying heart disease, limited cardiovascular reserve, or both experiences an SVT that is of abrupt onset and with an extremely rapid rate or when a patient has the propensity for the development of neurally mediated syncope. The typical pattern that is observed is the development of syncope or near-syncope at the onset of the SVT because of an initial drop in blood pressure. The patient often regains consciousness despite the continuation of the arrhythmia because of the activation of a compensatory mechanism. Completion of a standard EP test allows accurate identification of most types of supraventricular arrhythmias that may have caused the syncope. The study should be repeated during an isoproterenol infusion to increase the sensitivity of the study, particularly for detecting AV nodal re-entrant tachycardia in a patient with dual AV node physiology or catecholamine-sensitive atrial fibrillation (AF). According to the 2004 ESC Guidelines on Management of Syncope, an EP study is considered diagnostic of SVT as the cause of syncope in the presence of induction of a rapid supraventricular arrhythmia that reproduces hypotensive or spontaneous symptoms (see Table 29-3).[1] A supraventricular arrhythmia is diagnosed as the probable cause of syncope in less than 5% of patients who undergo EP testing for the evaluation of syncope of unknown origin. The probability of SVT as the cause of syncope is higher in patients who report a history of palpitations or heart racing before syncope.

Programmed Electrical Stimulation to Evaluate Ventricular Arrhythmias as the Cause of Syncope

VT is the most common abnormality that is uncovered during EP testing in patients with syncope. Among studies that have reported the results of EP testing in evaluating patients with syncope, VT was identified as the probable cause of syncope in approximately 20% of patients. In general, an EP test was interpreted as being positive for VT when sustained monomorphic VT is induced. The induction of polymorphic VT and ventricular fibrillation (VF) may represent a nonspecific response to EP testing. The diagnostic as well as prognostic importance of the induction of polymorphic VT, VF, or both remains uncertain.

According to the 2004 ESC Guidelines on Management of Syncope, an EP study is considered diagnostic of VT as the cause of syncope in the presence of induction of sustained monomorphic VT (see Table 29-3).[1] According to these guidelines, findings on EP testing that have less certain diagnostic value include the induction of polymorphic VT or VF in patients with Brugada syndrome or arrhythmogenic right ventricular dysplasia (ARVD) and in patients resuscitated from a cardiac arrest. These guidelines also state that the induction of polymorphic VT or VF in patients with ischemic or dilated cardiomyopathy has low predictive value.

Carotid Sinus Hypersensitivity

Syncope caused by carotid sinus hypersensitivity results from the stimulation of carotid sinus baroreceptors, which are located in the internal carotid artery above the bifurcation of the common carotid artery. Carotid sinus hypersensitivity is diagnosed by applying gentle pressure over the carotid pulsation just below the angle of the jaw, where the carotid bifurcation is located. According to the ESC 2004 Guidelines on Syncope, carotid sinus massage (CSM) is recommended in patients over the age of 40 years with syncope of unknown etiology after an initial evaluation.[1] CSM should not be performed in patients with known carotid artery disease because of an increased risk of stroke. Pressure should be applied for 5 to 10 seconds while continuously monitoring the ECG and blood pressure. If the response to CSM in the supine position is normal, the importance of repeating CSM in the upright position has now been well established.[13,14] The TT test makes it easier to perform CSM in both the supine and upright positions. The main complications associated with CSM are neurological. Because of this, CSM should be avoided in patients who have experienced transient ischemic attacks (TIAs), stroke within the past 3 months, or carotid bruits.

A normal response to CSM is a transient decrease in the sinus rate, slowing of AV conduction, or both. *Carotid sinus hypersensitivity* is defined as a sinus pause of more than 3 seconds' duration and a fall in systolic blood pressure of 50 mm Hg or more. The response to CSM can be classified as cardio-inhibitory (asystole), vasodepressive (fall in systolic blood pressure), or both. Carotid sinus hypersensitivity is detected in approximately one third of older patients who present with syncope or for falls.[1,15] The sensitivity of CSM for the diagnosis of carotid sinus hypersensitivity is increased by performing CSM with the patient in both the supine and upright positions.[13,14] Although it is common practice to perform CSM as part of a diagnostic EP study for syncope, a negative response to CSM in the supine position during an EP procedure does not exclude the diagnosis. Therefore repeat CSM in the standing position should be performed either before the EP study or at some point after the EP study. It is important to recognize, however, that carotid sinus hypersensitivity is also commonly observed in asymptomatic older patients.[16] Thus the diagnosis of carotid sinus hypersensitivity should be approached cautiously after excluding all other causes of syncope. Once diagnosed, dual-chamber pacemaker implantation is

Table 29-4 Recommended Tilt-Table Test Protocols

Supine pretilt phase of 5 minutes when no venous cannulation
Supine pretilt phase of at least 20 minutes when venous cannulation is used
Table tilted to 60 to 70 degrees
Passive tilt for 20 to 45 minutes
Use of either isoproterenol or sublingual nitroglycerine if the passive phase is negative (20 minutes)
For isoproterenol, infusion of 1 to 3 μg/min to achieve 20% to 25% increase in heart rate
For nitroglycerine, administration of 400 μg as a sublingual spray with the patient in the upright position
Positive result if syncope occurs

Table 29-5 Indications for Tilt-Table Testing

Class 1	Single unexplained episode of syncope in a high-risk setting Recurrent episodes of syncope in the absence of structural heart disease or in the presence of structural heart disease after other cardiac causes of syncope have been excluded When it will be of clinical value to demonstrate susceptibility to neurally mediated syncope
Class 2	When an understanding of the hemodynamic pattern may alter the therapeutic approach For differentiating syncope from the jerky movements of epilepsy For evaluating patients with recurrent unexplained falls For assessing recurrent presyncope or dizziness
Class 3	Assessment of treatment A single episode of syncope without injury and not in a high-risk setting Syncope with features typical of syncope because of neurally mediated hypotension when the result of the test will not affect treatment

recommended for patients with recurrent syncope or falls resulting from carotid sinus hypersensitivity.[17,18]

Tilt-Table Testing

The TT test is valuable for evaluating patients with syncope.[1,19] The recommendations for TT testing protocols are shown in Table 29-4.[1] Upright TT testing is generally performed for 20 to 45 minutes at an angle between 60 and 70 degrees. The sensitivity of the test can be increased, with an associated fall in specificity, by the use of longer tilt durations, steeper tilt angles, and provocative agents such as isoproterenol or nitroglycerin. When isoproterenol is used as a provocative agent, it is recommended that the infusion rate be increased incrementally from 1 to 3 μg/min to increase the heart rate to 20% to 25% greater than baseline. When nitroglycerin is used, a fixed dose of 400-μg nitroglycerine spray should be administered sublingually with the patient in the upright position. These two provocative approaches are equivalent in diagnostic accuracy. In the absence of pharmacologic provocation, the specificity of the test has been estimated to be 90%. It is important to recognize, however, that the specificity of TT testing decreases significantly when provocative agents are used.

The indications for TT testing are shown in Table 29-5.[1] It is generally agreed that upright TT testing is indicated in patients following a single episode of syncope in high-risk settings or in patients with recurrent syncope who do not have structural heart disease or in those with structural heart disease once cardiac causes of syncope have been excluded.[1] Upright TT testing is not necessary in patients who have experienced only a single syncopal episode that was highly typical for neurally mediated syncope and during which no injury occurred. It is also important to recognize that TT testing should not be used to assess treatment because (1) the reproducibility of a positive response to TT testing varies from 31% to 92%, (2) half of patients with an initial positive tilt response demonstrate a normal tilt response to either treatment or placebo, and (3) the mechanism of a positive response during TT testing does not correlate to that observed during spontaneous syncope as demonstrated with a loop monitor.[20-28]

Conclusion

In conclusion, EP testing and TT testing are important diagnostic tests when evaluating a patient with syncope. Although a large number of diagnoses can be established with an EP study, it is important to understand its important limitations. This is particularly true with regard to using EP testing to diagnose heart block or bradycardia. When a patient suspected of having a cardiac cause of syncope has a negative result in EP evaluation, it is often of value to recommend an external or implantable continuous loop event monitor.

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CHAPTER 30

Engineering Aspects of Pacemakers and Leads

Hiten Doshi, Shantanu Reddy, Michael J. Root, and Arjun Sharma

Introduction

The key functional aspects of pacemaker systems include the following:

- Produce cardiac excitation through an electrical stimulus (see Chapter 13)
- Control the rate of stimulation
- Detect (or sense) intrinsic cardiac activity and avoid competition with this activity
- Detect and categorize diagnostic data
- Store device and clinical events using memory (e.g., intrinsic tachycardia and diagnostic information)
- Permit external adjustment of functional parameters
- Facilitate interrogation of the memory and transmit data externally

Chapters immediately following this describe the clinical methods for applying these functions; this chapter describes the engineering aspects of pacemakers and leads.

General design constraints for a pacemaker include the following:

- An estimated 99.5% overall 5-year reliability of the pacemaker generator (AdvaMed guideline)
- Safety features such as warning of impending battery depletion, biostability, and biocompatibility of materials inside the human body
- Longevity of 5 to 10 years
- Weight of approximately 25 g or less
- Resistance to electromagnetic interference (EMI)
- Simplicity of use
- Patient information security

The devices must meet regulatory requirements for both safety and efficacy in multiple geographic areas. Biocompatibility issues potentially include corrosion and tissue reactions, including calcification, thrombogenesis, and toxicity. Design constraints are often at odds with each other; for example, the desired feature of greater battery longevity may be achieved with an undesirably large size. Testing for failure modes is complex; user technique, patient characteristics, and device properties may interact in complex mechanisms to produce failure. Testing therefore includes both intended use and foreseeable misuse

The visible structural components of the pacemaker system include the leads and their delivery systems, the implantable pulse generator (IPG) with its header and attachments for leads, the programmer, and a remote follow-up device.

The building blocks of the IPG include a power source (battery), integrated circuits, memory, dedicated components (e.g., capacitors, wireless telemetry receiver and transmitter), a hermetically sealed can, and the header.

Leads

Leads are complex mechanical systems that have to withstand biodegradation in the harsh environment of the body, repetitive flexural cycles in the heart, and compressive and tensile forces in the extravascular space.[1,2] The leads need to withstand conditions in intracardiac and intravascular locations, along the route to the venous entry site through tissue, and, lastly, the pocket location where the excess lead and the IPG reside. A lead potentially must survive multiple pulse generator replacements and should also be designed to be extracted from the body relatively atraumatically. Design characteristics that aid in extraction include a constant outer diameter of the lead with sufficient tensile strength. All these requirements must be met while providing for implanter preferences in handling characteristics and stability.

Leads are implanted into the venous system either via an introducer or directly into the vein. Commonly, the subclavian, cephalic, and axillary veins are accessed. Fluoroscopy is commonly used by the operator to navigate the lead into position (Figure 30-1), although non–radiography-dependent techniques have been described.

Pacing leads may be categorized as follows:

1. Endocardial or epicardial placement
   - **a.** Right atrium
   - **b.** Right ventricle

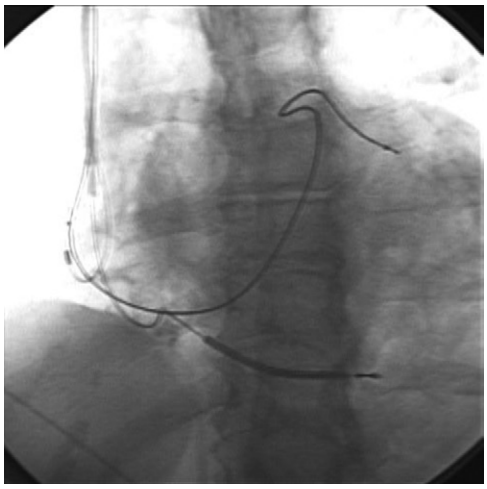

FIGURE 30-1 Fluoroscopy image of cardiac leads, including an atrial bipolar, dual-coil implantable cardioverter-defibrillator, and left ventricular lead.

FIGURE 30-2 An IS-1 pacemaker lead connector.

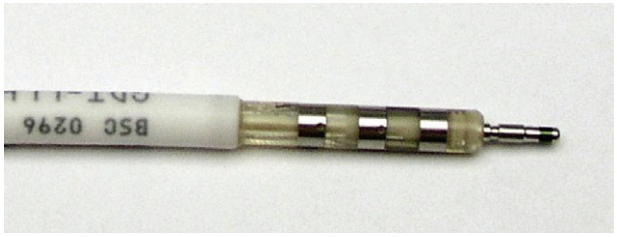

FIGURE 30-3 An IS-4 connector.

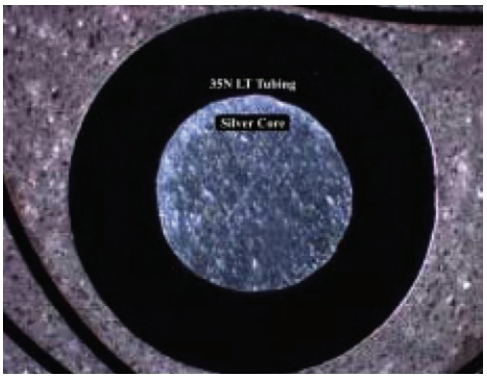

FIGURE 30-4 A cross-section of pacing conductor with MP35N and a silver core.

- **c.** Left ventricle
  - **i.** Placement via an epicardial coronary vein
  - **ii.** Epicardial active fixation surgically performed

2. Fixation types
- **a.** Active fixation (helical screw)
- **b.** Passive fixation (tines)
- **c.** Left ventricular
  - **i.** Passive
  - **ii.** Deployable structure

Leads can be identified as having three distinct sections: the lead connector, the lead body, and the electrodes.

Lead Connector

The connector assembly connects the lead to the IPG. The connectors of modern leads generally conform to industry standards, which specify lead characteristics to ensure that the lead of one manufacturer can be connected to the IPG of another manufacturer. The IS-1 connector is used for low-voltage pacing or sensing leads (Figure 30-2). The IS-1 connector enables up to two electrodes to be connected to the IPG within one single connector. Implantable cardioverter-defibrillator (ICD) leads may use the quadripolar connector (IS-4), which makes it possible to connect up to four individual electrodes to an IPG with a single connector (Figure 30-3). A natural extension of the quadripolar connector is to cardiac resynchronization therapy (CRT) leads, which makes it possible to position up to four electrodes over the left ventricle. This may provide options for addressing issues with left ventricular stimulation such as diaphragmatic stimulation and high pacing thresholds with electronic repositioning of the stimulation site. It is not unusual for leads to last 20 or more years; the operator may discover, on generator replacement, a lead with a currently nonstandard terminal pin length or diameter (e.g., 4.75 mm, 6 mm). Care should be taken to check the prior operative reports and device history to ensure the compatibility of the lead terminal end with the planned replacement generator header or to have adapters available to make the connection.

Lead Body

The lead body houses, protects, and isolates all the conductors. In addition to meeting strict functional requirements associated with conductor fatigue and insulation integrity, the lead body must be designed to impart specific handling characteristics to enable maneuvering of the lead into the desired position. Specific attributes include the stiffness and coefficient of friction. Stylet wires of various shapes and stiffness are used to facilitate lead tip positioning during the implantation procedure.

Most pacing leads use coiled conductors, in which either single or multiple wire strands are wound into a coil. A high-strength, corrosion-resistant nickel alloy known as MP35N is the most common material used in the manufacturing of pacing lead conductor wire. In some applications, an outer jacket of MP35N is combined with a silver core to lower resistance (Figure 30-4). A few leads used for left ventricular pacing use platinum-clad tantalum wire as well as wire consisting of MP35N with a tantalum core. Certain manufacturers also use cable conductors in low-voltage pacing leads (Figure 30-5). Cables are composite conductors consisting of very small wire strands that are bundled together. Most cable conductors use strands consisting of MP35N

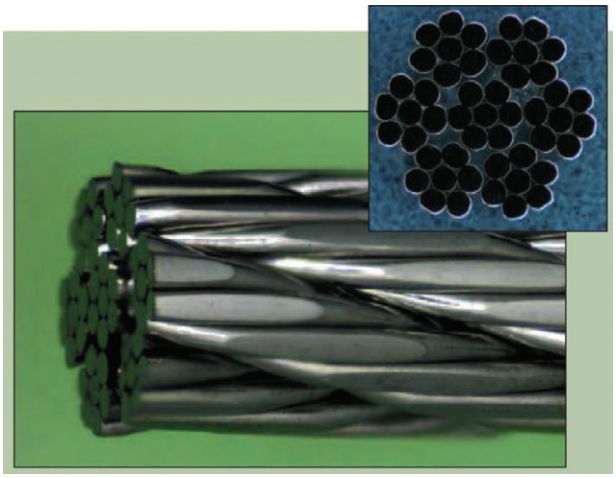

FIGURE 30-5 A cable with multiple wire conductors.

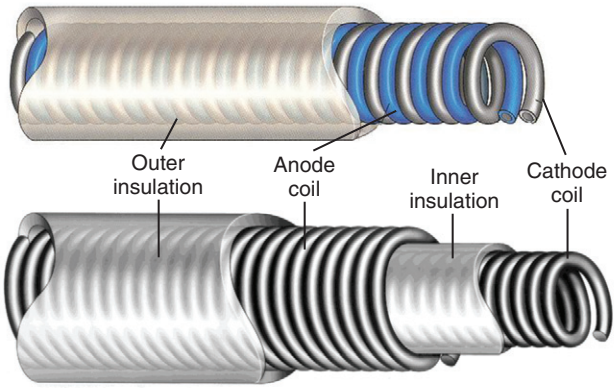

FIGURE 30-6 Co-radial and co-axial conductor wire arrangement in bipolar leads.

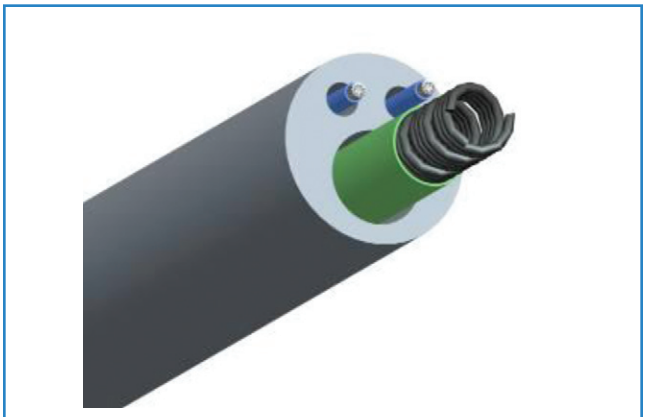

FIGURE 30-7 Multiple-lumen construction used in some left ventricular leads.

with a silver core. Pacing leads generally use either a co-radial or co-axial construction (Figure 30-6). In the co-radial construction, both anode and cathode conductors are coiled adjacent to each other, isolated from each other with a polymer insulator applied to the wire itself. The co-axial construction uses separate anode and cathode coiled conductors, isolated from each other through the use of an intermediate insulating polymer layer.

Some left ventricular leads have progressed from the co-axial and co-radial constructs to multi-lumen construction, which was used in the first endocardial ICD leads (Figure 30-7). The co-axial, co-radial, and multi-lumen construction methods rely on an outer insulation jacket that imparts structure to the lead body and also protects the conductors.

Pacing leads currently on the market use silicone rubber, polyurethane, or a co-polymer of silicone and polyurethane as the outer insulation. Both silicone rubber and polyurethane are used in various durometers, as chosen by the manufacturer, to impart specific mechanical attributes to the lead body. Silicone rubber has proven to be a flexible and biostable material. However, silicone rubber is susceptible to abrasion, especially when the lead is coiled and in contact with itself, another lead, or the IPG. Polyurethane is not susceptible to abrasion, but the 80A variant has been found to be highly susceptible to degradation, specifically environmental stress cracking. Polyurethane, depending on the application, may also have an undesirably high stiffness and is vulnerable to damage from the heat effects associated with electrocautery, which may be used during the implantation or replacement procedure. The silicone-polyurethane hybrid material was developed to combine the positive attributes of silicone and polyurethane into one material. Early experience with the material has been positive, with 2-year biocompatibility testing results showing minimal levels of degradation. However, the material may be vulnerable to electrocautery damage.

One of the most significant challenges a lead engineer must balance is the potential conflict between implanter preference and safety and reliability. Some physicians select very stiff leads on the basis of implant maneuverability. However, such a lead construct may promote tissue and vascular trauma and possibly cardiac perforation. Many physicians value size reduction (lower French size), which has been a significant market driver for lead development, but long-term malfunction-free rates have not always been adequate for small-size leads. If insulation thickness, material selection, and conductor design are not properly managed, catastrophic problems can occur, although there have been some notable exceptions.[3] The lead engineer must balance true clinical needs and benefits with market perceptions and ensure that the design of leads is safe and reliable. Given the variability of patient anatomy, patient activity level, and implanter technique, ensuring that in vitro test methods account for all potential clinical situations is a significant challenge. Understanding current product performance and leveraging the success of that particular design, while proceeding cautiously and in a data-driven manner with regard to changes, is perhaps the most successful technique to ensure a safe and effective product.

Electrodes

Fixation Methods

Pacing leads have an electrode at the distal end in contact with the myocardium. The distal electrode is usually the cathode. The electrode section of the lead may include a proximal electrode within the main lead body construct used as an anode. A lead with both cathode and anode electrodes is generally referred to as a *bipolar lead*, whereas a lead with only a cathode electrode is generally referred to as a *unipolar lead*. In unipolar leads, the

FIGURE 30-8 A passive-fixation lead with tines.

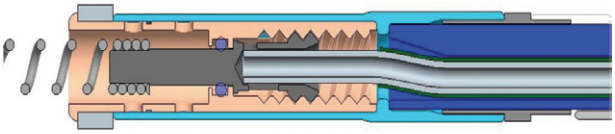

FIGURE 30-10 Cross-section of a lead with an extendable-retractable fixation mechanism.

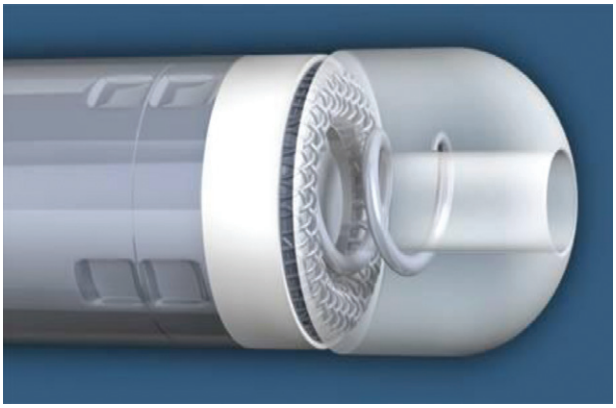

FIGURE 30-9 A fixed screw coated in mannitol.

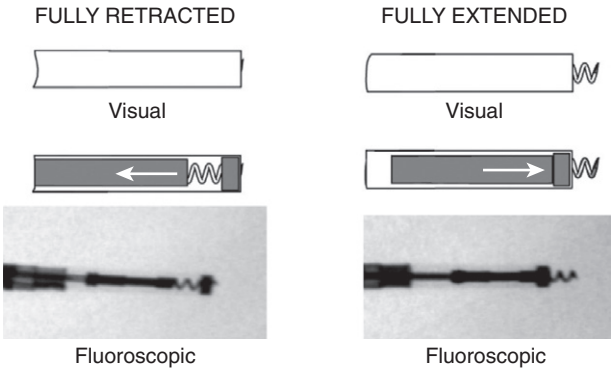

FIGURE 30-11 Diagrammatic and radiographic views of a lead with an extendable-retractable fixation mechanism.

housing of the IPG is used as the anode. Unipolar leads were historically used more frequently because of evidence that they were more reliable than bipolar leads and because they were smaller in diameter compared with bipolar leads. However, the reliability of bipolar leads has improved, and the issues with unipolar systems, such as oversensing of myopotentials and stimulation of pectoral muscle caused by charge concentration on the IPG housing, have decreased the popularity of unipolar leads over the past few decades.

The distal electrode needs to be designed to stimulate the myocardium and fixate the lead. The lead also serves as an antenna enabling the IPG to interpret cardiac rhythms. The potential difference between the anode and cathode electrodes as the depolarizing wavefront propagates across the electrodes is recorded and interpreted by the IPG to determine if a stimulus should be issued or inhibited. Electrode characteristics and spacing affect the recorded signal.

A passive fixation lead uses tines generally made of silicone rubber, that wedge within the trabeculae in the right atrium or the right ventricle. The electrode itself is positioned distal to the tine apparatus (Figure 30-8).

Active fixation leads are available in two forms: (1) the extendable-retractable variant and (2) the fixed-screw variant. Both designs use a helical screw (corkscrew); the screw itself can be the cathode electrode, or the screw may only be for fixation purposes with the actual cathode electrode separate from the fixation screw.

The fixed-screw variant (Figure 30-9) relies on a mannitol encapsulant, which dissolves within 2 to 3 minutes of introduction and enables passage of the lead into position without catching on anatomic structures. A common technique is to rotate the entire lead counterclockwise during passage to prevent snagging if the helix is exposed during passage. Once the lead tip reaches the desired location, after the fixation screw is exposed, the entire lead body is turned clockwise to fixate the lead in tissue. If repositioning is required, the lead body may be turned counterclockwise to disengage the lead.

The extendable-retractable variant has the screw retracted within the lead body during passage, which prevents catching of the lead on vascular and cardiac structures during passage (Figure 30-10). The fixation helix is then extended after the lead has been positioned. Helix extension occurs through the application of clockwise rotation to the terminal pin, which is transferred via the cathode conductor coil to a mechanism that converts this rotation into an extension of the screw. If repositioning is required, counterclockwise rotation of the terminal pin will retract the fixation helix. Most extendable-retractable leads use radiographic markers to help the operator determine when the helix is fully extended or fully retracted (Figure 30-11). The extendable-retractable active fixation leads for both pacing and ICD leads have become the most popular type of leads on the market. However, passive-fixation and fixed-screw leads also have important roles, partly driven by clinical need and benefit and partly by implanter preference. Advantages of the passive-fixation design include less injury at the electrode-tissue interface, resulting in generally lower pacing thresholds and a lower risk of myocardial perforation. The risk of cardiac perforation with an active-fixation lead may be higher in certain patients under certain circumstances (e.g., female gender, steroids administration, and apical placement; recent anterior or inferior infarction). The disadvantages of passive-fixation leads include limited locations for stable placement and a higher dislodgment rate, although the latter is highly

dependent on the implanter and his or her experience. In contrast, the active-fixation method produces greater myocardial injury and a slight tendency to higher early threshold rise, but this has been reduced by the use of steroid collars on the leads. Myocardial injury can manifest as a current of injury on electrogram analysis acutely, which helps confirm fixation. Active fixation has the advantage of having stable placement in most locations, including atrial locations other than the appendage, and in the right ventricular septum. Furthermore, active-fixation leads are generally easier to extract after long-term use.

FIGURE 30-12 An active fixation lead with steroid collar.

Design of Distal Electrodes

The design of the pacing electrodes is critical because their role is to transfer electrical charge to the myocardium effectively and efficiently. Myocardial stimulation is discussed in detail in Chapter 13; this chapter reviews the features of myocardial stimulation as they affect lead design and function. In brief, myocardial cells maintain a higher intracellular potassium (K^+) concentration and a lower sodium (Na^+) concentration. Electrogenic transmembrane ionic pumps result in a resting negative internal potential of approximately 90 mV compared with the surrounding extracellular space in the healthy myocardium and is less negative in diseased states. Depolarization of this transmembrane potential by a delivered electrical pulse results in the opening of Na^+ channels, with a resultant cascade of events generating an action potential and contraction. The lead design is important in minimizing the charge requirement to generate myocardial stimulation and also maintain a relatively stable pacing threshold under varying pathologic conditions such as acidosis and hyperkalemia or in the presence of antiarrhythmic drugs, all of which may elevate pacing threshold. In general, the lower the voltage threshold, the longer the pacemaker battery longevity. Furthermore, the impedance of the pacing circuit is carefully managed by minimizing conductor and connection impedance while maximizing tissue-electrode impedance. Increasing this interface impedance reduces current drain (I = V/R), which results in improved battery longevity. The cathode electrode may be in the form of a helical screw or a rounded electrode with shapes intended to concentrate charge and promote tissue stabilization. The second, proximal electrode serves as the anode and can be located from just over 1 mm to 16 mm from the cathode electrode (see Figure 32-8).

The charge required to stimulate the myocardium depends on myocardial excitability, distance from the electrode surface to excitable tissue, electrode polarization, microscopic surface area, electric field density, and macroscopic size. Myocardial excitability is a clinical property that may vary by location and pathologic processes and may necessitate lead repositioning. Increasing the distance between the electrode surface and excitable tissue increases the charge required to excite the myocardium. The placement of the electrode initiates a tissue reaction to the foreign body. Local cell death occurs with formation of a collagen capsule around the lead tip. The collagen capsule is inexcitable and effectively acts to distance the electrode surface from active myocytes. A number of methods have been used to minimize tissue reaction; a slowly eluting dose of 1 mg of dexamethasone is the most commonly used method and has been associated with reducing the increase in pacing thresholds observed after lead implantation (Figure 30-12).

Lead polarization occurs at the electrode-tissue interface and increases with the stimulation voltage.[4] Cathodal electrode stimulation produces a negative charge on the electrode. Beyond the electrode, the negative charge attracts positive ions such as Na^+ and hydrogen (H^+), often with associated water in the collagen capsule and the extracellular space. This charge bilayer is referred to as the *Helmholtz double layer*, which can be electrically modeled as a capacitor that stores charge. This lead polarization results in energy loss when pacing and, ideally, should be minimized. Lead polarization may also affect detection of the evoked response after pacing. Coatings and oxide layers such as iridium oxide, platinum black, and titanium nitride have been used; they improve charge transfer and reduce lead polarization. The use of these coatings has contributed to lower and more stable and predictable pacing thresholds. Increased microscopic surface area may reduce the resistive component of lead polarization. One method has used a sputtered iridium thin-film, fractal-coated lead cathode technology to increase the effective surface area of the electrode by 1000 compared with the geometric area.[5] Other methods of accomplishing this include porous, texturized, and laser-drilled lead cathode surfaces.

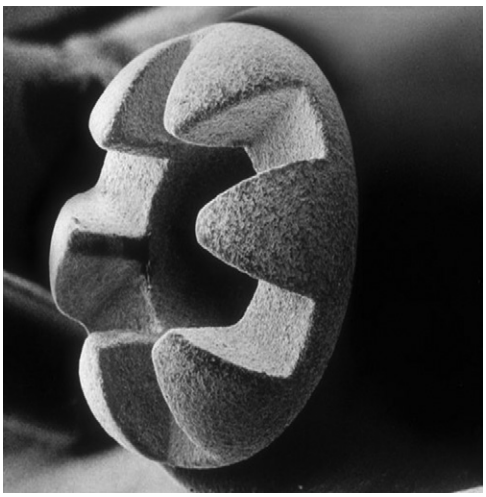

FIGURE 30-13 A distal electrode using edge effect to increase charge density in certain locations.

Methods to increase electrical field density have primarily used the effects of edges to concentrate the electrical field in multiple locations (Figure 30-13).

Lastly, a smaller macroscopic area has improved electric field density and lowers pacing impedance, which can contribute to increased IPG battery longevity. However, leads with a small cross-sectional area of the tip must be assessed clinically for the risk of penetrating or perforating the myocardium.

Lead Testing

Past failures of several polyurethane leads and the more recent high failure rate seen with a particular ICD lead have placed the spotlight on lead reliability. Although IPG failures are potentially catastrophic, they are much less common, and the IPG can be removed and replaced. In contrast, leads that have been in place for several years require specialized extraction procedures, with an accompanying risk depending on the experience of the operator and the center. To minimize lead failures in patients, leads engineers have focused their time and effort on improving their understanding of the use conditions, predicating lead performance, developing suitable bench tests, and using computer modeling and simulation techniques (see Video 30-1 at the Expert Consult site that accompanies this text).

Regulatory approval requires a clinical study with increases in both patient number and duration of follow-up with the more novel features of a lead. The U.S. Food and Drug Administration (FDA) has also put in place conditional approval of leads, which is contingent on a 5-year postmarket approval study with predefined clinical performance criteria. Long-term animal testing has been de-emphasized in recognition of the need for large numbers of patients over time to observe infrequent, time-dependent failures. In contrast, smaller Good Laboratory Practice animal studies are required.

Failure Modes

Despite advances in lead design, failures still do occur.[3] Beyond fairly acute phenomena such as dislodgment and cardiac perforation, common mechanical failure modes include conductor fracture and insulation failure.[6] Insulation failure tends to occur in locations of high motion or compressive or sheer stress and in areas where lead-on-lead and lead-on-IPG interactions occur. These areas are commonly in the IPG pocket, at or near the anchoring sleeve tie-down, and at venous access points or in any intravascular area where multiple leads may interact with each other. Conductor failure generally occurs in areas of repetitive and acute flexing; in areas of compression, such as when the lead passes between the clavicle and the first rib; and at sites of sheer forces, such as where the lead passes through a ligament or muscle layers (Figure 30-14). Acute flexural cycles may occur within the IPG pocket or within the vascular or cardiac portions of the lead trajectory. Certain areas of the lead may be susceptible to damage caused by implant handling, resulting in conductor disruption or a change in the bend radius of the lead. For these reasons, suture sleeve restraint areas are common sites of conductor fracture. In certain leads, connection sites inevitable in the design and the manufacturing process, such as conductor joints and insulation transitions, have proven to be vulnerable to fatigue failure. Leads engineers must therefore anticipate that repetitive flexing will occur at connection sites such as conductor joints and insulation transitions and must ensure that the design is capable of withstanding the anticipated service conditions. Manifestation of conductor fracture and insulation disruption includes sudden impedance changes, changes in signal amplitude, threshold increase, and, lastly, intermittent noise. The order in which these events occur varies, even in leads with a common failure mode. Long-term performance criteria for leads have not been clearly defined by the Heart Rhythm Society, but FDA postmarket surveillance studies suggest that a 5-year failure rate of 5% may be appropriate.

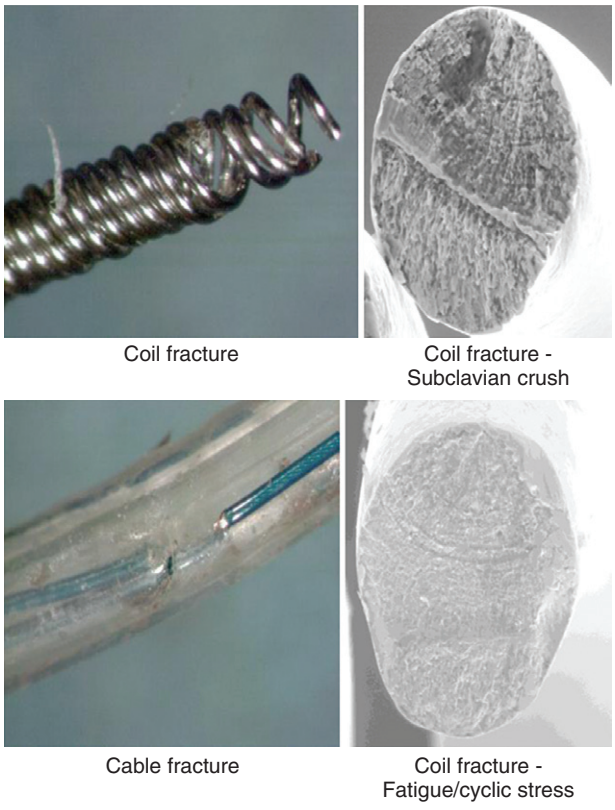

FIGURE 30-14 Types of pacing lead conductor fracture detected by scanning electron microscopy.

Special Considerations for Left Ventricular Leads

The construction and electrode configuration of left ventricular leads are briefly described here but are considered further in other chapters of this text. Left ventricular lead construction is significantly different from right ventricular pacing leads. Left ventricular leads need to be flexible enough that perforation of the thin-walled coronary vein does not occur acutely or chronically. This lead flexibility necessitates the use of a delivery system to access the coronary sinus. A subselecting guiding catheter may also be deployed into the target vein. Most left ventricular leads are deployed through a guiding catheter and over a guidewire into position in the target coronary vein.

Complex design issues of the lead include managing column stiffness to enable advancement, with flexibility in the distal section to enable tracking into a tortuous vessel. In addition, a low crossing profile (4 to 6 Fr) is desirable to facilitate passage of the lead into small, tortuous veins. Furthermore, a fixation method often is necessary for secure placement of leads within such veins (Figure 30-15). Thin-walled veins are not suitable for screw-fixation methods; therefore a preformed lead shape (canted tip, spiral, S-shaped) has been used to retain the lead in the coronary vein.

Placing epicardial, nontransvenous leads by minimally invasive or open-thoracic surgical methods is an alternative method when vascular access is not available for placement of a transvenous lead or in pediatric cases.

Potential areas for future development in left ventricular leads include increasing the number of electrodes, variable electrode

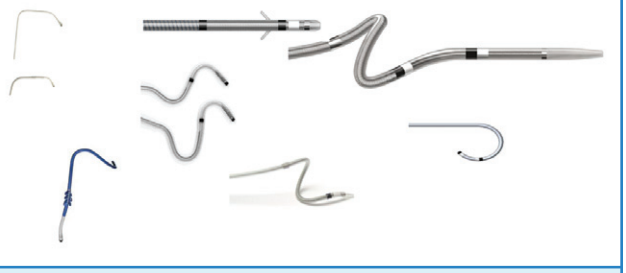

FIGURE 30-15 Left ventricular lead distal fixation methods.

position, improved stabilization shapes, reduced lead size, and improved delivery systems.

Pacemaker Implantable Pulse Generator

Battery

The sole source of power for IPGs is a battery. All IPG functions such as sensing and pacing are powered by the battery contained within the IPG. Zinc–mercuric oxide (Zn-HgO) batteries were used in the first IPGs that became available in 1960. This battery chemistry was developed by an American battery engineer, Samuel Ruben, in 1942 as a more reliable alternative to the ubiquitous Leclanché dry cell. Zn-HgO batteries were used by the military during World War II and, after the war, in wearable hearing aids. Other types of power sources, including rechargeable nickel-cadmium batteries and plutonium-238 nuclear power sources, soon became available as well, but Zn-HgO batteries remained the dominant power supply in the early IPGs. Their use in IPGs continued into the early 1970s.[8-10]

However, Zn-HgO batteries tended to form hydrogen gas, which causes an increase in internal pressure and could result in leakage. These batteries had a high self-discharge rate, in which battery capacity was lost as a result of parasitic chemical reactions. Furthermore, the discharge voltage was rather constant during most of the life of the battery but then decreased so rapidly near the end that there was little advance warning of battery depletion.

One of the biggest advances in IPGs occurred with the development of lithium battery technology. Lithium is the anode, or negative electrode, material in these batteries. Lithium batteries typically are characterized by high energy density. Higher energy density corresponds to greater longevity compared with other batteries, such as Zn-HgO batteries, of the same size. Lithium batteries enabled devices to last up to 5 to 10 years, a significant improvement over the 2 or so years attained with Zn-HgO batteries.

The first lithium battery designed for IPGs was implanted in 1972.[8-10] Since then, lithium batteries have been the power source of choice for IPGs. Various cathode, or positive electrode, chemistries have been developed for lithium IPG batteries, but lithium-iodine (Li-I_2) is the preferred chemistry for single-chamber and dual-chamber IPGs today. It provides high energy density for longevity at the low power levels required by IPGs.

Power requirements of IPGs may increase in the future as more advanced features are added, such as remote telemetry using radiofrequency and complex hemodynamic sensors. Li-I_2 may not be able to support these higher power operations, and other chemistries such as lithium–manganese dioxide (Li-MnO_2), lithium–silver vanadium oxide (Li-SVO), and lithium–carbon monofluoride plus silver vanadium oxide (Li-CF_x-SVO) will be needed.

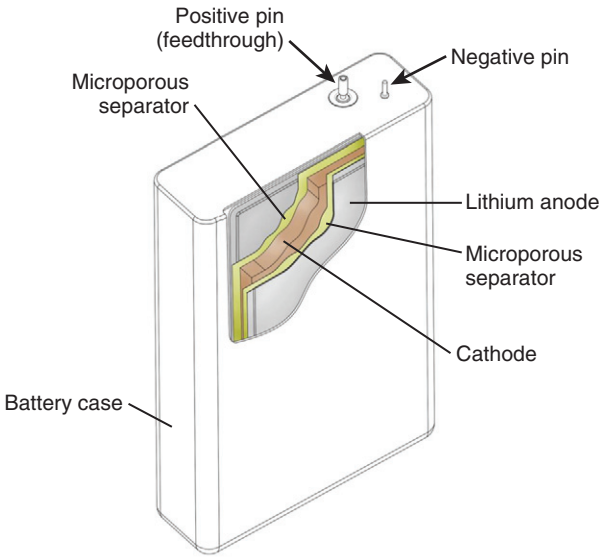

FIGURE 30-16 Basic components of an implantable pulse generator battery.

Design

The major components of a lithium battery are shown in Figure 32-16. The battery case may have a negative polarity, as shown in Figure 32-16, or a positive polarity, as with Li-I_2 batteries. All batteries, including the specialized batteries designed for IPGs, are composed of the same three basic active components—anode, cathode, and electrolyte. The anode, lithium in this case, gives up electrons to the IPG circuit, and the cathode accepts the electrons. The cathode is one or more of a number of diverse chemical compounds selected for the specific device application. The electrolyte completes the circuit inside the battery by means of ionic conduction. Most common battery types use liquid electrolyte solutions. Li-I_2 batteries use a solid-state electrolyte and are an exception to this.

Although the anode, the cathode, and the electrolyte make up the active components of a battery, other components are necessary to maximize its performance, make it practical to use, and ensure its safety and reliability. For example, it is important to prevent direct contact between the cathode and the anode while ensuring that both are mutually in contact with the electrolyte. This may be accomplished with a porous separator material. The separator is an electrical insulator that allows the ions in the electrolyte to move between the anode and the cathode. The entire battery electrode assembly and the electrolyte are contained within a hermetically sealed metal case in an IPG battery. Electrical connections to the IPG circuits are made at the positive and negative terminal pins. The positive pin usually is part of a hermetic glass-to-metal seal.

The most important design considerations for an IPG battery are reliability, small size, weight, and longevity as well as predictability when approaching the end of service life.

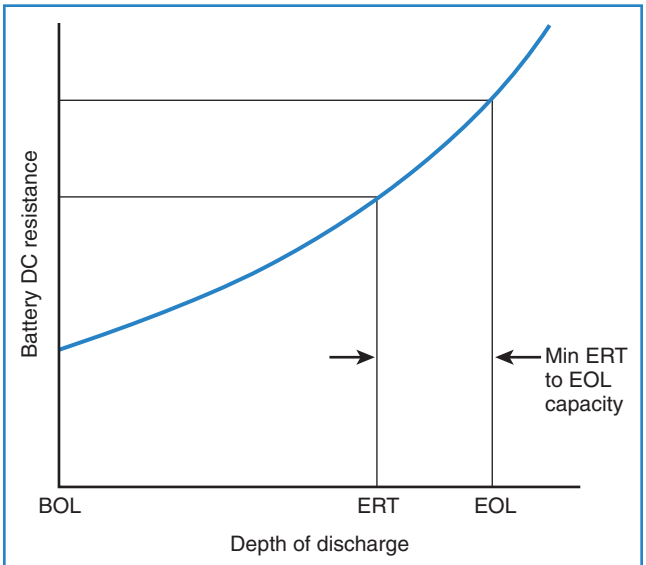

FIGURE 30-17 The change in internal resistance of a lithium-iodine battery during discharge. *BOL*, Beginning of life; *ERT*, elective replacement time; *EOL*, end of life.

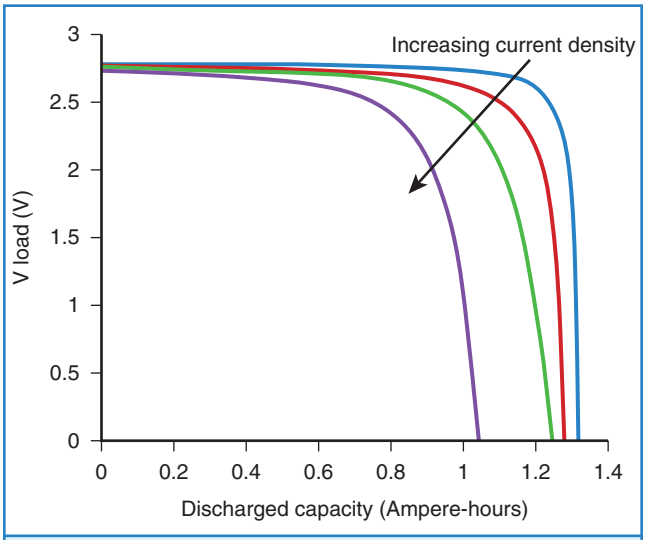

FIGURE 30-18 The effect of increasing internal resistance of a lithium-iodine battery during discharge as a function of discharge load. *(Modified from Untereker DF, Crespi AM, Rorvick A, et al: Power systems for implantable pacemakers, cardioverters and defibrillators. In Ellenbogen KA, Kay GN, Lau C-P, Wilkoff BL, editors*: Clinical cardiac pacing, defibrillation, and resynchronization therapy, *ed 3, Philadelphia, 2007, Saunders.)*

Reliability of any battery is defined by a number of factors, particularly the fundamental stability of the battery chemistry, mechanical design features, purity of the chemical components, and manufacturing capability. A major challenge for battery developers is to design high-energy-density batteries that minimize battery size without giving up longevity. IPG longevity depends on the battery chemistry, battery design (including size), and power consumption of the IPG. The most prevalent IPG battery chemistry today is Li-I_2, which produces voltages between 2.8 V and 2.5 V during use. IPG electronic components and circuits are designed to function in this voltage range. The iodine is stabilized by forming a complex with the polymer material poly-2-vinylpyridine. The battery chemistry is sometimes written as Li-I_2-PVP or Li-I_2-P2VP. Instead of a liquid electrolyte solution, Li-I_2 batteries use a solid-state electrolyte that is produced in situ from the reaction of Li with I_2 to yield lithium-iodide (Li-I). In addition to serving as the electrolyte, the Li-I formed lessens the direct reaction between Li and I_2 by serving as a mechanical barrier between the two electrodes; as a result, a separator is unnecessary. Direct reaction of Li with I_2 reduces the amount of active materials available for discharge and therefore decreases battery longevity.

As the Li-I_2 battery is discharged, Li-I continues to build up and eventually reduces the self-discharge reaction to an insignificant level. However, the increasing thickness of the Li-I layer also results in an increase in the internal resistance of the battery as the discharge proceeds (Figure 30-17). The internal resistance gradually increases during the service life of the battery, and the voltage of the battery decreases. The greater the discharge rate, the more rapidly the discharge voltage decreases. The increase in resistance continues until the battery can no longer support the power demands of the IPG. This characteristic provides a ready means to predict the end of battery life (Figure 30-18), allowing longevity to be determined with sufficient advance notice of battery end of life. Measurements of voltage and internal resistance, when coupled with the calculated predicted use based on programmed parameters (or past history of use), can provide an accurate prediction of remaining battery longevity. The nonlinear relationships shown in Figures 30-17 and 30-18 demonstrate why battery voltage alone is a poor indicator of remaining battery longevity. Traditionally, the clinician has assessed battery longevity by a rate change in response to the application of a magnet to the IPG. The magnet would force asynchronous pacing, the rate of which is an indicator of battery internal resistance. Now, a more useful estimate of remaining longevity can be obtained by interrogation of the IPG with a programmer.

The theoretical energy density of the Li-I_2 system is approximately 1.9 Watt-hours per cubic centimeter (Wh/cm^{-3}). Although real Li-I_2 batteries usually achieve less than 1 Wh/cm^{-3}, this is a high energy density compared with other commonly used batteries, and higher energy density results in either greater longevity or smaller battery size. However, Li-I_2 batteries can deliver long life only at low rates of discharge. This battery type is therefore well suited for IPGs because cardiac pacing therapy requires relatively low power levels. Although individual pacing pulses are in the order of tens of milliwatts (mW), they last for milliseconds and typically occur at a frequency of 60 to 70 pulses per minute. Thus the average power level for pacing therapy is generally in the order of tens of microwatts, depending on device programming and the therapy needs of the patient. Additional low power demands on the battery are related to IPG circuitry efficiency, including sensing, maintaining memory and, transiently with telemetry, communicating. Although the rate of power consumption of IPGs is low, the frequent application of pacing therapy, as well as the continuous background device operations, affects the longevity of a battery.

Battery Testing

An important challenge for IPG and battery developers is predicting the long-term performance of a battery. It is not always practical to simulate real use conditions, which last for 5 to 10 years or even longer, in battery tests. As a result, accelerated test protocols

are used to deplete the battery more quickly to obtain battery performance data in a shorter period. Accelerated tests discharge batteries at faster drain rates and, sometimes, higher temperatures. Faster drain rates shorten the time required to discharge the battery. Higher temperatures increase the rate of parasitic chemical reactions that can reduce the available capacity of the battery and thus negatively affect IPG longevity.

The results of accelerated tests are then used to develop battery performance models, which are subsequently used to predict the long-term performance under more realistic use conditions. The ability of battery performance simulations to accurately predict IPG longevity depends on a model that adequately describes battery behavior and a sufficient set of test data to use in the model.

Numerous tests are used to identify design and manufacturing process weaknesses that might result in battery failures. These weaknesses are then addressed through design and process improvements. Some of these tests are intended to evaluate the conditions that may be experienced after IPG implantation, whereas other tests assess the safety of the battery during abnormal mechanical and environmental conditions that may occur during shipping. Some of these tests have been defined by the United Nations.[10] Mechanical and environmental tests often are performed with batteries at different levels of depletion, typically at 0%, 50%, and 100% states of discharge. Commonly run tests for IPG batteries include the following:

- Exposure to high levels of mechanical shock and vibration
- Crushing or impact on the battery with extreme force
- Temperature shock—repeated, rapid change between high and low temperatures
- High pressure exposure
- Low pressure exposure
- High temperature storage
- Low temperature storage
  - External short circuit
  - Forced overdischarge—applying a load to drive a battery well past its normal end-of-life condition

Failure Modes

In some IPG failure modes, such as rapid discharge as a result of a short circuit in the IPG circuitry, the battery is not the cause, but rather the victim. Some failure modes originate within the battery. Battery failure modes lead to reduced power capability, decreased longevity and, in extreme cases, complete failure. Reduced performance may result in compromised therapy or reduced IPG functionality. Decreased battery longevity leads to a shortened device life. Complete battery failure means a device does not function at all.

One cause of reduced power output and decreased longevity is an increased internal resistance. This may occur if the internal battery electrode connections are not properly welded or if defects are present in the mechanical components themselves. In some cases, this can occur because of corrosion of the metal parts. A complete failure to function would ensue from complete detachment of the electrical connections, resulting in an open circuit.

Another source of high internal resistance leading to lower power output and shorter longevity is the excess formation of Li-I from the direct reaction between Li and I_2. One way for this to occur is long-term exposure to high temperatures greater than 50° C.

Table 30-1 Common Battery Failure Modes and Root Causes

BATTERY FAILURE MODES	ROOT CAUSES
Decreased longevity and reduced power capability	High internal resistance: Buildup of high resistance on electrodes (lithium-iodide in the case of lithium-iodine) High internal resistance: Poor welds in the current-carrying paths between the electrodes and terminal pins High internal resistance: Corrosion
Decreased longevity	Internal short circuit: Direct contact between positive and negative current paths from the electrode to the terminal pin Internal short circuit: Foreign materials or impurities Self-discharge Loss of hermeticity through seal or battery can weld seams
Loss of function	Open circuit caused by failed welds in the current-carrying paths

Self-discharge is the loss of active materials through parasitic chemical reactions that occur naturally. Battery capacity lost through self-discharge is not usable by the IPG and contributes to reduced longevity. This type of capacity loss for Li-I_2 batteries generally becomes extremely small once the initial Li-I layer is formed.

A short circuit within the battery decreases the longevity through parasitic reaction pathways that deplete the battery's active materials. Li-I_2 batteries cannot support high discharge rates; this tends to limit how rapidly the battery will completely discharge. One cause leading to internal short circuits is the direct connection between the anode and the cathode somewhere in the current path from the electrode to the terminal pin. Another cause is foreign material or certain impurities that are inadvertently incorporated into the battery during manufacturing. Other failure modes are listed in Table 30-1. However, battery failures are quite rare; in particular, Li-I_2 has a decades-long track record of high reliability.[9-12]

Pulse Generator Circuitry

Electrical Design

The basic design requirements include the functional elements described in the introduction but with a minimal current drain, and small size.[11] Minimizing the energy needed for the functions of the pulse generator (PG) is the one design parameter available to reduce battery size and still maintain device longevity. The building blocks of the electronic circuitry are depicted in Figure 30-19.

Mechanical Design

The mechanical design is dictated by the overall volume requirement of the PG, the electrical design, and the industry standards for lead connections (e.g., IS-1, IS-4) (Figures 30-20 and 30-21).

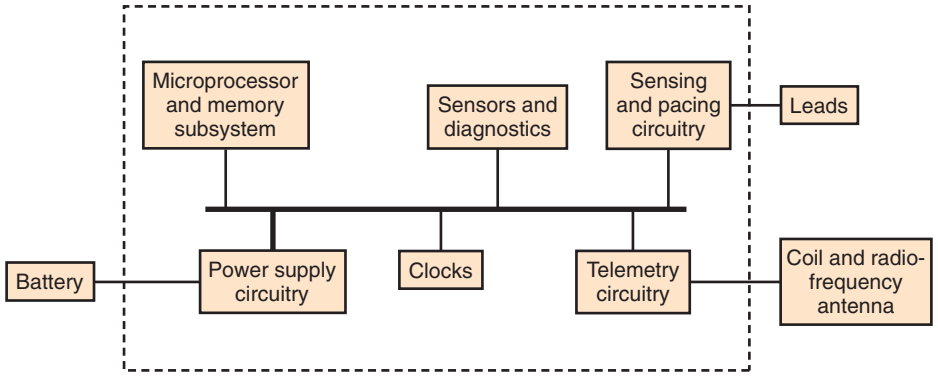

FIGURE 30-19 Block diagram of the major building blocks of the electronics in a pacemaker.

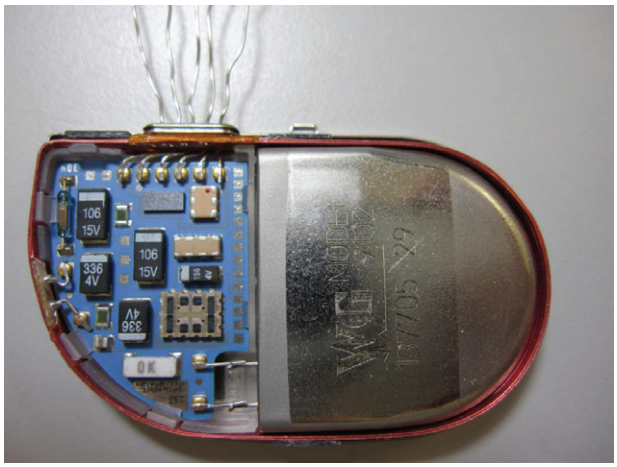

FIGURE 30-20 The inside of a pacemaker showing the hybrid circuit and battery. The battery is on the *right*; the hybrid circuitry, which includes an integrated circuit chip, is on the *left*. Around the perimeter is the telemetry coil. At the *top,* the feed-through wires are seen; they would normally enter the header.

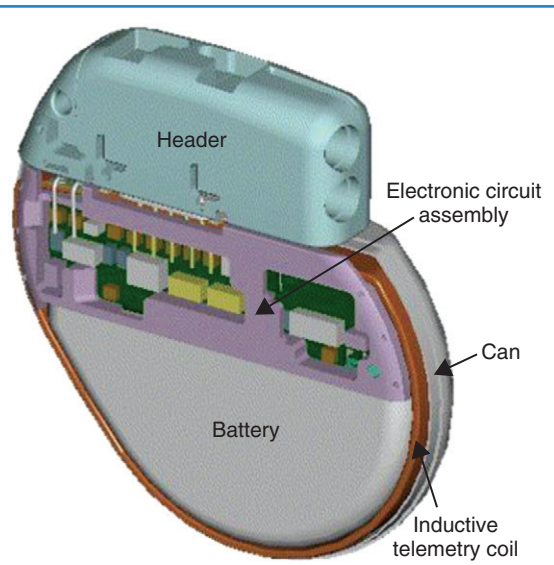

FIGURE 30-21 A pacemaker showing the header.

The PG comprises the metallic PG can and the header that houses the lead interconnect system. The PG is typically made from titanium because of titanium's strength, cost, ability to produce a hermetically sealed weld, and biocompatibility. The header typically has lead bores that receive the connector ends of leads. The leads are secured to the header and make electrical connection through the use of one or more set screws. Additional electrical connections may be made passively by spring connectors that allow insertion of the lead into the lead bores yet provide appropriate electrical connection with the lead conductors. Access to set screws is achieved through sealable slits in the silicone seal plugs that cover the head of the set screw. Seal plugs keep the conductors that are connected to the set screws electrically isolated from each other and from the surrounding body tissue, fluid, and muscularly generated electrical signals. Insulated feed-through wires run within the header from the connections to the titanium can.

Sensing Subsystem

Although the intracardiac leads provide high-fidelity electrocardiograms (ECGs) to the device, other noise sources such as skeletal muscle depolarization and electromagnetic interference (EMI) can adversely affect the appropriate detection of intrinsic cardiac activity. Therefore considerable effort and importance are placed on providing the device with the highest quality ECG signals. Assuming the lead is placed correctly, the sensing is designed to minimize noncardiac electrical signals. This is accomplished by EMI filters very near or at the point where the electrical connections enter the titanium can. The function of these is to eliminate high-frequency noise sources, which can be easily imparted onto the leads by welding equipment, fluorescent lights, cell phones, retail theft device trackers, and microwave ovens. Although these are the most notable and notorious sources, a large number of potential sources exist; thus great care is given to the design and testing of this function. Common mode noise rejection, differential amplification, or both may be used to reduce extracardiac signals. In addition to EMI filtering, further electrical filtering is performed on both hybrid and integrated circuits to eliminate skeletal muscle noise and maximize the signal in frequency ranges expected for P and R waves while avoiding amplification of the T waves. The threshold for detection of cardiac activity may be a programmable fixed signal size or may be variable and dictated by an automatic gain control algorithm. The sense amplifiers are blanked during stimulation and for a period

shortly thereafter to avoid detection of the stimulation artifact or polarization voltage. Timing circuits are used to dictate the periods of sensing in the various channels.

Pacing Subsystem

Pacing occurs only when needed, on the basis of the programmed parameters and the time since the last sensed or paced event. Minimizing pacing therapy or reducing the programmed pacing voltage improves device longevity. The pacing pulse is biphasic in nature to ensure that cardiac tissue is left in a charge-neutral state after the pace. This pulse is created by delivering a pseudo-constant voltage pace pulse followed by a recharge pulse. The charge-neutral pulse reduces the possibility of electroplating the electrode metal onto cardiac tissue as well as inappropriately sensing the after-potential. Limitations are placed on the maximum possible rate of pacing for safety.

Sensors and Other Diagnostic Circuits

Pacemakers also have additional circuits for managing power supplies for battery management, diagnostic functions, and various sensors for determining the optimal pacing rate. The following are some examples:

- Motion sensor (accelerometer): Motion does not accompany all physiological stresses; nonphysiological causes of motion may activate the sensor
- Minute ventilation sensor (impedance): Well-established normal relationship between ventilation and heart rate
- Cardiac contractility measurement (impedance)
- Temperature and oxygen measurement (not commercially used)

Internal Clocks

Pacemakers use at least one independent oscillator circuit to provide a timing reference, sometimes known as the *master clock*, for operating various other circuits. The oscillator typically derives its frequency from a crystal that vibrates at a known fixed frequency. Design considerations include keeping the frequency within a narrowly defined range and impervious to changes in temperature and other circuit fabrication parameters. Even though the temperature is highly stable once the pacemaker is implanted, the device needs to be able to handle a vast range because of transportation considerations. Additional circuits may derive multiple clocks of several other frequencies, as needed, by using the master clock. Any significant changes in the frequency of the master clock, even for a short period, can cause the pacemaker to malfunction because almost all the other circuits use the master clock directly or indirectly for their correct operation. Additional independent clocks with different designs may be used to detect any deviation of the master clock and take appropriate action to prevent harm to the patient. One form of degraded safe mode operation is to allow loss of pacing therapy but prevent active harm such as pacing too fast or pacing at the wrong time.

Microprocessor and Memory Subsystem

Microprocessors have been an integral component of pacemakers for at least 2 decades now. The increasing complexity and number of pacemaker algorithms and programmable parameters drove the decision to use this technology. Current pacemaker circuits for the various subsystems such as sensing, pacing, and various diagnostic functions previously described are controllable by the microprocessor although independent in their continuous operation. The higher level system function of changing the operating parameters of these circuits resides in the software executed by the microprocessor subsystem. The pacemaker software provides the interface to make it easy for the human user (physician or nurse practitioner) to control these circuits.

The severe power constraint of the pacemaker design affects the choice and use of all electrical circuits, and the microprocessor is no exception. As such, the microprocessor can easily draw much power and drain the tiny pacemaker battery in a very short amount of time (a few months) if it is not managed carefully. Several design trade-offs are involved in managing the microprocessor power drain.

The first decision is the choice of which microprocessor to use. Should one of the microprocessors readily available in the larger electronics industry be used? Should a custom microprocessor be created? Which architecture is best suited to execute pacemaker algorithms in the most efficient manner?

Electronics industry microprocessors are usually designed to operate at voltages typically much higher than those of circuits used in pacemakers, in part because the major design driver is computational speed. However, pacemakers need adequate computational speed at the lowest possible power drain; as a result, the majority of today's pacemakers use custom-fabricated microprocessors.

Pacemaker microprocessors use very slow clocks (a few kilohertz to a few megahertz at most). The microprocessors usually are connected to one or more of the following types of memories: read-only memory (ROM), static random access memory (SRAM), electrically erasable programmable read-only memory (EEPROM), or Flash-based memory (Adobe Systems, San Jose, CA). Pacemaker memory capacities typically range from a few kilobytes to a few megabytes. Pacemakers do not use any form of disk-based storage because of the power constraints and the inherent unreliability of moving parts.

Many methods are used to get the most efficient operation out of microprocessors. However, the most efficient microprocessor is still no match for dedicated low-power circuits used in a pacemaker, mostly for functions such as sensing. An energy-saving method involves turning off the microprocessor for the majority of the timing cycle. This means that the microprocessor is woken up to do its computation when a new event occurs and is put back into a dormant low-power "sleep" state as soon as it finishes its computation and delivers its decisions. A very rough estimate is that a pacemaker microprocessor spends more than 90% (or even >99%) of its entire lifetime of the device in its "sleep" state. Even during a relatively active period such as at implantation or during a follow-up, microprocessor use does not significantly rise; when the microprocessor is awake and executing software, it usually executes a tiny fraction of its code. The vast majority of pacemaker code is in place to handle situations that are rarely encountered. A large portion of the software in a pacemaker remains mostly unused on a beat-by-beat basis while the microprocessor executes a minimized number of computations. Typical functions on a beat involve figuring out the exact time to deliver the next pace pulse if the pacemaker is programmed to a rate-adaptive mode. The algorithms implemented in the software determine the ideal target heart rate based on sensor inputs and the current

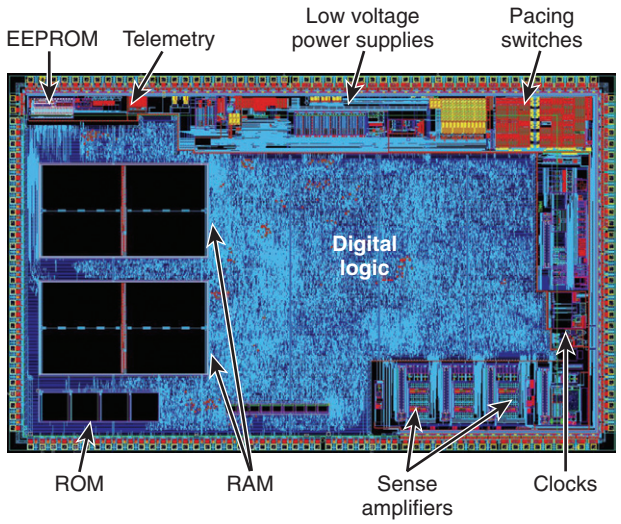

FIGURE 30-22 A mixed-signal integrated circuit. *EEPROM*, electrically erasable programmable read-only memory; *ROM*, read-only memory; *RAM*, random-access memory.

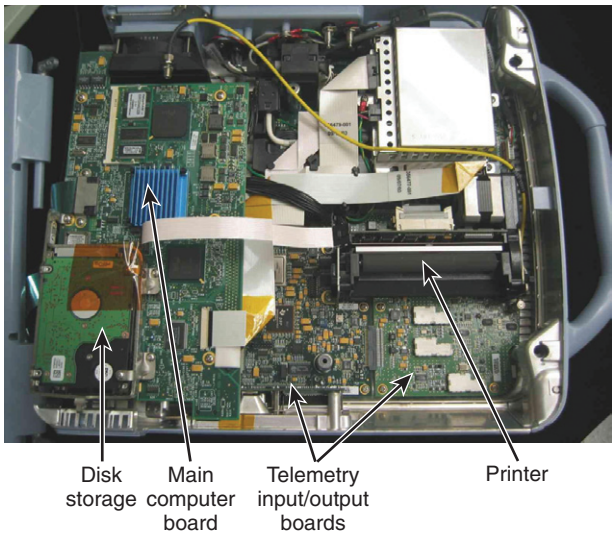

FIGURE 30-23 Internal view of a programmer. The components include the power supply, printer, disk storage, telemetry, and input/output boards.

programmed settings and compute the next time interval to deliver a pace pulse if the heart does not beat intrinsically.

The software typically is also responsible for initiating and collecting diagnostic data that would convey information about the patient's health to the physician. In addition, the pacemaker may also collect diagnostic information about its own performance to help diagnose and repair potential malfunctions.

Integrated Circuits

Pacemaker integrated circuits (ICs) may be purely digital or a mixture of analog and digital circuits, also known as *mixed-signal integrated circuits* (Figure 30-22). The electronic subsystems previously described are packed into two integrated circuits. The defining characteristics of pacemaker ICs are very high reliability, high complexity, low power consumption, and small volume. The ICs are housed along with other discrete components (resistors, capacitors) on a hybrid to form the core packaging for the electronics.

Telemetry Subsystem

Telemetry allows the physician to program the pacemaker noninvasively for individual patient needs after implantation. It also allows the noninvasive retrieval of diagnostic information stored in memory. Basic telemetry functionality has existed in pacemakers even before microprocessors were used. Current pacemakers typically use a combination of dedicated circuitry and microprocessor-based software to accomplish the communication functions of the system. Dedicated circuitry in the form of a receiver and a transmitter exists in the pacemaker to accomplish the low-level signal communication function with external devices such as a programmer recorder monitor (PRM) (Figure 30-23). The dedicated receiver circuitry does the work of deciphering encrypted incoming signals and notifies the microprocessor when it receives valid messages. The higher level function of message processing is typically carried out by the software. Correspondingly, when the microprocessor has something to transmit back, it pushes the data out via the transmit circuitry.

Security has become an important consideration in telemetry design because of patient privacy and security concerns.[12,13] With remote telemetry, the range (distance) at which the pacemaker telemetry is able to operate has increased. Manufacturers offer remote monitoring or follow-up solutions through specialized external devices that transmit their data over telephone lines, cellular networks, or other communication links that may be part of the Internet (Figure 30-24).[14] These technological advances also increase the potential risks of eavesdropping as well as unauthorized access to these devices.[15] Some privacy laws also require manufacturers to take reasonable steps to ensure that sensitive patient data remain protected. Manufacturers adapt various forms of cryptography solutions available in the computing and telecommunication industries to fit the size and power constraints of the pacemaker to address these security concerns. The security solution is also an integral part of external devices (programmer, remote monitor) designed and approved to communicate with the pacemaker.

Fault-Tolerant Design and Risk Management in Pacemakers

Product design is the first step in providing a reliable pacemaker. *Design validation* establishes, through objective evidence, that device specifications conform to user needs and intended uses. The safety aspect of the design needs to cover potential misuse in addition to intended use. *Design verification* confirms, by examination and provision of objective evidence, that specified requirements have been fulfilled. Manufacturers use numerous analytical and test methods (Box 30-1) to fulfill the validation and verification obligations to gain regulatory approval to market these devices. Many of these methods are used during the development of the pacemaker. The output of the design phase is a set of specifications. Once the design has been completed and the

FIGURE 30-24 Example of a remote follow-up cardiac rhythm management (*CRM*) system. *HF*, Heart failure; *BP*, blood pressure.

Box 30-1 Test and Analytical Methods Used in the Design and Manufacture of Pacemakers

Requirements analysis
Hazard analysis
- Failure modes and effects analysis
- Failure modes, effects, and criticality analysis

Stress testing
- Accelerated lifetime testing
- Thermal stress testing
- Vibrational stress testing
- Shock stress testing

Confidence/reliability testing
- Statistical sampling

IC testing
IC analog circuit simulations
IC digital logic simulations
IC timing simulations
Hybrid testing
Software testing
- Unit testing
- Integration testing
- Verification testing

Software analysis
- Inspection of the program source code
- Automated and manual software analysis to detect known forms of errors

Simulated use testing
Electromagnetic interference testing

IC, *Integrated circuit.*

Box 30-2 Food and Drug Administration Definitions of Faults

Fault (defect): Abnormal condition that may cause a reduction in, or loss of, the capability of a functional unit to perform a required function

Failure: The inability of a system to perform its required function within specified performance requirements

Fault tolerance: The ability of a functional unit to continue to perform a required function in the presence of faults or errors

Harm: Physical injury or damage to the health of people, or damage to property or the environment

Hazard: Potential source of harm

From http://www3.hi.is/pub/cs/2003-04/reliability/definitions/Fault_terms.html.

production of the device starts, automated testing is used at all levels of the manufacturing process to ensure that each individual device meets its specifications per the device master record.

Faults can lead to *failures*, which, in turn, can activate a *hazard*. Hazards can lead to *harm* (Box 30-2). Some failures may not activate hazards but may lead to loss of functionality, which can inconvenience the user (e.g., loss of a noncritical diagnostic feature). Some hazards may be naturally present in the operating environment of the device. If the hazard source is known, then preventing the hazard from turning into harm is a design challenge. For example, the use of magnetic resonance imaging (MRI) has been contraindicated by device manufacturers in the past. However, some devices have been designed to be safer with controlled use of MRI and are currently in various phases of the approval process.

Some environmental conditions can induce faults that can lead to failure (Box 30-3). In such cases, the environmental influence

Box 30-3 Examples of Environmental and Medical Hazards

Electromagnetic interference
- Medical equipment
- Home appliances
- Cellular phones
- High-voltage power lines
- Electronic article surveillance equipment

Lithotripsy
Therapeutic ultrasound
Transcutaneous electrical nerve stimulation
Electrocautery
Radiofrequency ablation
External defibrillation
Ionizing radiation
- Therapeutic radiation

Radioactive cobalt, linear accelerators, betatrons
- Cosmic (naturally occurring) background radiation
- High-energy x-rays, computer-aided tomography scans
- Radioactive impurities in materials

Diagnostic x-ray and fluoroscopic radiation
Magnetic resonance imaging

This is not an exhaustive list for all pacemakers. Please consult the appropriate product documentation.
From System Guide, *INSIGNIA I ULTRA, Boston Scientific Corporation.*

Box 30-4 Potential Failures and Possible Root Causes (Faults)

RANDOM COMPONENT FAILURES
Integrated Circuit Failures
- Silicon-controlled rectifier latch-up
- Impurities during fabrication
- Electrostatic discharge

SYSTEMIC DESIGN FAULTS THAT COULD LEAD TO FAILURE
Logic Errors in Circuits
Timing Errors
Software Error
- Incorrect or incomplete specifications
- Logic errors
- Improper error handling
- Inability to meet timing requirements
- Out of memory

This is not an exhaustive list. These examples are intended to provide an insight into the engineering challenges of designing a permanently implanted pacemaker.

Box 30-5 Example of a Transient Fault and Possible Mitigation

Single event upset is a change of state experienced by semiconductor devices from ionizing radiation. The effect of this is usually observed in large-scale integrated memories, where one or more "bits" of information may change their state.

Partial physical redundancy—such as the use of error-correcting memories using Hamming codes or cyclic redundancy check–based error detection and correction—can be an effective mitigation for this type of fault.

is also treated as a hazard. Ionizing radiation is an environmental hazard that carries the potential for inducing faults, which can cause device malfunction and lead to additional hazards.

Risk management plays a key role in the design decisions involved in managing hazards and their outcomes. Risk is evaluated along two dimensions: (1) the severity of a potential harm and (2) the estimated likelihood of encountering a hazard. Hazard analysis is a formalized development activity to manage this risk. Thus, ionizing radiation may induce random bit flips in memory, but error-correcting software may correct this. However, severely corrupted memory secondary to therapeutic radiation, if unused, may potentially go undetected until this portion of memory is first used. Accordingly, the ability of the device to function fully or partially in a safe manner becomes increasingly important. Examples of safe but degraded function include the lead safety switch—which automatically switches the pacing and sensing configuration from bipolar to unipolar if unusually high or low lead impedance is detected; and the reset mode—which is limited to basic life support function, with fixed pacing rate and amplitude.

Surgical electrocautery is another common medical environmental hazard, which, on occasion, may affect sensing, pacing, lead integrity, and the lead\tissue interface. At the time of this writing, the Heart Rhythm Society was in the process of developing a policy for perioperative care of patients with ICDs to mitigate this risk.

Fault-tolerant designs use various forms of redundancy to mitigate the effects of potential component malfunction and deliver appropriate performance that is transparent to the end user of the system (Box 30-4). When full performance cannot be delivered, a degraded but safe operation is provided. Unfortunately, the pacemaker cannot have complete redundancy of all subsystems, such as multiple batteries, multiple microprocessors, or sensing and pacing circuits, because of size and power constraints. Thus serious malfunctions do occur at a small but definite rate in all cardiac rhythm management devices.

Temporal redundancies, such as a simple re-attempt of an operation or a reset, may overcome the effects of many types of transient faults (Box 30-5). Safety monitors may be used to detect potentially unsafe operations and stop them before they can do harm. Some examples include:

- Runaway pacing protection
- Temporal checks—placing time limits on inherently dangerous operations such as manual burst pacing
- Self-checking software—use of various techniques such as range-checking inputs and outputs, data integrity checks, or timing checks

Some design or operational defects may be corrected after implantation by updating the pacemaker software noninvasively using telemetry. The ability to accomplish this type of repair operation must be designed and tested by the manufacturer before it is actually deployed in a field setting.

An important step in detecting potential device malfunction and observing normal aging of devices is the detailed analysis of pacemaker function in returned products. Returning all explanted pacemakers to the manufacturer is an important step in maintaining adequate reporting and in early recognition of potential device issues so that patient safety is improved.

Summary

Physicians caring for patients with pacemakers should have a fundamental understanding of these complex devices to appropriately care for their patients and recognize any device-related issues. Device malfunctions are infrequent and often are the result of complex interactions among the device, physician technique (actions), and patient issues. However, all the manufacturers provide backup technical assistance, which physicians should make use of when needed.

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CHAPTER 31

Pacing Technology and Its Indications: Advances in Threshold Management, Automatic Mode Switching, and Sensors

Chu-Pak Lau and Chung-Wah Siu

Since the first endocardial pacing lead implantation in 1958, pacemaker therapy has undergone remarkable technologic advances. For example, the number of circuitry components has increased from a mere two to three transistors in early pacemakers to nearly one million components with RAM (random access memory) sizes up to 124,000 bytes.[1] This increased sophistication has led to pacemaker features that the average pacemaker implanter may not have the time to understand or to program appropriately. In addition, threshold and sensor assessment may take up to 40% of time in an average follow-up (Figure 31-1).[2] Thus, automatic optimization of many pacing parameters has become a pressing need. This chapter reviews the current state of the art in three important modern pacemaker functions: (1) capture management, (2) automatic mode switching (AMS), and (3) implantable sensors. Particular attention is given to their indications and automaticity in programming.

Capture Management

The primary function of a pacemaker is to pace effectively at an efficient energy output. This depends on the pacing threshold, which varies significantly from individual to individual and within an individual over time. The latter may occur because of the spontaneous threshold rise after implantation, the occurrence of gross dislodgment or microdislodgment, diurnal changes, and the changes introduced by drugs and myocardial ischemia.[3,4] Thus, the ability to track threshold automatically will maximize patient safety, minimize battery drain for pacing, and, importantly, simplify programming. Box 31-1 presents a list of reasons for the need for automatic capture management.

An increase in demand for battery energy can result from some sensors. Whereas the piezoelectric sensor is energy inexpensive, the impedance sensor, such as is used to monitor minute ventilation, requires significant current consumption. More energy is required for the purpose of device monitoring, particularly for electrocardiogram (ECG) storage, which is becoming important for patients with atrial fibrillation (AF). With the use of multisite pacing (atrial pacing [Ap] for AF and ventricular pacing [Vp] for heart failure), minimizing pacing energy becomes critical. The longer survival of patients means that at least two thirds of those who receive a pacemaker will live long enough to need a replacement within the usual battery life of 7 years. Atrioventricular (AV) nodal ablation followed by permanent pacing provides symptomatic relief and enhancement of quality of life. This group of patients is younger, and a longer battery life is advantageous. All these changes occur simultaneously with an overall effort by manufacturers to reduce the size of the device.

From a clinical standpoint, variation in threshold may lead to an inadequate safety margin of stimulation. Such changes may result from the usual rise of threshold after implantation, from ischemia, and from antiarrhythmic medications. Finally, threshold measurement remains a time-consuming process, and if an alternative safe method is available, the burden of programming can be reduced.

Types of Capture Management

Several manufacturers have introduced algorithms for detecting ventricular, atrial, and left ventricular (in cardiac resynchronization therapy [CRT]) thresholds. The detection of an evoked response is based on either evoked response or impedance. Threshold data are used either on a beat-by-beat basis to ensure a paced response or intermittently to adjust output parameters.

St. Jude/Pacesetter Autocapture

The Autocapture pacing system was first introduced in the single-chamber Microny pacemaker from St. Jude Medical in 1995. (See Box 31-2 for information on the manufacturers referred to in this chapter.) It is designed to verify a response to each pacemaker stimulation that represents capture or myocardial depolarization and to automatically adjust the pacing output accordingly on a beat-to-beat basis. After a VP stimulus, the Autocapture algorithm opens an evoked response (ER) detection window for 46 ms after a 15-ms blanking period. Detection of an ER is used to diagnose capture. If an ER is not detected (loss of capture), a high-energy backup pulse of 4.5 V is discharged at 100 ms after the VP stimulus. If two consecutive backup pulses are delivered, the algorithm starts a stimulation threshold search by increasing the output to effect two consecutive captures (Figure 31-2). In single-chamber devices (Microny and Regency SR), a margin of 0.3 V is added. In addition, to avoid pacing at high output caused by diurnal fluctuation in threshold, the device automatically performs a threshold search once every 8 hours. Again a safety margin of 0.3 V is added to the detected threshold. In dual-chamber devices, the A-V interval is shortened to 50 ms (Ap) or 25 ms (atrial sensing [As]) to ensure overdrive of intrinsic ventricular rhythm. In the Affinity DR, automatic decrements and increments of output during threshold search are 0.25 V and

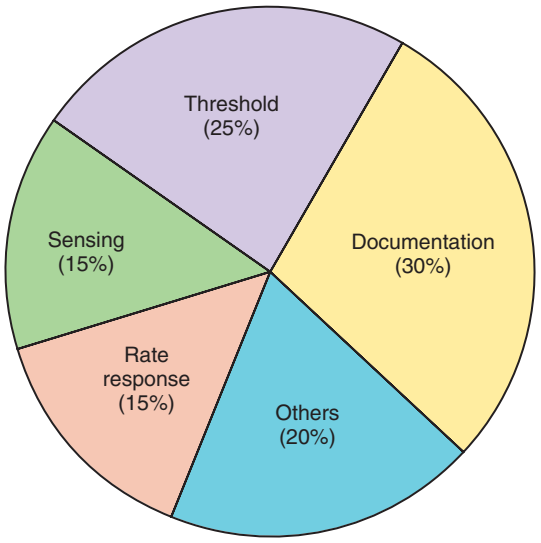

FIGURE 31-1 Time used for different activities during a routine pacemaker follow-up. *(From Marshall M, Butts L, Flaim G, et al: Predictors of time requirements for pacemaker clinic evaluation [abstract],* Pacing Clin Electrophysiol *18:952, 1995.)*

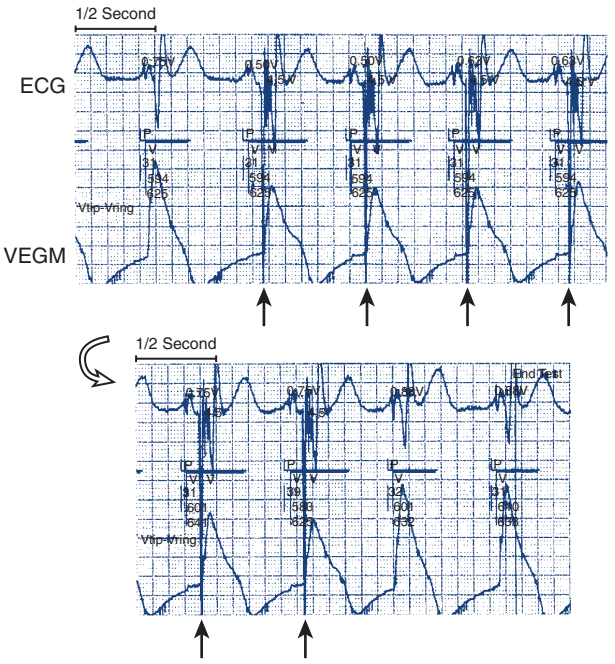

FIGURE 31-2 Autocapture threshold determination in a patient implanted with the Affinity. Successful ventricular capture was documented in the first beat. A reduction of ventricular output to 0.5 V resulted in failed capture (second beat), and a backup pulse (*arrow*) was emitted. An upward search then begins at increments of 0.125 V, and the search ends when two consecutive capture beats are achieved at 0.88 V. *VEGM*, Ventricular electrocardiogram (tip to ring).

Box 31-1 Needs and Potential Benefits of Capture Management

Increase in battery drain (e.g., sensors, electrocardiogram monitoring, and multiple-site pacing)
Increase in battery longevity
Two thirds of patients will be alive at the time of battery replacement
Pacing for populations such as those with atrial fibrillation and for those after atrioventricular nodal ablation
Reduction in battery size
Physiological/medical variations in threshold
Reduction in time for pacemaker programming

Box 31-2 Pacemaker Manufacturers and Models

Biotec, S.P.A., Bologna, Italy
Biotronik GmbH & Co., Berlin, Germany (Inos)
Cardiac Pacemakers Inc., St. Paul, Minn.
Cook Pacemakers Corporation, Leechburg, Pa.
ELA Medical, Rougement, France (Chorum DR, model 7034/7134; Talent DR, model 223)
Guidant CPI, St. Paul, Minn. (Discovery, model 1273/4/5; Meridian DR, model 1276; Pulsar Max DR, model 1270; Vigor DR, model 1230/2/5)
Intermedics Inc., Freeport, Tex. (Marathon DR, model 294-09)
Medtronic Inc., St. Paul, Minn. (AT 500 DDDRP, model AT500/500C; Kappa, models 400 and 700; Thera DR, model 7960/1/2)
Siemens Pacesetter Ltd., Solna, Sweden
Sorin Biomedica, Saluggia, Italy (Living 1, Living 1 Plus)
St. Jude Medical Pacesetter, St. Paul, Minn. (Affinity DR, model 5330/1; Trilogy DR, model 2364)
Telectronics Pacing System, Englewood, Colo. (Meta DDDR, models 1250, 1254, 1256)
Vitatron BV, Dieren, The Netherlands (Clarity DDDR, Model 860/2/5; Diamond, model 800/801/820/840)

Box 31-3 Factors Affecting Capture Detection

Electrode polarization
Fusion beats (false negative → ↑output)
Ventricular capture + intrinsic beat
Pseudo-fusion beats (false positive → ↓ output)
Pacing spike (and failure of capture) + intrinsic beat
Algorithm related: unipolar pacing, bipolar sensing
Adequate evoked response (>2.5 mV)
Other applications: atrial, epicardial, and left ventricle

0.125 V, respectively (see Figure 31-2). In addition, beat-to-beat capture verification has only recently been extended to atrial stimulation in the Zephyr pacemaker by St. Jude Medical (ACP confirm), as the small atrial electrical signal represents a major challenge in discrimination between the ER signal and the pace-induced after-polarization (see below).

Efficacy

Factors that affect the Autocapture's detection of an ER are listed in Box 31-3. One major challenge to this approach is the difficulty in distinguishing the ER signal and the pace-induced after-potential. A large electrode polarization artifact relative to the size of the ER can affect ER detection. This can be reduced with the use of low-polarization electrodes (made possible by increasing

the microscopic electrode-tissue interface area).[5] An alternative is to use a biphasic waveform that comprises a fast precharge followed by a negative postcharge to minimize the polarization effect.[6] In one study, the effect of a modified fast prepulse on the Autocapture was tested in 45 patients with leads from two manufacturers (Medtronic 4024 Cap Sure, and Pacesetter 1450 K/T and 1470 T leads).[7] Whereas the ER was independent of the type of pacing pulse, the polarization artifact was significantly less during the modified pulse compared with the conventional pacing pulse, resulting in an improved efficacy of the Autocapture algorithm (94% vs. 71% success rate in ER detection). An adequate ER amplitude of greater than 2.5 mV is recommended before activation of the Autocapture algorithm; this was present in 93% of 60 patients in one study.[8] Neither the clinical data nor the conventional electrical parameters were effective in predicting the size of the ER signal. Body posture and exercise had relatively little effect on the ER.[9] Recently, a new ER algorithm measuring the depolarization integral (area) instead of ER signal amplitudes (voltage) to determine ER has enhanced the accuracy of capture verification; in fact, the algorithm allows ER determination even with old high-polarization bipolar leads. Because of enhanced sensitivity, it has become possible to distinguish a small atrial ER from a pace-induced after-potential.

In a multicenter study, 113 patients received the Pacesetter Microny SR+ and were followed up for 1 year. ER was satisfactory for Autocapture in 102 of 113 patients.[10] Even though ER was stable over time it correlated poorly with the R wave at the time of implantation. Acute and chronic pacing thresholds measured at the clinic using a standard surface ECG VARIO threshold test significantly correlated with that derived from the Autocapture, although the Autocapture threshold was higher (0.11 ± 0.22 V) because of the way in which threshold was derived. During Holter recordings, no failure of ventricular capture occurred, and backup pulses were used in 1.1% of all paced beats. Most of these were caused by fusion or pseudo-fusion beats (87%), undersensing of either the R wave or the ER (4.6%), and was the true cause of loss of capture in only 7%. Although these did not affect pacing performance, the need for backup pulses may negate the energy saving by the Autocapture itself. Similar positive results from the Autocapture algorithm in the medium term for safety and efficacy have been published.[11,12]

Projected increases in battery longevity afforded by the Autocapture have been reported.[13,14] Compared with the factory-set pacemaker setting of 5 V, the Autocapture reduced the energy drain in the Microny SR+ (with 0.35 Ah) and increased device longevity by 53%. For the Regency SR+ with a larger battery (0.79 Ah), the increase in device longevity was even more significant (245%). However, when the conventional output was reduced to 2.5 V, the benefit of the Autocapture on battery life was much less impressive.[13,14]

Clinical Implications

The main benefits of any automatic capture management algorithm are patient safety and effective capture during threshold changes. Programming of threshold can be simplified as the Autocapture threshold has been significantly correlated with bedside threshold assessment. The energy saving would be more important in patients with chronic high thresholds. Conversely, fusion and pseudo-fusion beats appear to be the main limitation, not only because they reduce battery energy but also because they may lead to erroneous threshold determination.[15]

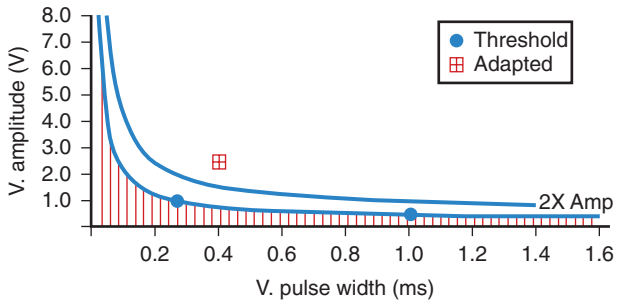

FIGURE 31-3 Ventricular capture management (Medtronic Kappa 700). The device has determined the rheobase (at 1 ms) and chronaxie and recommends a safety margin of twice the amplitude threshold.

Boston Scientific Automatic Capture

Likewise, the automatic capture algorithm from Boston Scientific also provides a beat-to-beat verification of myocardial capture based on the ventricular ER. The ventricular voltage output is automatically adjusted to 0.5 V above the measured threshold. When loss of capture occurs, a backup pacing pulse 1.5 V higher than the measured threshold is delivered 100 ms after the primary stimulus. When loss of capture is confirmed for two cycles out of four beats, an automatic threshold test will check for the new threshold.

Biotronik Capture Control

The Logos pacemakers measure the ER signals from several successful capture beats to generate a reference curve, against which failure of capture is compared.[16,17] No backup pacing pulses are present, but persistent loss of capture results in the increase of pulse output in 2-V steps. After a programmable period, the output is reduced to the programmed value. This algorithm ensures patient safety through beat-by-beat capture verification.

Medtronic Ventricular Capture Management

The Kappa 700 pacemakers incorporate a threshold assessment based on ER: The Pacing Threshold Search (ambulatory) and Capture Management Threshold Test (bedside). During the procedure, the threshold at the Rheobase is determined at 1 ms by amplitude decrement until loss of capture and then by amplitude increment until capture is confirmed. The chronaxie is then determined by doubling the programmed amplitude and decreasing the pulse width (and subsequently increasing the amplitude to capture). A recommended pacing setting is then determined (Figure 31-3). The physician can use the ambulatory threshold data to automatically adjust threshold (adaptive), use the data only for monitoring, or turn off the algorithm. A minimal adapted output needs to be programmed. The ventricular capture management can be activated once every 15 minutes for 42 days and is not a beat-by-beat threshold tracking algorithm.

Automatic Mode Switching

Because the ventricular response of a DDD pacemaker is dependent on the atrial rate, rapid VP can occur in a DDD pacemaker

during episodes of atrial tachycardias (AT), especially during AF (Figure 31-4). This is managed in contemporary pacemakers by using an algorithm known as *automatic mode switching*. Patients with dual chamber pacemakers will develop AT for several reasons: (1) Nearly one half of patients receiving pacemakers have sinus node disease, and a substantial proportion of these patients have bradycardia-tachycardia syndrome. (2) As many as 30% of patients with complete AV block either have coexistent bradycardia-tachycardia syndrome or will develop this problem with time.[18] (3) A dual chamber pacemaker is often used in patients after AV nodal ablation for refractory AT. (4) The incidence of AF increases markedly with age.[19]

Several registries and controlled trials have generated data on the incidence of AF. From 1988 to 1990, 12.9% of Medicare pacemaker recipients who received dual-chamber pacemakers had underlying paroxysmal AF.[20] After implantation of a dual-chamber pacemaker, patients have an overall 2% to 3% per year risk of developing AF. In patients with sinus node disease, the risk of developing paroxysmal or persistent AF is increased to 8% per year.[21-24]

Conventional or specially designed pacemakers can convert automatically to another pacing mode under a variety of circumstances.[25-32] The term *automatic mode switching* is now used to define an automatic function whereby a device is designed to switch temporarily to a nonatrial tracking destination mode during an AT and to switch spontaneously back to the original mode on resumption of sinus rhythm.

Components of an Automatic Mode Switching Algorithm

The components of AMS function include (1) AT detection, (2) pacemaker response during AMS, and (3) resynchronization to sinus rhythm or atrial paced rhythm at AT termination.

Atrial Tachycardia Detection

A device can detect AT in four main ways (Table 31-1): (1) Most devices use a *rate cutoff* criterion, in which a sensed atrial rate exceeding a programmable value will result in AMS. Some systems are designed to avoid mode switch during atrial ectopic beats or short runs of AT. For example, four short cycles of seven consecutive beats are required before AMS occurs in the Medtronic Kappa 700. Interval number summation is used in the incremental and decremental counter of the Meta DDDR for short cycles and long cycles, respectively. (2) Some devices use a *mean atrial rate*, or matched atrial rate, based on a moving value related to the duration of the prevailing sensed atrial cycle as a criterion to move toward AMS. AMS will occur when the matched atrial interval has shortened to a predetermined duration. This algorithm is used in the Medtronic Thera DR, the Kappa 400 (GEM DR ICD), and the St. Jude Trilogy DR+/Affinity family. Because the process is gradual, the rapidity of AMS will depend not only on the AT detection rate or interval but also on the pre-existing sinus rate. It is easier for the matched atrial interval to reach the tachycardia detection interval when AT occurs in the setting of a higher resting

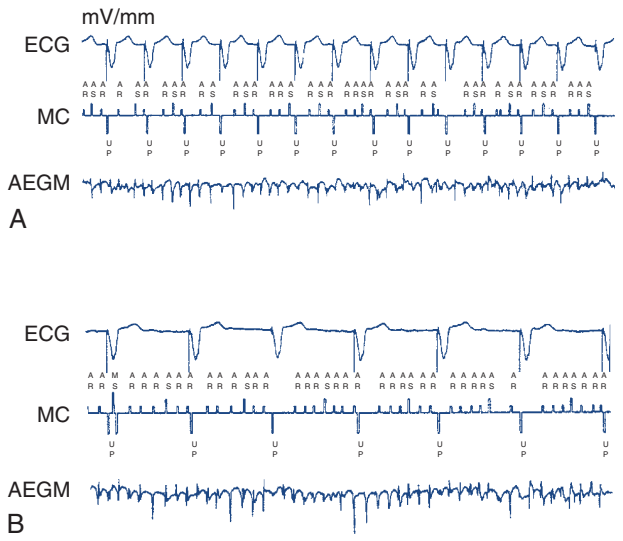

FIGURE 31-4 A, Rapid ventricular response in a patient with complete atrioventricular block with a Medtronic Kappa 400 pacemaker. The patient developed an episode of atrial fibrillation (AF) when the automatic mode switching (AMS) function was turned off. AF was detected by the atrial channel, and ventricular pacing occurred at an upper rate of 112 beats/min. **B,** Activation of AMS function in the pacemaker resulted in conversion to the DDI(R) mode with a ventricular rate at 60 beats/min. *AEGM*, Atrial electrocardiogram; *ECG*, surface electrocardiogram; *MC*, marker channel. *(From Lau CP, Leung SK, Tse HF, Barold SS: Automatic mode switching of implantable pacemakers. I: Principles of instrumentation, clinical and hemodynamic considerations,* Pacing Clin Electrophysiol *25:967–983, 2002.)*

Table 31-1 Classification of Different Methods of AT Detection in Current AMS Algorithms

CRITERION	EXAMPLES	INDICATIONS FOR MODE SWITCHING
Rate cutoff	Pulsar/Vigor/ Meridian/Discovery	Incremental/decremental counter
	Inos/Logos	Ratio of short/total cycles (e.g., 4 of 7 consecutive cycles)
	Kappa 400/700	Ratio of short/total cycles (e.g., 4 of 7 consecutive cycles)
	Marathon DR	Consecutive short cycles
	Meta DDDR (model 1254/1256)	Incremental/decremental counter
Running average rate	Thera DR	Matched atrial interval computed from prevailing atrial rate
	Trilogy DR Affinity	Filtered atrial interval
Sensor-based physiological rate	Clarity/Diamond	Single beat outside a physiological rate band (15 or 30 beats/min)
	Marathon DR	SmarTracking rate range (accelerometer sensor)
	Meta DR (model 1250)	Sensor-controlled PVARP
	Living 1/Living 1 Plus	Sensor-indicated rate to define tachycardia detection
Complex	Marathon DR	SmarTracking and rate cutoff
	AT 500	Rate cutoff and PR relationship

AT, *Atrial tachycardia;* AMS, *automatic mode switching;* PVARP, *postventricular atrial refractory period.*

sinus rate than from a sinus bradycardia. This is because the matching atrial interval starts from a shorter baseline duration on its gradual way to reach the tachycardia detection interval. (3) Sensors can be used to determine the physiological rate (e.g., Diamond and SmarTracking in Marathon). To take into account the fluctuation in sinus rate, a physiological heart rate range based on the sensor-indicated rate is used to define sinus rhythm, and rates beyond the upper end of the physiological range will activate AMS. (4) Complex algorithms are a combination of algorithms, or they use additional criteria (often from implantable cardioverter-defibrillators [ICDs]) to distinguish AF and other rhythms. For example, a PR logic and a rate criterion are instrumented in the AT500 (Medtronic, Inc.) to detect AF and AT.[33]

Destination Mode

Either the VVI(R) mode or the DDI(R) mode is used. No studies have been performed on the relative merits of the VVI(R) mode versus the DDI(R) mode. Obviously, during AMS, no AV synchrony occurs, and the DDI(R) is functionally equivalent to the VVI(R) mode. Theoretically, the DDI(R) mode may avoid AV dissociation when a sinus pause occurs at AT termination if the AMS algorithm has not yet resynchronized to sinus rhythm. The VVI mode during AMS has been described as VDI because the maintenance of As controls the perpetuation or termination of AMS, but this designation does not strictly conform to the standard pacemaker code. However, when AF is undersensed during AMS, atrial pacing in DDI(R) destination mode may paradoxically perpetuate paroxysmal AF. Apart from passive handling of AT in terms of the AMS algorithm, some devices deliver an active pacing intervention on the detection of frequent atrial ectopic beats, which are thought to herald the onset of AF, or an active pacing to terminate AT.

Resynchronization

Some AMS algorithms use the same onset criteria to resynchronize after AT termination, and some others, for example, Thera DR, use slower criteria of resynchronization to avoid intermittent AMS during short runs of AT.

The Ideal Automatic Mode Switching Algorithm

An ideal AMS algorithm (Table 31-2) should have an appropriate onset speed after AT begins. Prolonged rapid VP caused by a slow algorithm or oscillation between mode switching and tracking during short-lasting AT in a fast algorithm will result in undesirable ventricular rate fluctuation, AV dissociation, or both. It is clear that speed of response and rate stability are two competing parameters. Atrial and ventricular responses during AMS should result in a pacing rate appropriate to the pathophysiological state of the patient. In general, this rate is sensor determined. At the termination of AT, and to avoid AV dissociation during the process, the algorithm should resynchronize to sinus rhythm at the earliest opportunity. Many algorithms incorporate a rate fallback mechanism to ensure smooth rate control during mode transitions. With ideal sensing and programming, these characteristics are dependent entirely on the AMS algorithm.

In clinical practice, however, arrhythmia-related and sensing-related issues affect the sensitivity and specificity of the AMS response significantly. *Sensitivity* of an AMS algorithm refers to its ability to detect AT (i.e., avoid false-negative response), whereas *specificity* refers to the absence of AMS during sinus rhythm (i.e., avoid false-positive response) (Table 31-3). With AMS algorithms, the greater the sensitivity, the lower is the specificity, and vice versa.

Table 31-2 Characteristics of an Ideal AMS Algorithm

CHARACTERISTICS	REMARKS
Onset	Is rapid and avoids high-rate ventricular pacing without causing frequent mode oscillations during unsustained AT
Response	Avoids excessive rate fluctuation Avoids inappropriate atrial pacing
Resynchronization	Restores AV synchrony to sinus rhythm at the earliest opportunity
Sensitivity	Has the ability to sense AT of varying rates and signal sizes Has the ability to sense atrial flutter
Specificity	Avoids switching during VA cross-talk, sinus tachycardia, and extraneous electrical noises

AMS, Automatic mode switching; AV, *atrioventricular;* AT, *atrial tachycardia;* VA, *ventriculoatrial.*

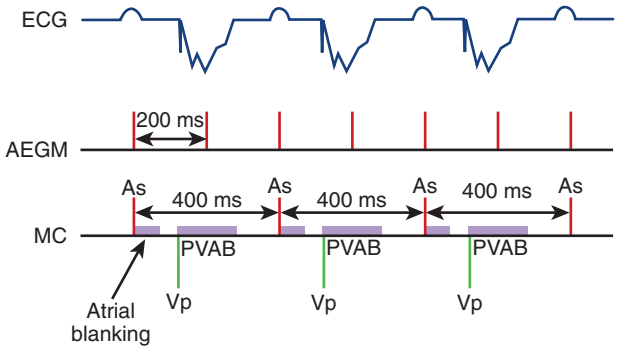

FIGURE 31-5 Sensing of atrial flutter (2:1) by a DDD pacemaker. The atrial flutter cycle length is shorter than the sum of the A-V interval plus the PVAB. The blanking periods are shown in purple. Every alternate flutter wave falls in the PVAB, resulting in 2:1 sensing. *AEGM*, Atrial electrocardiogram; *ECG*, surface electrocardiogram; *MC*, marker channel; *PVAB*, postventricular atrial blanking period. *(From Lau CP, Leung SK, Tse HF, Barold SS: Automatic mode switching of implantable pacemakers. I: Principles of instrumentation, clinical and hemodynamic considerations,* Pacing Clin Electrophysiol *25:967–983, 2002.)*

Automatic Mode Switching Sensitivity

As most AMS algorithms detect AT by a rate cutoff criterion, a slow atrial rate (e.g., atrial rate slowing after antiarrhythmic medications) may fall below the tachycardia detection rate, and AMS will not occur. Conversion of AF to atrial flutter is a special situation in which alternate flutter waves coincide with the postventricular atrial blanking period (PVAB), and the effectively detected atrial rate falls below the tachycardia detection rate and prevents AMS (Figure 31-5).

Table 31-3 Factors Affecting AT Detection in Dual-Chamber Pacemakers with AMS Algorithms

	UNDERDETECTION (SENSITIVITY)	OVERDETECTION (SPECIFICITY)
Arrhythmia related	Atrial flutter	Sinus tachycardia
	AF with small or widely varying signal amplitudes	—
	Slow atrial tachycardia (actual or drug-induced)	—
Pacemaker related		
Lead configurations	—	Unipolar sensing (far-field sensing and myopotentials)
		Low atrial lead positions
		Lead in the coronary sinus
		Dual-site atrial or bi-atrial sensing
Atrial sensitivity	Insufficient atrial sensitivity to sense AF	
Atrial blanking	Reduced sensed AT rate	Inadequate blanking in A–V interval and after ventricular pacing
A–V interval	Reduced sensed AT rate (some devices)	—
PVARP	Reduced sensed AT rate (some devices)	PVARP-mediated AMS: AMS can occur during sinus tachycardia or ectopy
VA cross-talk	—	Increased sensed atrial rate

AF, *Atrial fibrillation;* AMS, *automatic mode switching;* AT, *atrial tachycardia;* AV, *atrioventricular;* PVARP, *postventricular atrial refractory period.*

In the currently available devices, the postventricular atrial refractory period (PVARP) is opened (completely or on a conditional high rate) to enhance AMS. In other words, sensing occurs in the second part of the PVARP beyond the PVAB. The latter is designed to prevent far-field R-wave sensing. Atrial undersensing may occur because of an inappropriately long PVAB. Undersensing can often be avoided by appropriate adjustment of the PVAB, provided the atrial channel exhibits no far-field sensing. The widely varying amplitude of atrial ECG in AF, both temporally in a patient and between patients, can result in AMS failure when the atrial sensitivity is programmed incorrectly. During electrophysiological study, acutely recorded atrial ECGs (ECGs) during AF and sinus rhythm show similar mean amplitude, but the variability in amplitude is substantially wider and the minimum amplitude considerably smaller in AF compared with sinus rhythm (minimum atrial ECG: 1.4 ± 1.1 and 2.0 ± 0.8 mV, respectively).[34] A high-programmed atrial sensitivity may cause As of far-field signals or noise, whereas a low atrial sensitivity can lead to undersensing during AF (Figure 31-6).[35] Optimal programming of atrial sensitivity for AMS requires three times the safety margin compared with two times for sinus P-wave sensing (Figure 31-7).[35]

Far-field sensing of the tail end of the QRS complex by the atrial channel is the most common cause of a false-positive AMS response. Such far-field sensing of the QRS complex (almost always from a paced beat) causes VA cross-talk in opposite direction to the well-known form of AV cross-talk. Several investigators have studied the incidence of far-field R wave as recorded by an atrial-lead VDD system or a single-lead VDD system.[36-38] In general, unipolar As, paced QRS complex, longer dipole lengths (30 vs. 17.8 mm), and septal and low right atrial implants may predispose to far-field R-wave sensing. In one study, at an atrial sensitivity of 0.1 mV, all 30 bipolar leads had a far-field R wave sensed.[38] The median far-field QRS complex sensing threshold was 0.3 mV, and it occurred at 67 to 202 ms following the VP stimuli. These have implications on the highest atrial sensitivity and the duration of blanking period needed. In addition to atrial sensitivity, VA cross-talk occurs when the PVAB is too short or when the QRS is too long. Anything that prolongs the QRS complex (e.g., flecainide, amiodarone, or hyperkalemia) favors such VA cross-talk. Without PVAB programmability, false AMS from such far-field R-wave sensing can often be corrected by decreasing the atrial sensitivity. Less commonly, oversensing of atrial signals can occur within the A-V interval. In such a case, the atrial blanking period connected to the initial part of the A-V interval (post-atrial blanking period) must terminate before the A-V interval has timed out. Thus, double sensing of the P wave (near-field), especially caused by a large after-potential following Ap or sensing of the early part of the spontaneous QRS complex (far field), can occur within the A-V interval. Far-field sensing of the spontaneous QRS complex during the A-V interval is probably less common than sensing the terminal part of the QRS complex beyond the PVAB. The atrial channel can sense the early part of the spontaneous QRS only if it is detected before the ventricular channel senses it as a near-field signal.

In some devices with algorithms based on the matched atrial rate or interval, AMS can occur following a series of short-long cycles, where the short cycles occur within the A-V interval (As-Ar or Ar-As), despite the fact that the long cycles exceed the duration of the tachycardia detection interval. Problems related to As within the A-V interval could be eliminated by extending the atrial blanking period to encompass the entire A-V interval—either as a factory-set feature or by means of a special programmable option. Signal detection during the A-V interval beyond the atrial blanking period is designed to optimize the detection of AF. Improved AMS algorithms should now make sensing within the A-V interval unnecessary and obviate atrial oversensing.

A low-lying atrial lead or one in the coronary sinus may pick up both atrial and ventricular signals. The recent use of dual-site—right-atrial (with a posteriorly situated lead near the coronary sinus) and bi-atrial—pacing necessitates special algorithms or optimal lead positioning to avoid far-field R-wave sensing or even double sensing of the P wave. The latter may occur when the atrial conduction time between the two atrial sites is longer than the atrial blanking period (Figure 31-8). The sensitivity and specificity of AMS can now be validated by ECG and data storage of current implanted devices.

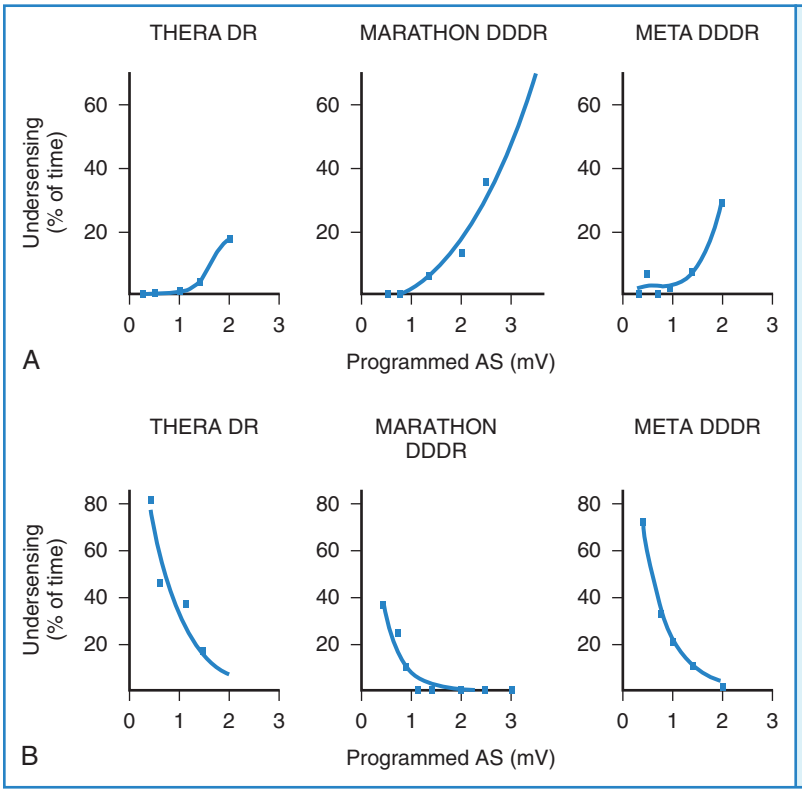

FIGURE 31-6 Effect of programmed atrial sensitivity in three mode switching pacemakers during persistent atrial fibrillation (AF). **A,** Significant undersensing of AF began to occur when the sensitivity was above 1 mV. **B,** Minimum oversensing of noise occurred when the sensitivity level was above 2 mV. *(From Leung SK, Lau CP, Lam CT, et al: Programmed atrial sensitivity: A critical determinant in atrial fibrillation detection and optimal automatic mode switching,* Pacing Clin Electrophysiol *21:2214–2219, 1998.)*

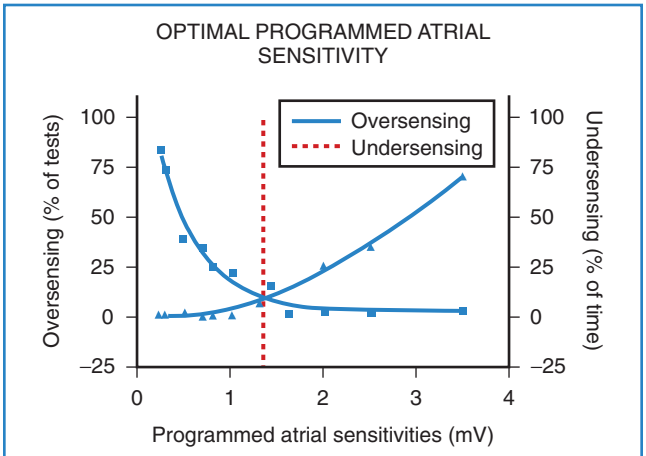

FIGURE 31-7 Optimal programmed atrial sensitivity level for mode switching. This occurred at 1.3 mV, which was three times the safety margin, compared with the sinus P wave. *(From Leung SK, Lau CP, Lam CT, et al: Programmed atrial sensitivity: A critical determinant in atrial fibrillation detection and optimal automatic mode switching,* Pacing Clin Electrophysiol *21:2214–2219, 1998.)*

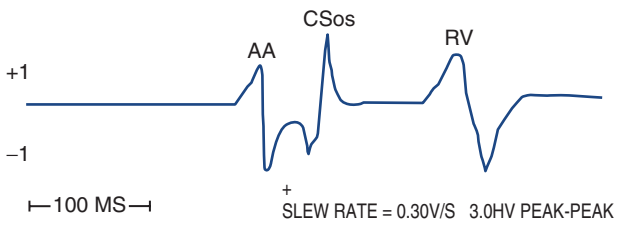

FIGURE 31-8 An atrial electrocardiogram recorded from a pacing system analyzer from a wide atrial bipole (low right atrial as anode, high right atrial as cathode) as used in dual-site right atrial pacing. Note the wide separation of the atrial electrocardiogram and the far-field R wave. *AA*, Right atrial appendage electrogram; *CS_{OS}*, atrial electrocardiogram just below CS_{OS}; *RV*, far-field right ventricular electrocardiogram. *(From Lau CP, Leung SK, Tse HF, Barold SS: Automatic mode switching of implantable pacemakers. I: Principles of instrumentation, clinical and hemodynamic considerations,* Pacing Clin Electrophysiol *25:967–983, 2002.)*

Automatic Mode Switching Diagnostics

AMS diagnostics provide an assessment of the frequency and pattern of AT episodes. These data may be useful for consideration of pacemaker mode reprogramming, such as from a dual-chamber mode to the VVIR mode when a patient develops permanent AF, and to assess the need for adjunctive antiarrhythmic and anticoagulation drug therapies in patients with a large number of AF episodes, long duration of AF episodes, or both. Indeed, recent studies suggest that asymptomatic episodes of AF occur at least 12 times more frequently than do symptomatic episodes in patients with implantable rhythm control devices.[39,40] Although these episodes may not be symptomatically relevant, their impact on thromboembolism and heart failure is probably similar to that of symptomatic episodes and may require similarly aggressive treatment. Indeed, AMS was used 66% of the time in patients with a known history of AT or AF and in 55% of the time in patients without this history.[39] However, the critical issue is the specificity of the recorded episodes characterized as

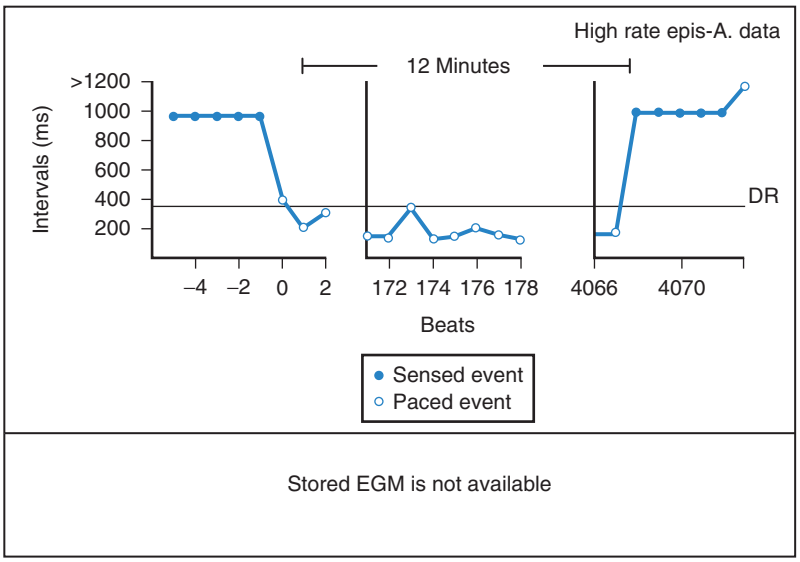

FIGURE 31-9 A recording of the atrial cycle length at the onset, during, and at termination of an episode of atrial fibrillation (AF) in a patient with paroxysmal AF with a Medtronic Thera DR pacemaker. An episode of high atrial rate beyond the atrial detection rate of 350 ms that lasted for more than 4000 cycles was recorded. *(From Lau CP, Leung SK, Tse HF, Barold SS: Automatic mode switching of implantable pacemakers. I: Principles of instrumentation, clinical and hemodynamic considerations,* Pacing Clin Electrophysiol *25:967–983, 2002.)*

AT or AF, which is now better defined through recording of atrial ECGs.

Event Counters

In general, event counters record the number of intrinsic and pacemaker-mediated events that occur during an event recording period. These counters are either triggered by the onset of a high atrial rate or AMS (Figure 31-9). Some current devices also allow patients to trigger the event counter, using an external magnet, to record data for a preset number of beats. This feature is useful for documentation and assessment of the pattern of symptomatic AF episodes.[41] Either the AMS counter or the atrial high rate episode monitor can be used for the detection and assessment of AT or AF episodes.

The AMS counter records the actual number of mode switches that occur. Previous studies on the Medtronic Thera DR pacemaker have demonstrated that in 12% to 40% of patients, mode-switching episodes were not attributed to AT. As described above, the majority of inappropriate mode switching was due to far-field R wave, or near-field A-wave sensing of atrial paced beats. Furthermore, the mode switch count recorded is affected by the speed of response, the sensitivity of the algorithm, and the speed of resynchronization to sinus rhythm or atrial paced rhythm as well.[42-50]

Theoretically, the atrial high-rate episode monitor should be independent of the mode switch algorithm and should be more accurate than the AMS counter. For example, intermittent atrial undersensing can mimic frequent short episodes of paroxysmal AF by registering repeated AMS (Figure 31-10). Seidl and colleagues suggested that optimal programming of the atrial high rate episode monitor in the Medtronic Thera DR pacemaker could reliably detect AT with high sensitivity and specificity.[44] However, false-negative detection during short episodes of AF and false-positive detection due to far-field R-wave oversensing were still observed. A specific pattern of oscillations in the atrial rate profile consistent with atrial oversensing has been described (Figure 31-11). With additional criteria to exclude oversensing, off-line analysis of the recorded signals can significantly reduce false-positive detection to 2.9%.[45]

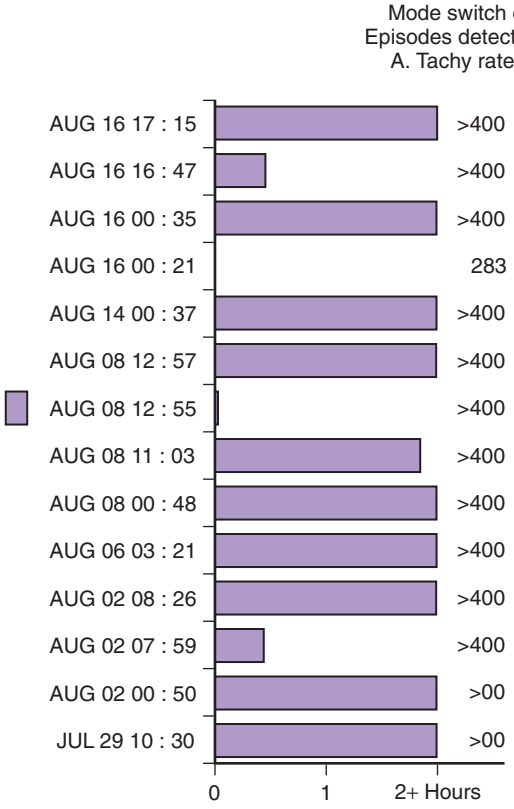

FIGURE 31-10 Mode switch episode log in the same patient as in Figure 31-9 who developed persistent atrial fibrillation (AF) 4 years later. Note the very close spacing between each recorded episode, which gave an impression of very frequent paroxysms of AF. However, this was probably due to mode switching in and out of persistent AF due to AF undersensing.

Histograms

Histograms provide details of the pacing operation of the device (e.g., As-Vs, As-Vp, Ap-Vs, Ap-Vp, and ventricular ectopy) and of the AMS operations and also provide the number of AF episodes (Figure 31-12). The rate histogram during the mode switch episodes may be useful for identification of inappropriate mode switching. When mode switching episodes occur in the atrial rate of 175 to 250 beats/min, it may represent double counting because of oversensing either far-field or near-field events. Episodes where the atrial rate is greater than 400 beats/min are likely to represent true AF, if lead fracture and myopotential sensing can be excluded.[46]

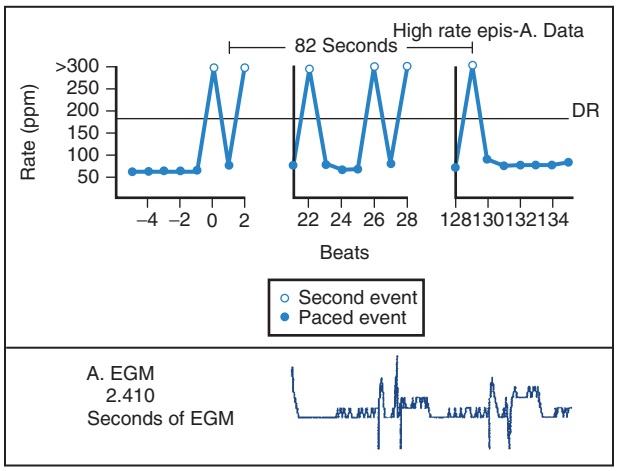

FIGURE 31-11 Double atrial sensing in a dual-site pacing device leading to rate fluctuation prior to atrial mode sensing (AMS). The short-long sequence induced rate oscillation, and when the mean atrial rate was reached, sustained AMS was induced. Atrial electrocardiogram clearly showed double P-wave sensing. *(From Lau CP, Leung SK, Tse HF, Barold SS: Automatic mode switching of implantable pacemakers. I: Principles of instrumentation, clinical and hemodynamic considerations,* Pacing Clin Electrophysiol *25:967–983, 2002.)*

Stored Atrial Electrocardiogram

A number of devices have telemetered atrial ECGs that allow online assessment of pacemaker operations. These are very useful to assess atrial sensing issues when adjusting the parameters of AMS. The incorporation of the stored atrial ECG data is very useful in confirming the etiology of the recorded arrhythmia (see Figures 31-11 and 31-13). Atrial stored ECGs can increase the accuracy of the event counters and identify the type of atrial arrhythmias.[47-50] They may provide important insight on the onset and termination of the arrhythmias (Figure 31-13). In a recent study, when atrial ECGs were available for confirmation, it was found that as many as 62.7% of mode switching episodes were erroneously executed.[44] In patients with an implanted single-lead VDD system, only 35% of 235 episodes of suspected AF were confirmed as AF, whereas the other episodes were diagnosed to be atrial undersensing.[50] At present, most devices provide only limited duration of stored atrial ECGs due to the limitation of pacemaker memory capability.

In Guidant pacemakers, the number of events and the duration of the dual-channel (atrial and ventricular) ECGs are programmable, being limited to a cumulative maximum of 40 seconds (2 ECGs of 20 seconds' duration or up to 20 ECGs of 2 seconds' duration). Some other devices allow the recording of a single-channel compound ECG consisting of superimposed atrial and

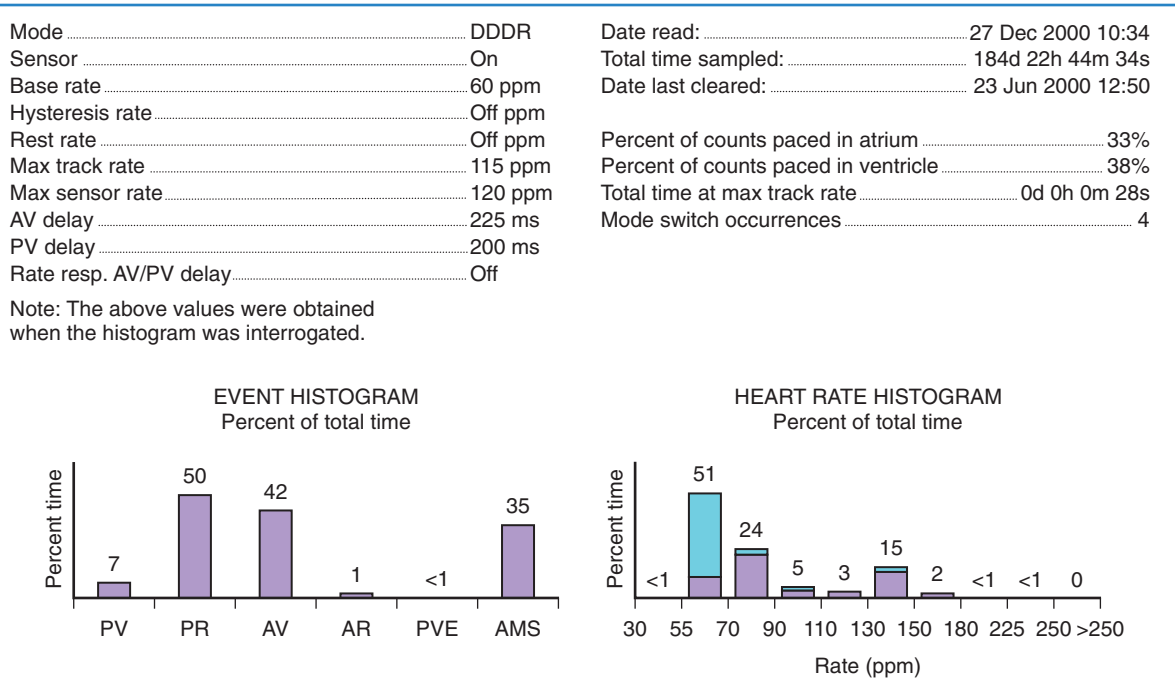

FIGURE 31-12 Pacemaker operation histogram from the Affinity DR (St. Jude Medical). Four episodes of mode switches were recorded. In addition, the histograms showed that the patient was in atrial mode switching (*AMS*) for 35% of the time, which gives an idea of the amount of atrial fibrillation burden during the recording period.

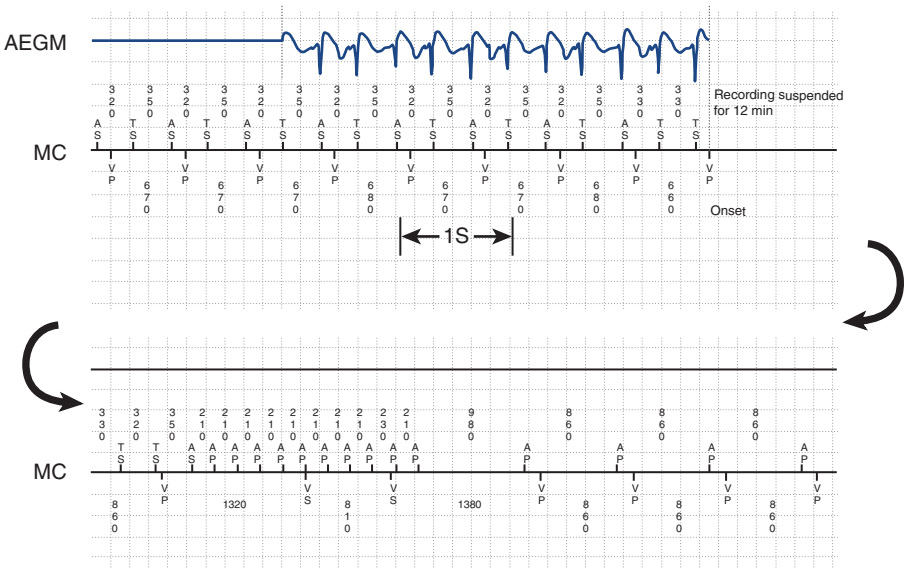

FIGURE 31-13 Atrial electrocardiograms recording at the onset of atrial tachycardia (AT) (Model AT500, Medtronic, Inc.), validating an appropriate AT detection. The AT lasted for about 12 minutes (recording suspended) and terminated spontaneously. *AEGM*, Atrial electrocardiogram; *As*, atrial sense; *Ap*, atrial pace, *AT*, atrial tachycardia; *MC*, marker channel; *Vp*, ventricular pace; *Vs*, ventricular sense; *Ts*, tachycardia sense.

ventricular components in a single channel (AV or summed ECG). This combined arrangement may make it difficult to differentiate atrial flutter from far-field R-wave sensing by the atrial channel. ECG recordings can be programmed to be triggered by AT, by other arrhythmias, and by an externally applied magnet during symptomatic episodes. The stored ECGs are able to demonstrate the actual signals that triggered the recording, whether or not an arrhythmia occurred. ECG storage in many pacemakers now begins at the time of the trigger. The standard for pacemakers should be the storage of ECGs with annotations (these do not consume much memory) at the start of the arrhythmia or from a predetermined time before the trigger. Such pacemakers are now becoming available.

Atrial Fibrillation Burden

Several clinical studies have attempted to use AMS diagnostics to evaluate the effects of Ap on the total burden of AF (both symptomatic and asymptomatic episodes).[51,52] This provides a powerful tool to assess the effectiveness of a therapy to treat AF (Figure 31-14). However, the accuracy of the measurement of AF burden by using the AMS diagnostics is limited by the following factors: (1) the specificity and sensitivity of the AMS diagnostics as described, (2) the availability of the atrial stored ECG to confirm AF, and (3) the storage capacity of the pacemaker data logs because the event counters in most pacemakers can easily be saturated.

Clinical Benefits

The hemodynamic benefits of maintaining a regular ventricular rate have been reported.[53-57] Anecdotal reports of the symptomatic benefit of AMS and improvement of tachycardia-related symptoms by avoiding a rapid-paced ventricular rate at the onset of AT are also available. A randomized, crossover, prospective study has reported on the addition of AMS in patients after AV nodal ablation and DDDR pacing.[58] In this study, 48 patients were randomly assigned to DDDR pacing with and without activation of AMS. It was found that the VVIR mode alone was the least well tolerated, and the DDDR with mode switching was the most acceptable (Figure 31-15). Patient-perceived well-being was superior with AMS activated than with AMS inactivated, and early crossover was observed in 3% and 19% of patients, respectively. This study documented a short-term symptomatic benefit of AMS over conventional DDDR mode in a population with high AT incidence.

Whether different AMS algorithms may have an impact on symptoms was the subject of another study.[59] Three different AMS onset criteria (mean atrial rate, "4 of 7" and "1 of 1") of an AMS algorithm were injected into an implanted DDDR pacemaker (Thera DR models 7142, 7952, and 7960i; Medtronic, Inc.) in a group of patients with frequent AT episodes. The faster AMS criteria, 4 of 7 and 1 of 1, were better tolerated than were the slow-onset criteria using mean atrial rate (Figure 31-16). Conversely, the fast-responding algorithms led to shorter but more frequent episodes of AF that were sensed, suggesting that the device may be switching in and out of AMS because of lack of stability. This study demonstrated that different types of AMS algorithms might also have an impact on patients' symptoms. An inappropriate AMS algorithm can have a deleterious effect on patients' symptoms. For example, in the first version of the DDDR Meta, frequent mode switching can result in AV dissociation, which may cause more symptoms than AF itself.[60] In patients with a high sinus rate, undesirable mode switching will occur during sinus rhythm. The extended ventricular escape interval caused by mode switching will prevent VP, as the device will function in a DDI/VVI mode.[61] In the presence of a prolonged P-R interval, this may lead to a very long A-V interval and pacemaker syndrome.[62]

Two recent studies on the stability of the sinus node after AV nodal ablation questioned the long-term clinical benefit of AMS.[63,64] In one study, after AV nodal ablation and implantation of a DDDR device, patients were symptomatically better and

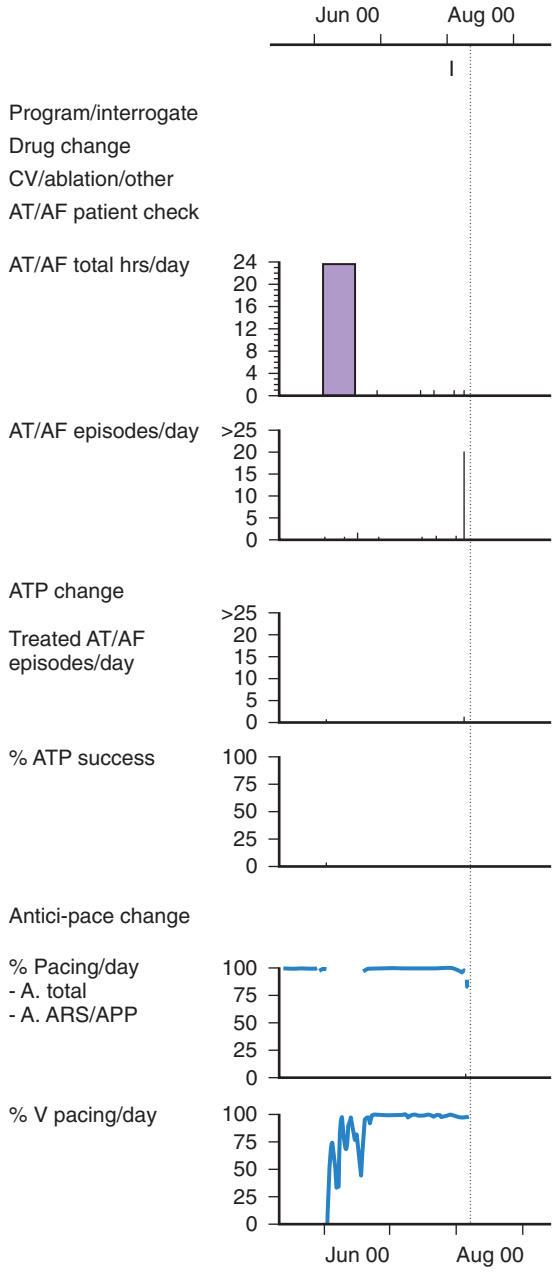

FIGURE 31-14 Atrial fibrillation (*AF*) diagnostics from a DDDR pacemaker with atrial tachycardia (*AT*)/AF therapy (AT500, Medtronic Inc.). A period of persistent AF (June 2000) was documented by the total AF duration of nearly 24 hours per day. The corresponding atrial pacing was minimal in this pacemaker-dependent patient.

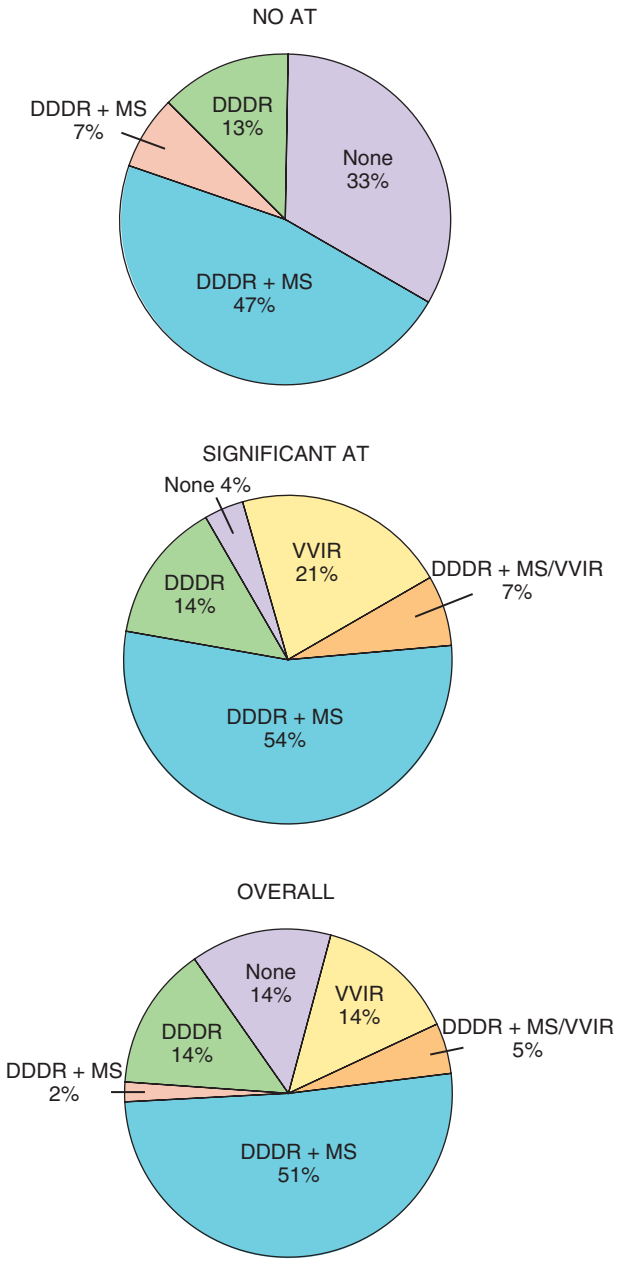

FIGURE 31-15 Preferred pacing modes in patients with and without atrial tachycardia (*AT*) during a randomized mode study. DDDR with atrial mode sensing activated (DDDR + MS) was the most preferred mode, independent of the presence of AT before implantation. *(From Kamalvand K, Tam K, Kotsakis K, et al: Is mode switching beneficial? A randomized study in patients with paroxysmal atrial tachyarrhythmias,* J Am Coll Cardiol *30:496–504, 1997.)*

achieved better quality of life and NYHA class, compared with a control group of patients with continuation of medical therapy.[63] The long-term maintenance of sinus rhythm was poor in the ablated and paced group. As many as 24% developed chronic AF by 12 months, necessitating reprogramming DDDR pacemakers to the VVIR mode. In another study, 12 of 37 patients developed chronic AF at 6 weeks after AV nodal ablation versus 0 of 19 in those who continued medical treatment.[64] The cause was most likely the withdrawal of antiarrhythmic medications after AV nodal ablation but also possibly an atrial proarrhythmic effect of the ablation and pacing procedure. However, should a dual chamber device be implanted after AV nodal ablation, AMS remains an integral part of device therapy to avoid the occurrence of rapid VP during AF.

Illustrative Types of Automatic Mode Switching

See material posted at www.expertconsult.com/.

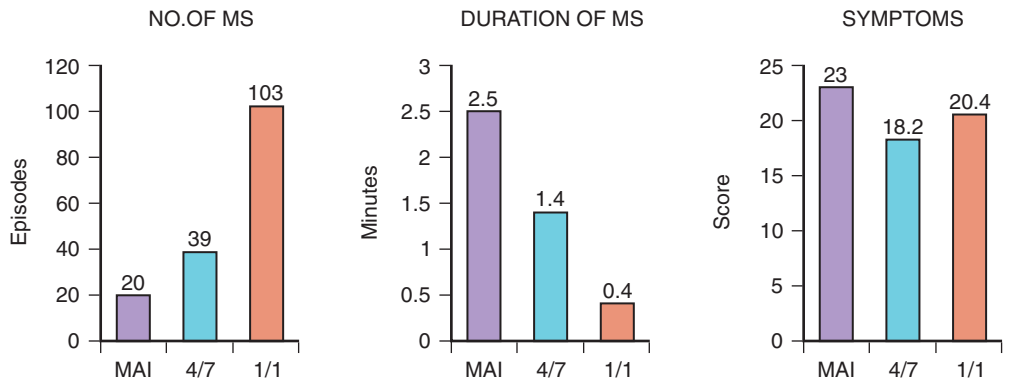

FIGURE 31-16 Effect of different mode onset criteria on mode switch frequency and duration and symptoms. *MA1, 4/7, 1/1*, automatic mode switching (AMS) algorithm based on the mean atrial rate, 4 of 7 high atrial rate events, or one atrial ectopy only. *MAI*, Matching atrial interval. *(From Marshall HJ, Kay GN, Hess M, et al: Mode switching in dual chamber pacemakers: Effect of onset criteria on arrhythmia-related symptoms,* Europace *1:49–54, 1999.)*

Follow-up and Troubleshooting

A detailed evaluation (based on pacemaker diagnostics and ambulatory recordings) of atrial arrhythmias both before and after implantation is essential to select the type of AMS algorithms and programmed settings. It is essential during implantation to maximize the amplitude of the atrial ECG in sinus rhythm and minimize the far-field R-wave signals by appropriate atrial lead placement. A bipolar atrial lead should be implanted in a patient expected to use AMS frequently. It may also be preferable to use a closely spaced atrial bipole to minimize far-field R-wave sensing.

Because of the highly variable AF amplitudes, a routine setting of nominal atrial sensitivity margin or two times the atrial sensitivity margin may not be adequate for optimal AT or AF detection. If an episode of AF becomes available, sensitivity adjustment can be guided by the measured amplitude of the atrial ECG. Leung and associates have suggested that the optimal atrial sensitivity setting for AMS appears to be at three times versus two times the detected amplitude of the atrial ECG in sinus rhythm.[35]

Incorrect programming of these parameters (or suboptimal pacemaker design) may create a number of problems, including loss of specificity, such as sensing sinus tachycardia on exercise as pathologic tachycardia, withholding AMS because of inappropriate selection of atrial sensitivity, atrial blanking periods and related timing cycles, or all of these.

AMS failure caused by atrial events occurring within the atrial blanking periods was reported in a series of 7 patients with Meta DDDR (Model 1254).[60] All patients experienced palpitations. In 6 of 7 patients, AMS failure was due to atrial flutter, with alternate flutter waves falling within the atrial blanking periods (values: 120 ms after atrial sensed/paced event and 150 ms for PVAB). In these patients, relatively slow atrial flutter was related to drugs used to control AF. By either shortening the A-V interval or prolonging the A-V interval and PVARP so that flutter waves could be sensed outside the atrial blanking interval, normal AMS function was restored. In 1 of 6 patients, the cause of AMS failure was due to a low atrial ECG amplitude during AF, and it was corrected by reprogramming atrial sensitivity.

Palma and colleagues systematically evaluated the effect of varying atrial sensitivity, A-V interval, and detection criteria for AMS in 18 patients.[65] Pacemaker models studied included the Meta DDDR (Model 1254, Medtronic, Inc.), the Thera DR (Model 7940, Medtronic, Inc.) and the Relay (Model 293-03 Intermedics, Inc.). Although an atrial sensitivity of 1 mV allowed correct sensing of sinus rhythm in 13 of 14 patients (93%), only 43% of the patients had effective AMS during AF. A-V intervals between 120 and 200 ms were found to be most effective to detect AF, whereas AF sensing was reduced when a longer A-V interval was used. The use of stringent criteria for AF detection might interfere with AMS onset. This study points out the importance of adjusting the conventional pacing parameters to optimize AMS function.[60]

Overall experience with AMS has been satisfactory so far. Barring economic considerations, all pacemakers should possess an AMS function as one of their programmable options. AMS allows the benefits of AV synchrony to be extended to a population with existing or threatened AF. These devices are indicated in all patients with the bradycardia-tachycardia syndrome. They should also be considered in patients with sinus node disease without paroxysmal AF, obstructive hypertrophic cardiomyopathy, or any condition that predisposes patients to paroxysmal AF. Indeed, like the rate-adaptive function (R), it could be argued that all patients should receive a device with AMS capability because it is not possible to predict which patients will eventually develop AF (or atrial chronotropic incompetence in the case of the rate-adaptive function). Many algorithms have been used by different manufacturers, and these algorithms do not all behave similarly. Optimal care of the patient with a pacemaker requires a thorough knowledge of his or her arrhythmia history, atrial ECG amplitude (in sinus rhythm and AT), basic timing cycles required for all AMS algorithms, and the characteristics of the various available algorithms.

Implantable Sensors

In the presence of abnormal cardiac automaticity and conduction, physiological pacing aims to maintain the heart rate and restore the sequence of cardiac activation. It is assumed that sensors should mimic the behavior of the healthy sinus node response to exercise and nonexercise needs. The atrial ECG can be used for rate control when sinoatrial function is adequate. However, a high proportion of pacemaker recipients have either established or

progressive abnormal sinoatrial function occurring either at rest or during exercise. Such chronotropic incompetence is commonly caused by medications or ischemia or occurs in association with sick sinus syndrome. In addition, the atrium may be unreliable for sensing or pacing in some patients (such as during AF or paroxysmal AT), so it is necessary to use sensors as an alternative means to simulate sinus node responsiveness. These problems prompted the development of nonatrial implantable sensors for cardiac pacing. In addition, the role of sensors has also been expanded to include functions other than rate augmentation, such as the monitoring of cardiac hemodynamics during heart failure and ventricular arrhythmias. Although a number of implantable sensors to detect exercise have been proposed or instrumented in pacing devices, to date, no single sensor has the ability to simulate the ideal sinus rhythm behavior.

Sensor Classification

Sensors derived from a common technical principle share similar hardware requirements and sensor stability as well as similar drawbacks and limitations.[66] Thus, it is more practical to classify sensors according to the technical methods that are used to measure the sensed parameter (Table 31-4). During isotonic exercise, body movements (especially those produced by heel strike during walking) result in changes in acceleration forces that act on the pacemaker. Sensors that are capable of measuring the acceleration or vibration forces in the pulse generator are broadly referred to as *activity sensors*. The sensing of body vibrations is, therefore, a simple way to indicate the onset of exercise. Technically, detection of body movement can be achieved using a piezoelectric crystal, an accelerometer, a tilt switch, or an inductive sensor. Each of these devices transduces the motion of the sensor either directly into voltage or indirectly into measurable changes in the electrical resistance of the crystal. Although it is a tertiary sensor, activity is the most widely used control parameter in rate-adaptive pacing because of its ease of implementation and its compatibility with standard unipolar and bipolar pacing leads. Minimal or no energy expenditure is required for such a system, and because the sensor does not need to have contact with body fluid, it is usually stable over time. Other advantages are that all the hardware is within the pacemaker case, it does not depend on the electrode arrangement, and it can be used with standard unipolar and bipolar pacing electrodes. This makes it ideal for combining it with other sensors and for pacemaker upgrading. It is used often as a backup sensor when a new sensor is being investigated. However, as a group, because body movement has

Table 31-4 Major Classes of Sensors Used in Rate-Responsive Pacing*

		EXAMPLES	
METHODS	**PHYSIOLOGICAL PARAMETERS**	**MODELS**	**MANUFACTURERS**
Vibration sensing	Body movement	Activitrax, Legend, Thera, DX2, Kappa Sensolog, Sensorhythm, Trilogy Relay, Dash, Marathon Excel Ergos Swing	Medtronic, Inc. Pacesetter Intermedics CPI Biotronik Sorin
Impedance sensing	Respiratory rate Minute ventilation Stroke volume, pre-ejection period, right ventricular ejection time Ventricular inotropic parameter	Biorate Chorus RM Legend plus, DX2, Kappa Precept Diplos, Inos	Biotec ELA Medical Medtronic, Inc. CPI Biotronik
Ventricular evoked response	Evoked Q-T interval Evoked R-wave area ("gradient")	TX, Quintech, Rhythmx Prism CL	Vitatron Telectronics
	PHYSICAL PARAMETERS		
Special sensors on pacing electrode	Central venous temperature dP/dt Right atrial pressure Pulmonary arterial pressure Peak endocardial acceleration	Kelvin 500 Nova MR Thermos Deltatrax, Model 2503 Best of Living	Cook Pacemakers Intermedics Biotronik Medtronic, Inc. Sorin
	CHEMICAL PARAMETERS		
	pH Mixed venous oxygen saturation Catecholamine levels	OxyElite	Medtronic, Inc. Siemens

**Classified according to method of technical realization.*
dP/dt, *Rate of change in pressure.*

only a loose relationship to workload, the sensor-indicated rate has low proportionality, and physical activities that do not involve body movement will not be detected by these sensors.

Impedance is a measure of all factors that oppose the flow of electric current and is derived by measuring resistance to an injected subthreshold electric current across a tissue. This principle has been used extensively for measuring respiratory parameters and relative stroke volume in situations involving invasive monitoring.[67,68] The elegant simplicity of impedance has enabled it to be used with implantable pacing leads, including both standard pacing leads and specialized multi-electrode catheters. The pulse generator casing has been used as one electrode for the measurement of impedance in most of these pacing systems. Impedance can be used to detect relative changes in ventilatory mechanics, right ventricular mechanical function, or their combination. Relative motions between electrodes for impedance sensing also lead to changes in impedance measured, and this is inversely related to the number of electrodes used to measure impedance. In rate-adaptive pacemakers, motion artifacts are usually the result of arm movements that cause the pulse generator to move within the prepectoral pocket, thereby changing the relative electrode separation between the pacemaker and the intracardiac electrodes.[69] Because arm movement accompanies normal walking, these artifacts in the impedance signal occur with both walking and upper limb exercises. Similarly, exogenous electrical interference such as diathermy may lead to erroneous sensing.

The intracardiac ventricular ECG resulting from a suprathreshold pacing stimulus has been used to provide several parameters that can guide rate modulation. The area under the curve inscribed by the depolarization phase of the paced ventricular ECG (the intracardiac R wave) has been termed the *ventricular depolarization gradient* or *paced depolarization integral* (PDI).[70] In addition to depolarization, the total duration of depolarization and repolarization can be estimated by the interval from the pacing stimulus to the intracardiac T wave (the Q-T or stimulus-T interval). Both these parameters are sensitive to changes in heart rate and circulating catecholamines and can be derived from the paced intracardiac ECG with conventional pacing electrodes. Because a large polarization effect occurs after a pacing stimulus, a modified waveform of the output pulse that compensates for after-potentials is needed to eliminate this effect so that these parameters can be accurately measured.

The last group of sensors comprises those that are incorporated into the pacing lead. These dedicated sensors allow the chemical compositions of the bloodstream or intracardiac hemodynamics to be measured and may result in a more physiological sensor system. However, the long-term stability of these sensors is questionable. They are also energy expensive. Examples of these specialized leads include thermistors (used to measure blood temperature), piezoelectric crystals (used to measure right ventricular pressure), optical sensors (used to measure oxygen [SvO_2]), and accelerometers at the tip of pacing leads. Some of these sensors measure highly physiological parameters. These include the measurement of pH, catecholamines, SvO_2, and right ventricular pressure.[71,72]

These sensors have only a limited application in the field of rate-adaptive pacing because their long-term stability in the blood environment is questionable, but some important developments have occurred in this field, and these sensors may open the possibility for ambulatory monitoring of intracardiac environment using an implanted device;. Included in this group are sensors that detect right ventricular dP/dt as an index of contractility and an accelerator sensor at the tip of a pacing lead to monitor the peak endocardial acceleration, which has the possibility for optimizing the AV interval.[73-81]

Characteristics of an Ideal Rate-Adaptive Pacing System

The normal human sinus node increases the rate of its spontaneous depolarization during exercise in a manner that is linearly related to oxygen consumption (VO_2). Because this response undoubtedly has evolutionary advantages, the goal of rate-adaptive pacemakers that modulate pacing rate by artificial sensors has been to simulate the chronotropic characteristics of the sinus node (Table 31-5). However, it is uncertain whether the sinus node provides the ideal rate response in patients who require permanent pacemakers. Nevertheless, until evidence indicating otherwise becomes available, rate-adaptive pacemakers will strive to reproduce this physiological standard. Keeping these uncertainties in mind, the ideal rate-adaptive pacing system should provide pacing rates that are proportional to the level of metabolic demand. One of the best indicators of sensor proportionality is the correlation between the sensor-indicated pacing rate and the level of oxygen consumption during exercise (Figure 31-17). In general, parameters such as minute ventilation and the paced Q-T interval are proportional sensors. Some sensors using specialized pacing leads are also highly proportional. For example, a properly functioning SvO_2 sensor will result in a rate closely related to oxygen consumption during exercise.

Table 31-5 Characteristics of an Ideal Sensor for Rate-Responsive Pacing

CONSIDERATIONS	EXAMPLES AND REMARKS
SENSOR CONSIDERATIONS	
Proportionality	Oxygen saturation sensing has good proportionality.
Speed of response	Activity sensing has the best speed of response.
Sensitivity	QT sensing can detect non–exercise-related changes such as anxiety reaction.
Specificity	Activity sensing is affected by environmental vibration. Respiratory sensing is affected by voluntary hyperventilation.
TECHNICAL CONSIDERATIONS	
Stability	Stability of early pH sensor was a problem.
Size	Large size or requirement for additional electrodes may be a problem. Energy consumption must not unduly harm pacemaker longevity. Energy consumption must not unduly harm pacemaker longevity.
Biocompatibility	It is important for the sensor to be in direct contact with the bloodstream.
Ease of programming	Programming was difficult in early QT-sensing pacemakers.

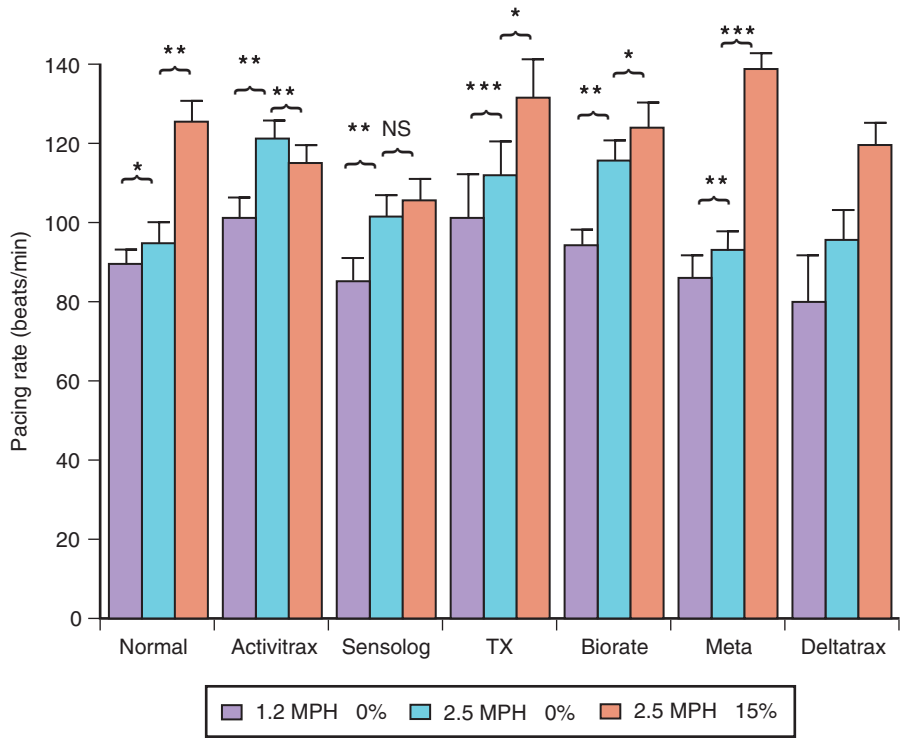

FIGURE 31-17 Brief activities are used to evaluate the proportionality of rate response of some common sensors. Maximal heart rate was derived from a 3-minute walking test done at different speeds (1.2 and 2.5 mph) and on different slopes (0% and 15%). No significant change in pacing rate was observed when patients with the Sensology pacemaker ascended an incline, whereas the pacing rate decreased significantly in patients with the Activitrax during the same activity. *NS*, Not significant; *, $P < .05$; **, $P < .01$; ***, $P < .001$; *Tx*, QT sensing pacemaker. *(From Lau CP, Butrous GS, Ward DE, et al: Comparison of exercise performance of six rate-adaptive right ventricular cardiac pacemakers,* Am J Cardiol *63:833–838, 1989.)*

In addition, an appropriate speed of response of the pacing rate to the onset of and recovery from exercise is an essential feature of a rate-adaptive pacing system. The change in pacing rate should occur with the kinetics (or speed of response) of a sensor that is similar to that of the sinus node. An anticipatory response of the heart rate occurs in many individuals before exercise. With both supine and upright isotonic exercises, heart rate and cardiac output increase within 10 seconds of the onset of exercise.[82,83] Both cardiac output and sinus rate increase exponentially, with a half-time that ranges from 10 to 45 seconds, the rate of rise being proportional to the intensity of work.[82] At the termination of upright exercise, a delay of approximately 5 to 10 seconds occurs before cardiac output starts to decrease, followed by an exponential fall with a half-time of 25 to 60 seconds. If the rate decay is faster than is physiologically appropriate, adverse hemodynamic consequences may occur in the presence of a substantial drop in heart rate. In one study, pacing rate was reduced either abruptly or gradually after identical exercise, and it was shown that an appropriately modulated rate recovery was associated with a higher cardiac output, lower sinus rate, and faster lactate clearance than with an unphysiological rate recovery pattern. Appropriate adjustment of the rate recovery curve is important to enhance recovery from exercise.

The exercise responses of six different types of rate-adaptive pacemakers (with sensors for activity, Q-T interval, respiratory rate, minute ventilation, and right ventricular dP/dt) were compared with normal sinus rate in one study (Figure 31-18).[84] The results of this study demonstrated that the activity-sensing pacemakers best simulated the normal speed of rate response at the start of exercise. The rate response of activity sensors is usually immediate (no delay time), and the time needed to attain half the maximal change in rate occurred within 45 seconds from the onset of exercise. The maximal change in pacing rate is reached within 2 minutes of beginning an ordinary activity such as walking. The respiratory rate and the right ventricular dP/dt sensors had a longer delay time. The slowest sensor to respond to exercise was an early version of the QT-sensing pacemaker, which required up to 1 minute to initiate a rate response, and the maximal change in pacing rate was attained only in the recovery period following a short duration of exercise.

Exercise is but one of the many physiological requirements for variation in heart rate. Emotions such as anxiety may trigger a substantial change in heart rate. The sinus rate is higher when an individual moves from the supine posture to the upright posture, with a fall in the cardiac output. Isometric exercise also results in an increase in cardiac output and heart rate in most individuals. The changes in heart rate that occur during various physiological maneuvers (e.g., Valsalva maneuver), baroreceptor reflexes, and anxiety reactions may also be potentially important. An appropriate compensatory heart rate response is especially important in pathophysiological conditions such as anemia, acute blood loss, or other causes of hypovolemia. The artificial sensor should be sensitive enough to detect exercise needs and nonexercise needs for changes in heart rate and yet be specific enough not to be affected by unrelated signals arising from both internal and external environments. Although the ideal sensor should provide these functional characteristics, it must also be technically feasible to implement, with a reliability that is acceptable with modern implantable pacemakers (see Table 31-5).

The overall chronotropic response obtained with a rate-adaptive pacing system is dependent on three major factors: (1) the intrinsic properties of the rate-control parameter, (2) the algorithm used to relate changes in the sensed parameter into changes in pacing rate, and (3) the way in which the pacing system is programmed. Each of these factors can dramatically change the rate modulation actually observed with a rate-adaptive pacing

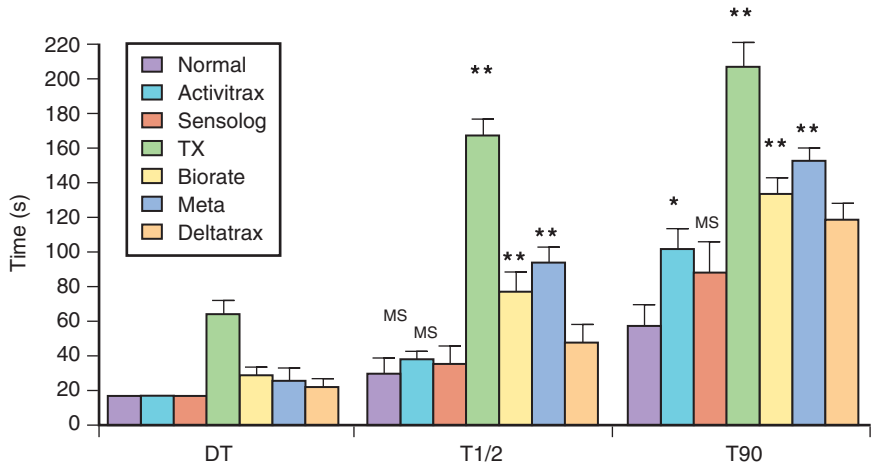

FIGURE 31-18 Speed of rate response of different pacemakers during walking at a nominal speed (2.5 mph at 0% gradient). The normal sinus rate responds almost immediately, one half of the change being achieved in less than 30 seconds and most of the change within 1 minute. This speed of response was most closely simulated by the activity-sensing pacemakers. Significant differences were derived by comparing the response times of each pacemaker ($T\frac{1}{2}$ and T90) with those of the normal sinus response. Ninety percent of the maximal rate for this exercise was reached within the exercise period in all patients, except in those with the QT-sensing pacemaker (*TX*), and these patients achieved this pacing rate only in the recovery phase. *DT*, Delay time; *$T\frac{1}{2}$ and T90*, times needed to reach 50% and 90% of maximal heart rate. *(From Lau CP, Butrous GS, Ward DE, et al: Comparison of exercise performance of six rate-adaptive right ventricular cardiac pacemakers,* Am J Cardiol *63:833–838, 1989.)*

system. In addition, an appropriate rate-control algorithm or clever programming can overcome the intrinsic limitations of many sensors. In contrast, inappropriate programming of a pacing system can distort the chronotropic response of an otherwise ideal sensor, which will result in a poor clinical outcome. Thus, clinical input is required to achieve optimal results with any rate-adaptive pacemaker.

Sensor Combination

See material at www.expertconsult.com/.

Automaticity

See material at www.expertconsult.com/.

Clinical Outcome

The ultimate goal of pacemaker therapy is to improve symptoms and quality of life, and these criteria have been used to compare pacing modes. In terms of symptomatology, VVIR pacing is superior to VVI pacing. However, the overall contribution of improved control of symptoms to enhanced quality of life is probably small in the usual pacemaker recipient in whom quality of life is already close to that of age-matched normal individuals.[85] No comparative study of sensors and their effects on symptomatology or quality of life has yet been completed. A patient-randomized, double-blinded crossover study was done in 10 patients using the combined activity and minute ventilation dual-sensor VVIR pacemaker for-high grade AV block and chronic or persistent paroxysmal AF. The patients in this study performed 2 weeks of out-of-hospital activity in the activity only, minute ventilation only, and dual-sensor VVIR and VVI modes. Patients were assessed on their perceived general well-being by using visual analog scale scores, Specific Activities Scale functional status questionnaire, and objective improvement by standardized daily activity protocols and graded treadmill testing. Subjective perception of exercise capacity and functional status was significantly reduced in the VVI mode compared with the VVIR modes. However, no clear advantage of dual-sensor VVIR pacing over activity sensor pacing was demonstrated. Four of the 10 patients preferred the activity VVIR mode, 3 preferred the dual-sensor mode, and 3 had no preference. Three patients found dual-sensor VVIR the least acceptable, 3 patients found minute ventilation least acceptable, and 1 patient found both dual-sensor and minute ventilation sensor pacing unacceptable. There was no significant difference in the objective performance among the 3 VVIR modes. These are not unexpected results, which suggests that no major differences exist among sensors and their combinations in gross clinical terms. However, the overall numbers of patients studied were small and hence the data do not have sufficient statistical power to unveil less-than-major differences, which may be important for assessing the long-term effects of a pacing mode. The difficulty of multiple comparisons and the order of pacing modes studied are further limitations. Lukl and colleagues also assessed quality of life with regard to cardiovascular symptoms, physical activity, psychosocial and emotional functioning, and self-perceived health during DDD and dual-sensor VVIR pacing.[86] Significant improvement during DDD pacing was demonstrated in all subgroups of patients (sick sinus syndrome, patients with chronotropic competence or incompetence, and patients with high-degree AV block). The overall result shows that DDD pacing offers better quality of life than does dual-sensor VVIR pacing. Thus, dual-sensor VVIR pacing cannot compensate for the lack of AV synchrony. Because most rate-adaptive pacemakers have an activity sensor, it is of interest if the addition of a minute ventilation sensor contributes to better clinical performance. A preliminary study suggests that, although the maximal exercise capacity may not be affected by the combined sensor, better rate-adaptation profiles may enhance quality of life.[87]

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CHAPTER 32

Pacemaker Insertion, Revision, and Extraction

Mark H. Schoenfeld

It would be too ambitious an undertaking to address in a single chapter such diverse pacemaker themes as implantation, revision, and extraction. This chapter, however, presents the author's personal perspective on the subject(s). The goal is to provide information that is readable for clinicians and students in the field, without being overly encyclopedic.

Implantation

As with most things in life, preparation is everything; that is, one must "plan the work, then work the plan." The determination to embark on pacemaker implantation includes the assumption that the implanter has had the appropriate degree of training, has maintained proficiency in this area, and understands the specific indications for a particular procedure as delineated in the ACC/AHA/HRS guidelines for device implantation. The maintenance of a minimum procedural volume is essential, and, indeed, the number of implants performed by an individual is inversely related to the development of complications at the time of implantation. In addition, preparation entails anticipation of all the resources and personnel required to perform the operation, including a sterile operating arena (whether operating room or catheterization laboratory), standard operating room instruments, pacemaker leads and generators, corresponding pacer programmers, pacer system analyzers, anesthesia/sedation, fluoroscopy, and emergency equipment (e.g., pericardiocentesis sets). The presence of an experienced nurse or technician who can make the necessary threshold determinations is also indispensable. The role of the "pacemaker manufacturer's representative" in this regard remains highly controversial and continues to raise both quality assurance issues and ethical concerns.

Deciding on an operating strategy is crucial. This is especially true in complicated cases—patients with pre-existing pacer or defibrillator systems with pacer dependence; patients with congenital cardiovascular abnormalities such as persistent superior vena cava syndrome with previous demonstration of subclavian vein thrombosis; or patients in whom individualization of therapy dictates something "special" (e.g., contralateral placement in a mastectomy patient, placement of the device as a function of the patient's left-handedness or right-handedness, or cosmetic concerns necessitating a submammary implant).

The use of antibiotic prophylaxis before implantation has long been debated. Meta-analysis, however, suggests that prophylaxis may, indeed, be very important in minimizing device-related infections. Generally, an antistaphylococcal antibiotic is administered "on-call" to the procedure with continuation of this antibiotic for 24 hours following the implantation. The site of peripheral intravenous placement—this should be ipsilateral to the anticipated site of implant so as to allow for dye injection and radiographic imaging of central venous anatomy in cases where percutaneous subclavian or cephalic vein access is difficult—should also be considered preoperatively. The anticoagulated patient poses a particular challenge both preoperatively and perioperatively. Warfarin (Coumadin) is generally withdrawn to achieve an international normalized ratio (INR) of less than 2; cephalic cutdown and strict hemostasis are encouraged; and warfarin is resumed postoperatively, preferably *without* the adjunct of intravenous heparin or enoxaparin (with which significant pocket hematomas have occurred). Some have demonstrated, however, that implantation may take place without withholding warfarin and without untoward bleeding problems.

The choice (and number) of leads must also be considered. Passive-fixation leads are typically associated with less elevation in acute threshold level, but active-fixation leads may be selected when potential dislodgment is a significant concern. This might be anticipated, for example, in cases of smooth-walled dilated right ventricles, amputated atrial appendages in patients having undergone earlier open-heart surgery, or right ventricular outflow tract lead positioning. In addition, active-fixation leads may be more easily removed in the unlikely event that extraction is a future consideration. Pacing configuration (unipolar vs. bipolar) is also an important issue to contemplate. On the one hand, unipolar leads are typically smaller in diameter and easier to introduce; in many cases, two unipolar leads may be introduced primarily through a single venotomy or even through a single peel-away introducer. However, unipolar systems have many potential disadvantages, including myopectoral stimulation, myopotential inhibition, and sensing of unipolar spikes by simultaneously implanted defibrillators. On the other hand, bipolar lead systems have had a number of associated advisories related to insulation degradation and subclavian crush syndrome. Compatibility of the selected lead(s) with the designated pulse generator must be ensured.

Epicardial or subxiphoid placement of pacer systems is typically reserved for those individuals who cannot undergo effective pacing via the transvenous route (e.g., a patient who has a mechanical tricuspid valve replacement) or who are simultaneously undergoing thoracotomy for other reasons. Limited surgical approaches using a trans-atrial implantation technique have also been described.

Transvenous pacing is usually the preferred route, with use of the cephalic vein, the subclavian vein, or the axillary vein; it is rare to employ the external or internal jugular veins. Identification of a reasonably sized brachial or antecubital vein by placing a tourniquet around the arm is a good predictor that the patient will

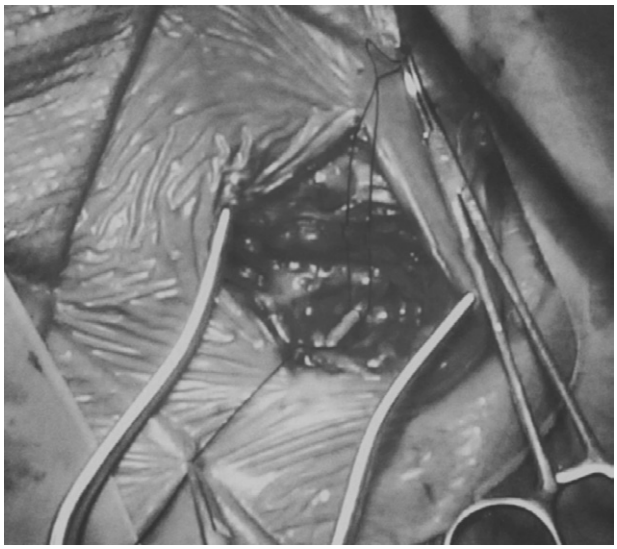

FIGURE 32-1 Isolation of cephalic vein.

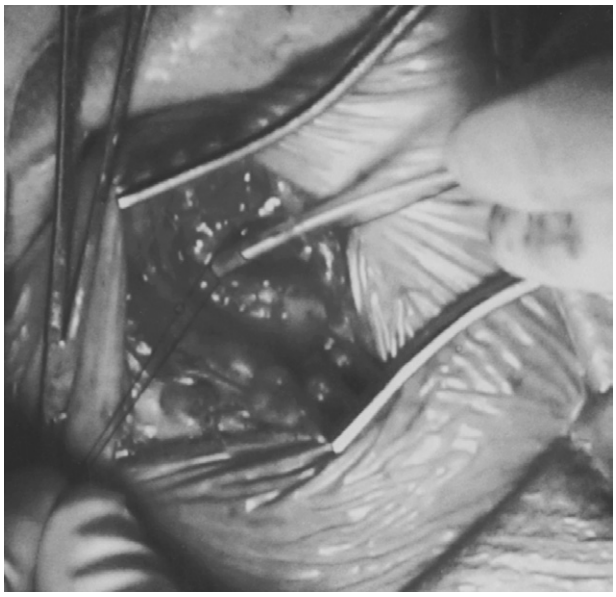

FIGURE 32-2 Insertion of lead through venotomy in cephalic vein.

have a usable cephalic vein more proximally. After meticulous preparation, draping, and administration of local anesthesia, a circumlinear incision is made; dissection follows down to the delto-pectoral fat pad, beneath which courses the cephalic vein (Figure 32-1). Many implanters choose to access the subclavian vein percutaneously *before* making such an incision, in the belief that the anatomies of the clavicle and the first rib are better appreciated "from the outside." Nothing, however, precludes using the subclavian approach from *within* the incision if the cephalic vein is not encountered. The distinct advantages to looking for the cephalic vein first are as follows: (1) It avoids the potential risk of pneumothorax, subclavian artery puncture associated with attempts at subclavian vein puncture, or both; (2) it may avoid trauma to the lead incurred in the subclavian crush syndrome or associated with the peel-away introducer technique; (3) it provides yet another avenue of access not available to those implanters who are accustomed to only the subclavian puncture technique, and (4) in cases of subsequent revision, it allows the use of an unused subclavian vein. Ligatures are applied proximally and distally to the site of the venotomy (Figure 32-2). It is particularly important to tie off the distal ligature (usually with 3-0 silk) before introducing the lead to prevent significant back-bleeding should a small cephalic vein avulse with manipulation. Vein lifts that are typically supplied with the pacemaker electrodes can be abrasive; the author prefers to use a curved iris forceps. The lead should be visually inspected before introducing it to ensure that no defects are present at the very outset before manipulation.

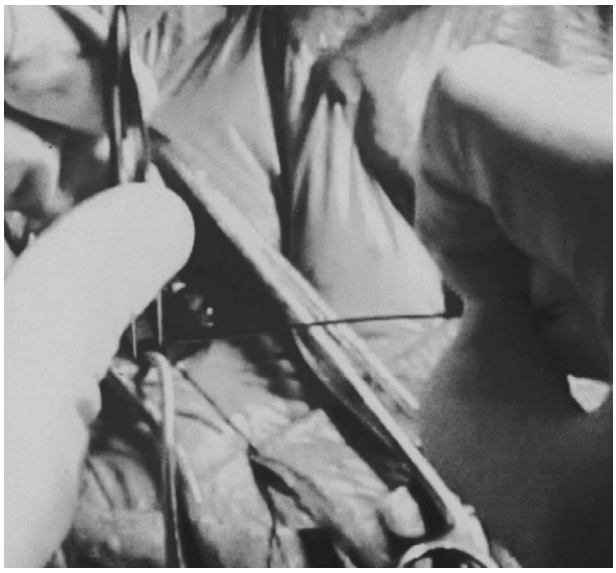

FIGURE 32-3 Insertion of guidewire through cephalic vein; first lead already inserted through venotomy.

Often a venotomy through the cephalic vein will accommodate both atrial and ventricular leads. Occasionally, only one (or neither) may be introduced primarily, because the vein is either too small or tortuous. In such cases, one may consider introducing a guidewire through the cephalic vein and then using a peel-away introducer technique through the cephalic vein to introduce one or both leads (Ong-Barold technique; see Figures 32-3 and 32-4). Again, great care should be taken while advancing the introducer (use of a Gerard forceps to raise the flap of the venotomy may be helpful here) to avoid avulsing the cephalic vein, and fluoroscopic visualization of the advancing introducer may be helpful to track its course along the guidewire. Percutaneous subclavian vein access has been made possible largely by the peel-away introducer technique, which allows access to be achieved through the Seldinger technique and removal of the sheath subsequently from the retained pacemaker lead. A variety of techniques has been reported. The subclavian window approach entails puncturing near the apex of the angle formed by the first rib and clavicle and aiming medially and in the cephalic direction.

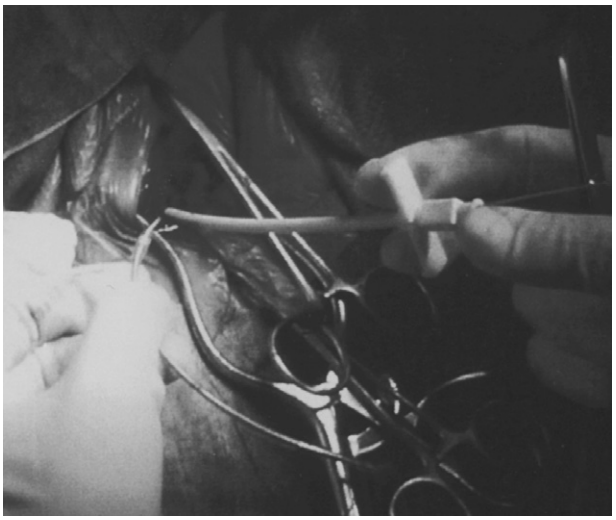

FIGURE 32-4 Insertion of peel-away introducer over guidewire through cephalic vein; first lead already inserted through venotomy.

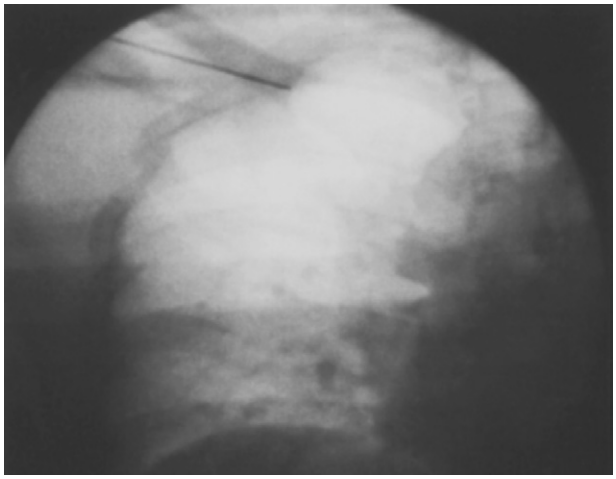

FIGURE 32-5 Fluoroscopic visualization of introducer needle for obtaining subclavian vein access.

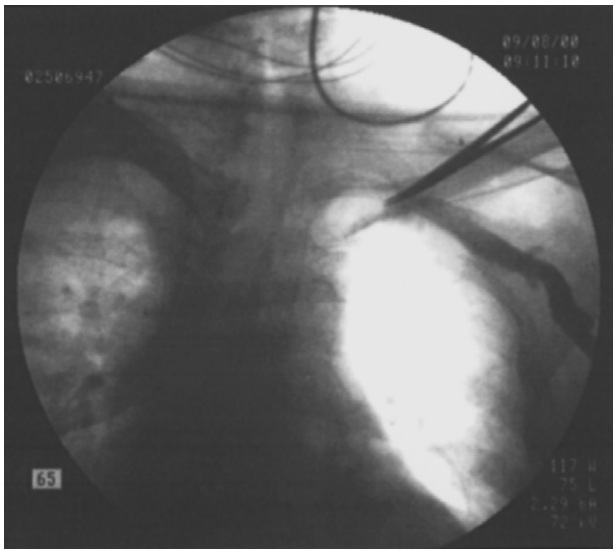

FIGURE 32-6 Peripheral dye injection for venography to guide needle for subclavian vein access.

The medial aspect of this approach has a better success rate and a lower risk of pneumothorax and vascular injury compared with a more lateral entry because the vein is a larger target and the apex of the lung is more laterally situated. The tighter binding between the first rib and clavicle may, however, result in the subclavian crush phenomenon with insulation failure, particularly in the case of bipolar coaxial polyurethane leads. The "safe introducer technique," as described by Byrd, relates to a safety zone between the first rib and clavicle, extending laterally from the sternum in an arc. More lateral approaches may avoid soft tissue entrapment (subclavius muscle, costocoracoid ligament, and costoclavicular ligament) and may, therefore, extend lead longevity. Cannulation of the extrathoracic portion of the subclavian vein (the axillary vein) has been increasingly used, with puncture made anteriorly to the first rib, maneuvering posteriorly and medially, but remaining lateral to the juncture of the first rib and clavicle; in the more lateral locations, care must be taken to avoid puncturing the subclavian artery. The use of radiography has been advocated during the introduction of needles, whatever may be the technique chosen, to confirm point of entry and subsequent trajectory (Figure 32-5); in some cases, dye injection with venography may facilitate venipuncture (Figure 32-6), particularly in cases where access has been difficult and the risk of subclavian vein thrombosis exists. This may be particularly effective in guiding venipuncture when using the axillary vein approach. Occasionally, Doppler techniques to facilitate vein localization and venipuncture may be used. In patients who have superior vena cava, innominate vein obstruction, or both, stent dilation has been considered to achieve access without going to the contralateral chest. Once access to the subclavian vein has been achieved, an incision must be made to allow for the development of the pocket if the puncture was percutaneous and not from within the wound. The peel-away-introducer technique then allows for passage of the introducer over the guidewire and subsequent passage of the pacemaker lead through the introducer. If the leads are small (especially if unipolar), both may be guided through a single introducer. More commonly, the guidewire is retained after passage of the first lead to allow for the passage of a second introducer and pacemaker lead, which obviates the need for a second venipuncture (Figure 32-7); alternatively, two guidewires may be passed through a single percutaneous introducer with subsequent sliding of the introducer over each guidewire separately to provide independent access for each of two pacing leads. Occasionally, a recently introduced lead may cause problems (e.g., a need to switch from a passive fixation to active fixation lead) with loss of previously established venous access. In such cases, a blade may be used to slit the insulation of the lead to be sacrificed, a guidewire wedged through this insulation, and the lead advanced with a guidewire as a unit so that the guidewire enters the vascular space. With the guidewire held in place, the lead to be sacrificed may be advanced slightly so as to disengage it from the guidewire; in this manner, the guidewire is retained within the vascular

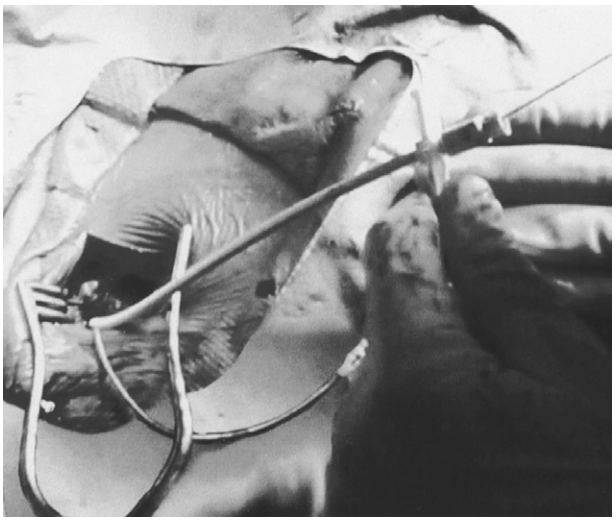

FIGURE 32-7 Peel-away introducer technique with retained wire for subclavian access.

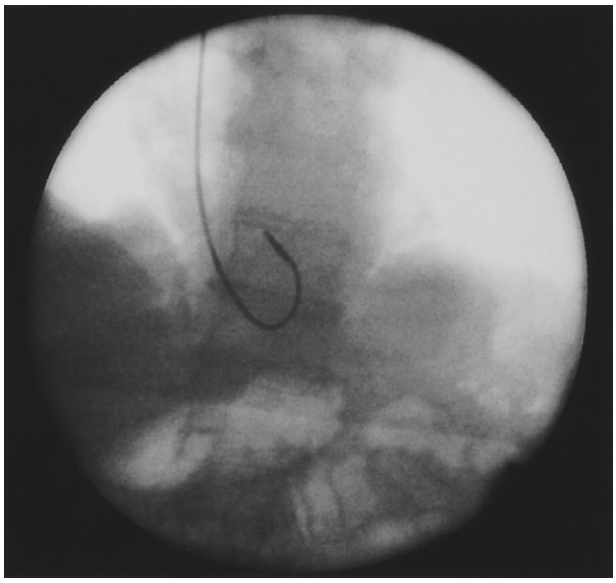

FIGURE 32-9 Prolapse of ventricular lead across tricuspid valve.

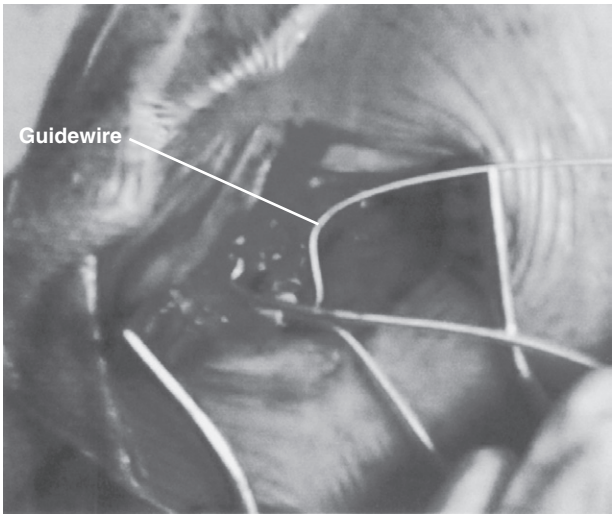

FIGURE 32-8 Insertion of guidewire under insulation of lead to be sacrificed, to re-establish venous access.

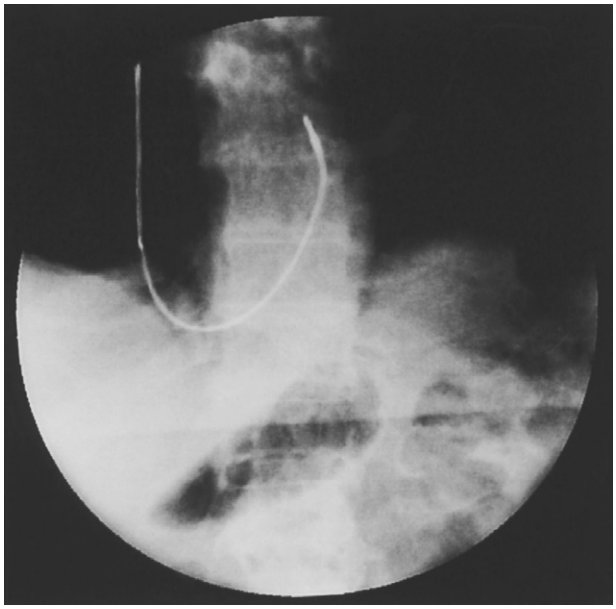

FIGURE 32-10 Passage of ventricular lead into right ventricular outflow tract, with plan to pull back and allow lead to "drop" into right ventricular apex (subtraction image).

space, the old lead may be removed, and a new lead may be placed through a peel-away introducer placed over the guidewire (Figure 32-8). The technique required for lead manipulation may vary as a function of the lead used and the cardiac chamber to be accessed. For right ventricular apex positioning, one approach is to prolapse the lead across the tricuspid valve (Figure 32-9). The other commonly employed approach is to create a curve on the stylet and guide the lead to the right ventricular outflow tract, subsequently withdrawing the lead until it drops into the right ventricular apex position (Figure 32-10); this approach ensures that passage has been achieved into the right side of the heart and reduces the inadvertent placement of the lead into the coronary sinus. With any lead manipulation, great care must be undertaken to avoid dislodgment of other leads already in place, particularly if these have been recently placed. In addition, placement of the leads may result in the induction of ventricular arrhythmias and trauma to the atrioventricular node or right bundle (of great concern in patients with pre-existing left bundle branch block), dictating the need for backup equipment for external pacing and defibrillation. Placement of the ventricular lead in patients with persistent left superior vena cava may be particularly challenging. The loop-de-loop technique is used in which the lead enters the dilated coronary sinus from the left superior vena cava and is

banked off the right atrial wall to re-enter the right ventricular apex. An active fixation lead is recommended for stabilization of position in this case (Figure 32-11). Occasionally patients may require placement of the lead in the right ventricular outflow tract; for example, to minimize electrical interaction with a previously implanted right ventricular apex defibrillator lead, an active fixation bipolar lead should be employed (Figure 32-12). The optimal position for right ventricular pacing to promote cardiac hemodynamics (e.g., apical versus outflow tract) is still being debated, but to date, no definitive answer has been found.

Biventricular pacing has been increasingly used as a method to facilitate cardiac resynchronization therapy, most commonly during defibrillator placement and, to a lesser extent, to alleviate symptoms of heart failure in patients who are not candidates for defibrillator implantation. Placement of a second ventricular lead to enable left ventricular pacing has been accomplished via the coronary sinus approach, though epicardial or trans-septal approaches may on occasion be used. Engaging the coronary sinus can be difficult, especially in patients who have undergone previous cardiac surgery; it is most easily achieved via left-sided implantation. Of the many techniques that have been devised, the most common one is cannulation of the coronary sinus, which may be achieved with a deflectable electrophysiology catheter and confirmed by obtaining left atrial recordings. Thereafter, a sheath may be advanced over the electrophysiology catheter, which is then removed. Balloon-occlusive venography with dye injection may then delineate the coronary sinus anatomy and allow for subsequent placement of a coronary sinus lead into a branch allowing for biventricular pacing. This may require tracking of the lead along a guidewire, a so-called *over-the-wire* approach. Alternative methods to engage the coronary sinus ostium include searching with a glidewire over which a sheath is subsequently advanced and using special preformed catheters such as Amplatz catheters that allow for subsequent passage of a guidewire once the ostium is localized. On occasion, guidewires or glidewires may be necessary to maintain access within the coronary sinus while a separate sheath-guidewire combination is used to pass the coronary sinus lead. Fixation of coronary sinus leads is predominantly passive, though efforts are currently under way to develop alternative methods of fixation.

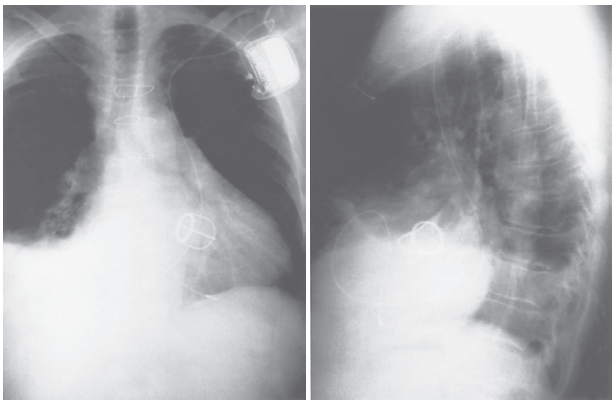

FIGURE 32-11 Active fixation ventricular pacing lead inserted via persistent left superior vena cava, through coronary sinus, and via loop-de-loop into the right ventricular apex in patient with Starr-Edwards valve prosthesis.

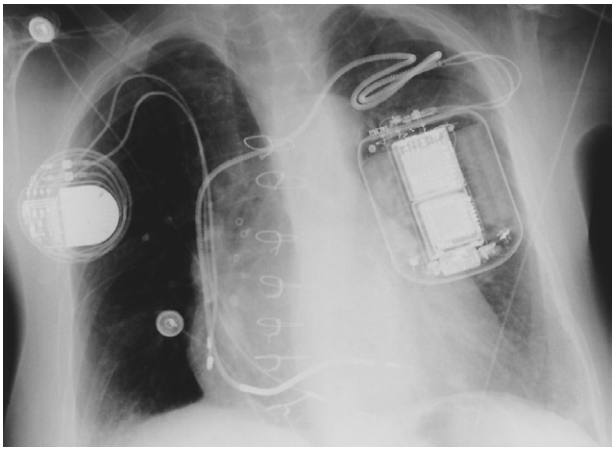

FIGURE 32-12 Patient with right-sided pacer and left-sided defibrillator, with active-fixation ICD lead positioned in right ventricular outflow tract to minimize interaction with right ventricular apical pacing lead. *ICD*, implantable cardioverter defibrillator.

Manipulation of the atrial lead primarily entails using a straight stylet initially to pass the lead through the vein into the right atrium and then replacing it with a curved stylet. Great care must be exercised, as with manipulation of any stylet, to avoid getting heme on the stylet lest it occlude the lumen of the lead and thereby prevent the passage of other stylets that might be required. In the case of a preformed (J-shaped) passive-fixation atrial lead, engagement of the atrial appendage is the goal and may be appreciated fluoroscopically by the "dog wag" appearance of the engaged lead as it moves with atrial contraction. For active-fixation leads, it is important to test the screw mechanism before attempting passage. Active-fixation atrial leads are either preformed J-shaped ones or require the implanter to form a J by passage of a J-shaped stylet; in either case, it is useful to watch the screw mechanism extend under a magnified fluoroscopic image and then torque the body of the lead clockwise slightly for further stabilization. Less experienced implanters have the misconception that the use of an active-fixation lead per se ensures active fixation and greater stability. It is critical to test fluoroscopically for stability of the lead fixation with gentle traction, particularly as the J-shaped stylet is being withdrawn from the atrial lead. Ironically, better sensing and pacing thresholds may often be achieved with passive-fixation leads; however, active fixation enables positioning the leads in patients with prior atriotomy or who require positioning of the lead in a less orthodox location within the atrium. As to special positioning of atrial leads, some preliminary work has explored the potential benefit of preventing atrial fibrillation by pacing at the Bachmann's bundle, by interatrial septum pacing, or by both. Dual-site right atrial pacing and bi-atrial synchronous pacing in some studies have been more effective in the prevention or reduction of atrial fibrillation, compared with single-site right and left atrial pacing. Typically, dual-site right atrial pacing consists of pacing simultaneously from leads positioned in the high right atrium and coronary sinus ostium; the proposed mechanism responsible for antifibrillatory effects is a reduction of activation times in the atrium, especially in areas of conduction delay.

A question that frequently arises is how best to place atrial leads in a patient who is in atrial fibrillation or flutter at the time of implantation. One approach is to acutely cardiovert the patient

to sinus mechanism, provided no significant risk of thromboembolic phenomena (as assessed by recency of the arrhythmia, trans-esophageal echocardiography, previous anticoagulation, etc.) exists. Another method is to blindly position the lead and use an active-fixation lead, in particular, to allow for a variety of test positions as assessed by atrial signals and electrocardiographic mapping. Cardioversion could be undertaken thereafter in the latter case, or it may occur spontaneously in the case of the paroxysmal fibrillator.

In some situations, the implanter may opt for a single-lead dual-chamber system, particularly for patients with heart block but with normal sinus node function and without atrial arrhythmias. Current models allow for bipolar atrial sensing with ventricular pacing and sensing (unipolar or bipolar), although leads that also allow for atrial pacing have been studied. The advantage of this approach is that atrioventricular synchrony may be achieved with a single lead. It is important to size a patient with regard to cardiac configuration so as to choose a lead with appropriate spacing between the atrial bi-pole and ventricular electrodes. It is ideal to have the atrial electrodes contacting the atrial wall (as opposed to sitting in the blood pool), also allowing enough slack to accommodate changes in atrial electrode positioning that may arise with respiration or change in body position.

Fluoroscopic confirmation of positioning is important, not only in the anteroposterior views but also in utilizing right and left anterior oblique views to assess patients with anteriorly rotated hearts and either confirm or rule out the placement of a lead within the coronary sinus.

Following placement of the lead(s), use of the pacer system analyzer is crucial in evaluating sensing thresholds, pacing thresholds, and lead impedance and for the possibility of diaphragmatic stimulation at high output—either through atrial leads (phrenic nerve stimulation) or ventricular leads (through a thin-walled right ventricle). For active-fixation leads, whether in the atrium or in the ventricle, demonstration of an initial injury current is particularly useful in confirming fixation.

Perhaps the most important step in pacemaker implantation is lead anchoring. An anchoring sleeve minimizes trauma by being sutured (typically a 0-silk) to the underlying lead insulation, conductor, or both (Figure 32-13). The right balance must be achieved between anchoring the sleeve too securely and anchoring it not securely enough; it is easier to bury the sleeves with a purse-string suture with leads implanted via the cephalic route than via the subclavian route. In addition, repeat fluoroscopy should be undertaken once anchoring has been performed to make sure that lead position, redundancy, or both remain stable at baseline as well as with deep breathing. Enough slack should be provided to accommodate tall individuals, particularly those with large respiratory excursions, to prevent undue tension or retraction of the lead. The leads are then connected to the connector block of the generator; it is critical to ensure that the set screw sites are adequately tightened (including both poles in the case of bipolar leads) by gentle tugging on the lead. Application of sterile adhesive over the set screw site may minimize current drain through this locale.

Creation of the generator pocket, either with Metzenbaum scissors or forceps or blunt finger dissection, is followed by placement of the generator inside the pocket. It is useful to irrigate the pocket with antibiotic solution. Hemostatic thrombin-containing preparations, absorbable meshes, or both may sometimes be instilled or left within the pocket. Any redundant or excess lead should be placed *under* the can so that future generator replacements will not be compromised by inadvertent slicing of the lead(s). In some cases, placement of the generator and lead within a Dacron pouch ("Parsonnet pouch") (Figure 32-14) may allow for more ideal stabilization and anchoring of the system in the prepectoral fat and thereby minimize generator migration and extrusion, or the so-called *twiddler's syndrome*. In some patients, a submammary generator placement may be considered for cosmetic reasons; the lead electrodes may be tunneled from the infraclavicular site of entry to the inframammary incision by using a long needle, a guidewire, and an introducer/dilator technique similar to the retained guidewire technique described earlier (Figure 32-15). After insertion of the generator into the pocket,

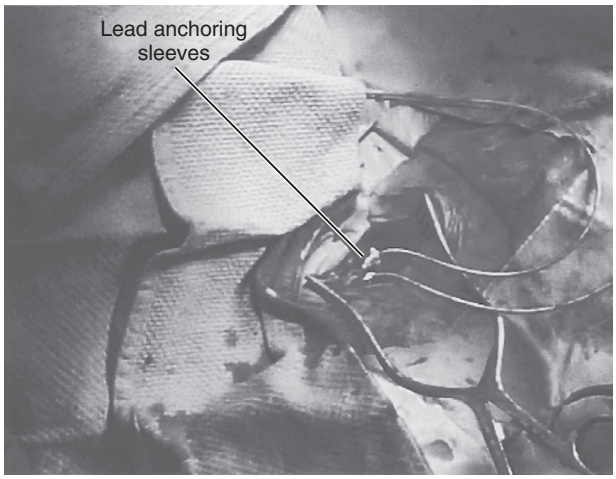

FIGURE 32-13 Use of anchoring sleeves for fixation of pacer leads to underlying fascia.

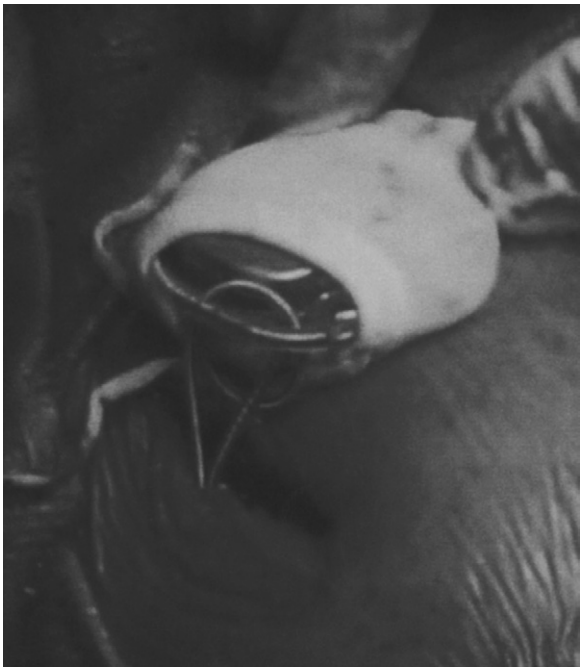

FIGURE 32-14 Use of Parsonnet pouch.

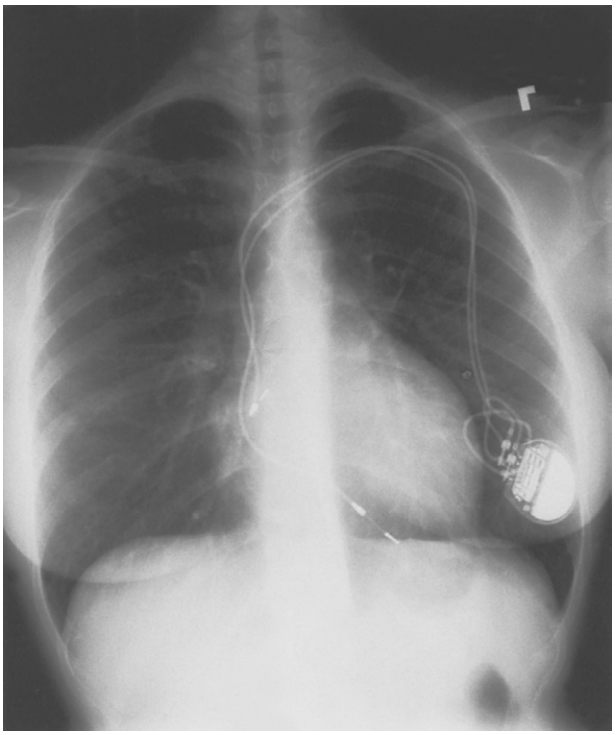

FIGURE 32-15 Atrial and ventricular leads inserted via a left subclavian approach, tunneled to a left submammary location for generator placement.

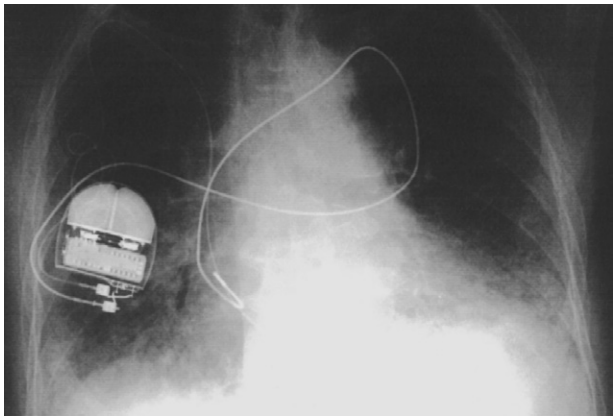

FIGURE 32-16 Right-sided pacer generator and ventricular lead, with the atrial lead placed via the left side and tunneled over to the contralateral generator site.

fluoroscopic confirmation of lead stability is important to rule out lead retraction during this process. Potential complications associated with pacemaker implantation are numerous but fortunately uncommon and have been well described elsewhere. A clear inverse relationship exists between operator experience and complication rate; a direct relationship is associated with the use of subclavian puncture. Preparedness for any eventuality, as discussed previously, remains an important goal. Although problems with bleeding are usually readily apparent, as in complications due to arrhythmia induction, the two most worrisome issues likely to be encountered are sudden hypoxemia and hypotension, which may occur independently or together. The former raises the possibility of pneumothorax, oversedation, or air embolism (when the introducer technique is employed), whereas the latter may include a variety of issues such as ongoing bleeding (suspected or otherwise), hypovolemia, medication, left ventricular dysfunction, pneumothorax, or cardiac tamponade. Some of these complications may lead to a vicious downward spiral; it is, therefore, incumbent on the implanter to keep close scrutiny on the vital signs, oximetry, and rhythm and remain in constant communication with the other team members in the operating arena who are monitoring these factors.

Pacemaker Upgrades, Revisions, and Generator Replacements

On occasion, it may be necessary to upgrade an existing pacemaker system. This is most commonly encountered in patients with single-chamber ventricular systems who experience pacemaker syndrome, which may be overt or subclinical; this would warrant a switch to a dual-chamber system. Increasingly, patients with congestive heart failure are requiring an upgrade to a biventricular system. Considerable operator experience is required for this upgrading procedure; initial reports of these procedures were associated with a remarkably high complication rate, but it is hoped that it has been reduced over time. Obtaining previous operative notes is extremely useful to ascertain which vein was previously used. If the original route was subclavian, was it because there was no identifiable cephalic vein, or was it the implanter's preference? If the latter, an accessible cephalic vein may well be available to accommodate the new atrial lead, which would require the cutdown technique as previously described. If no cephalic vein is available, the subclavian vein must be used. In case of any doubt as to the viability of the vein vis-à-vis the risk of thrombosis, dye injection of the ipsilateral brachial or axillary vein is helpful. Otherwise, percutaneous subclavian vein entry through the skin or from within the wound is undertaken, with great care to avoid needling or cutting the insulation of the previously implanted lead. Radiographic visualization of the searching needle trajectory is particularly useful in this situation.

If subclavian vein thrombosis is present or the infraclavicular space is too tight to accommodate a second lead (even the smallest unipolar available), then access may be attempted via the contralateral chest with tunneling of the new lead under the skin to the original pacer site (Figure 32-16). The alternative would be to abandon the original site altogether and place a new dual-chamber system via the contralateral chest. If the new lead is to be implanted and tunneled back, a smaller incision can be used; once again, anchoring is of vital importance. For tunneling, a Kelly clamp can be advanced bluntly in the subcutaneous tissue from the receiving (original) site to the satellite (contralateral) site. The free terminal end of the new atrial lead may be placed through a Penrose drain with a gentle tie applied around the drain just distal to the lead connector. The free end of the Penrose drain is then grasped and pulled through the tunnel, back to the original implantation site; the tie is released and the drain is then removed. Alternative approaches include the use of a guidewire and the peel-away introducer technique (introduced from the original site

to the satellite location), with passage of the terminal end of the new lead back through the sheath to the original site; a chest tube may also serve as the tunneling conduit. Great care must be taken to strive for a tunnel that is deep (as close as possible to the overlying muscle) and to avoid traumatizing the lead during the tunneling process.

Less commonly, the contralateral site may be used for the new lead, as well as for the creation of a new pacemaker pocket with placement of the new generator. Under these circumstances, the original lead is then tunneled under the skin, by using the same procedure described above, to the new (satellite) location. Depending on the available remaining length of the original lead, a lead extender may be required to traverse the distance to the new site.

Not infrequently, existing lead(s) may deteriorate because of insulation breach or conductor fracture. Placement of a new lead is then required, either through the original site or via the contralateral chest. The same techniques apply, as discussed above, with an upgrade from a single-chamber system to a dual-chamber system. The implanter may decide to abandon the original site altogether and place a new system via the contralateral chest, leaving the original system intact, removing only the old generator (with capping and anchoring of the old lead[s]) or removing of all of the previous hardware (generator and leads). Provided no evidence of infection or erosion is present, old leads may be retained, that is, without mandating extraction.

Generator replacement has been an increasingly important procedure, whether to meet elective replacement indicators or because of device advisories; this undoubtedly reflects the enhanced longevity of patients with pacemakers. It is a commonly undertaken procedure but its importance is often minimized; in fact, it requires a lot of advance thinking. This is particularly the case for the patient with pacer dependence. It is important to establish whether any escape rhythm is present by slowly lowering the programmed rate. If no spontaneous rhythm emerges, consideration must be given to how to maintain perfusion when the old generator is disconnected from the chronic leads. Temporary transvenous pacing or noninvasive external (Zoll) pacing are alternative solutions to quickly changing from the old generator to the new generator (provided that the implanter has nimble hands!). For unipolar systems, as soon as the generator is lifted out of the pocket, capture will be lost; to facilitate conversion to a new generator, a "money clip" may be externally attached to the generator with its associated alligator clip connected to the skin retractor at the pocket site. The new generator must be compatible, either primarily or through adapters, with the existing leads; knowledge of the previous system is therefore critical—with regard to lead manufacturer, nature of the terminal pin, and polarity. Visual inspection of the leads and determination of thresholds and impedances—at baseline as well as with gentle traction on the leads—are all important maneuvers that must be undertaken to make sure that lead replacement is not required (in addition to generator replacement). Rarely, repair of a conductor fracture may be undertaken using splicing techniques; occasionally, a terminal pin modification may be made with splicing techniques if an otherwise-needed adapter is unavailable. Not uncommonly, an anchoring sleeve may be applied with sterile silicone adhesive to repair an insulation breach in the lead. One note of caution that applies to generator changeovers is as follows: An alarmingly higher incidence of infections is noted compared with primary implants because insufficient attention is paid to meticulous aseptic technique during these more ambulatory procedures.

Management of Pocket Hematoma, Erosion, Infection, and Pacer Extraction

In the perioperative time frame, it is not uncommon to encounter pacer pocket hematomas, particularly (1) if the procedure has been associated with venous back-bleeding at the lead insertion site, (2) if arterial bleeding has been encountered, or (3) if a tear has been made outside the fascial plane during creation of the pocket; the use of anticoagulation or aspirin and, increasingly, clopidogrel, will also predispose the patient to problems in this regard. Arterial bleeding will result in the rapid formation of a sizable and enlarging hematoma and requires immediate exploration. In the case of less dramatic hematomas, cautious observation is warranted to watch for undue tension on the overlying pocket wall and subsequent tissue necrosis. Needle aspiration of the pocket may result in some decompression but should generally be avoided because it will not remove clots and may, in fact, introduce infection.

Rarely, the decision may be that the generator will be removed and not replaced. For example, certain patients elect to have the device removed because of ongoing implant-related discomfort that does not dissipate with time (so-called *pacemakerodynia*). It is always wise to review the original indications for pacer implantation while considering the removal of a device without replacement to avoid second-guessing the past decision.

The decision to remove one or more extant leads is the more difficult one than the decision to actually perform the corresponding procedure. Unequivocally, device-associated infection is best treated by removal of all associated hardware. The decision to do less—that is, clean the site and the pacemaker and plan for reimplantation at the same site or a distant site—has been reported but is not recommended. Once the skin barrier has been broken, colonization occurs and infection is likely; if the erosion or infection occurred because of previous indolent infection at the time of implantation or by secondary seeding, then clearly infection was present at the outset.

Extraction of leads may be undertaken transvenously or through a more extensive open-heart surgical approach (i.e., sternotomy or thoracotomy). An intermediate procedure called the *trans-atrial approach* has been described by Byrd; it is reserved for patients whose leads are not accessible or removable through the inferior vena cava or the superior vena cava. During this procedure the right atrium is exposed when the third or fourth right costal cartilage is removed, the pericardium is opened, and a purse-string suture is placed in the right atrium; a biopsy instrument is then inserted through the purse-string, and the lead is pulled out of the atrium.

Some clinicians have made a clear the distinction between extraction and simple lead removal: In the former, the leads are more difficult to take out of the patient. A policy conference of the Heart Rhythm Society has proposed that "extraction" apply to the removal of any transvenous lead that has been implanted more than 1 year ago or that requires the use of tools beyond standard stylets or simple traction. Indeed, the procedure can be quite challenging and potentially dangerous, even in experienced hands. In one large database, the risk of incomplete or failed extraction increased with implantation duration, less experienced physicians, ventricular leads, noninfected patients, and younger patients. Major complications were reported in 1.4% of patients (<1% at centers with more than 300 cases), and complication risk was associated with increased number of leads removed, female

gender, and less experienced physicians. The risk includes death, nonfatal hemopericardium or tamponade, hemothorax, arteriovenous fistula, need for transfusion, pulmonary embolism, and stroke. Unequivocally, a learning curve associated with extraction techniques does exist. The procedure is rarely emergent. As is the case with pacer implantation, the physician embarking on extraction must be prepared in advance to address any emergent complication, with particular emphasis on defibrillation, pericardiocentesis, cardiac surgical backup, or all of these. Large-bore intravenous access and arterial line monitoring are essential. Temporary pacing leads should be inserted in all patients who are pacer dependent.

Three transvenous approaches have been described for lead removal: (1) mechanical, (2) laser, and (3) electrosurgical. Mechanical approaches entail traction on the lead; removal by simple pulling was more easily achieved decades ago with leads that were made of silicone rubber and were nontined or short-tined. During application of the lead, direct traction by pulling on the lead (preferably with a standard lead stylet inserted within) is undertaken, with just enough force to feel the tugging of the heart without inducing chest pain, mechanical embarrassment with hypotension or tamponade, or ventricular arrhythmias. Such force may be applied for minutes, although in the past, various weights or elastic bands were used to allow constant traction for a period of days. Excessive force may result in stretching or tearing of the lead or may induce damage either in the vein or at the tissue-electrode interface.

Improved fixation techniques used to minimize lead dislodgment have ironically led to increased difficulty with lead extraction when required. As a result, countertraction and counterpressure techniques and devices have been developed to facilitate extraction. The use of locking stylets has made it far easier to apply direct traction. The superior lead extraction approach entails opening the pocket and using lead clippers to remove the terminal connector from the pacer lead to be extracted. The insulators and outer conductor coil (in the case of coaxial leads) are trimmed back to expose the inner conductor coil, and the opening of this coil is then broadened with a coil expander. Sizing of the inner conductor coil is then undertaken, typically with a set of variably sized gauge pins, to select the largest locking stylet that will fully enter the inner conductor coil. The locking stylet is then introduced and advanced to the lead tip. In some stylets, counterclockwise rotation may be required (Cook Vascular, Leechburg, PA), whereas in others (Wilkoff stylet, Cook Vascular), removal of a latch pin and pushing of the locking cannula forward are required to activate the locking mechanism. In yet another model (Spectranetics, Colorado Springs, CO), a lead-locking device stylet has a fine, wire mesh stretched over its entire length; the mesh is released once the stylet is advanced and by bunching up holds the lead along its entire length (Figure 32-17). Tugging on the stylet to ensure the adequacy of locking is followed by ligating the end of the lead insulation with 2.0 suture and tying the suture ends to the locking stylet loop handle. This handle is flattened and placed through a preselected sheath set (telescoping inner and outer sheaths).

Standard sheaths are made of a plastic, such as Teflon (E.I. DuPont, Wilmington, DE) or stainless steel. The latter are used typically during initial entry into the central venous circulation and are used to cut through dense fibrosis near the subclavian site; then they are exchanged with the more flexible plastic sheaths that are used to negotiate through the various curves encountered along the venous path. Continuous and moderate tension is applied on the locking stylet as first the metal set and then the plastic sheaths are advanced to disrupt the fibrotic deposits (the outer sheath has a sharp cutting edge that is advanced over its inner sheath). Fluoroscopic guidance is deemed essential, on the basis of the recognition that misdirected dilators may result in serious vascular injury, particularly at curvatures in the vein where the more flexible plastic sheaths are required (Figure 32-18). If too much tension is applied to the lead–locking stylet combination, the same risks associated with conventional external traction may arise: tearing the lead, avulsing the vein or heart wall, or disengaging the locking stylet from the lead. The larger sheath is advanced over the inner sheath, while the smaller sheath is always kept on the leading edge in a telescoping forward movement. A snow plow effect may arise with scar tissue that is peeled away from the venous wall and pushed in front of the

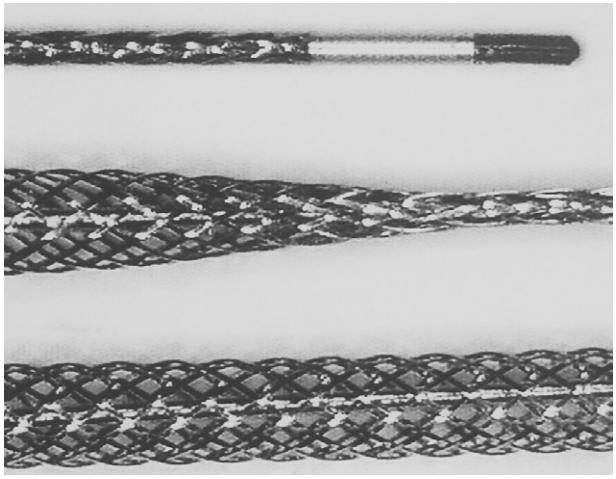

FIGURE 32-17 Special mesh locking stylet that expands along the entire length of the lead to be extracted.

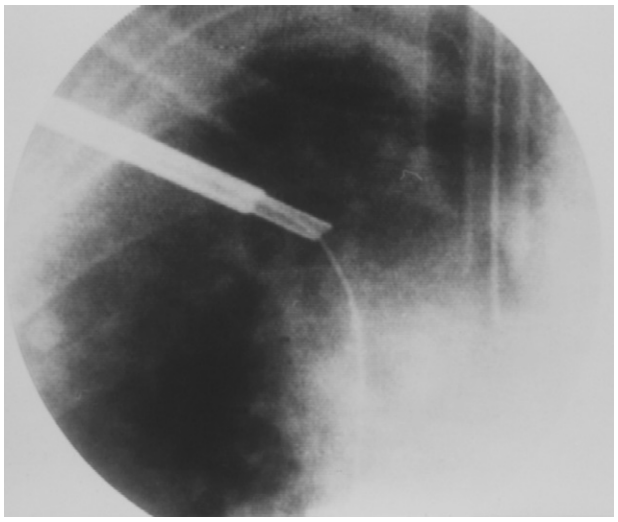

FIGURE 32-18 Use of telescoping (inner and outer) extraction sheaths over the lead to be removed.

FIGURE 32-19 Cross-section of excimer laser sheath.

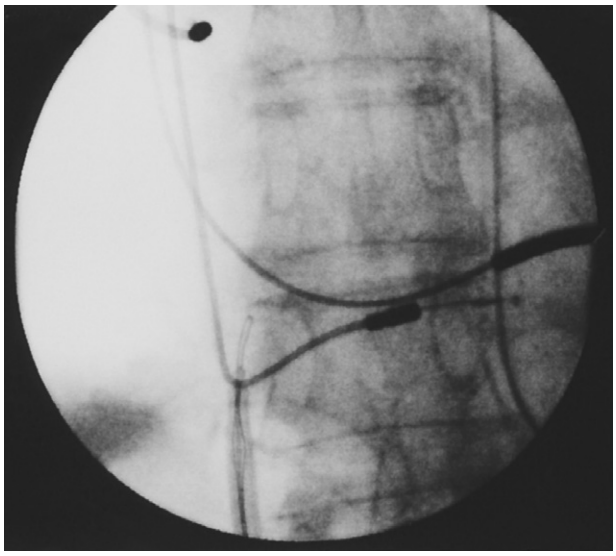

FIGURE 32-20 Fluoroscopy of the right ventricular apical lead being extracted from a femoral approach/snare technique in a patient with a dual-chamber pacing system and separate defibrillator lead in the right ventricular outflow tract.

sheaths, thereby preventing further advancement of the dilators. When the sheath set approaches the lead tip near the tissue–electrode interface, the outer sheath is removed and reversed so that its blunt end faces the myocardium and countertraction is then applied against the myocardial surface to release the lead tip. In some cases, after a chronic (noninfected) lead is removed, the retained sheath may be used to place a guidewire and then a peel-away dilating sheath is used to guide the placement of the new pacemaker lead; occasionally, balloon venoplasty may be required as an adjunct.

Powered sheaths have been developed to reduce the need for traction and counterpressure. The laser sheath is used to deliver excimer laser energy fiberoptically to the distal end of the sheath to dissolve the encapsulating fibrotic tissue in circumferential fashion (Figure 32-19). The laser has a very short depth of penetration, affecting only tissue that is in direct contact with the end of the sheath. This releases the lead from its tissue attachments, thus facilitating advancement of the sheath over the lead. An electrosurgical dissection sheath using radiofrequency energy with a more directed sheath tip is currently under active investigation.

Snares may be employed to apply indirect traction in extracting lead(s) by using a femoral approach. The snare device is used to encircle the free tip of the pacing lead or a loop of the lead, with traction then applied from below (Figures 32-20 and 32-21). The approach may be challenging because it is often difficult to ensnare a lead, but it may be less injurious because the coring out of surrounding fibrotic tissue is not required in this approach; nonetheless, the operator must be aware of the associated risks, femoral vein injury and thromboembolism, as well as the same potential complications associated with traction of the lead from above. The technique is indicated (1) if the lead to be extracted is not accessible from the venous entry site, (2) if the lead has been cut or fractured, or (3) if there has been retraction of the lead into the central venous circulation, intracardiac space, or both. The author's group found the technique to be particularly well

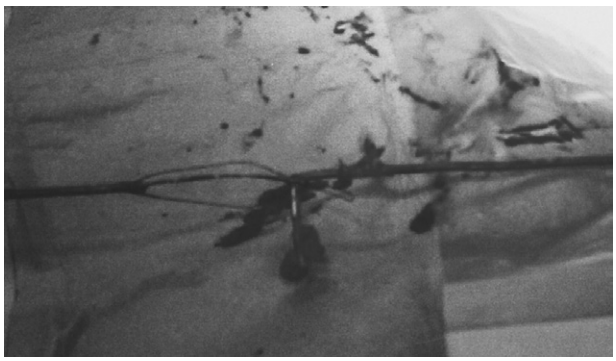

FIGURE 32-21 Right ventricular pacing lead after removal via the snare technique (same patient as Figure 34-20).

suited to removing atrial leads under the Accufix advisory associated with fracture of the inner retention J-shaped wire, particularly if this wire is protruding. If the lead is still anchored in the pectoral region, it must first be freed. Thereafter, a sheath with a hemostatic valve is placed via the femoral vein to the inferior vena cava level just below the atrium, and through this the grasping tool is deployed. Tools available for this include a deflecting tip guidewire and Dotter helical basket retriever, pigtail catheter, or Amplatz catheter; special countertraction sheaths are also available.

It is clear that lead extraction is a procedure that is not undertaken lightly, may be hazardous, and requires specialized training and careful deliberation and preparation. Indeed, in some series (e.g., Accufix leads), the risk of extraction over time has exceeded that associated with retention of the lead. In some cases (e.g., infected pacer systems), extraction is essentially unavoidable, but

precedents for abandonment without extraction of noninfected leads do exist.

Conclusion

Implantation and revision techniques have remained relatively constant over time. What remains paramount is an appreciation of the goals of implantation; thoughtful preparedness with regard to materials and approaches that will be required; anticipation of potential problems that will need to be addressed; and, perhaps most important, an experienced implanter who can respond appropriately when difficulties are encountered. Above all, complacency should be avoided because unfamiliar and unexpected circumstances do tend to arise.

Acknowledgment

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CHAPTER 33

Current Indications for Temporary and Permanent Cardiac Pacing

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In the past few decades, improvements in device technology and surgical techniques have made permanent pacemaker implantation a readily performed minor surgery with a low likelihood of major complications. Similarly, temporary pacemaker insertion can often be performed at the bedside quickly and safely with a relatively limited set of tools. Nevertheless, employing cardiac pacing in a given situation remains a major clinical decision, as it has the potential for life-altering consequences for the patient. In 2008, the American College of Cardiology, the American Heart Association, and the Heart Rhythm Society (ACC/AHA/HRS) jointly issued an updated set of guidelines for cardiac pacing on the basis of a comprehensive review of available clinical data and expert opinion.[1] This chapter refers to this document frequently and makes use of the ACC/AHA/HRS conventional division of indications into class I, class IIa, class IIb, and class III. The European Society of Cardiology separately released a set of guidelines for pacemaker implantation in 2007, making use of the same system for classifying indications.[2]

The ACC/AHA/HRS and ESC guidelines also classify the supportive data for each recommendation by assigning a level of evidence (LOE, see Appendix Table 33-1).* It is notable that of the 71 specific ACC/AHA/HRS recommendations relating to permanent cardiac pacing in adults, only 3 have LOE A, 29 have LOE B, and 39 have LOE C. In some instances, the lack of randomized trials reflects a broad consensus on the standard of care and the absence of alternatives to cardiac pacing for symptomatic bradycardia. In many other instances, however, particularly for class II indications, data from large clinical trials are scarce. The guidelines should, therefore, not be adhered to blindly but should be seen as a framework to assist with clinical decision making. Accordingly, the aim of this chapter is to review the indications for cardiac pacing in adults, including temporary pacing, permanent pacing, and multiple-site pacing, with special attention to clinical dilemmas and specific clinical situations. Device therapy in pediatric and adolescent patients and in patients with congenital heart disease will be reviewed separately.

Indications for Permanent Pacing

Bradyarrhythmias

Permanent pacing is most commonly employed to treat bradyarrhythmias, which can result from dysfunction of the specialized cardiac conduction system or dysfunction of the autonomic nervous system or from iatrogenesis. Therefore, the aim of this section is to provide a pathophysiologic framework for considering cardiac pacing in terms of the anatomic compartments required for normal cardiac rhythmicity.

Disorders of Sinoatrial Conduction

The functions of the sinus node are impulse generation, impulse transmission, and modulation of heart rate in response to autonomic inputs. Patients suffering from sinus node dysfunction manifest one or more of several distinct electrocardiographic abnormalities, including sinus bradycardia, sinus pauses, bradycardia alternating with tachyarrhythmias, and failure to augment heart rate appropriately with exercise (see Appendix Table 33-2). Typically, such patients will complain of lightheadedness, fatigue, syncope, or activity intolerance. The main diagnostic tool for establishing the diagnosis of sinus node dysfunction is continuous ambulatory electrocardiographic monitoring for a period determined by the frequency of the patient's symptoms.

No randomized trials demonstrating that pacing improves survival in patients with sinus node dysfunction have been conducted, and at least one small series suggests that short-term prognosis is good in this patient population.[3] Thus, the primary role for pacing is to treat symptoms, prevent adverse events such as syncope, and permit therapy with drugs that slow heart rate, as required to treat other medical conditions. Before considering pacemaker implantation, reversible causes of sinus node dysfunction should be ruled out (Table 33-1). The indications for permanent pacing in sinus node dysfunction are summarized in Appendix Table 33-3. When sinus pauses or bradycardia coincide temporally with the patient's symptoms and a causal link can be established, a pacemaker is indicated; this is a class I indication. Conversely, when the patient's typical symptoms occur during periods when monitoring reveals a normal heart rate, pacemaker implantation would not be expected to provide any benefit; this is, therefore, a class III indication.

It should be emphasized that when the vagal tone is high, particularly during sleep, episodes of sinus bradycardia are common in healthy individuals. Thus, in inpatients or outpatients with cardiac monitors, pauses and periods of slow heart rate are frequently seen and can be of uncertain clinical significance. Similarly, symptoms of lightheadedness, syncope, and activity intolerance are not specific and can occur for a number of reasons. Thus, the decision to implant a pacemaker in a patient with evidence of sinus bradycardia and suggestive symptoms but without a clear

*Appendix tables are available on the Expert Consult site for this text.

Table 33-1 Reversible Causes of Sinus Bradycardia and Atrioventricular Block

TYPE OF CAUSE	SPECIFIC CAUSE
Cardiac	Myocardial ischemia Viral myocarditis Lyme disease Rheumatic fever Endocarditis Post–cardiac surgery Post–cardiac transplant Athletic training
Autonomic nervous system	Neurocardiogenic syncope Carotid hypersensitivity Vagal stimulation
Drugs and medications	β-Adrenergic blockers Calcium channel blockers Clonidine Digitalis Ivabradine Reserpine, methyldopa Class IA antiarrhythmic drugs Class IC antiarrhythmic drugs Class III antiarrhythmic drugs General anesthetics Tricyclic antidepressants Phenothiazines Lithium Phenytoin Cholinesterase inhibitors
Hypothermia	
Hypothyroidism	
Neurologic	Elevated intracranial pressure Spinal cord injury
Electrolyte imbalances	Hypokalemia Hyperkalemia Hypercalcemia
Pulmonary	Obstructive sleep apnea Prolonged hypoxia

causal link can be a difficult one. In such situations, we favor a thorough workup for other cardiac and noncardiac causes of the patient's symptoms. Particularly in older adults, we have found that polypharmacy is an often-overlooked cause for lightheadedness and syncope and should be ruled out before pacemaker implantation is considered. When no other cause can be identified, pacemaker implantation is a class IIa indication. Such patients should be advised that when a causal link has not been established between bradycardia and their symptoms, a pacemaker might not provide any benefit.

In patients with suspected sinus node dysfunction, particularly in those manifesting some degree of activity intolerance, exercise testing can be a very helpful adjunctive assessment of sinus node function. Chronotropic incompetence is often defined as failure to achieve a heart rate of 80% of age-adjusted maximum predicted heart rate with exercise.[4] However, the critical issue in such cases is whether heart rate is sufficient to meet physiologic demands. The clinician should, therefore, not place too much importance on the specific rate achieved but should determine whether sinus node function is the main factor limiting the patient's ability to exercise. Where this is the case, pacemaker implantation is warranted; this is a class I indication, even when heart rate is normal at rest and sinus pauses are not identified on monitoring.

The usefulness of invasive electrophysiology testing in determining the need to implant a pacemaker is limited, primarily because abnormalities in electrophysiologic parameters are not, in general, predictive of clinical events. Nevertheless, for patients with syncope who are undergoing electrophysiology testing and in whom other causes have not been identified, profound abnormalities of sinus node function may tip the balance of considerations in favor of pacemaker implantation; this is a class IIa indication.

Finally, a clinical situation frequently encountered is evidence of sinus node dysfunction manifested by sinus pauses or resting bradycardia in the absence of symptoms. At present, data suggesting that implantation of a pacemaker in such patients prevents adverse events or prolongs life are not available. Pacemaker implantation in the asymptomatic patient with sinus node dysfunction is therefore not recommended (class III). However, when sinus node dysfunction is marked (resting heart rate persistently less than 40 beats/min while awake), the ACC/AHA/HRS guidelines do recognize a class IIb indication for pacing in those who are at least minimally symptomatic. Often, a simple exercise test is sufficient in these patients to establish whether clinically significant sinus node dysfunction is present. However, in patients who cannot exercise because of comorbidities, pacemaker implantation can be considered.

Disorders of Atrioventricular Conduction

The function of the atrioventricular (AV) node is to delay impulse propagation from atria to ventricles to the extent necessary to optimize ventricular filling. This delay varies physiologically over a large range and is heavily influenced by autonomic tone and heart rate. The function of the bundle of His, which passes from the AV node to the ventricle through the central fibrous body, is to transmit the electrical impulse rapidly from the atrium to the ventricle. Conduction time through the bundle of His is rapid and does not vary with heart rate under normal conditions. Conduction slowing or block can occur in the AV node, the bundle of His, or both, and characteristic electrocardiogram (ECG) patterns are present, as well as differences in prognosis, depending on the location and severity of the block. In general, when the block is above the level of the His bundle (supra-His), prognosis for progression to a high-grade block is better than when the block is at or below the level of the His bundle (intra-His or infra-His).[5] Symptoms caused by an AV block can include fatigue, lightheadedness, and syncope; a persistent high-grade AV block can result in heart failure caused by bradycardia and loss of AV synchrony and can predispose to ventricular arrhythmias.

First-Degree Atrioventricular Block

First-Degree AV block is defined as P-R interval exceeding 0.2 seconds and is often reflective of incipient AV nodal disease, though it can be a normal finding in patients at rest with high vagal tone. Recent data from the Framingham cohort suggest that in the long term, patients with first-degree AV block have a

significantly higher risk of requiring pacemaker implantation and have a higher mortality rate.[6] However, with a few exceptions (discussed below), the short-term prognosis for those with isolated first-degree AV block is excellent, so pacemaker implantation is, in general, not indicated in asymptomatic patients as a prophylactic measure (class III). However, a few indications for pacing are recognized for first-degree AV block (summarized in Appendix Table 33-4).

Some patients with marked first-degree AV block (P-R interval >0.3 seconds) have symptoms that may warrant pacemaker implantation.[7] In these patients, ventricular activation is so delayed that the subsequent atrial activation occurs shortly after the QRS complex on the surface ECG, resulting in atrial contraction against closed AV valves (Figure 33-1). Patients with severe left ventricular dysfunction and markedly prolonged P-R intervals may experience hemodynamic compromise caused by impaired ventricular filling and diastolic AV valvular regurgitation.[8] Often, reducing the dosages of AV nodal blocking medications in these patients can shorten the P-R interval and improve symptoms. Where this is not possible, restoration of AV synchrony with dual-chamber pacing and a normal AV delay can solve the problem, and this is a class IIa indication. However, ventricular pacing under these circumstances carries with it the potential deleterious effects of intraventricular dyssynchrony, so consideration should be given to biventricular pacing in such instances, especially when left ventricular function is not normal (see below).

Finally, patients with several neuromuscular diseases (see Appendix Table 33-5) often have rapidly progressive AV conduction system disease. Even in asymptomatic patients with these disorders, marked first-degree AV block should prompt consideration of pacemaker implantation as a prophylactic measure.

Type I Second-Degree Atrioventricular Block

Second-degree AV block is divided into type I and type II on the basis of the ECG pattern. In type I, the P-R interval lengthens before the nonconducted beat and shortens on the first beat after the nonconducted beat (Wenckebach conduction); in type II, the P-R interval is fixed. In general, type I second-degree AV block suggests a supra-His level of block and is associated with a more benign prognosis, while type II occurs with intra-His or infra-His conduction system disease and has a higher rate of progression to complete heart block.[5] It should be remembered that in pathologic conditions, it is possible for any component of the conduction system, even the structures below the AV node, to exhibit Wenckebach conduction. Thus, type I second-degree AV block has a benign prognosis only when it is caused by supra-His block, which is usually the case when the QRS is narrow.

Regardless of the level of block, patients with symptomatic bradycardia resulting from second-degree AV block from irreversible causes or essential drug therapy should undergo permanent pacemaker implantation (class I). In the setting of high vagal tone such as sleep or in highly conditioned athletes at rest, type I second-degree AV block is frequently observed and is a normal finding.[9] For asymptomatic patients, pacemaker implantation is therefore not recommended (class III). However, as with first-degree AV block, patients with type I second-degree AV block can have symptoms caused by loss of AV synchrony, and pacemaker implantation should be considered for this indication (class IIa) as well as for symptomatic bradycardia. Indications for pacing in type I second-degree AV block are summarized in Appendix Table 33-4.

High-Grade Atrioventricular Block

Patients with type II second-degree AV block (Figure 33-2) have a higher rate of progression to third-degree AV block, particularly in the setting of intraventricular conduction abnormalities. From the point of view of cardiac pacing, advanced second-degree AV block and third-degree AV block should be grouped together in a single high-risk category, and pacemaker implantation is the only reasonable treatment when reversible causes cannot be identified (see Appendix Table 33-6). Randomized clinical trials comparing pacing with conservative management are not available, but considerable nonrandomized evidence exists that pacing for patients with high-grade AV block results in a prolongation of life and reduction in morbidity.[10]

Third-degree AV block and consequent AV dissociation are almost always symptomatic, though the symptoms can vary in

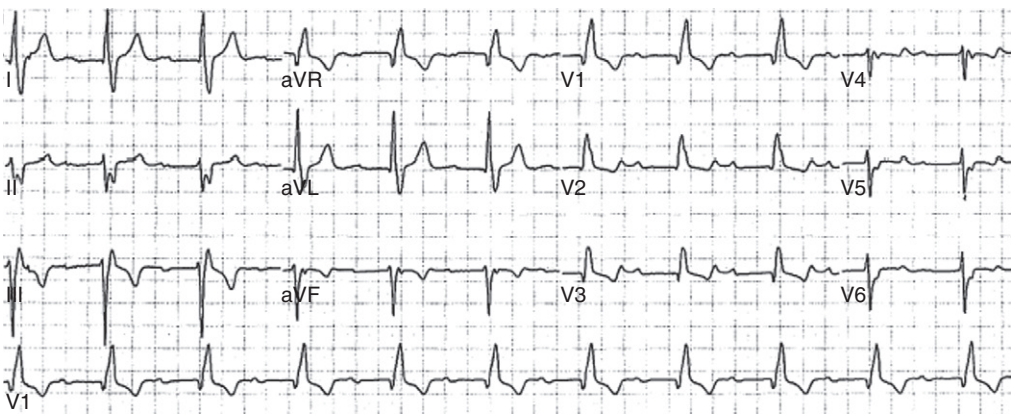


FIGURE 33-1 Twelve-lead electrocardiogram showing sinus rhythm with a prolonged P-R interval of 400 ms. This can lead to symptoms caused by atrioventricular dyssynchrony that improve after implantation of a dual-chamber pacemaker.

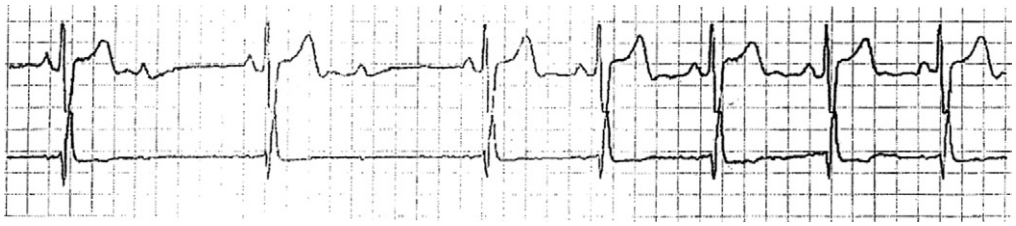


FIGURE 33-2 Rhythm strip showing 2:1 atrioventricular conduction on the left associated with a faster sinus rate and 1:1 AV conduction on the right with slower sinus rate. This is diagnostic of a Mobitz type II infra-His block and is an indication for permanent pacemaker implantation.

severity from mild dizziness and exercise intolerance to syncope or even sudden death, depending on the rate of the escape rhythm. In addition to medications that affect AV nodal conduction, a number of reversible causes of high-grade AV block, including myocardial ischemia, exist, and these should be ruled out before considering permanent pacing (see Table 33-1). Often, a careful history and an ECG are sufficient to rule out reversible causes of complete heart block, but where uncertainty remains, it is appropriate to perform further diagnostic testing. Brief periods of third-degree heart block can occur in situations of high vagal tone; where these are transient or occur exclusively in sleep and are accompanied by adequate escape rhythms, pacemaker implantation is not always warranted.

Advanced second-degree and third-degree AV block can be paroxysmal, with long intervening periods of 1:1 AV conduction, or can occur exclusively with exercise. When such paroxysmal heart block cannot be attributed to reversible causes, pacemaker implantation is a class I indication in almost all clinical situations, even in asymptomatic patients in the presence of pauses longer than 3 seconds, escape rate less than 40 beats/min, escape rhythm that originates below the AV node, cardiomegaly, or left ventricular dysfunction. In asymptomatic patients with third-degree heart block, normal cardiac size and function, and an escape rate longer than 40 beats/min, permanent pacemaker implantation is a class IIa indication.

AV block can be difficult to diagnose in the setting of atrial fibrillation. However, a slow regular escape rhythm in atrial fibrillation suggests the presence of high-grade AV block, as do long pauses. When symptoms caused by bradycardia are present, pacemaker implantation is warranted (class I). When pauses in atrial fibrillation exceed 5 seconds, pacemaker implantation is a class IIa indication.

Disorders of Intraventricular Conduction

The functions of the distal limbs of the conduction system (bundle branches, fascicles, and Purkinje fibers) are to transmit the electrical impulse rapidly to ventricular muscle and to ensure coordinated activation of the ventricles. The bundle of His bifurcates into the right bundle branch and the left bundle branch at the crest of the interventricular septum. Bundle branches then ramify into complex networks of specialized conduction fibers, known as *fascicles*. On the left, this complex fascicular system is conventionally divided into the left anterior fascicle and the left posterior fascicle. Dysfunction and failure of impulse transmission can occur in any combination of these bundles and fascicles, with or without superimposed AV block, leading to a variety of intraventricular conduction disturbances. Cardiac pacing has a role in a subset of patients with intraventricular conduction system disease (see Appendix Table 33-7).

Hemiblocks and Bundle Branch Block

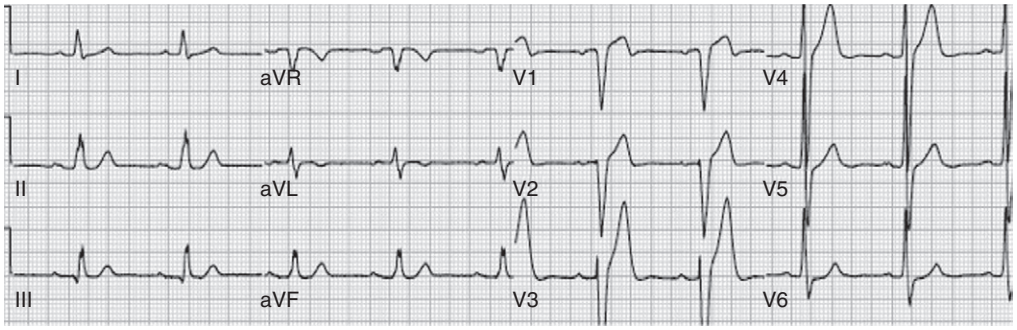
Individuals without conduction system disease may develop bundle branch block or fascicular block at very high heart rates, during tachyarrhythmias, or, less commonly, at very low heart rates (phase 4 aberrancy). Also, a small percentage of normal healthy individuals have right or left bundle branch block as a congenital variant. In general, block of a single fascicle (right bundle branch block, left anterior hemiblock, or left posterior hemiblock), with or without accompanying first-degree AV block, does not warrant consideration of pacemaker implantation without evidence of high-grade AV block.[11] The only major exceptions to this rule are patients with selected neuromuscular diseases, in whom any fascicular block may warrant consideration of pacemaker implantation because of the unpredictable nature of disease progression (class IIb).

Although complete left bundle branch block can be seen in the presence of disease of both the anterior and posterior fascicular systems (particularly in the setting of a large myocardial infarction), it more commonly results from a proximal lesion in the conduction system and should not be grouped with bifascicular blocks. If a patient presents with bundle branch block with left-axis, first-degree AV block and syncope, it may be reasonable to assess intraventricular conduction with an invasive electrophysiology study. An H-V interval less than 0.1 seconds or the finding of pathologic infra-His block with pacing may warrant consideration of pacemaker implantation.[12]

When complete left bundle branch block alternates with right bundle branch block, it suggests the presence of severe, widespread infra-His conduction system disease. The same is true when right bundle branch block with left anterior hemiblock alternates with right bundle branch block with left posterior hemiblock. Whether this alternation occurs within a single ECG or rhythm strip, or on successive ECGs recorded on separate days, this condition carries a high risk for progression to complete heart block and is a class I indication for pacemaker implantation, even in the absence of symptoms (Figure 33-3).

Chronic Bifascicular Block

Chronic bifascicular block is present with involvement of one of the left-sided fascicles plus the right bundle branch. *Trifascicular block* is a somewhat confusing term often used to refer to



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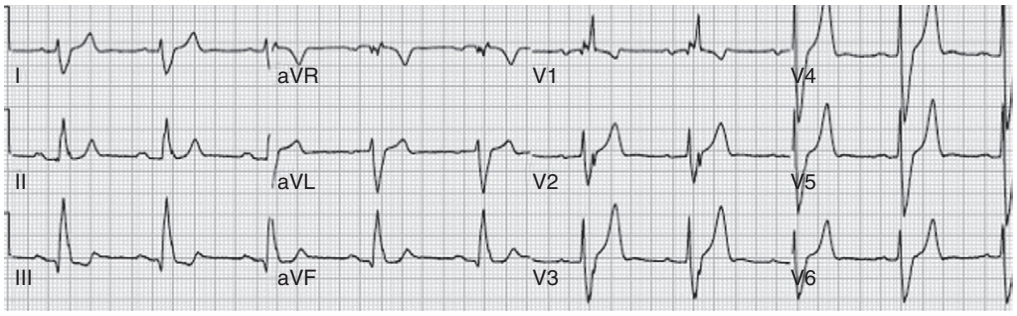

B

FIGURE 33-3 **A,** Twelve-lead electrocardiogram (ECG) showing sinus rhythm with left bundle branch block. **B,** Twelve-lead ECG in the same patient when he presented with syncope. The ECG shows right bundle branch block. Alternating bundle branch block signifies significant infra-His disease and is an indication for pacemaker implantation.

bifascicular block in the presence of first-degree AV block. The prognostic significance of bifascicular blocks varies according to the site of the block and the presence or absence of other forms of heart disease. With a few important exceptions (detailed below), the annual rate of progression to complete heart block in the asymptomatic patient is low, even though most patients who develop third-degree AV block have bifascicular block at some point.[13] When bifascicular block is accompanied (even transiently) by type II second-degree AV block, advanced second-degree AV block, or third-degree AV block, a high risk of progression to complete heart block is present, and pacemaker implantation is warranted whether or not symptoms are present (class I).

Syncope should prompt a thorough evaluation in patients with infra-His conduction system disease manifested by bifascicular block or trifascicular block.

When noncardiac causes have been excluded, it is important to consider ventricular tachycardia as a cause of syncope, especially when mild-to-moderate left ventricular dysfunction is present. When such patients are candidates for implantable cardioverter defibrillator (ICD) implantation, dual-chamber devices should be favored in the presence of infra-His conduction system disease to ensure AV synchrony in the event of paroxysmal AV block.

Occasionally, asymptomatic patients with infra-His conduction system disease are taken to the electrophysiology lab for other reasons. A prolonged H-V interval (<0.1 seconds) or the finding of nonphysiologic pacing-induced infra-His block warrant consideration of pacemaker implantation in these patients, even if they are asymptomatic (class IIa).

Disorders of the Autonomic Nervous System

The cardiovascular system, and the sinoatrial (SA) node and AV node within the heart, are richly innervated with parasympathetic and sympathetic fibers. Particular forms of autonomic nervous system dysfunction can cause symptomatic bradycardia, which, in some cases, can be responsive to cardiac pacing (see Appendix Table 33-8).

Carotid Sinus Hypersensitivity

Carotid sinus hypersensitivity occurs in patients in whom mechanical stimulation of the carotid body in the neck causes a vagal discharge that results in bradycardia. In some patients, asystole and syncope can ensue. For patients with recurrent syncope associated with carotid sinus stimulation and less than 3 seconds of ventricular asystole on carotid sinus pressure, permanent pacing is indicated (class I). When carotid sinus hypersensitivity is present with syncope, but the syncope is not clearly precipitated by carotid stimulation or any other identifiable cause, pacemaker implantation is a reasonable consideration (class IIa). However, in the absence of syncope, pacemaker implantation is not indicated for carotid hypersensitivity, even when vague symptoms such as

dizziness or lightheadedness coincide with carotid stimulation (class III).

Neurocardiogenic Syncope

Neurocardiogenic syncope, also known as *vasovagal syndrome*, results from a pathologic cardiovascular reflex, in which the final common pathway diverges into a peripheral vasodepressor response and a cardioinhibitory response. The vasodepressor response consists of an abrupt decrease in peripheral vascular resistance caused by withdrawal of sympathetic tone, resulting in hypotension and associated symptoms. The cardioinhibitory response involves sinus bradycardia (and occasionally sinus arrest) with or without AV block caused by vagal stimulation of SA and AV nodes. Patients with severe cardioinhibitory response can have asystole anywhere from seconds up to a minute.

A typical history for vasovagal syncope includes a prodrome of malaise with nausea or lightheadedness preceding syncope. Symptoms can be triggered by emotional stress, physiologic stress of any kind, volume depletion, abrupt postural changes, and vagal stimuli such as micturition, defecation, or coughing. Tilt-table testing provides a useful way to classify these patients into those having a predominantly vasodepressor response and those having a predominantly cardioinhibitory response. Classifying patients in this way is essential before any consideration of pacemaker implantation, as patients with predominantly vasodepressor response will not respond to cardiac pacing.

Even in patients with some degree of cardioinhibition, SA nodal and AV nodal functions are typically normal, so cardiac pacing is not first-line therapy. The large, randomized, placebo-controlled Vasovagal Pacemaker Study II (VPS-II) has been performed to test pacing in neurocardiogenic syncope.[14] The results showed no aggregate benefit to pacing in general, though it may be reasonable to use pacing in certain subpopulations (patients with prolonged asystole, minimal prodrome, or no response to other treatments). For patients with symptomatic documented cardioinhibition either on tilt-table testing or spontaneously, a class IIb indication for permanent pacing is present, if the bradycardia is refractory to lifestyle changes and maneuvers. For patients in high-risk occupations (transportation, construction, operation of heavy machinery) or for those with prolonged periods of asystole (<5 seconds), pacemaker implantation may be the safest course. However, these patients should be cautioned that pacing will not prevent attacks and may not be sufficient to abort the attacks once they are in progress. The main role for pacing in these situations is to blunt the severity of the episodes, and in some cases, when minimal prodromal symptoms are present, pacing can provide additional time for the patient to undertake abortive maneuvers.

Iatrogenic Bradycardia

Bradycardia can result from a variety of iatrogenic causes, most commonly from medications but also from cardiac procedures and cardiac surgery.

Medications

All patients presenting with symptomatic bradycardia should be thoroughly questioned about medication use, and, where possible, medications that cause bradycardia should be discontinued. Commonly prescribed classes of medications that can cause bradycardia are listed in Table 33-1. In many instances, these medications may have strong indications (for example, β-blockers in patients with coronary artery disease). It may, therefore, be necessary to implant a permanent pacemaker, which will help continue therapy with essential medications (class I). The risks of pacemaker implantation should be carefully weighed against the risk of discontinuing the medication in question, and pacemaker implantation should only be undertaken when the risk/benefit profile is favorable. In this context, it should be emphasized that clinically relevant doses of AV nodal blocking agents commonly unmask pre-existing AV nodal disease but typically do not cause AV block in patients with otherwise normal conduction. In one series, while 41% of patients with high-grade AV block experienced short-term resolution with cessation of nodal blocking drugs,[15] more than half these patients subsequently experienced recurrence of high-grade AV block off the medication. Only about 15% of patients with high-grade AV block while on nodal agents had lasting resolution of AV block with cessation of drug therapy. Thus, it is important to monitor closely even those patients with short-term resolution of AV block after cessation of nodal agents, as the majority of these individuals will eventually need pacemaker implantation.

Procedures and Surgeries

The AV conduction axis can sustain significant damage during cardiac surgery, particularly aortic and mitral valve surgery, and temporary pacing is often necessary post-operatively.[16] When AV conduction does not recover after a reasonable period (we typically wait 7 days), a permanent pacemaker should be implanted (class I).[17,18]

Catheter ablation of the AV junction with pacemaker implantation is frequently used to treat rapid atrial fibrillation that is refractory to medical therapy. These patients should always receive a permanent pacemaker (class I) regardless of the level and rate of the escape rhythm. In general, we favor pacemaker implantation at least 3 to 4 weeks before AV junction (AVJ) ablation to minimize the risk of lead dislodgment during catheter ablation. Because these patients are dependent on ventricular pacing, consideration should be given to biventricular pacing after AVJ ablation, to minimize the deleterious effects of right ventricular (RV) apical pacing in those who are susceptible (typically patients with left ventricular ejection fraction [LVEF] <45%) and to provide a backup pacing system in the event of malfunction of a pacing lead.

Patients who develop unintended third-degree or high-grade AV block caused by catheter ablation for AV nodal re-entrant tachycardia or accessory pathway ablation should undergo permanent pacemaker implantation. Because nodal function can recover in these patients, it may be reasonable to delay pacemaker implantation, if necessary, with use of temporary pacing, until it is clear that the loss of AV nodal function is permanent. Rarely, the patient with ventricular pre-excitation undergoes a catheter ablation procedure that disrupts AV nodal conduction without affecting the accessory pathway. The patient is then dependent on accessory pathway conduction for the transmission of the impulse from the atrium to the ventricle. In this circumstance, antegrade conduction over the accessory pathway should be assessed with exercise testing or with pacing in the electrophysiology laboratory to make sure that the conduction is robust over a physiologic range of heart rates. Pacemaker implantation should be considered if accessory pathway conduction is not robust, if accessory

pathway function decreases over time, or if accessory pathway ablation becomes necessary, leaving the patient without a functional AV communication.

Tachyarrhythmias

Although medications, catheter ablation, and ICD implantation are the primarily modalities for treating tachyarrhythmias, cardiac pacing does have a role in certain circumstances, both for termination of supraventricular tachyarrhythmias and for prevention of triggered ventricular arrhythmias (see Appendix Table 33-9). Although pacing is used in the automatic detection and termination of ventricular tachycardia, pacing systems with this capacity should also have the ability to defibrillate in the event that pacing accelerates the rhythm or causes degeneration into ventricular fibrillation. Pacemakers without ICD function should therefore not be implanted for detection and termination of ventricular tachycardia.

Termination of Supraventricular Tachyarrhythmias

In the treatment of recurrent, symptomatic supraventricular tachycardia (SVT) that cannot be controlled with catheter ablation or medications, cardiac pacing has a role. When pacing reproducibly terminates the arrhythmia and arrhythmia detection is reliable, it is reasonable to implant a pacemaker (class IIa), even in the absence of conduction system dysfunction or any other indication for cardiac pacing. Because overdrive pacing of SVT can occasionally result in atrial fibrillation (especially at shorter cycle lengths), patients with accessory pathways that can conduct rapidly in the antegrade direction should not receive anti-tachycardia pacing (class III) because of the risk of causing pre-excited atrial fibrillation that degenerates into ventricular fibrillation.

Prevention of Ventricular Tachyarrhythmias

In vulnerable patients, slow heart rates cause increased dispersion of ventricular repolarization and predispose to pause-dependent polymorphic ventricular tachyarrythmias (VTs; torsades de pointes). A typical initiation begins with a pause, followed by a beat in which repolarization is prolonged, and a tightly coupled premature ventricular depolarization that starts a run of polymorphic VT. In situations where VT is clearly pause dependent and sustained and is not related to a reversible cause, pacemaker implantation is warranted, regardless of the Q-T interval (class I), particularly if the resting heart rate is slow. In patients with congenital long QT syndrome (LQTS) that is high risk by genotype or family history, pacing is warranted to minimize the risk of VT (class IIa). Often, such patients will also have an indication for a defibrillator, so ICD implantation may be preferred to implantation of only a pacemaker.

Multiple-Site Pacing

Multiple-site pacing has emerged in the past decade as a novel approach to optimizing electrical and mechanical synchrony. In selected patients with heart failure caused by systolic dysfunction and intraventricular conduction disturbances, biventricular pacing can dramatically improve symptoms and decrease mortality. Multiple-site atrial pacing to improve atrial function and reduce atrial fibrillation has also been explored, but a role for this modality has yet to be established with large clinical trials.

Biventricular Pacing in Heart Failure

Dyssynchronous ventricular contraction caused by abnormal ventricular activation can be deleterious. Many patients with heart failure caused by left ventricular (LV) systolic dysfunction have broad QRS intervals arising from the involvement of the intraventricular conduction system, and some have a broad QRS intervals in the setting of frequent RV apical pacing. Two landmark clinical trials, Comparison of Medical Therapy, Pacing, Defibrillation in Chronic Heart Failure (COMPANION) and Cardiac Resynchronization-Heart Failure trial (CARE-HF), have established a role for biventricular pacing or cardiac resynchronization therapy (CRT) in selected patients with heart failure with reduced ejection fraction, both for reduction of symptoms and reduction in mortality.[19,20] These studies included patients with LVEF 35% or less and QRS interval less than 0.12 seconds regardless of the type of intraventricular conduction abnormality. Thus far, the guidelines have focused on patients with New York Heart Association (NYHA) class III and ambulatory class IV symptoms who are already on recommended medical therapy. The importance of ensuring that patients with heart failure are on medical therapy cannot be overemphasized, as patients can move from NYHA class III/IV to class I on medications alone, and the ejection fraction can improve significantly. Among these patients, biventricular device implantation for restoration of mechanical synchrony is a class I indication for those in sinus rhythm and class IIa for those in atrial fibrillation or who depend on ventricular pacing. Although the guidelines do not describe an indication for patients with NYHA class IV symptoms who depend on positive inotropes or are nonambulatory, we have occasionally found that such patients can benefit dramatically from CRT, to the point of weaning the patients off inotropes so that the patients can leave the hospital.[19,21]

Recently, results from the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT) trial[22] have shown that with biventricular ICD implantation, a significant reduction occurs in mortality rates and hospitalizations for heart failure, even in NYHA class I/II patients, which has raised the possibility of a considerable expansion in the indications for CRT.[19] At the time of the writing of this chapter, these data did not yet affect clinical practice but are likely to have a major impact in the near future. As for now, the 2008 ACC/AHA/HRS guidelines recognize a class IIb indication for patients with LVEF less than 35% and NYHA class I or II heart failure when pacemaker implantation is planned for other indications and frequent ventricular pacing is expected.

Multiple-Site Atrial Pacing

Atrial fibrillation is often caused by fibrosis and electrical remodeling in atria, with or without chamber enlargement. Patients with atrial fibrillation may therefore manifest intra-atrial conduction delay (broad P waves), which can serve as a substrate for re-entry as well as for frequent atrial ectopy that can trigger atrial fibrillation. Synchronous atrial activation may reduce the potential for repolarization inhomogeneity, as well as for triggered premature atrial depolarizations, and thereby reduce the frequency of episodes of atrial fibrillation.

A number of small clinical series and one moderate-sized randomized trial have been performed to evaluate the potential for multiple-site atrial pacing to reduce atrial fibrillation. Thus far, with the possible exception of patients with marked intra-atrial

conduction delay that manifests as surface P-wave duration less than 0.18 seconds, no benefit in terms of symptoms, reduction in atrial fibrillation, or adverse cardiac events have been reported.[23] Therefore, no recognized indication for pacing to prevent atrial fibrillation in patients without any other indication for permanent pacing (class III) exists at present.

Permanent Pacing in Specific Clinical Situations

Myocardial Infarction

It is common for patients to sustain damage to the cardiac conduction system from myocardial infarction (MI), and the guidelines recognize a separate class of indications for this group of patients, since acquired AV block in the post-MI setting has a distinct prognostic significance. As with all patients manifesting intraventricular conduction disturbances, all symptomatic AV blocks that are not transient warrant permanent pacing (class I). The guidelines also recognize additional class I indications for patients who have no symptoms but have persistent second-degree AV block with alternating bundle branch block, third-degree AV block, and transient second-degree or third-degree AV block that is believed to be either intra-His or Infra-His. Pacemaker implantation can also be considered for patients with persistent second-degree or third-degree AV block that is supra-His (class IIb). However, AV block that is transient and not accompanied by intraventricular conduction defects or that is accompanied only by left anterior fascicular block has a low rate of progression to complete heart block, and prophylactic pacemaker implantation is not recommended (Appendix Table 33-10). Similarly, bundle branch block or fascicular block without AV block does not warrant pacemaker implantation, nor does persistent first-degree AV block with bundle branch block that predates the infarction (class III).

Dilated Cardiomyopathy

Patients with ischemic or nonischemic dilated cardiomyopathy constitute a distinct group of high-risk patients who tend not to tolerate bradyarrhythmias, AV dyssynchrony, or intraventricular dyssynchrony. In addition, they often require medications that can worsen their sinus node dysfunction and AV block. For that reason, we generally have a lower threshold to initiate device therapy for class IIa and class IIb indications in this population. All patients with dilated cardiomyopathy who have indications for permanent pacing should be evaluated for the need for biventricular pacing as well as the need for a defibrillator before any device implantation.

Hypertrophic Cardiomyopathy

Some patients with hypertrophic cardiomyopathy develop steep pressure gradients across the LV outflow tract (LVOT), at rest or with provocation. These patients can then develop varying degrees of LV outflow obstruction, leading to chest discomfort, dyspnea, lightheadedness, and syncope. For most patients, a combination of medical therapy and either surgical myectomy or alcohol septal ablation can provide definitive relief from outflow tract obstruction. However, when either of these is contraindicated or unsuccessful, pacemaker implantation has a role. RV apical pacing can cause ventricular dyssynchrony and thereby result in the reduction of LVOT pressure gradient and obstruction.

Some randomized clinical trials have demonstrated subjective improvement in symptoms as well as in physiologic endpoints, but others have shown no overall improvement in the quality of life or any alteration in the course of the disease.[24,25] Patients with hypertensive hypertrophic cardiomyopathy and older adults may be subpopulations that derive more benefit, whereas pacing is more difficult in those with rapid atrial rates or brisk AV nodal conduction. Overall, data are inconclusive but certainly do not support the idea of routine pacing in these patients. However, the guidelines do recognize a class IIb indication for medically refractory symptomatic hypertrophic cardiomyopathy with resting or provoked outflow tract obstruction (Appendix Table 33-11). Asymptomatic patients, those with symptoms that are medically controlled, and those with symptoms but no documented outflow tract obstruction are not candidates for pacing (class III).

After Cardiac Transplantation

Patients who have undergone cardiac transplantation often experience sinus bradycardia, particularly in the immediate post-transplant period. Slower atrial rates and chronotropic incompetence can negatively impact the cardiac rehabilitation process and significantly delay hospital discharge. When this bradycardia is not expected to resolve, permanent pacing is a class I indication. Even when some resolution in bradycardia is expected over several months to a year, permanent pacing can be considered if the post-transplant recovery process is limited by bradycardia (class IIb).

Patients who have received transplants are also vulnerable to coronary vasculopathy, which frequently manifests as conduction system dysfunction.[26,27] Therefore, after transplantation, pacemaker implantation can be considered in patients with recurrent syncope of undetermined cause, even without clear evidence of bradyarrhythmia (class IIb). Conduction system dysfunction can also be evident in acute rejection. While comprehensive data are not available on the long-term prognosis of patients with bradyarrhythmias and syncope in the setting of rejection, it is reasonable to consider permanent pacing if the bradyarrhythmia is persistent, even after the rejection has been controlled (Appendix Table 33-12).

Indications for Temporary Pacing

Temporary cardiac pacing can be a life-saving treatment in many clinical situations, but it also poses some risk for serious complications. In this section, we briefly review the modalities available for temporary pacing, followed by the major indications for temporary pacing.

Temporary Pacing Modalities

Temporary cardiac pacing can be achieved with any of several modalities (see Table 33-2). Precordial percussion can result in ventricular systoles in the setting of an asystolic arrest and can be used until transcutaneous electrodes can be placed. In general, given its morbidity, transcutaneous pacing should be reserved for emergent situations and ideally in unconscious or sedated patients.[28,29] Esophageal pacing is similarly morbid and often

Table 33-2 Modalities for Temporary Pacing

	ENDOCARDIAL (VENOUS)	CUTANEOUS	ESOPHAGEAL	EPICARDIAL	PERCUSSION
Chamber	Both	Ventricle	Atrium	Both	Ventricle
Prolonged use	Yes	If sedated	No	Yes	No
Application	Any indication	Emergency	Atrial pacing Pediatrics	Postoperative only	Witnessed bradycardic arrest

requires relatively large amounts of current delivery for ventricular capture. It is seldom used in adult patients but may have a role in infants and children for the diagnosis and pace termination of atrial arrhythmias. Epicardial lead placement is usually performed as a prophylactic measure against bradycardia after cardiac surgery. It is common for inflammation to occur around the epicardial pacing leads, which results in a rise in pacing threshold and ultimately failure of the pacing system.[30]

Patients requiring sustained temporary pacing should, in general, have transvenous pacing systems placed to reduce morbidity and achieve more reliable pacing. Given the risk of infection, cardiac perforation, and more commonly, lead migration and failure, temporary transvenous pacemakers should be used for as short a period as possible. Patients with temporary transvenous pacing systems should be on bedrest under continuous monitoring, preferably in an intensive care unit (ICU), and should have daily threshold testing and imaging with chest radiography to confirm the appropriate positioning and functioning of the pacing lead.

Asystole

Pacing is part of the advanced cardiac life support algorithm for asystole and should be initiated promptly on identification of ventricular asystole. Care should be taken to distinguish asystole from fine ventricular fibrillation, as pacing has no role in treating the latter rhythm. Because asystolic cardiac arrest is not usually caused by primary conduction system dysfunction, pacing often is of limited value; nonetheless, it should be undertaken as indicated in the algorithm. In general, the prognosis for asystolic cardiac arrest is poor.

Acute Myocardial Infarction

A variety of conduction disturbances can occur during acute MI, and any component of the conduction system can be involved. The ACC/AHA guidelines on the management of acute MI contain a section on the indications for temporary pacemaker insertion based on the prognostic significance of various bradyarrhythmias in the setting of acute MI.[31]

Sinus bradycardia alone should not, in general, prompt temporary pacemaker insertion for prophylactic purposes. If the bradycardia potentiates ischemia or causes heart failure or hypotension and is not responsive to vagolytic agents such as atropine, then temporary pacing is indicated. In general, given the potential for increasing myocardial oxygen demand and worsening infarction with the administration of chronotropic agents such as isoproterenol or other β-adrenergic agents, pacing is preferable. First-degree AV block and type I second-degree AV block during MI occur in a substantial number of patients (particularly, in those with inferior MI), and as with sinus bradycardia, neither should prompt pacemaker insertion for prophylaxis of high-grade AV block when a narrow QRS complex is present (class III). It is reasonable to consider pacemaker implantation in high-grade AV block (type II second-degree AV block or third-degree AV block) with a narrow QRS interval, though many of these patients will have an adequate escape rhythm.

Table 33-3 Risk Score for Prediction of High-Grade Atrioventricular Block in Acute Myocardial Infarction

ABNORMALITY	POINTS
First-degree AV block	1
Type I second-degree AV block	1
Type II second-degree AV block	1
LAFB or LPFB	1
RBBB or LBBB	1
TOTAL SORE	**RISK OF COMPLETE HEART BLOCK**
0	1.2%
1	7.8%
2	25%
3	36.4%

AV, Atrioventricular; LAFB, *left anterior fascicular block;* LPFB, *left posterior fascicular block;* RBBB, *right bundle branch block;* LBBB, *left bundle branch block.*
Modified from Lamas GA, Muller JE, Turi ZG, et al: A simplified method to predict occurrence of complete heart block during acute myocardial infarction, Am J Cardiol *57:1213–1219, 1986.*

The development of new intraventricular conduction abnormalities in acute MI, particularly in conjunction with an anterior MI, is ominous and portends a worse prognosis in terms of the infarct size, hemodynamics, and the development of a complete heart block. A simple risk score (Table 33-3) has been devised to stratify patients and identify the development of a complete heart block in the setting of an acute MI.[32] Temporary pacemaker placement should be considered for patients at a moderate-to-high risk of progression to complete heart block, even without symptoms or hemodynamic compromise. These include patients with preexisting intraventricular conduction system disease with new AV block and patients with new intraventricular conduction system disease (see Appendix Table 33-13). It should be emphasized that these guidelines are distinct from those governing the indications for permanent pacing after the acute phase of MI. Many patients

will need pacing only for the acute phase, particularly after successful revascularization.

Bradyarrhythmias

In patients with significant bradycardia accompanied by symptoms of cerebral hypoperfusion, hemodynamic compromise, heart failure, or cardiac ischemia is present and in whom chronotropic agents are either ineffective or contraindicated, temporary pacemaker insertion should be considered. Often, such patients will ultimately require permanent pacemaker implantation, but necessary cardiac pacing should not be delayed while the workup for the cause of bradycardia is under way. Many reversible causes of bradycardia and conduction system abnormalities exist (see Table 33-1), and temporary pacing can be invaluable while the appropriate diagnostic testing is performed. Temporary pacing may also be required for pacemaker-dependent patients who require lead or device revision, with an obligatory delay between explantation of an old device and implantation of a new device (for example, in pacemaker lead infection).

Some patients presenting with high-grade AV block, either persistent or paroxysmal, have minimal symptoms at rest and are not hemodynamically compromised. The question thus arises whether all of these patients should receive temporary pacing. As a general rule, the location and rate of the escape rhythm are the critical determining factors in these situations. Patients may have persistent complete heart block with a supra-His escape rhythm of 50 to 60 beats/min, normal blood pressure, and minimal symptoms at rest. These patients should be on bedrest with transcutaneous pacing available at the bedside, but temporary pacemaker placement is not necessarily warranted. However, patients with even brief paroxysms of high-grade AV block with an inadequate escape rhythm, wide QRS escape rhythm, or with evidence of intra-His or infra-His conduction system disease should undergo temporary pacemaker insertion, given the unpredictable and often sudden nature of a paroxysmal AV block.

Tachyarrhythmias

In patients with bradycardia-dependent ventricular tachycardia, temporary pacing can be a life-saving treatment. Particularly in acquired LQTS, when changes in repolarization are often caused by the transient effects of drugs, temporary pacing at rates between 85 and 100 beats/min can be very effective in preventing polymorphic ventricular tachycardia until the high-risk period has passed.

Patients with refractory tachyarrhythmias who do not respond to medications may respond to overdrive pacing. Given the risks of temporary pacemaker insertion, this strategy should be undertaken only in the persistently symptomatic patient after a failure of medical therapy and when electrical cardioversion is not desirable. Atrial flutter can often be readily terminated with this strategy. Overdrive pacing of VT can result in the acceleration of the rhythm as well as ventricular fibrillation, so this maneuver should only be undertaken in an intensive care setting, where the care team will be ready for emergent defibrillation should it become necessary. The same principle applies for any SVT when ventricular pre-excitation is present.

Some evidence suggests that after cardiac surgery, atrial pacing can result in a lower incidence of postoperative atrial fibrillation. While this is not a sufficient reason to place a temporary transvenous pacing system, it may be reasonable to use a dual-chamber strategy in patients who receive epicardial pacing systems at the time of surgery.

Temporary Pacing for Hemodynamic Indications

Patients with severe LV dysfunction who are hospitalized with rest symptoms or hemodynamic compromise can sometimes benefit from pacing. When ventricular filling is impaired because of marked first-degree AV block or type I second-degree AV block, a trial of temporary dual-chamber pacing may be beneficial. When the QRS interval is prolonged, a trial of biventricular pacing with a temporary system can sometime help determine whether a permanent biventricular system should be implanted.

Periprocedural Pacing

Patients undergoing noncardiac surgery often present with chronic conduction disturbances. In the vast majority of instances, temporary pacing is not necessary. General anesthesia is safe in patients with chronic asymptomatic sinus bradycardia, first-degree AV block, type I second-degree AV block with normal QRS, and bifascicular block, with a very low rate of high-grade intraprocedural AV block. The main exceptions to this rule are patients who present for surgery with complete heart block, high-grade second-degree AV block, or with any symptomatic bradyarrhythmia. If surgery is urgent, temporary pacemaker implantation can be considered in these patients. Elective surgery should be deferred in this situation to permit further diagnostic testing and treatment, possibly to include pacemaker implantation.

It is controversial whether every patient with baseline left bundle branch block undergoing catheterization of the right ventricle or right ventricular endomyocardial biopsy should receive a temporary pacemaker. About 5% to 10% of patients with catheter introduction in the right ventricle will develop transient right bundle branch block. For patients with baseline left bundle branch block, this can result in complete heart block and asystole, and it may be reasonable to place a temporary pacemaker in these patients. In most cases, iatrogenic right bundle branch block is transient but can last for hours and up to several days.

Summary

Cardiac pacing has emerged as a safe, reliable, and highly effective treatment for a subset of cardiac rhythm abnormalities. As with any treatment, proper patient selection is essential to success. This chapter has provided a summary of current indications for cardiac pacing as outlined in the most recent ACC/AHA/HRS guidelines, with special attention to frequently encountered clinical dilemmas. It should be emphasized that in deciding whether or not to initiate pacing, the clinician should always bear in mind not only the specific guidelines but also the level of supporting evidence and the presence or absence of alternatives to cardiac pacing. Particularly with permanent pacemakers, device implantation imposes a lifestyle change for the patient, and thus it is critical to integrate patient preference into the clinical decision making process. Finally, although pacemakers have been in widespread clinical use for several decades, the indications for pacing are rapidly evolving and undoubtedly will expand as more clinical data on patient selection and outcomes become available and as pacing technology continues to improve.

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CHAPTER 34

Cardiac Pacing Modes and Terminology

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Pacemakers have the capability of sensing intrinsic cardiac activity and responding to sensed events depending on the pacing mode. Cardiac pacing terminology has evolved as the devices have become more sophisticated. Pacemakers have different programmable rates, pacing modes, and timing cycles that allow them to function predictably and respond to different circumstances. Understanding of pacing terminology and timing cycles (Tables 34-1 and 34-2) is important to differentiate between appropriate and inappropriate pacemaker functions.

Pacing Nomenclature

A five-letter pacing mode nomenclature has been adopted (see Table 34-1).[1] The first letter refers to the chamber being paced (**O**mitted or absent, **A**trium, **V**entricle, and **D**ual for atrium and ventricle), the second letter refers to the chamber being sensed (**O**mitted or absent, **A**trium, **V**entricle, and **D**ual for atrium and ventricle), and the third letter refers to the response of the pacemaker to a sensed event (**O**mitted or absent, **I**nhibit, **T**rigger or tracking, and **D**ual for inhibit and trigger). The fourth letter refers to the rate modulation or rate adaptive response to activity (**R**ate adaptive, and **O**mitted or absent rate response), and the fifth letter refers to multiple-site pacing (**O**mitted or absent, **A**trium, **V**entricle, and **D**ual for atrium and ventricle).

Pacing Modes

Available pacing modes depend on the location and number of leads implanted. Indications, advantages, and disadvantages of different pacing modes are reviewed in Table 34-3.

Single-Chamber or Dual-Chamber Asynchronous Pacing

Asynchronous pacing refers to continuous atrial pacing, ventricular pacing, or both at a specific rate, regardless of the presence or absence of an intrinsic atrial event, ventricular event, or both (Figure 34-1, *A*). Such pacing mode is symbolized as AOO, VOO, or DOO. These pacing modes are used in limited circumstances, such as when pacemaker-dependent patients (without ventricular sensed events) are exposed to noise or artifact (e.g., electrocautery), which could result in asystole due to oversensing and pacing inhibition if the pacemaker has been programmed in a non-asynchronous pacing mode. Nevertheless, asynchronous pacing is often seen when the device is at the end of its life or when a magnet is placed over the pulse generator.

Single-Chamber (Atrial or Ventricular) Inhibited Pacing

Pacemakers with an atrial lead can be programmed to an atrial-inhibited mode referred to as AAI, whereas devices with a ventricular lead can be programmed to a ventricular-inhibited mode (VVI). The AAI pacing mode refers to atrial paced, atrial sensed, and inhibition of pacing output in response to an atrial sensed event (P wave), whereas the VVI pacing mode refers to ventricular paced, ventricular sensed, and inhibition of pacing output in response to a ventricular sensed event (R wave). Therefore the single chamber (atrium or ventricle) will only be paced if no sensed event (P wave or R wave) is detected faster than the programmed lower rate limit (LRL). In contrast, the single chamber (atrium or ventricle) will not be paced if a sensed event is detected (inhibited pacing) at a rate faster than the LRL (Figure 34-1, *B* and *C*).

Dual-Chamber (Atrioventricular) Sensing and Sequential, P-Synchronous Pacing with Inhibition (DDD)

The DDD pacing mode requires at least an atrial lead and a ventricular lead. The DDD mode refers to atrial and ventricular pacing as well as atrial and ventricular sensing with dual function (inhibit and trigger pacing) in response to an intrinsic atrial sensed event or a ventricular sensed event. In the DDD mode, the pacemaker will pace both the atrium and the ventricle (atrioventricular [AV] sequential pacing), with programmed AV delay if the intrinsic atrial and ventricular rates are below the LRL. If the atrial rate is slower than LRL, the device will pace the atrium while *inhibiting* ventricular pacing if an intrinsic ventricular event is sensed within a predetermined AV delay. If an atrial sensed event is faster than the LRL without an intrinsic ventricular event, the pacemaker *inhibits* atrial pacing but *triggers* ventricular pacing (P-synchronous pacing) after a predetermined AV delay (Figure 34-1, *D*). Finally, pacing will be completely *inhibited* if the intrinsic atrial and ventricular rates are above the LRL. This pacing mode is the most commonly used in dual-chamber devices (DDD or DDDR) and biventricular pacemakers (DDDOV or DDDRV).

Dual-Chamber (Atrioventricular) Sensing and Sequential, Non–P-Synchronous Pacing with Inhibition (DDI)

The DDI pacing mode refers to pacing both the atrium and the ventricle, sensing both the atrium and the ventricle and inhibiting pacing in response to an intrinsic atrial sensed event or a ventricular sensed event. In contrast to DDD, the DDI mode lacks the *trigger* or P-synchronous pacing in response to an atrial sensed event. Thus the pacemaker will not *trigger* ventricular pacing after

Table 34-1 Revised NASPE/BPEG Generic Code for Antibradycardia, Adaptive-Rate, and Multiple-Site Pacing

POSITION				
I	**II**	**III**	**IV**	**V**
CHAMBER(S) PACED	**CHAMBER(S) SENSED**	**RESPONSE TO SENSING**	**RATE MODULATION**	**MULTIPLE-SITE 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.*
From 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 *25(2):260–264, 2002.*

Table 34-2 Abbreviations and Description of Cardiac Events and Timing Cycles in Single-Chamber, Dual-Chamber, and Biventricular Pacemakers/Devices

CARDIAC EVENTS/TIMING CYCLES (ABBREVIATION)	DESCRIPTION
SINGLE-CHAMBER (ATRIAL OR VENTRICULAR) PACEMAKER	
Atrial sensed event (P/AS)	Sensed a native **A**trial depolarization (**P** wave)
Atrial paced event (A/AP)	Delivered **A**trial **P**acing output
Ventricular sensed event (R/VS)	Sensed a native **V**entricular depolarization (Q**R**S complex)
Ventricular paced event (V/VP)	Delivered **V**entricular **P**acing output
Atrial blanking period (AB)	Atrial sensing amplifier is "blind" and will not detect or respond to atrial sensed event
Ventricular blanking period (VB)	Ventricular sensing amplifier is "blind" and will not detect or respond to any ventricular sensed event
Atrial refractory period (ARP)	An atrial sensed event will be noted but ignored, without affecting pacemaker timing cycle
Ventricular refractory period (VRP)	A ventricular sensed event will be noted but ignored, without affecting pacemaker timing cycle
Lower rate limit (LRL)	Minimum pacing rate
Upper rate limit (URL)	Maximum pacing rate
Maximum sensor rate (MSR)	Maximum pacing rate by rate-responsive sensor
DUAL-CHAMBER (ATRIAL AND VENTRICULAR) PACEMAKER	
Atrioventricular sequential pacing (AV)	Atrial paced event followed by paced ventricular event
P-synchronous V-pacing (PV)	Atrial sensed event followed by paced ventricular event
VA Interval (VAI)	Interval from ventricular sensed or paced event to atrial paced event
AR (AP-AS)	Atrial paced event followed by ventricular sensed event
AV interval or delay (AVI)	Programmed atrioventricular pacing interval
Paced AV interval (Paced AVI)	AV interval/delay from atrial paced event (A) to ventricular paced event (V)
Sensed AV interval (Sensed AVI)	AV interval/delay from atrial sensed event (P) to ventricular paced event (V)
Maximum or upper tracking rate (MTR)	Maximum ventricular pacing rate allowed in response to high sensed atrial rates
Postatrial ventricular blanking period (PAVB)	Period when ventricular sensing is "OFF" after an atrial paced event
Post-ventricular atrial blanking period (PVAB)	Period when atrial sensing is "OFF" after a ventricular paced or sensed event
Post-ventricular atrial refractory period (PVARP)	Period after a ventricular event when the device can sense but not track an atrial event
Total atrial refractory period (TARP)	Sum of AVI and PVARP
Rate-responsive AV delay (RRAVD)	AV delay that adjusts by shortening as the rate increases.
CARDIAC RESYNCHRONIZATION THE RAPY/PACEMAKERS	
Biventricular pacing interval or LV offset (V–V)	Timing gap between RV and LV pacing
RV refractory period (RVRP)	An RV sensed event maybe noted but ignored, without affecting RV pacing timing cycle
LV refractory period (LVRP)	An LV sensed event maybe noted but ignored, without affecting LV pacing timing cycle
LV protection period (LVPP)	Period after a ventricular paced or sensed event that prevents inappropriate pacing during vulnerable period

Table 34-3 Indications, Advantages, and Disadvantages of Commonly Used Pacing Modes

PACING MODE	INDICATION/ ADVANTAGES	DISADVANTAGES
Asynchronous (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 pacing (AAI, VVI)	AAI: sick sinus syndrome with intact AV node; preserves AV synchrony VVI: atrial fibrillation with slow VR and single-lead ICDs AAI/VVI 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) VVI has a higher incidence of atrial arrhythmias[10]
DDD, DDDRV (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 less battery longevity
DDI	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)[2,9]
VDD	Appropriate sinus node function with AV node disease (e.g., MDT RV lead model 5038); dual chamber with high atrial pacing threshold to minimize battery depletion	Lack of atrial pacing Potential AV dyssynchrony at lower rate limit
DVI	Severe sinus bradycardia/ standstill and atrial lead malfunction (oversensing)	Asynchronous atrial pacing Potential AV dyssynchrony

AV, Atrioventricular; VR, *ventricular regurgitation;* ICDs, *implantable-cardioverter-defibrillators;* MDT, *Medtronic, Inc.;* RV, *right ventricular.*

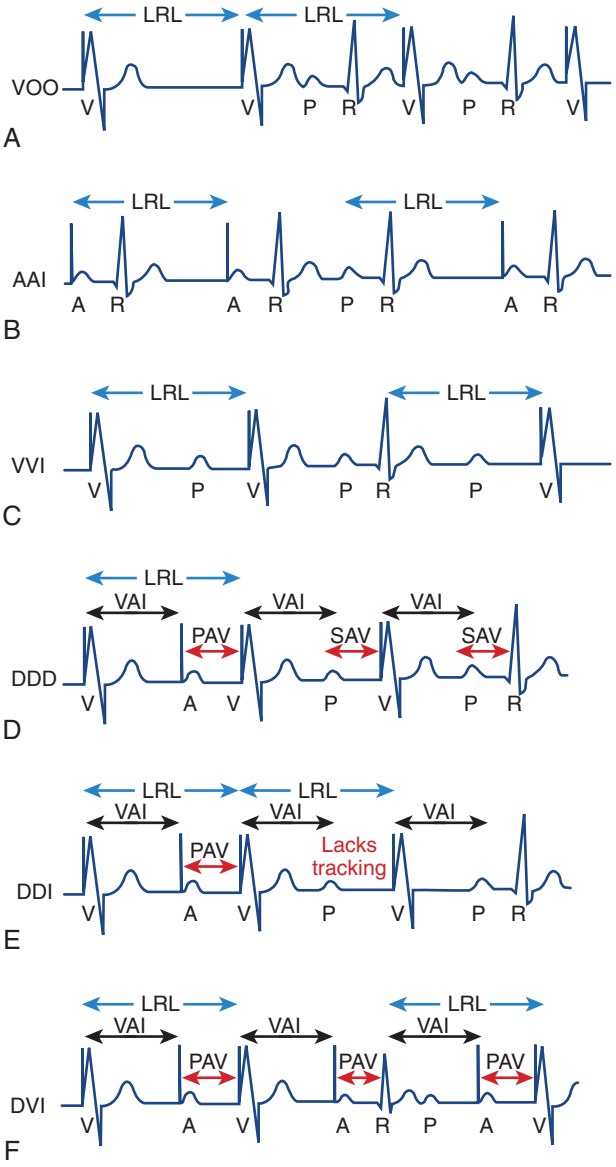

FIGURE 34-1 Different pacing modes. *LRL,* Lower rate limit; *P,* intrinsic P wave; *A,* atrial paced event; *R,* intrinsic R wave; *V,* ventricular paced event; *VAI,* ventriculoatrial interval; *PAV,* paced atrioventricular interval; *SAV,* sensed atrioventricular interval.

an atrial sensed event, but atrioventricular sequential pacing will occur only after atrial pacing if no intrinsic ventricular event is present (Figure 34-1, *E*). The overall advantage is that it can function as two different atrial and ventricular pacemakers (AAI with a backup VVI). For example, in a patient with a high-degree AV block, a sinus rate of 80 beats/min, and a programmed LRL of 60 beats/min, the pacemaker will *inhibit* atrial pacing, but it will pace the ventricle at LRL with the development of AV dyssynchrony due to lack of the *trigger* or *tracking* feature. However, when the atrial rate drops below 60 beats/min, the pacemaker will pace both chambers at the LRL with preservation of AV synchrony.

Overall, the most commonly used pacing modes are VVI, DDD, and DDI without rate response or VVIR, DDDR, and DDIR with rate response. VDD and DVI are less commonly used pacing modes. The VDD mode refers to ventricular pacing only and atrial and ventricular sensing with *inhibition* and *tracking* function in response to a sensed event. This pacing mode is indicated in patients with normal sinus node function with AV nodal disease, as atrial pacing is not required. This dual-chamber pacing mode may be used with single-pass leads that incorporate both atrial and ventricular electrodes within a single lead body or in subjects with normal sinus node function and appropriate atrial sensing but a high atrial pacing threshold. DVI refers to atrial and ventricular pacing, ventricular sensing only, and inhibition to a ventricular sensed event. This mode lacks atrial sensing, and thus it

will pace the atrium asynchronously at the LRL. This mode was used in first-generation pacemakers and thus is more of historical significance (Figure 34-1, *F*). However, DVI can still be used in patients with significant sinus bradycardia or atrial standstill and atrial lead malfunction (oversensing), in which atrial pacing is mandated (asynchronous pacing). Other pacing modes have a more historical use, such as VAT (ventricular pacing only, atrial sensing only, and tracking response), which could be used on pacemaker-dependent patients to avoid inhibition of ventricular pacing due to ventricular lead oversensing.[2-4]

Timing Cycles

Recognition of normal pacemaker function versus abnormal pacemaker function on the electrocardiogram (ECG) requires a clear understanding of pacemaker timing cycles. Overall, timing cycles are based on cardiac events such as atrial sensed events and ventricular sensed events (referred to as "P" and "R," respectively), and atrial paced events or ventricular paced events (referred to as "A" and "V", respectively). Appropriate sensing of cardiac events allows appropriate function and adaptation of the pacing mode, such as mode switching or noise reversion response (described below). Abbreviations and descriptions of pertinent cardiac events and pacemaker timing cycles are provided in Table 34-2.

Asynchronous pacing modes (AOO, VOO, and DOO) have the simplest timing cycle (they lack blanking and refractory periods) since there is neither sensing nor mode of response (see Figure 34-1, *A*). Thus, AOO or VOO have a fixed pacing interval, regardless of cardiac events, which depends on the programmable LRL. In addition, DOO has a programmable AV interval (AVI) as well as a ventriculoatrial (VA) interval that depend on the LRL. In contrast, non-asynchronous pacing modes have more timing cycles, including blanking and refractory periods.

Blanking and Refractory Periods

These are basic timing periods that avoid oversensing of inappropriate signals such as evoked potentials and repolarization. During the blanking period, the sense amplifier is "off" or "blind" and will not detect any event. Physiologically, this resembles the absolute refractory period during the cardiac action potential. The main purpose is to avoid cross-talk and oversensing related to evoked potentials. In contrast, the sensing amplifier is "on" during the refractory period and therefore allows detection of rapid signals or cardiac events. Physiologically, this corresponds to the relative refractory period of the cardiac action potential. Sensed events during this period are included in the counters but are ignored and generally do not trigger or reset timing cycles. The presence or absence of blanking and refractory periods depends on specific features of a manufacturer's pulse generator as well as on the programmed pacing mode (Figure 34-2). Some blanking and refractory periods are not programmable.

Single-chamber pacing modes have simpler blanking and refractory periods. AAI would start an atrial blanking period (ABP) and an atrial refractory period (ARP) after an atrial sensed or atrial paced event, which would avoid oversensing atrial evoked potentials, atrial repolarization, or ventricular depolarization. Similarly, VVI would start a ventricular blanking period (VBP) and a ventricular refractory period (VRP) after a ventricular sensed or ventricular paced event to avoid oversensing of ventricular evoked potentials and T waves (Figure 34-2, *A* and *B*).

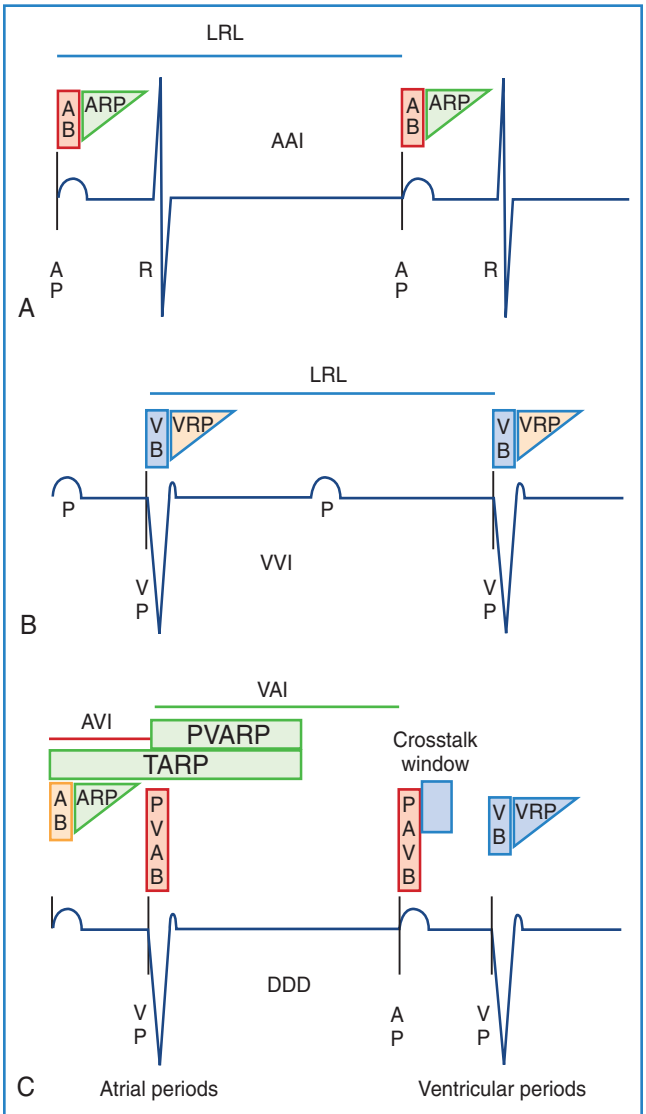

FIGURE 34-2 Blanking and refractory periods with different pacing modes. **A,** A-A interval (*AAI*) mode. **B,** V-V interval (*VVI*) mode. **C,** DDD mode. *LRL,* Lower rate limit; *AB,* atrial blanking period; *ARP,* atrial refractory period; *VB,* ventricular blanking period; *VRP,* ventricular refractory period; *AVI,* atrioventricular interval; *VAI,* ventriculoatrial interval; *PVARP,* postventricular atrial refractory period; *TARP,* total atrial refractory period; *PVAB,* postventricular atrial blanking period; *PAVB,* postatrial ventricular blanking period.

Conversely, dual-chamber pacing modes have more complex timing cycles (Figure 34-2, *C*). An atrial paced event starts a postatrial ventricular blanking (PAVB) to avoid ventricular oversensing during atrial pacing, whereas a ventricular paced or sensed event starts a PVAB to avoid atrial oversensing during ventricular pacing. If an atrial pacing artifact were to be detected on the ventricular channel, ventricular pacing would be inhibited (*cross-talk*), resulting in potential asystole in a pacemaker-dependent patient. Thus blanking periods are safety mechanisms that prevent cross-talk. Following the PAVB is a timing period called the *ventricular triggering period* or *cross-talk sensing window,* and in the event that a ventricular sensed event occurs during this period, *safety pacing* will take place. Safety pacing is a

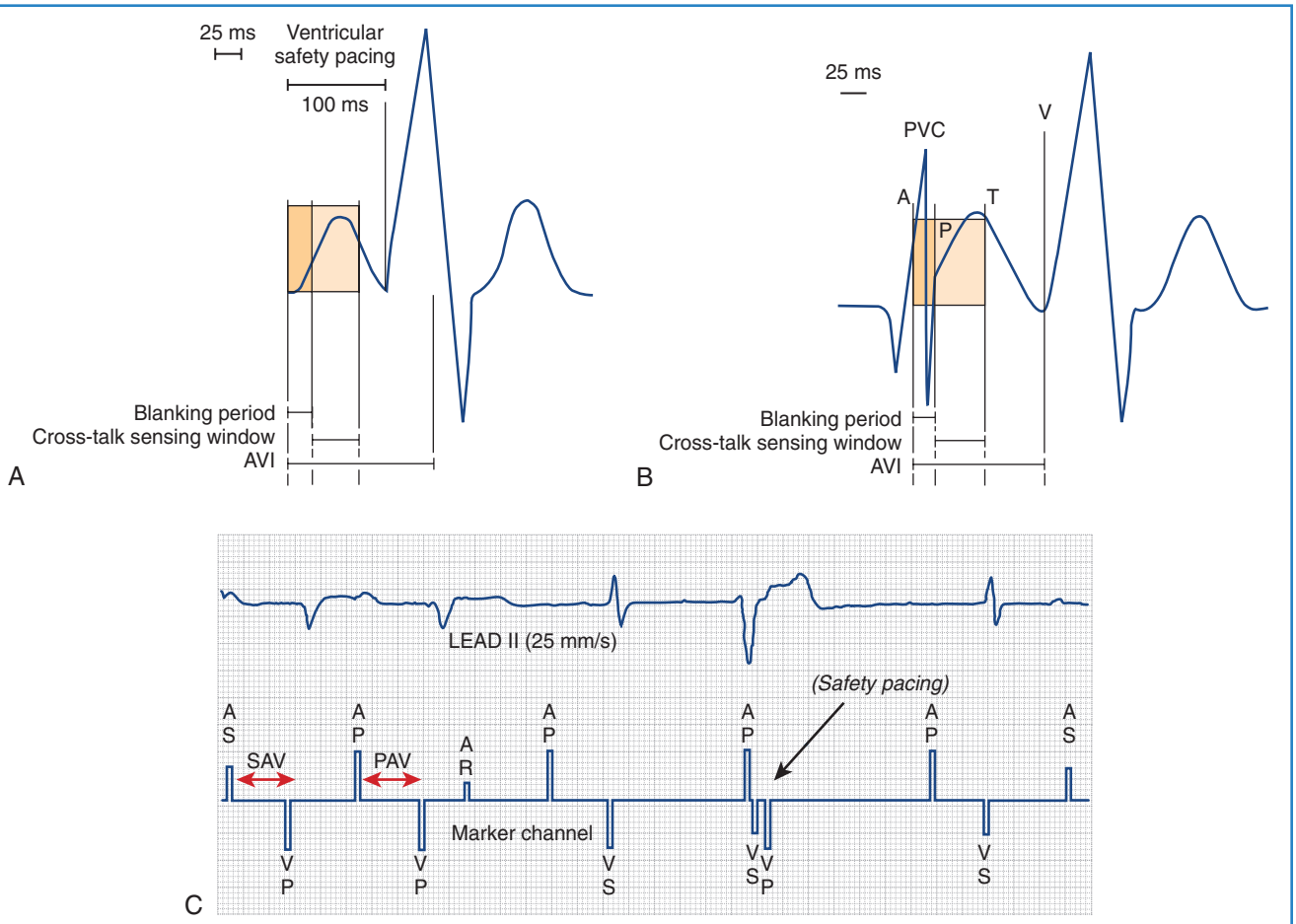

FIGURE 34-3 Blanking period, cross-talk sensing window, and safety pacing. **A,** Represents ventricular safety pacing at 100 ms when ventricular amplifier senses an event during cross-talk sensing window. **B,** Premature ventricular contraction (*PVC*) is not sensed, since it falls within postatrial ventricular blanking followed by ventricular pacing (*VP*) after completion of the atrioventricular interval (*AVI*).[4] **C,** PVC occurs simultaneously as the lower rate limit times out and delivers an atrial paced event. Inappropriate safety pacing (100-ms AVI) occurs, since the PVC is sensed during the cross-talk window. *PAV,* Paced AV interval; *SAV,* sensed AV interval. (***A*** *and* ***B,*** *From Ellenbogen KA, Wood MA:* Cardiac pacing and ICDs*, ed 4, Malden, MA, 2005, Blackwell.)*

feature in which ventricular pacing occurs at an AVI typically shorter than the programmed AVI, often about 100 to 120 ms (programmable interval in some devices), to prevent ventricular asystole. Therefore, cross-talk should be suspected if AV pacing occurs at shorter than programmed AVI (Figure 34-3). Cross-talk can be resolved by extending the PAVB period, decreasing atrial output, or decreasing ventricular sensitivity.[2-4]

Furthermore, an atrial sensed event or an atrial paced event starts ARP and AVI. After the AVI is timed out, the pacemaker will deliver a ventricular paced event if no intrinsic ventricular sensed event is noted. A ventricular sensed event or a ventricular paced event starts VRP and postventricular atrial refractory period (PVARP). The VRP avoids sensing the evoked response and T wave, whereas PVARP avoids inappropriate atrial oversensing of ventricular repolarization, tracking of retrograde P wave, or both. The total atrial refractory period (TARP) is the sum of AVI and PVARP (see Figure 34-2, *C*). During TARP, any atrial sensed event noted does not affect the timing cycle. As a consequence, TARP limits the maximum tracking rate (MTR) in the DDD (P-synchronous) mode, as well as the upper rate limit (URL) or maximum sensor rate (MSR) in a non–P-synchronous mode and a rate-adaptive response, respectively. Thus, lengthening TARP will subsequently decrease the MTR, URL, or MSR. Atrial sensed events falling in TARP may not be tracked in a DDD pacing mode, but they will be detected and counted to detect higher atrial rates and trigger the mode-switch algorithm. PVARP should be extended to include a retrograde P wave only if VA conduction is present. Inappropriately short PVARPs can lead to a sensed retrograde P wave after a premature ventricular contraction (PVC), which will start an AVI followed by a ventricular paced event. This can set up a cycle of sensed retrograde P waves, causing an *endless-loop pacemaker tachycardia,* also called *pacemaker-mediated tachycardia* (PMT). PMT is a form of AV dyssynchrony or *VA synchrony*. PMT should be suspected when P-synchronous ventricular pacing is noted at the MTR with a sudden onset that occurs after PVC (Figure 34-4, *A*). Commonly, PMT may also be seen during atrial threshold testing, such as auto threshold, which causes a ventricular paced event after loss of atrial capture. This, in turn, leads to retrograde VA conduction with initiation of PMT if the atrial sensed event occurs beyond PVARP. More complex algorithms cause suspicion of PMT when the VP-P interval is stable, and they will confirm PMT if the measurement of the VP-P interval remains stable after alteration of the next P-V interval (Figure 34-4, *B*).[5] However, if the VP-P

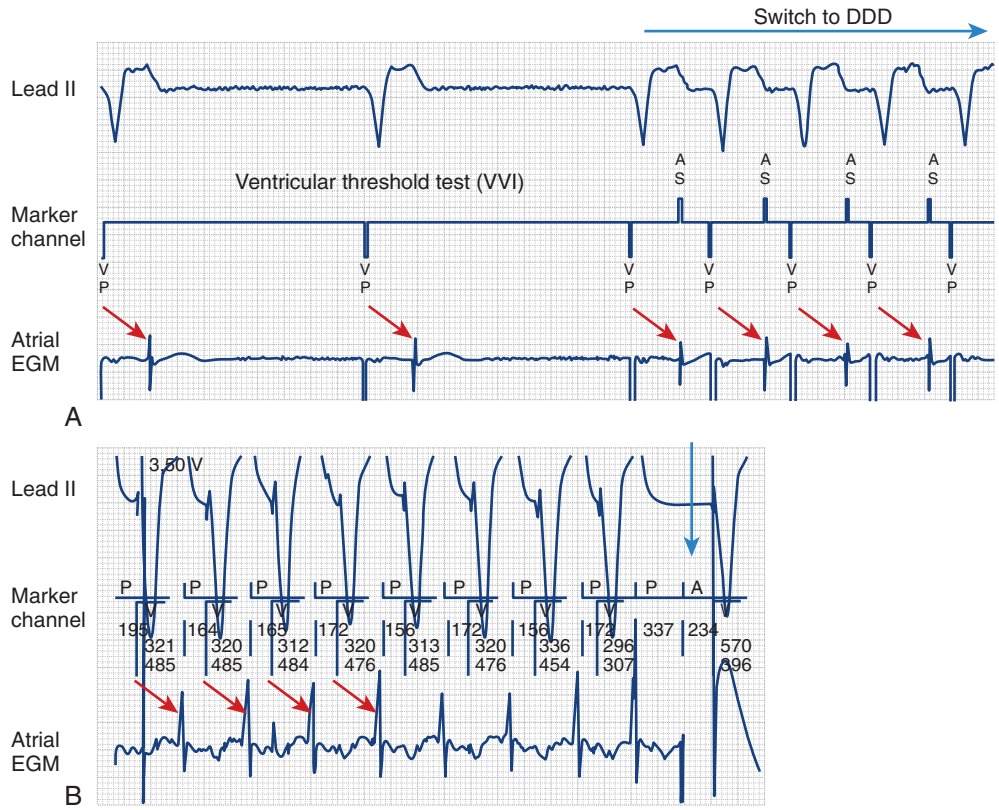

FIGURE 34-4 Pacemaker-mediated tachycardia (PMT). **A,** PMT initiated once the V-V interval (VVI) pacing mode switches to DDD during the ventricular pacing threshold. Red arrows illustrate VA timing from VP to atrial electrogram (*EGM*), which is only sensed and tracked after the device changes to the DDD mode. **B,** VP-P interval (*red arrow*) remains stable after changing the PV interval or sensed AV interval (P-synchronous pacing), which confirms retrograde VA conduction and PMT. Sequential atrial and ventricular pacing (*blue arrow*) is delivered to terminate PMT.[4] *(From Ellenbogen KA, Wood MA:* Cardiac pacing and ICDs*, ed 4, Malden, MA, 2005, Blackwell.)*

interval lengthens or shortens after changing the P-V interval, the device excludes PMT and continues with P-synchronous tracking of the atrial rhythm. All device manufacturers have algorithms to interrupt suspected PMT. The most common algorithms include a withholding of a single ventricular pacing output, an extension of PVARP for a single cycle, and interruption of P-synchronous pacing after the AVI is met followed by sequential AV pacing (see Figure 34-4, *B*).[5-7]

Base-Rate Behavior

Pacemakers from different manufacturers vary in their responses to sensed events. Dual-chamber pacemakers have been historically designed with a ventricular-based timing system. Designation of timing system, for example, atrial-based timing system, ventricular-based timing system, or hybrid-based timing system—gained importance with the innovation of rate-adaptive pacing. As long as the LRL pacing remains stable, no difference is discernible between atrial and ventricular timing systems.[2-4]

Ventricular-based timing is characterized by a predetermined VA interval (VAI), which starts after a ventricular sensed event and will time out the next atrial paced beat. A ventricular sensed event (e.g., PVC) during the VAI will reset the VAI. The ventricular rate is determined by the sum of VAI and AVI (Figure 34-5, *A*). A ventricular sensed event during the AVI terminates the AVI and initiates VAI. Therefore, the resulting A-A interval is shorter (slightly faster rate than programmed LRL) based on a P-R interval shorter than the programmed AVI.

Atrial-based timing is characterized by an A-A interval that will time out the next atrial paced beat and subsequently determine pacing rate. A sensed R wave during AVI (intrinsic AV conduction) inhibits ventricular pacing but does not change basic A-A timing, and the ventricular rate stays at the LRL. A sensed R wave during VAI resets the A-A timing, and thus the ventricular rate maybe slightly slower than the programmed LRL (A-A plus AVI; Figure 34-5, *B*).

The main difference between atrial-based timing and ventricular-based timing can be demonstrated in patients with underlying 2:1 AV block at a lower rate. During 2:1 AV block, AV (AP-VP) and AR (AP-VS) events alternate. The ventricular-based timing may increase pacing rate during AR, but the LRL is never violated. Atrial-based timing results in alternating cycles that are either faster or slower than the LRL but never the same as the programmed LRL (Figure 34-6, *A*).

Currently, most pacemakers have modified atrial-based timing or hybrid-based timing designated to avoid the potential rate variations or limitations that could occur with a pure atrial-based timing system or a ventricular-based timing system. These hybrid-based timing algorithms vary among different manufacturers (Figures 34-5, *C,* and 34-6, *B*).[5-7] For example, atrial-based timing

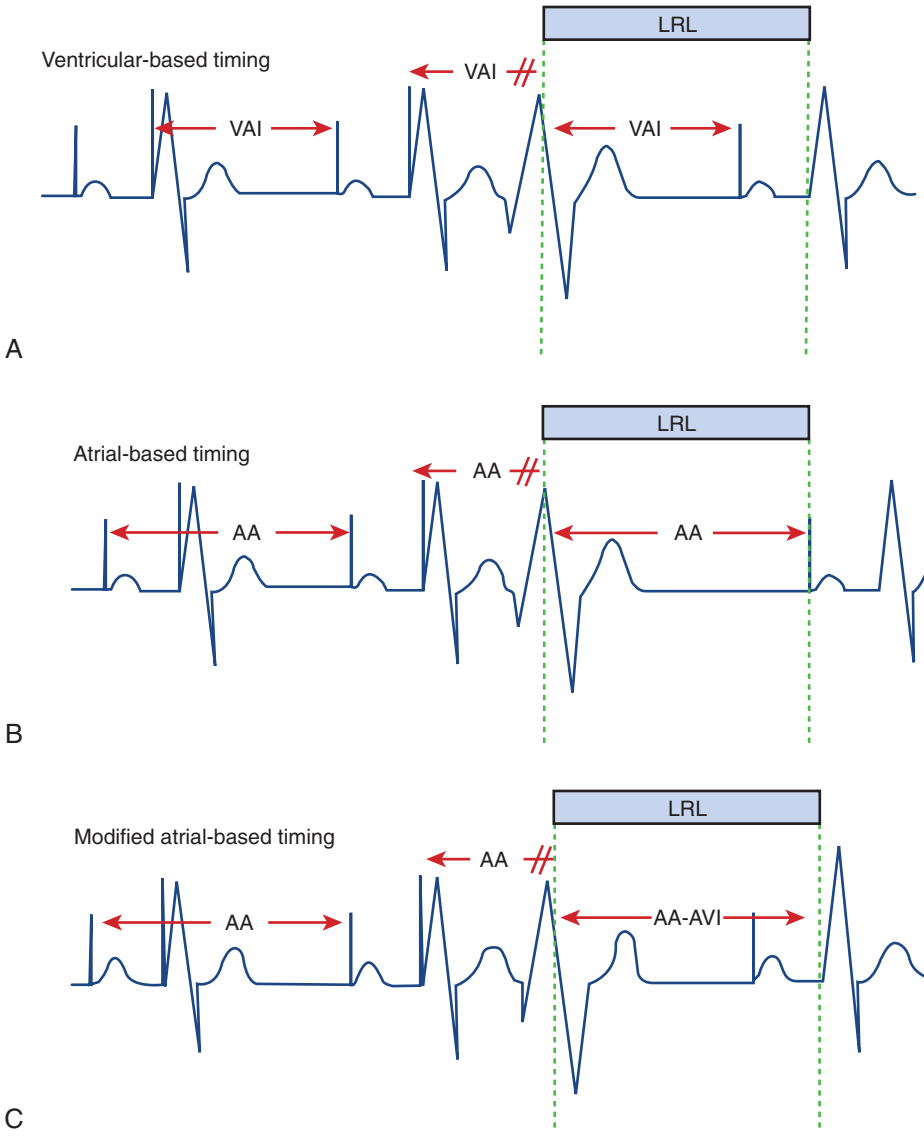

FIGURE 34-5 Response to premature ventricular contraction (PVC) with different base-rate timings. **A,** Ventricular-based timing; reset of V-A interval (*VAI*) after PVC, followed by atrial paced event on completion. **B,** Atrial-based timing; reset of A-A interval after PVC, violating lower rate limit (*LRL*) after adding A-V interval (*AVI*). **C,** Modified atrial-based timing; adjustment of A-A interval after PVC by subtracting AVI from AAI to maintain LRL. *(Modified from Ellenbogen KA, Wood MA:* Cardiac pacing and ICDs*, ed 4, Malden, MA, 2005, Blackwell.)*

may change to ventricular-based timing after PVC (ventricular sensed event), whereas a sensed R wave during the AVI (intrinsic AV conduction) is ignored and does not reset the A-A interval (see Figure 34-5, *C*).

Atrioventricular Interval or Delay

All dual-chamber contemporary devices have a differential AVI, or *AV delay*, that depends on whether the atrium is paced or sensed (Figure 34-7, *A*). This is based on the native atrial depolarization being commonly sensed 20 to 60 ms after the onset of the P wave.[8] In contrast, the P wave starts immediately after an atrial paced event. For example, if AVI is programmed at 160 ms for an atrial sensed event as well as an atrial paced event, the true ECG-based P-R interval following an atrial sensed event would be 180 to 220 ms compared with 160 ms in the atrial paced event. Therefore, the AVI started by an atrial sensed event (also referred to as the *P-V interval*) should be shorter than the one that follows an atrial paced event. The main purpose of differential AVI is to provide a similar functional P-R interval and adequate ventricular filling, regardless of an atrial sensed event or an atrial paced event. Most pacemakers allow programming of different paced AVIs and sensed AVIs, with differences up to 100 ms.[5-7]

Dynamic or rate-adaptive AV delay is a feature that allows shortening the AVI as the atrial rate increases, either during sinus rhythm or during sensor-driven pacing (Figure 34-7, *B*). This feature is intended to mimic the normal physiology, in which the P-R interval shortens as the heart rate increases to optimize cardiac output. Subsequently, this allows atrial tracking at faster rates because of a shorter TARP (AVI + PVARP). Different manufacturers have different methods to achieve a dynamic AVI. The most common method is linear shortening of the AVI from a

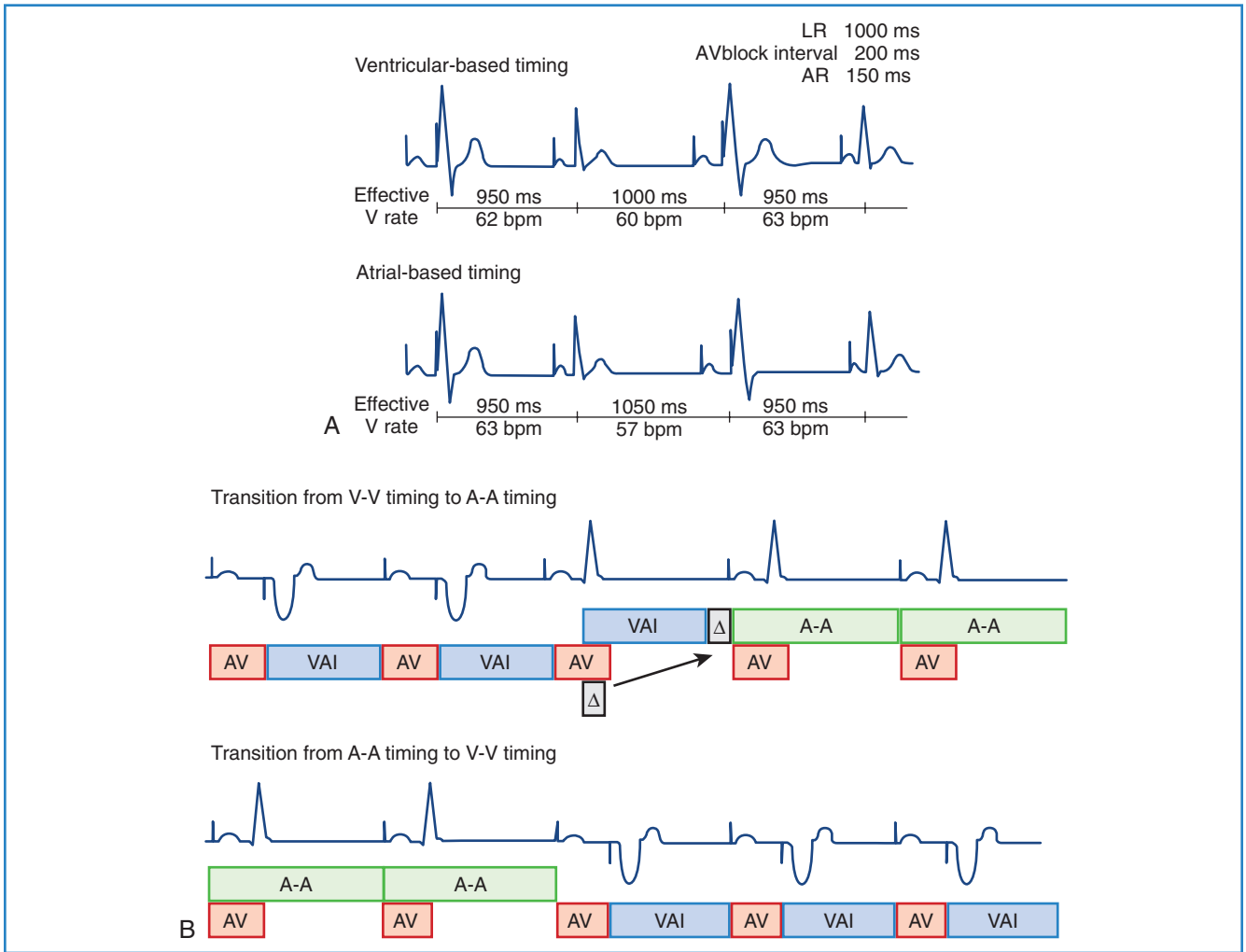

FIGURE 34-6 Atrial, ventricular, and hybrid base-rate behavior. **A,** Ventricular and atrial-based timing with underlying 2:1 atrioventricular (AV) block (AV block interval is longer than atrial rate). *Top*: AV block interval is slightly longer than atrial rate, hence the rate alternates with the rate at the lower rate limit (LRL; 60 beats/min) and slightly faster than the LRL (63 beats/min) in ventricular-based timing. *Bottom:* Atrial-based timing violates LRL with an alternating faster (63 beats/min) and slower (57 beats/min) ventricular rate than programmed LRL. **B,** Hybrid-based timing.[6] *Top*: Timing changes from ventricular based to atrial based after a ventricular sensed event is noted (Δ, difference between P-R interval and A-V interval in the first cycle during which intrinsic conduction occurs). Δ is applied to next V-A interval (*VAI*) to provide a smooth transition without affecting V-V intervals. *Bottom:* Timing changes from atrial based to ventricular based when intrinsic AV nodal conduction is no longer present. (***A,*** *From Ellenbogen KA, Wood MA:* Cardiac pacing and ICDs*, ed 4, Malden, MA, 2005, Blackwell; and Siemens-pacesetter;* ***B,*** *From Insignia I* Ultra System Guide*, models 1190/1290/1291, St. Paul, MN, 2006, Guidant Corporation.)*

programmed baseline AVI to a programmed minimum AVI. Another method is stepwise shortening of the AVI.[5-7]

AV hysteresis has significantly changed over the years. This term refers to the alteration of the AVI, depending on AV nodal conduction. Of historical interest, *negative hysteresis* refers to shortening of the AVI to maintain a paced ventricular rhythm.[2] This was available when a high percentage of ventricular pacing was thought to have beneficial effects and remains useful in biventricular pacemakers to ensure a high percentage of ventricular pacing. AV hysteresis, previously known as *positive hysteresis*, describes alterations in the paced AVI to promote intrinsic AV conduction.[2,3] Contemporary algorithms, such as minimal ventricular pacing and search AV, achieve a similar purpose.[6,7] *AV hysteresis* is no longer used because newer algorithms with better defined behavior are now available. These algorithms are described below.

Upper Rate Behavior

The MTR or the upper rate limit (URL) controls the upper rate behavior of pacemakers. The MTR modulates the upper tracking rate behavior in dual-chamber P-synchronous pacing modes, whereas the URL refers to the maximum allowed pacing rate, regardless of the pacing mode. MTR or URL and PVARP are initiated after a paced or sensed ventricular event. After a P wave has been sensed and after completion of the AVI, ventricular pacing will be delivered only if the MTR or URL has timed out.

Atrial sensed events (such as sinus tachycardia) terminate the VAI and initiate an AVI. P-wave–synchronous pacing occurs with a 1:1 AV relationship as long as the atrial rate is between the programmed LRL and MTR. The AVI and the MTR must complete their cycles to deliver ventricular pacing. If the atrial rate is faster than TARP (AVI + PVARP), some P waves are not tracked,

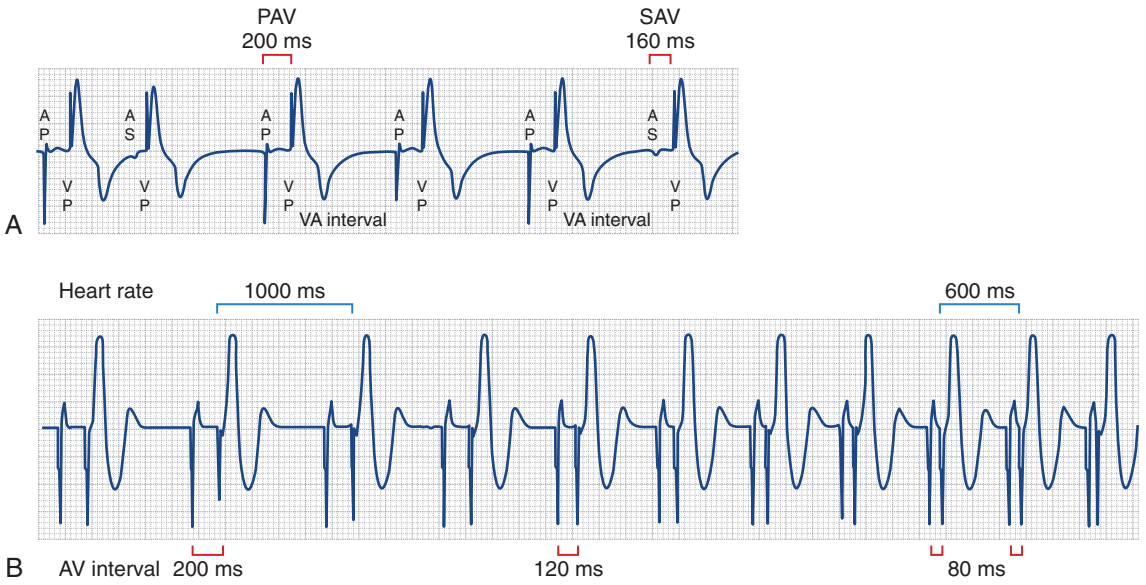

FIGURE 34-7 Differential and dynamic atrioventricular (*AV*) interval. **A,** Electrocardiogram tracing demonstrates differential AVI with paced AVI of 200 ms and sensed AVI of 160 ms. **B,** Tracing demonstrates a dynamic AV delay with gradual shortening of paced AVI as the sensor-indicated rate increases. *AS*, Atrial sensed event; *AP*, atrial paced event; *VP*, ventricular paced event; *VA interval*, ventriculoatrial interval; *SAV*, sensed AV interval; *PAV*, paced AV interval. (***B,*** *From* Insignia I Ultra System Guide, *models 1190/1290/1291, St Paul, MN, 2006, Guidant Corporation.)*

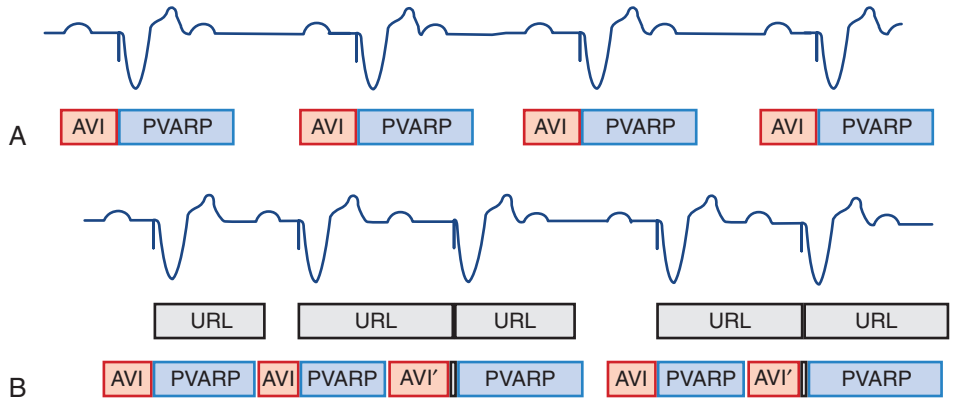

FIGURE 34-8 Upper rate behavior. **A,** 2:1 fixed block behavior; every other P wave falls within the post-ventricular atrial refractory period (*PVARP*) and, as a result, tracking with ventricular pacing does not occur. **B,** Atrioventricular (AV) Wenckebach behavior; atrial rate is faster than the maximum tracking rate (MTR) with progressive prolongation of the AV delay (to avoid violation of the MTR) until a P wave falls into the PVARP, which results in lack of ventricular pacing. *URL*, Upper rate limit; *AVI*, atrioventricular interval; *AVI′*, extension of AVI to meet the URL. *(Modified From* Insignia I Ultra System Guide, *models 1190/1290/1291, St Paul, MN, 2006, Guidant Corporation.)*

and the pacemaker behaves similar to a 2:1, 3:1 AV block and so on, depending on the atrial rate (Figure 34-8, *A*). Thus, a long PVARP results in a fixed AV block response at a relatively low tracking rate. This may be an important issue in some patients since abrupt changes in pacing rate with intermittent lack of tracking can result in significant symptoms.[2,3,9]

In addition, pacemakers may mimic AV nodal Wenckebach behavior (e.g., "electronic" Wenckebach) when the atrial rate exceeds the MTR. *AV nodal Wenckebach behavior* is characterized by a progressive P-V interval prolongation until a sensed P wave falls into PVARP and is ignored by the pacemaker, resulting in a pause (see Figure 34-8, *B*). Wenckebach behavior will occur with atrial rates between the MTR and TARP, which can be calculated as the Wenckebach interval (WI = MTR – TARP).[2,4] For example, a programmed MTR of 400 ms and TARP of 350 ms (AVI 125 + PVARP 225) results in a Wenckebach interval of 50 ms, which means that Wenckebach behavior will occur within a 50-ms range (P-P interval 350 to 400 ms). Moreover, 2:1, or fixed block, pacemaker behavior occurs when the P-P interval is shorter than 350 ms. Nevertheless, Wenckebach behavior will not occur if the Wenckebach interval is 0 (e.g., MTR 400, TARP [AVI 250 + PVARP 150]), but a 2:1 or fixed AV block pacemaker behavior will occur as soon as the P-P interval is faster than the MTR (see Figure 34-8, *A*).

Special Pacing Features

Rate Smoothing or Atrial/Ventricular Rate Stabilization

Rate smoothing (RS) or *atrial/ventricular rate stabilization* (ARS/VRS) is a variation of upper rate behavior. ARS/VRS, or RS, was developed to prevent marked changes in A-A and V-V intervals not only at the URL but also when sinus rhythm (SR) is interrupted by profound bradycardia or asystole. Single-chamber and dual-chamber non–P-synchronous pacing modes operate between the LRL and the URL (the MSR, if rate-adaptive response is enabled), whereas P-synchronous pacing modes operate between the LRL and the MTR. This feature is recommended in patients with large symptomatic variations in ventricular rate, such as sinoatrial disease, atrial flutter/fibrillation, premature atrial and ventricular contractions, and Wenckebach pacemaker behavior (Figure 34-9). Most recently, biventricular devices have added VRS and RS in an attempt to increase the percentage of biventricular pacing during conducted atrial arrhythmias. These algorithms vary among different manufacturers.[6,7] For example, RS can be programmed to percentage change (3% to 24% in 3% increments) between V-V cycles. Importantly, this feature is typically unavailable if rate drop response (described below) is enabled.

Hysteresis

Hysteresis is a feature found in single-chamber and dual-chamber pacemakers. In an attempt to maintain intrinsic atrial and ventricular activation, both single-chamber and dual-chamber pacemakers use this feature to allow intrinsic conduction after a sensed P or R wave has occurred. (Figure 34-10, *A*).[2-6] For example, a pacemaker programmed with an LRL of 60 beats/min and hysteresis offset of 10 beats/min (60 – 10 = 50 beats/min) will pace at 60 beats/min until an intrinsic event (P or R wave) is sensed above the LRL (>60 beats/min). Hysteresis rate of 50 beats/min will allow an extra 200 ms for another sensed P or R wave to occur. In the case of adaptive-rate modes, hysteresis rate is below the sensor-indicated rate instead of the LRL. However, if no intrinsic event (P or R wave) is sensed above the sensor-indicated rate or the LRL, the pacemaker will continue to pace at 60 beats/min. To overcome this limitation and in an attempt to allow the intrinsic native rhythm to appear, scan or search hysteresis was later introduced to periodically decrease the pacing rate to the hysteresis rate after a specific number of cycles (Figure 34-10, *B*).[2,5,6]

A more contemporary form of hysteresis is referred to by some manufacturers as *sudden bradycardia response* or *rate drop response*. This feature was developed and is used primarily to treat vasovagal or neurocardiogenic syncope.[5-7] The purpose of this feature is to allow pacing that is faster than the LRL when the intrinsic rate decreases below a specified programmed rate. Figure 34-11 demonstrates rate drop response (Medtronic, Inc.) pacing at an intervention rate of 100 beats/min for a programmable duration only if the heart rate drops more than the programmed heart rate drop of 25 beats/min (from 95 beats/min to <70 beats/min) within a programmed detection window. As another example, a hysteresis of –30 and an LRL of 90 will not

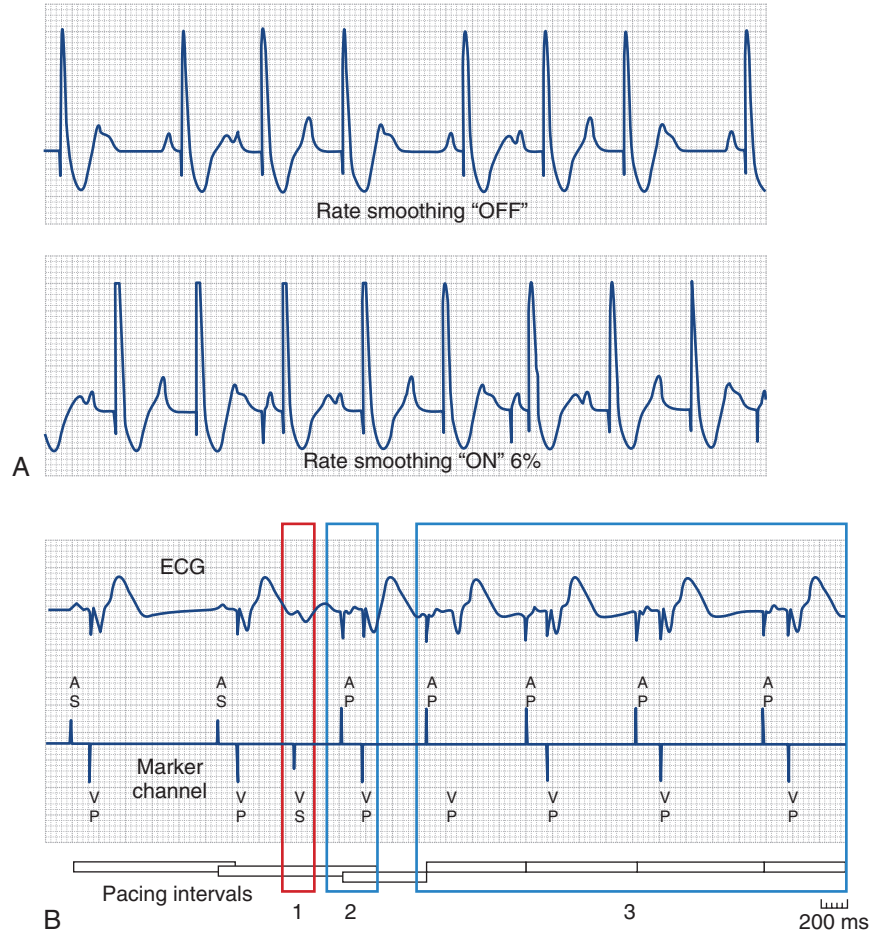

FIGURE 34-9 Rate smoothing/ventricular rate stabilization. **A,** *Top panel:* Atrial rate above the maximum tracking rate causes atrioventricular (AV) Wenckebach pacemaker behavior with subsequent irregular ventricular rate. *Bottom panel:* Rate-smoothing feature at 6% is enabled, which will only allow the R-R interval to extend up to 36 ms over the former R-R interval (6% of 600 ms or 100 beats/min). **B,** After a sensed postventricular cross-talk (PVC) (*1*), ventricular rate stabilization causes AV sequential pacing (*2*) at previous V-V (PVC) interval plus interval decrement, with a gradual prolongation of AV sequential pacing (*3*). (***A*** *and* ***B,*** *From Insignia I Ultra System Guide [Models 1190/1290/1291], St Paul, MN, 2006, Guidant Corporation; Boston Scientific; and Medtronic Concerto. In* Resynchronization therapy and defibrillator reference guide, *Minneapolis, MN, 2008, Medtronic, Inc.)*

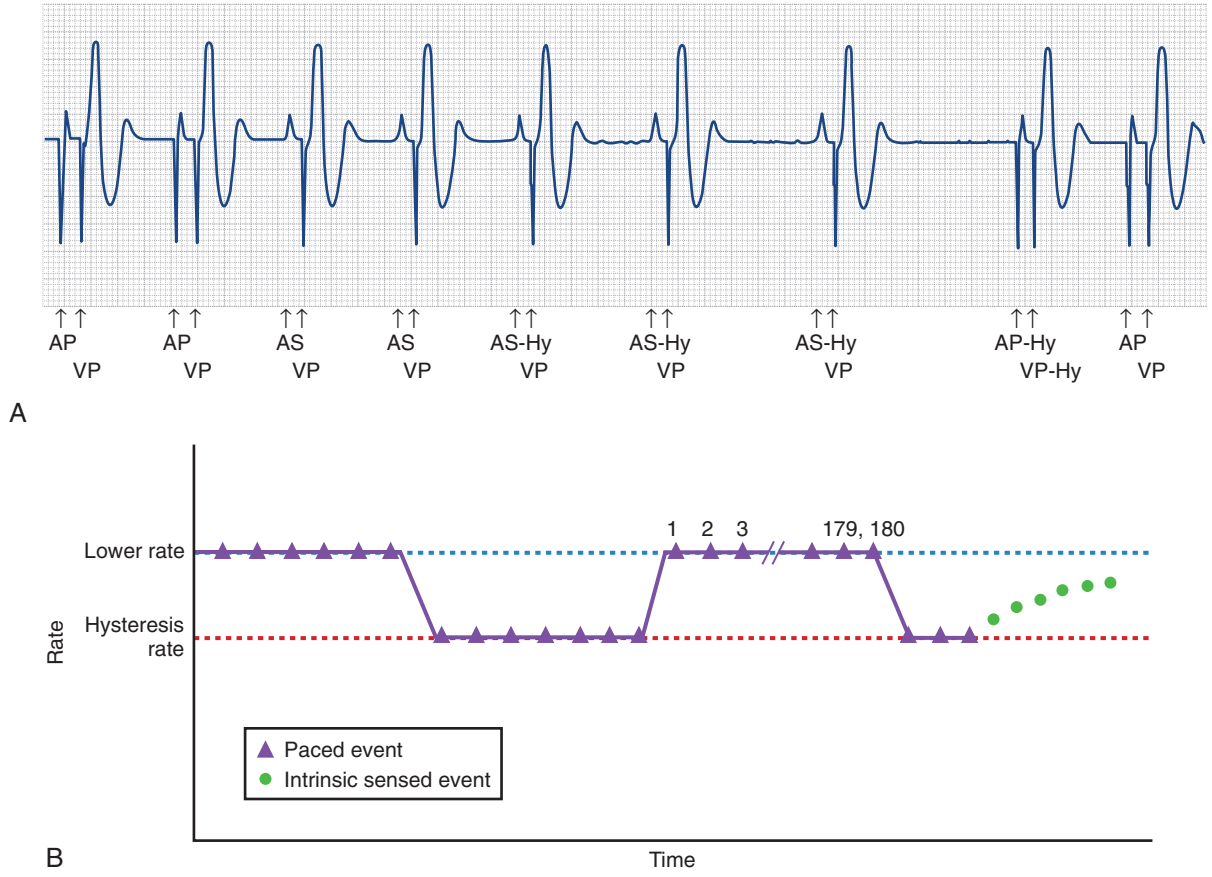

FIGURE 34-10 Rate hysteresis. **A,** Electrocardiogram tracing demonstrates activation of rate hysteresis after a single nonrefractory sensed atrial event above the lower rate limit (LRL). However, rate hysteresis is deactivated after a single atrial pace at the hysteresis rate. **B,** Scan hysteresis; the pacing rate is lowered (after every 180 consecutive paced cycles) to the hysteresis rate for the programmed seven cardiac cycles. In contrast to the first scan, pacing at the LRL is inhibited after an intrinsic rhythm (above hysteresis rate) is noted during the second scan. *AS*, Atrial sensed event; *AP*, atrial paced event; *VP*, ventricular paced event; *AS-Hy*, atrial sensed hysteresis; *AP-Hy*, atrial paced hysteresis LRL. (***A,*** *From* Insignia I Ultra System Guide, *models 1190/1290/1291, St Paul, MN, 2006, Guidant Corporation.* ***B,*** *From Cylos Pacemaker Feature Handbook. In* Premium dual-sensor pacemaker family, *Lake Oswego, OR, 2006, Biotronik Inc.)*

pace until the heart rate drops below the programmed hysteresis rate (60 beats/min). Once the heart rate drops below 60 beats/min, the device will pace at an LRL of 90 beats/min for a specific predetermined or programmed number of timing cycles. After the programmed number of paced beats is met, a prolonged escape interval is permitted to allow intrinsic conduction above the hysteresis rate.

Algorithms to Promote Intrinsic Atrioventricular Conduction

Different manufacturers have developed algorithms to promote intrinsic AV nodal conduction and minimize ventricular pacing. This feature obtained special attention after the deleterious effects of frequent ventricular pacing, such as exacerbation of heart failure and increased risk of atrial fibrillation, were recognized.[9,10]

AV Search Hysteresis

This was the first algorithm to promote AV conduction.[2-4] Specific details of AV hysteresis vary among different manufacturers.[5,6] This algorithm may also be referred to as *AV hysteresis* or *ventricular intrinsic preference* (VIP). Essentially, these algorithms allow programming a baseline AVI and delta (Δ) AVI, or AVI extension. Thus, AVI + Δ promotes intrinsic AV conduction (Figure 34-12, *A*). In the event that AV sequential pacing is present, the device will periodically extend the AV delay by the programmed Δ for up to a programmed number of consecutive cardiac cycles in an attempt to allow intrinsic conduction. If no intrinsic AV conduction is noted at AVI + Δ, AV pacing will revert to the baseline programmed AVI. Another variation of this algorithm is a gradual extension of the AVI up to the programmed extension.

Managed Ventricular Pacing

The MVP algorithm allows two pacing modes, alternating AAI and DDD on demand (Figure 36-12, *B*).[7] After an atrial sensed or atrial paced event, intrinsic conduction is allowed; however, after transient loss of AV conduction, a backup ventricular paced beat is delivered. Persistent loss of AV conduction, defined by this algorithm as 2 of 4 consecutive nonrefractory A-A intervals

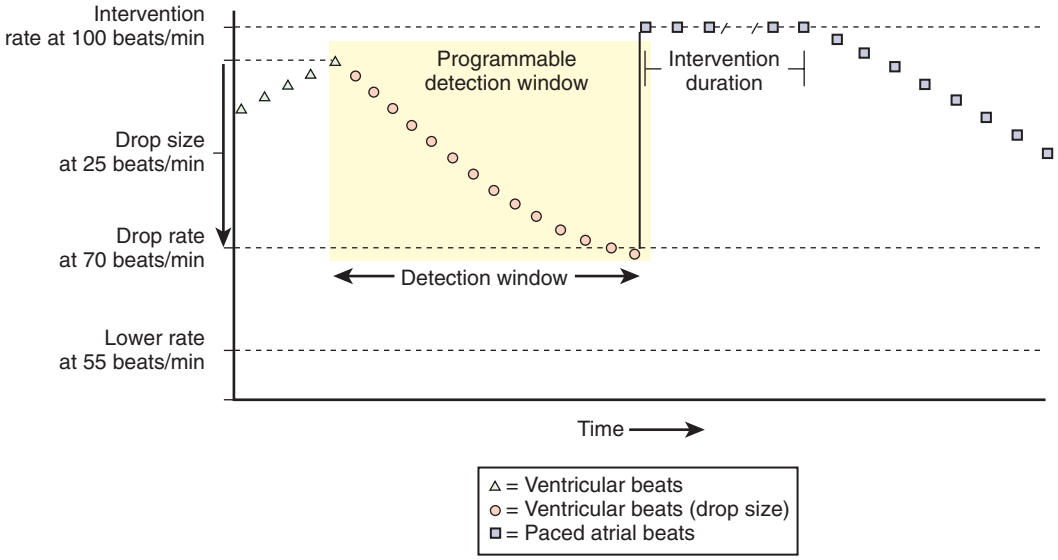

FIGURE 34-11 Rate drop response in a DDD pacing mode. Pacemaker intervenes with elevated pacing rate for brief period after a specified programmable heart rate drop occurs. Pacing rate slowly decreases by 5 beats/min until the intrinsic rate is sensed or the lower rate limit is reached. *(From Medtronic Adapta, Versa, Sensia. In* Pacemaker reference guide, *Minneapolis, MN, 2006, Medtronic, Inc.)*

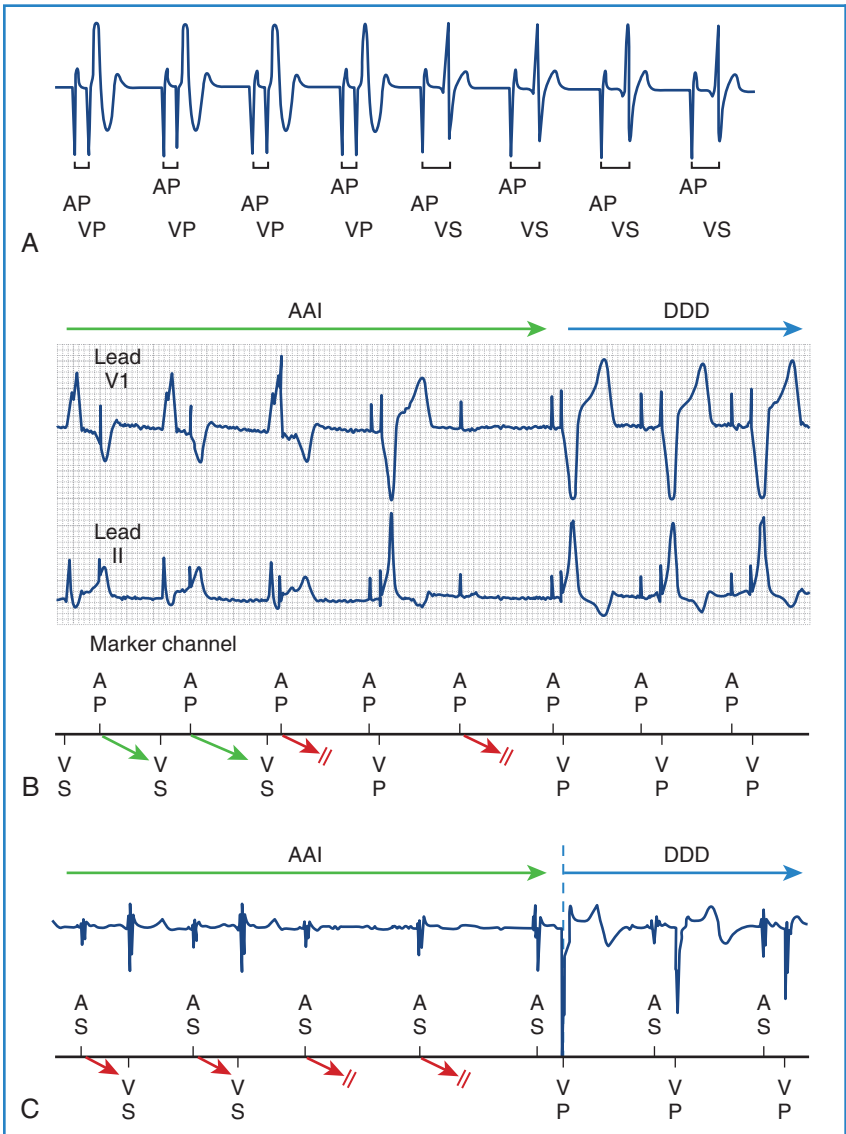

FIGURE 34-12 Algorithms to promote intrinsic atrioventricular (AV) conduction. **A,** AV hysteresis; intrinsic R waves are sensed after A-V interval (AVI) is lengthened to a programmed delta AV delay allowing intrinsic AV conduction. **B,** Managed ventricular pacing; A-A interval (AAI) mode switches over to DDD after two of four A-A intervals (AAIs) without R wave (AV Wenckebach); however, backup ventricular pacing is delivered after transient loss of AV conduction. **C,** Sorin SafeAAIR2; AAI changes to DDD mode after two consecutive P waves without intrinsic AV conduction (high-degree AV block). *(**A,** Modified from* Insignia I Ultra System Guide, *models 1190/1290/1291, St Paul, MN, 2006, Guidant Corporation.)*

without an R event, will switch to the DDD pacing mode. The algorithm periodically assesses for return of AV conduction after 1 minute of DDD pacing, and AAI is restored when intrinsic AV conduction returns. The MVP algorithm has been shown to promote intrinsic AV conduction with an 85% reduction of cumulative ventricular pacing compared with DDD/R.[11]

AAISafeR2 Sorin

AAISafeR2 (Figure 34-12, *C*) is a more complex and tolerant algorithm to minimize ventricular pacing.[2,3,12] First-, second-, and even third-degree AV blocks are allowed up to a preset level before the algorithm switches to the DDD pacing mode. The algorithm will automatically change to DDD at the preprogrammed AV delay if any of the following occur: (1) two consecutive blocked P waves (high-degree AV block), (2) more than three blocked P waves within 12 cycles (second-degree AV block), (3) ventricular pause above a programmed duration between 2 and 4 seconds, and (4) more than six consecutive abnormal PR/AR intervals above a certain programmed value (first-degree AV block, PR >350 ms, and AR >450 ms). This last criterion for first-degree AV block can be disabled. This algorithm will attempt to assess and restore intrinsic AV conduction after 12 consecutive sensed R waves or 100 DDD cycles have occurred. AAI pacing will be disabled until the next time the device is programmed if "persistent" AV conduction abnormality is noted, defined as more than 50% of the time in DDD mode. However, if AV block is detected during exercise (heart rate >100 beats/min), the event will not add to the counter for persistent DDD operation. Finally, while in DDD(R) mode after an episode of persistent AV block, the device will assess for intrinsic AV conduction and attempt to return to AAI(R) every morning when the patient awakens.

Algorithms to Avoid Competition of Native and Paced Atrial Rhythm

These algorithms are incorporated to avoid inappropriate atrial pacing during the atrial relative refractory period with consequent induction of atrial tachycardia, atrial flutter, or atrial fibrillation.

Noncompetitive Atrial Pacing

If a refractory atrial sensed event occurs within PVARP, a programmable (300-ms default) noncompetitive atrial pacing (NCAP) interval is initiated.[2,3,7] No atrial pacing will occur during the 300-ms NCAP, even if the programmed VAI is completed. VAI will be extended until the 300-ms NCAP expires. If a new atrial sensed event occurs during NCAP, the 300-ms NACP is reset. In case the atrial paced event is delayed by NCAP, the PAV interval will be shortened in an attempt to keep the ventricular rate stable (Figure 34-13).

Atrial Protection Interval

This algorithm shortens the PVARP for each interval where the pseudo-Wenckebach window is less than 125 ms, providing a noncompetitive pacing window of 125 ms.[3] By shortening the PVARP, the atrial sensed event will reset the VAI or the A-A interval depending on the base-rate behavior (ventricular-, atrial-, or hybrid-based timing).

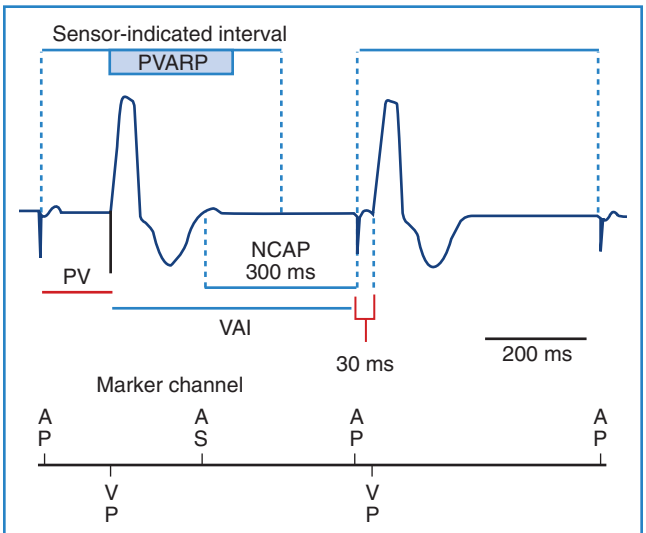

FIGURE 34-13 Noncompetitive atrial pacing (*NCAP*). An atrial sensed event during the postventricular atrial refractory period (*PVARP*) will start NCAP (300 ms), which will extend atrial pacing beyond sensor-indicated interval to avoid atrial arrhythmia induction by premature atrial pacing. Subsequent A-V interval (AVI) will be shorter to maintain the programmed lower rate limit. *(Modified from Medtronic Adapta, Versa, Sensia. In* Pacemaker reference guide, *Minneapolis, MN, 2006, Medtronic, Inc.)*

Sinus Preference

This algorithm is comparable with rate hysteresis and intends to maintain atrial sensing.[2,3,7] This allows a gradual decrease of the sensor-indicated pacing rate to a lower rate in search of SR. SR is allowed to predominate if it is detected within the programmable lower rate. However, if the sinus rate is not detected at the programmed lower rate for eight paced beats, the paced rate will gradually increase to the sensor-indicated rate. This operation restarts once a programmable search interval times out. Sinus preference cannot be enabled with the MVP algorithm, and it is temporarily disabled if the pacemaker switches to a nonatrial tracking mode.

Arrhythmia-Search Algorithms

Arrhythmia-search algorithms vary among different manufacturers; however, they are all intended to identify and properly mode switch in response to atrial tachyarrhythmias, including atrial tachycardia, atrial flutter, and atrial fibrillation.

Blanked Atrial Flutter Search

This algorithm will extend PVARP and VAI to uncover an atrial sensed event, if one falls within the ABP. If a second atrial sensed event is noted above the MS rate limit, the pacemaker will add it to the counters to mode switch.

Atrial Flutter Response

If an atrial sensed event occurs within PVARP, an atrial response window starts a 260-ms interval, which will restart if another atrial event is sensed.[2,6] In the absence of an atrial sensed event,

an atrial paced event will occur only in the presence of at least 50 ms before the LRL interval is met. A ventricular paced event will occur, with or without atrial pacing, if no sensed event is noted at the LRL interval (Figure 34-14).

Mode Switch

Mode switch refers to the ability to change automatically from one pacing mode to another in response to a rapid atrial rate. Therefore, this feature is used in patients with paroxysmal supraventricular tachycardia to eliminate tracking of atrial tachyarrhythmias. A counter should complete a specified number of short P-P intervals to mode switch to a nonatrial tracking mode, such as DDI(R) and VVI(R). Similarly, the mode switch reverts to the prior atrial tracking mode when a specified number of long P-P intervals are met. It is essential to sense atrial events that occur during part of the AVI and PVARP to avoid undersensing of atrial tachyarrhythmias. In contrast, PVAB is important to avoid atrial oversensing because of ventricular pacing, which could potentially cause an inappropriate mode switch. Shorter PVAB allows detection of higher atrial rates, whereas longer PVAB is more likely to undersense atrial tachyarrhythmias. Automatic mode switching is described in more detail in Chapter 33.

Fallback

This feature is intended to avoid abrupt symptomatic pauses related to Wenckebach behavior and fixed block once mode switch criteria have been met.[2,3] Once the pacing mode has switched, the device will gradually decrease the ventricular paced rate to the sensor rate or to the fallback LRL (Figure 34-15). The fallback time determines how quickly the rate will decrease to the sensor-determined rate or to the fallback LRL. When the atrial rate slows below the MTR or the fallback rate, AV synchrony is restored. This feature may vary among different manufacturers.

Response to Magnet Application

Responses to magnet application may vary depending on the programming of the device and its manufacturer.[2,3,5-7] In general, sense amplifiers will be disabled during magnet application, resulting in asynchronous pacing in single-chamber (VOO, AOO) or dual-chamber pacemakers (DOO). However, the individual specifics for magnet application should be understood for each pacemaker. Some pacemakers have a programmable feature to turn "off" magnet response, whereas others may "enable" storage of diagnostic electrograms with magnet application. In addition, some pacemakers will not display asynchronous pacing when in a "reset mode." Moreover, pacemakers from some manufacturers will continue to pace asynchronously for a number of beats after magnet removal, while others may have different pacing rates that may also vary depending on battery status.

Noise Reversion Response

Noise reversion response is a feature designed to identify inappropriately sensed artifacts, such as electromagnetic interference (EMI). Many sources of EMI exist in today's world. Noise response algorithms also vary from manufacturer to manufacturer.[2,3,6,7] The basic principle of noise reversion is to tag continuous signals as "noise" in ARP or VRP with nonphysiological rates exceeding 400 to 600 cycles/min (7 to 10 Hz). Noise reversion response will switch the pacing mode to an asynchronous mode at the LRL in non–rate-adaptive pacing modes or to the sensor-indicated rate in rate-adapting pacing modes in most devices (Figure 34-16).

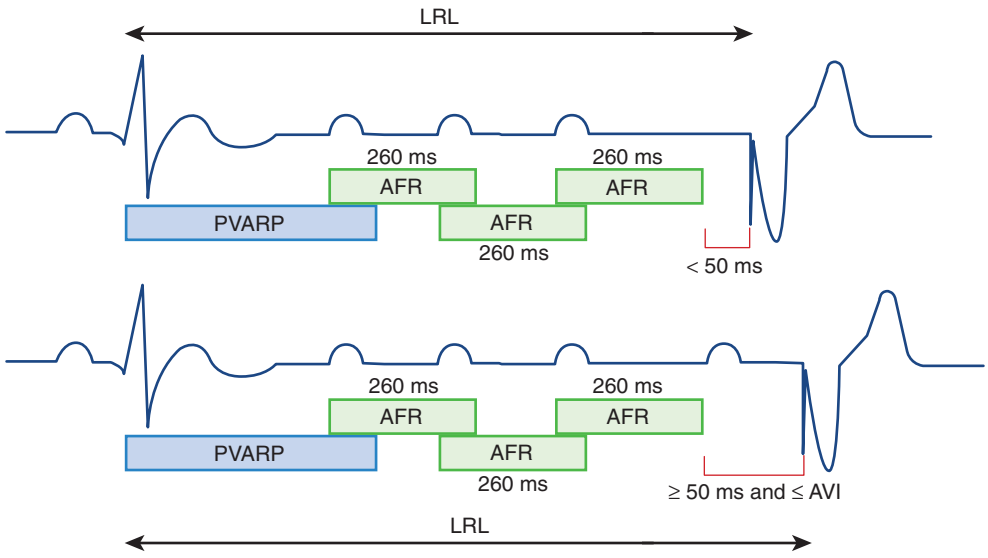

FIGURE 34-14 Atrial flutter response (*AFR*) with different programmed lower rate limit (*LRL*). *Top,* Sensing of an atrial event within the PVARP starts a 260-ms AFR window, which is restarted if another atrial event is sensed. This will continue as long as atrial sensed events are noted on an AFR window. However, ventricular pacing will occur once the LRL is met. *Bottom,* In contrast to the top panel, atrioventricular sequential pacing will occur only in the presence of at least 50 ms before the programmed LRL. *AVI,* Atrioventricular interval. *(Modified from* Insignia I Ultra System Guide, *models 1190/1290/1291, St Paul, MN, 2006, Guidant Corporation.)*

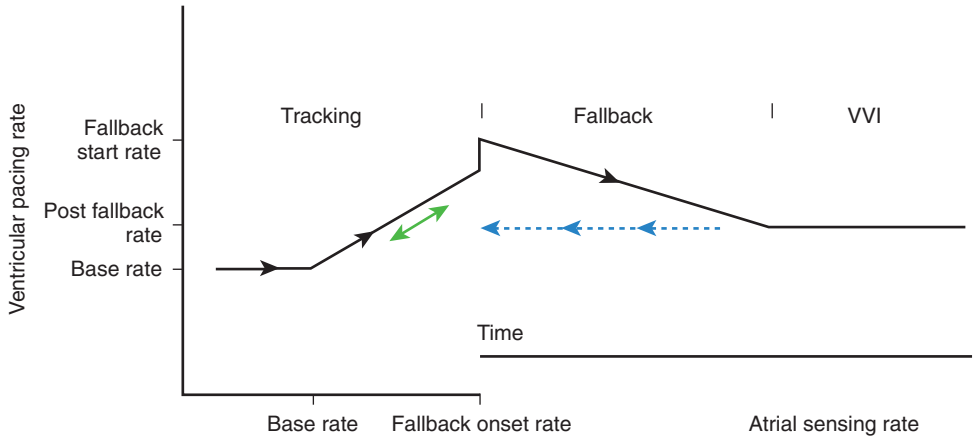

FIGURE 34-15 Fallback behavior. Atrioventricular (AV) sequential (DDD) pacing (*green arrow*) occurs between base rate and fallback or mode switch (MS) threshold. Rapid atrial rates will trigger MS to the V-V interval (*VVI*) pacing mode, with a pacing rate that will gradually decrease to a programmed fallback rate. DDD pacing mode will be restored after atrial rate decreases (*blue arrow*) below MS or fallback onset. *(Modified from Hayes DL, Asirvatham SJ, Friedman PA: Pacemaker and cardiac resynchronization timing cycles and electrocardiography. In Hayes DL, editor:* Cardiac pacing, defibrillation and resynchronization. A clinical approach, *Chichester, West Sussex, UK, Hoboken, NJ, 2008, Wiley-Blackwell.)*

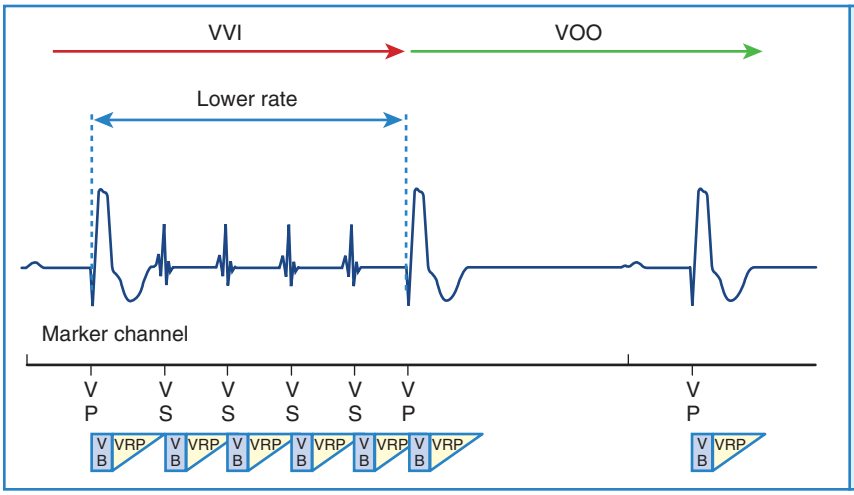

FIGURE 34-16 Noise reversion response. A ventricular event sensed during the ventricular refractory period (*VRP*) will reinitiate the initial VRP and the ventricular blanking period after ventricular pacing. Persistent sensing of ventricular events during VRP that occur at nonphysiological rates will be tagged as "noise," with subsequent switch to an asynchronous (VOO) pacing mode. *(Modified from Medtronic Adapta, Versa, Sensia. In* Pacemaker reference guide, *Minneapolis, MN, 2006, Medtronic, Inc.)*

Special Biventricular Cycle Timing and Pacing Features

Left Ventricular Refractory and Protection Periods

Biventricular pacing should be maximized to provide optimal symptomatic and survival benefit.[9,13] Even though biventricular devices base their timing cycle on RV sensed and paced events, *LV refractory and protection periods* are important to maximize cardiac resynchronization therapy (CRT) without increasing the risk of inducing ventricular arrhythmias.[3,13,14] These periods are programmable by some manufacturers. Similar to the right VRP, the *LV refractory period* (LVRP) is initiated after a left ventricular VP or VS event. LVRP will ignore LV sensed events without resetting or affecting the LV pacing timing cycle. The purpose of LVRP is to avoid inappropriate loss of CRT due to LV oversensing. For example, T-wave oversensing could inhibit LV pacing, which can be avoided by increasing LVRP to include the T wave. However, a long programmed LVRP will shorten the LV sensing window.

The *LV protection period* (LVPP) prevents inappropriate LV pacing during the LV vulnerable period, such as with LV PVC, which could induce ventricular tachyarrhythmias. However, a long programmed LVPP limits the MTR or MSR and can potentially inhibit CRT at higher pacing rates. This period is available only if LV sensing and pacing are enabled. Importantly, a ventricular sensed event in LVPP will inhibit only LV pacing without affecting RV pacing for bradycardia support.[14]

V–V Timing

A programmable RV-LV delay (better known as *V-V delay*, or *LV offset*) has been recently added to most biventricular devices to allow different timing between RV and LV pacing. The first generation of biventricular devices had nonprogrammable

simultaneous RV and LV pacing. This was developed in an attempt to improve the clinical response by improving resynchronization between RV and LV activation. Programmable V-V delay varies among different manufacturers.[14,15] Some allow LV pacing to occur from 0 to 100 ms before RV pacing, whereas others allow LV pacing even after RV pacing. However, conflicting results have been reported from different studies with regard to the optimal V-V delay as well as the utility of ECG-based optimization of V-V delay.[2,9]

Biventricular Trigger or Ventricular Sense Response

Biventricular trigger (BiVT), also known as *ventricular sense response*, was developed in an attempt to promote biventricular resynchronization in the event of frequent premature ventricular contractions and atrial tachyarrhythmias after mode switch has occurred to a nontracking mode. BiVT will provide biventricular pacing between the LRL and the URL or the MTR.[14,15] Some manufacturers have a programmable BiVT maximum pacing rate, which will limit this feature below the MTR in dual-chamber devices. BiVT, together with VRS or RS (described above), is intended to further increase resynchronization therapy.

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All references cited in this chapter are available online at expertconsult.com.

CHAPTER 35

Hemodynamic Aspects of Cardiac Pacing

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Since the implantation of the first permanent pacemaker in 1958, the understanding of the hemodynamic principles and consequences of cardiac pacing has steadily progressed. Instead of merely supporting chronotropic function, cardiac stimulation aims at closely emulating normal physiology. The progresses made are attributable to technologic advances and, in particular, to a deeper understanding of cardiovascular physiology during stimulation. In permanently paced patients, the ideal "physiological stimulator" should preserve or restore three main functions: (1) chronotropy, by adapting the pacing rate to the patient's activity, (2) atrial function and atrioventricular (AV) synchrony, to optimize ventricular filling, and (3) ventricular activation sequence, to optimize the synchrony and performance of ventricular contraction. The adverse consequences of right ventricular (RV) apical stimulation are notorious and justify the avoidance of optional ventricular capture. Cardiac resynchronization plays an important role, particularly in patients presenting with congestive heart failure (HF) and electromechanical dyssynchrony. Therefore, the aims of physiological cardiac pacing are to (1) instantaneously optimize cardiac function according to the patient's activity status, and (2) preserve atrial and ventricular mechanical and electrical (prevention of arrhythmias) functions in the long term. This chapter reviews hemodynamic principles, which have prompted the development of physiological cardiac stimulation.

Heart Rate: Restoration of Normal Chronotropic Function

Cardiovascular Physiology

Cardiac output (CO) is the product of heart rate (HR) and stroke volume (SV), calculated as the difference between left ventricular (LV) end-diastolic (ED) and end-systolic (ES) volumes. HR is mainly under the influence of the autonomic nervous system and circulating catecholamines. LVED volume depends on the (1) circulating volume, (2) cardiac filling pressures, (3) contributions of atrial systole, and (4) ventricular relaxation, and LVES volume depends on (1) cardiac afterload and (2) ventricular contractility (Figure 35-1). The Frank-Starling law correlates the ventricular filling pressures with ventricular systolic ejection volumes as a function of the LV systolic performance (Figure 35-2).[1] The respective contributions of these variables to cardiovascular performance are influenced by age; physical fitness; the presence, type, and severity of underlying heart disease; and the prescription of pharmaceuticals. In healthy individuals, during exercise, up to a 300% increase in CO is mostly contributed by an increase in HR and more modestly to an increase in stroke volume (SV).[2] On the one hand, the contribution of the increase in SV is more important in endurance athletes. In the presence of LV systolic dysfunction, on the other hand, the increase in SV during exercise is limited by a reduced contractile reserve, and the increase in CO is even more dependent on variations in HR.

Chronotropic Dysfunction

Chronotropic Incompetence

The term *chronotropic incompetence* (CI) describes an insufficient HR relative to the metabolic needs of the organism, during exercise or under stress caused by emotional disturbance, pain, and so on. The definition of CI has not been standardized. It has been defined as the inability to reach, during an exercise test, a maximal HR more than 75% to 80% of the theoretical maximal HR calculated by Astrand's formula (220 – Age). Others consider that the absolute peak HR during exercise must be more than 100 or 120 beats/min.[3] Wilkoff determined the HR response to exercise in a mathematical model, which includes age, resting HR, intensity of exercise, and functional capacity (FC) in the equation:

$$\text{FC effort} = [(220 - \text{Age} - \text{Resting FC}) \times (\text{Exercise METS} - 1)/(\text{Peak exercise METS} - 1)] + \text{Resting FC}$$

In contrast to others, this method is not limited to a single value of HR at peak exercise and takes the activity of the patient into consideration. It does, however, require the performance of a cardiorespiratory exercise test with measurements of expired gases during maximal exercise up to the anaerobic threshold to avoid underestimating CI. Because of the limited relevance of definitions based purely on statistics, a functional definition is usually adopted in clinical practice; this definition includes determining whether CI is symptomatic and whether it limits exercise capacity.

The incidence of CI varies with the definition applied, though it may reach 60% among permanently paced patients. Its origin is atrial or ventricular. Sinus node dysfunction (SND) is the most frequent cause of atrial CI, observed in 25% to 40% of cases, and the incidence increases with age.[4] A few patients presenting with permanent atrial fibrillation maintain a normal chronotropic

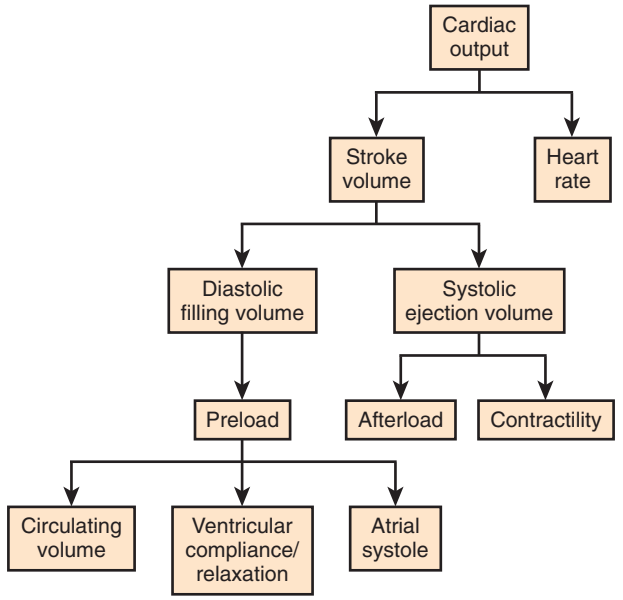

FIGURE 35-1 Physiological determinants of cardiac output.

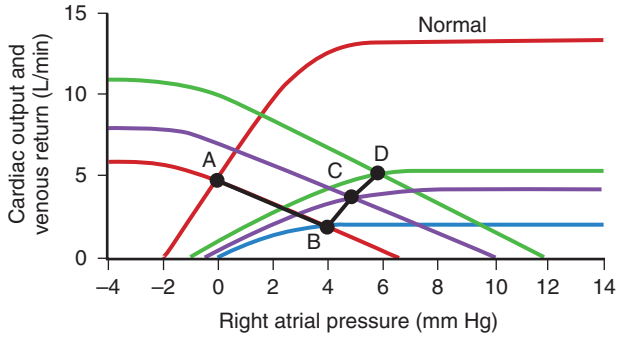

FIGURE 35-2 Frank-Starling curves before (*red curve*) and after the development of acute myocardial infarction and severe left ventricular dysfunction (*blue curve*). The *purple curves* show the sympathetic compensatory effect on filling pressure and left ventricular ejection fraction (*B* to *C* point): right shift of the pressure-volume curve with low ventricular function, higher filling pressure, and low cardiac output. The *green curve* indicates a slower effect of fluid retention and myocardial recovery (*C* to *D* point). A change in preload on stroke volume and cardiac output is more important with a normal ejection fraction compared with left ventricular dysfunction. *(Reprinted with permission from Guyton AC, Hall JE:* Textbook of medical physiology, *ed 11, St Louis, 2005, Elsevier.)*

function during exercise. However, they have inappropriate tachycardia, bradycardia, or both in alternans. The severity of CI in patients presenting with high-degree AV block increases with age and with the increasingly distal location of a block along the His-Purkinje system. Rarely dissociated from disorders of impulse formation or propagation, CI may be associated with autonomic dysfunction, as well as with myocardial ischemia.[5] Further investigation is warranted if myocardial ischemia is suggested by clinical presentation, particularly since its incidence is threefold higher among patients with coronary artery disease.

CI can be effectively managed using one of two main pacing modes: (1) In the presence of AV block without associated SND, the P-wave–synchronous VDD or DDD modes allow the synchronization of ventricular contraction with atrial systole with a programmable AV delay. The maximum tracking rate must be adapted to the patient's characteristics, including habitual physical activities, age, and underlying cardiac status. In order to prevent the development of pseudo-Wenckebach periodicity or 2:1 AV block during exercise, the upper tracking rate must not exceed the total atrial refractory period (TARP), which is postventricular atrial refractory period (PVARP) plus AV delay. Most pacemakers allow fixed programming of these intervals or, using automatic adaptive algorithms, their variation in response to HR. The AV delay can also be modulated beat-by-beat in response to the preceding cycle. Adaptation of the AV delay is often preferred to modulate TARP, as a shortening of the PVARP gives rise to the risk of triggering pacemaker-mediated tachycardia (PMT) during exercise. State-of-the-art algorithms effectively prevent the onset of PMT. (2) Sensor-driven pacing allows the adaptation of HR to exercise in the atrium (AAIR), the ventricle (VVIR), or both chambers (DDDR, DDIR). Several sensors have been tested; however, a detailed description of each is beyond the scope of this chapter. Currently, the most frequently used sensors are accelerometers and motion sensors, minute ventilation sensors (which track variations in thoracic impedance), and QT interval sensors. Minute ventilation is less sensitive than motion sensing, though its performance is higher during sustained physical exercise. Some devices have combined these sensors. Much work is in progress to develop more physiological and automatically adaptive (closed-loop) sensors. Verification of the programming of the sensor adapted to the patient's activity—by analysis of the stored histograms or by a 24-hour ambulatory electrocardiogram (ECG) or exercise test, if necessary—is important.

Hyperchronotropism

Excessively rapid atrial or ventricular pacing may be a source of LV dysfunction. In animal models, long-term, rapid ventricular pacing has been shown to cause a more rapid and severe deterioration of LV function than does atrial pacing. Therefore, all causes of excessively rapid permanent pacing must be identified and corrected to eliminate the risk of induced ventricular dysfunction. These causes include PMT, adverse effects of preventive algorithms against atrial arrhythmias, ventricular response to atrial tachycardias, sensing anomalies, poorly programmed sensors and, rarely, dysfunction of electronic internal circuits (runaway pacemaker). These complications are prevented or detected during programming or interrogation of the pulse generator. A proper programming of the PVARP at rest and during exercise and its extension after ventricular extrasystoles prevent the onset of PMT. If these measures fail, algorithms of PMT termination by atrial pacing or extension of the PVARP are helpful. Finally, all pacemaker models allow programming of mode switch at a selected atrial rate to prevent the tracking of supraventricular tachycardias by the ventricles.

Optimal Heart Rate

The optimal lowest ventricular pacing rate at rest and the highest ventricular pacing rate during exercise vary among patients as a function of age, physical conditioning, and underlying cardiovascular status.

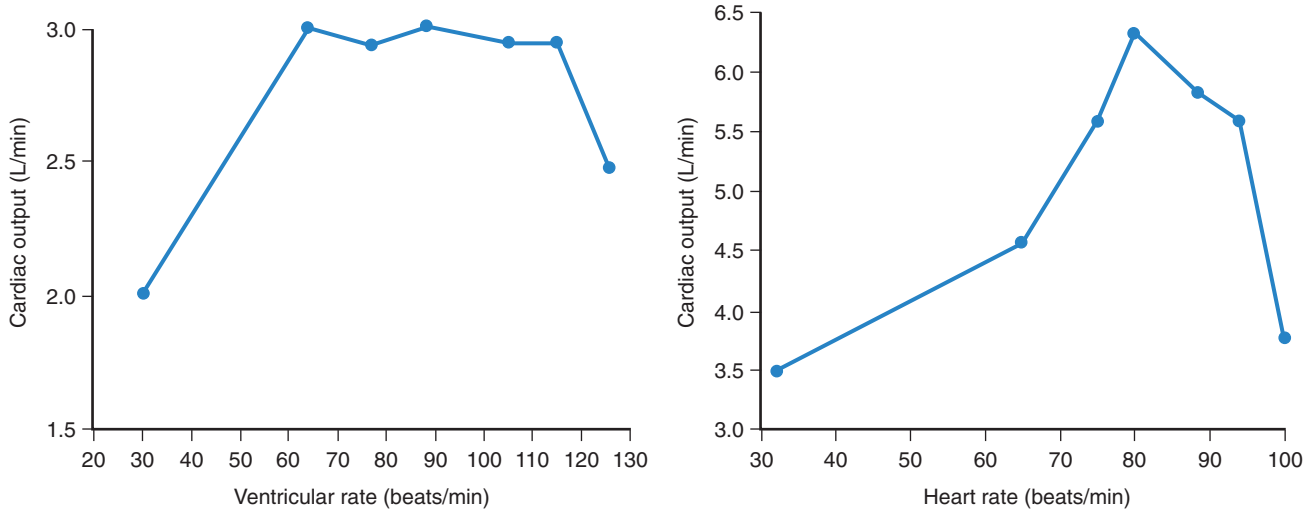

FIGURE 35-3 *Left,* Flat curve. *Right,* Peaked curve. *(From Sowton E: Haemodynamic studies in patients with artificial pacemakers,* Br Heart J *26;737–746, 1964.)*

Lower Ventricular Pacing Rate

In the early days of cardiac pacing, Sowton et al studied the optimal lowest pacing rate by measuring CO and left and right filling pressures in patients presenting with complete AV block.[6] The highest CO and lowest filling pressures were associated with pacing rates between 55 and 90 beats/min and a mean of 71 beats/min. CO/ventricular pacing rate curves showed roughly two distinct profiles. Flat curves (Figure 35-3, *left*) were most often associated with normal myocardial contractility and a stable CO as HR increased. Peaking curves (see Figure 35-3, *right*) were often observed in the presence of LV dysfunction, showing greater variations in CO with changes in HR. At the fastest HR, CO levels fell, reflecting the shortened diastolic filling time and alteration in LV compliance.

In clinical practice, the lowest pacing rate is often set between 50 and 70 beats/min, as observed on average in healthy individuals at rest. At less than 50 beats/min, CO decreases proportionally with HR, which must be avoided in the presence of HF. In patients with coronary artery disease or ventricular hypertrophy and diastolic dysfunction, excessively rapid pacing decreases coronary perfusion and ventricular filling. Furthermore, excessively rapid pacing shortens the life of the pulse generator.

Maximal Ventricular Pacing Rate

The upper ventricular pacing rate, whether atrial tracking driven or sensor driven, must also be tailored on the basis of the patient's habitual activities and underlying cardiovascular status. An excessively slow upper pacing rate causes exercise-induced chronotropic insufficiency, and an excessively rapid pacing rate may be deleterious. Kindermann et al ascertained the theoretical, optimal, maximal pacing rate corresponding to the increase in maximum VO_2 (oxygen rate) measured during cardiorespiratory exercise testing in patients with a normal or less than 45% LV ejection fraction (EF), the majority of whom were paced in DDD mode.[7] The mean optimal pacing rate was 86% of the theoretical maximal HR in patients with a normal LVEF, and 75% in patients with a depressed LVEF. It is noteworthy that programming of the upper pacing rate was excessively high in the majority of patients. Furthermore, in most patients, maximal VO_2 rapidly reached a plateau during exercise testing, regardless of systolic LV function. According to Fick's principle, a VO_2 that remains stable despite an increase in HR (in presence of a stable arteriovenous O_2 difference) indicates a decrease in SV.

A decrease in CO along with an excessively rapid HR is associated with three main mechanisms: (1) development of myocardial ischemia, (2) decrease in LV diastolic filling, and (3) unfavorable force/HR ratio. The complex interaction of these mechanisms explains why one cannot predict the optimal ventricular pacing rate from measurements of baseline LVEF only. Likewise, the optimal pacing rate during exercise calculated as a percentage of the theoretical maximal HR must be interpreted cautiously. Under some conditions, including ongoing myocardial ischemia, arrhythmias, and so on, the optimal maximal HR estimated on the basis of the maximal CO may not be optimal for individual patients.

Heart Rate and Cardiac Resynchronization Therapy

The long-term effects of atrial pacing at a rate faster than the sinus rate in recipients of cardiac resynchronization therapy (CRT) devices programmed in DDD/DDDR mode are only indirectly understood. First, continuous atrial pacing might increase the inter-atrial conduction delay and accentuate the left heart AV dyssynchrony (see Atrial Conduction Delay). In addition, several studies have found a link between increased mortality and long-term elevation of HR in unpaced patients with or without HF. Finally, a slower HR may promote angiogenesis. For the time being, and pending additional information, the recommendation is to keep the backup atrial pacing rate below the sinus rate, except in the presence of chronotropic insufficiency.

Preserving Atrial Function and Atrioventricular Synchrony

Atrial Function

Atrial systole plays an important hemodynamic role. (1) It augments LV filling and promotes its contractility by the Frank-Starling mechanism. (2) It keeps the mean atrial pressure at a low level and facilitates the venous return to the heart. (3) It allows the presystolic closure of the AV valves, preventing VA valvular regurgitation with a sudden decrease in the pressures immediately after atrial contraction. Furthermore, the atria influence peripheral vasomotor activity and water-electrolyte balance by neurohormonal mechanisms mediated by the autonomic nervous system and b-type atrial natriuretic peptide. These mechanisms altogether participate directly or indirectly in the regulation of the main determinants of CO, that is, preload, afterload, and contractility.

The hemodynamic importance of atrial function varies highly among individuals. In healthy subjects, the contribution of atrial systole to ventricular SV is approximately 20% at rest and 30% during exercise. The contribution of atrial systole to CO during vigorous effort is gradually supplanted by HR. However, the relative importance of atrial systole increases with age, with abnormal ventricular diastolic function, and within certain limits, with the deterioration of LV systolic function.[8]

Atrioventricular Synchrony

A proper AV synchronization is key for the efficacious hemodynamic contribution of atrial systole. Conversely, complete AV dissociation is hemodynamically detrimental. Atrial systole occurring when the mitral valve is closed activates (1) atrial and pulmonary neurohumoral stretch receptors, (2) vagal activity, and (3) the production of atrial natriuretic peptide. These effects may cause a fall in systemic arterial pressure and a variety of manifestations known as *pacemaker syndrome* when occurring in permanently paced patients. It has been described in approximately 20% of patients paced in the VVI/VVIR mode, whose atrial activity is sinus, though it may occur in any pacing mode in the presence of AV dyssynchronization. AV synchronization is electrical and mechanical, left and right. While electrical and mechanical dyssynchronies usually coexist, their correlation is not systematic (see Atrial Conduction Delay). "Electrical" AV dyssynchrony manifests as an abnormal PR interval or AV dissociation on surface ECG, and "mechanical" AV dyssynchrony is defined as a LV diastolic filling time less than 40% of the cardiac cycle, accompanied by an abnormal transmitral Doppler profile. In the case of cardiac pacing, left AV mechanical synchrony is hemodynamically the most important and is preserved by programming an appropriate AV delay. The main determinants of the AV delay are AV conduction time, intra-atrial and inter-atrial conduction times, and intraventricular and interventricular (VV) conduction times.

Atrial Conduction Delay

The intra-atrial and inter-atrial conduction delays are measured from the onset of the P wave to (1) the para-Hisian atrial ECG (normally 30 to 60 ms), and (2) to the distal coronary sinus atrial ECG (normal 60 to 90 ms), respectively. Prolonged atrial conduction delays may cause left AV dyssynchrony with a foreshortened mechanical AV delay, apparent on mitral Doppler as a short LV filling period and truncated A wave. The main causes of prolonged atrial conduction delays—apparent on surface ECG as a more than 120-ms P-wave duration, notching of the P wave, and a foreshortened segment between the end of the P wave and the onset of QRS (Figure 35-4)—are (1) slowing of intra-atrial conduction due to heart disease, and (2) a latency of paced atrial capture. The latter is responsible for greater conduction delays than is apparent during sinus rhythm and mandates the routine programming of a 30 ms to 40-ms longer paced than sensed AV delay. The latency of atrial capture can be considerably amplified by several factors, including type and location of the pacing lead and its interface with the myocardium, pacing rate, abnormal electrolyte or metabolic status, the effect of medications, and myocardial disease. Heart diseases most often associated with anomalous atrial conduction are valvular (rheumatic mitral disease, in particular), hypertrophic, ischemic, and hypertensive. Programmers allow a choice of separate AV intervals for sensed P waves versus paced P waves in order to offset this phenomenon. While left atrial dilation is often associated with prolonged atrial conduction time, this correlation is low, except in the case of rheumatic mitral valve disease.[9]

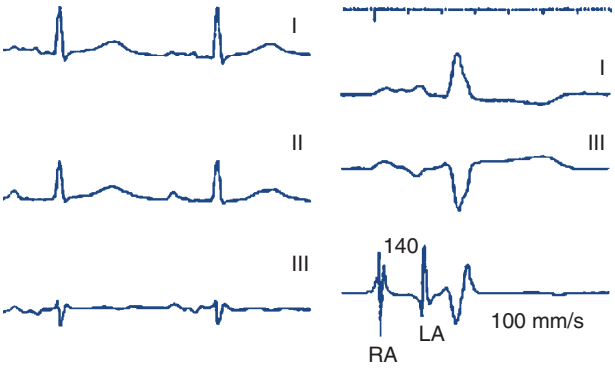

FIGURE 35-4 Surface electrocardiogram: high-degree interatrial block with 170-ms P-wave duration. The terminal portion of the P wave is negative in lead III with left superior axis (–30). The three intracardiac electrocardiograms (*lower right tracing*), sensed by a composite bi-atrial lead, correspond to right atrial (*RA*), left atrial (*LA*), and far-field R waves. The interatrial delay is 140 ms.

In the majority of patients, prolonged intra-atrial conduction is associated with slowing of AV conduction, probably due to atrial lesions similar to those found in SND; this association is found in 30% of patients. PR prolongation compensates for the delayed atrial conduction and limits its effects on left AV synchrony. In the presence of normal AV conduction and major intra-atrial and inter-atrial conduction delays, left atrial contraction is delayed, sometimes to the point of encountering a closed mitral valve. The main consequences are (1) a decreased LV SV, and (2) the activation of neurohumoral responses due to atrial distension. On the one hand, programming of the AV delay based on surface ECG alone is unlikely to remedy this situation. On the other hand, the echocardiographic transmitral filling pattern enables the optimization of left AV synchrony (see Atrioventricular Optimization Methods).

Prevention and Management of Atrial Conduction Delay

In patients with long inter-atrial conduction times, different technical solutions may help prevent pacing-induced AV

dyssynchrony in the left heart. This applies mainly to patients presenting with permanent, complete AV block or to those patients who need ventricular stimulation for hemodynamic indications such as hypertrophic obstructive cardiomyopathy. These patients may benefit from one of the following two choices:

1. *DDD pacing with a paced AV delay up to 250 ms to 300 ms to restore the atrial contribution concealed by shorter AV delays* (Figure 35-5). However, this option, which lengthens the TARP and limits exercise capacity by lowering the 2:1 Wenckebach point, is acceptable mainly in inactive patients.

2. *Bi-atrial synchronous DDD pacing.* In addition to its probable antiarrhythmic effect, this pacing mode confers significant hemodynamic benefits in difficult situations, verified during temporary pacing. By preempting left atrial systole by 30 ms to 75 ms, it restores normal left AV synchrony (Figure 35-6) and enables the programming of conventional AV delays. When conventional DDD pacing was compared with DDD bi-atrial pacing by using different AV delays and a fixed pacing rate, DDD bi-atrial pacing was shown to increase CO by a mean of 23% ± 6% and lower pulmonary capillary wedge pressure by a mean of 27% ± 13%. The benefit decreased as the AV delay increased.[10]

It is generally possible to increase the programmed AV delay at the cost of a long TARP and a decrease in the maximal atrial tracking rate during exercise. Depending on the position of the lead and the distribution of intra-atrial morphologic abnormalities, atrial pacing might lengthen or shorten atrial conduction time, with a high interindividual variability. A septal implantation of the atrial lead often allows the shortening of conduction delays. If an atrial lead has already been implanted in the appendage, an alternative dual right atrial pacing, or bi-atrial stimulation, using a second lead placed at the coronary sinus ostium or within the coronary sinus, can be considered. One must also pay attention to the prolongation of the AV delay, which, during CRT, might compromise resynchronization by promoting spontaneous AV conduction.

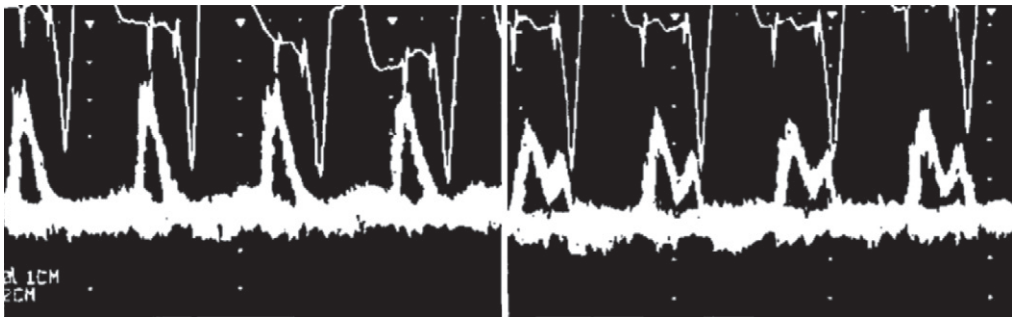

FIGURE 35-5 Adverse hemodynamic consequences of major intra-atrial conduction delay in a patient permanently paced in the DDD mode for bradycardia. A standard AV delay of 150 ms results in a short filling time and single pulse mitral flow (*left panel*). Increasing the AV delay to 250 ms restores normal AV synchrony (*right panel*). *(From Daubert JC, Pavin D, Jauvert G, Mabo P: Intra- and interatrial conduction delay: Implications for cardiac pacing,* Pacing Clin Electrophysiol *27:507–525, 2004.)*

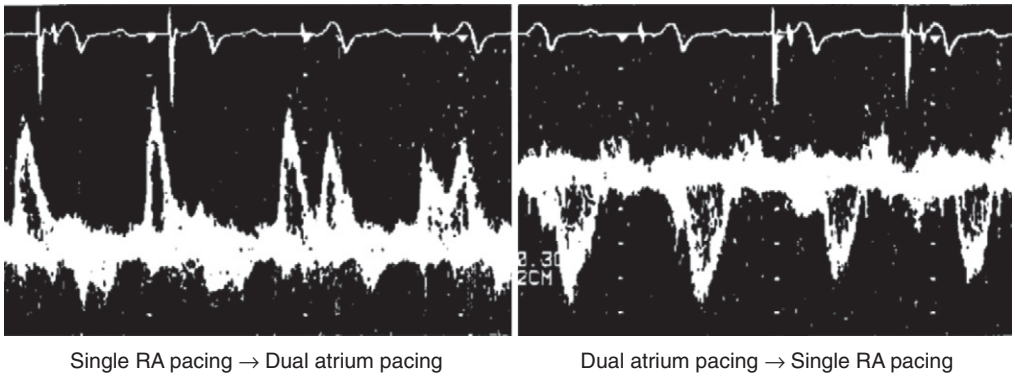

FIGURE 35-6 Instantaneous hemodynamic changes induced by bi-atrial synchronous DDD pacing versus standard DDD pacing in a patient with long inter-atrial conduction time. *Left,* Switch from standard to bi-atrial pacing instantaneously corrects the baseline atrioventricular dyssynchrony in the left heart. *Right,* Switch from biatrial to standard DDD causes a prominent decrease in aortic velocity-time integral. *(From Daubert JC, Pavin D, Jauvert G, Mabo P: Intra- and interatrial conduction delay: Implications for cardiac pacing,* Pacing Clin Electrophysiol *27:507–525, 2004.)*

Late Atrial Sensing and Cardiac Resynchronization Therapy

In the presence of major intra-atrial conduction delay between the sinus node and the atrial pacing site, atrial sensing is delayed. The interval between atrial sensing and ventricular sensing is foreshortened, with a risk of inhibited biventricular pacing or fusion beats. Repositioning the atrial lead or modulating or ablating the AV node may be necessary.

The clinical effects of fused spontaneous and paced QRS in recipients of CRT systems remain uncertain. Indirect arguments suggest that fusion complexes are not necessarily adverse.[11] In limited studies, at least a similar hemodynamic benefit was observed in patients at rest in whom resynchronization was achieved by LV stimulation alone, with fusion via the right bundle branch, or by biventricular stimulation.[12] Furthermore, the absence of first-degree AV block predicts a response to CRT. Either the presence of AV block is a prognostic factor associated with more severe heart disease or its absence is associated with a higher likelihood of fusion or "concealed resynchronization."[13] Nevertheless, pending further studies, the current recommendation is to avoid or limit biventricular simulation with fusion to the extent possible.

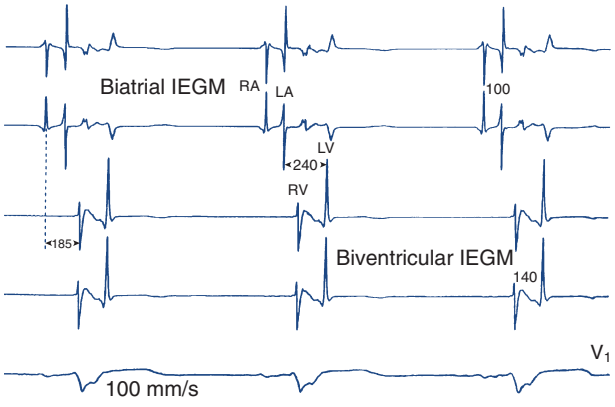

FIGURE 35-7 Intracardiac recordings from four permanent leads at time of device implant. The P-R interval is normal on surface electrocardiogram (ECG). However, the intracardiac ECGs show marked VV conduction delay (140 ms) resulting in major left atrioventricular dyssynchrony (LA – LV = 240 ms). *RA*, Right atrium; *LA*, left atrium (distal coronary sinus); *RV*, right ventricle; *LV*, left ventricle (posterolateral vein); *IEGM*, intracardiac electrogram.

Atrioventricular Synchrony During Exercise

During exercise, sympathetic activity facilitates AV nodal conduction, and a shortening of AV delay that is inversely proportional to the HR is observed. Implantable pacemakers are able to reproduce this phenomenon in patients with AV block.[14] The rate-adaptive AV delay shortens AV delay, usually linearly with acceleration of the HR, up to the shortest programmable value.[15] This offers several benefits: (1) improvements in hemodynamic function and cardiopulmonary performance while preserving proper AV synchrony during exercise[16]; (2) ability to increase the maximal synchronous HR during exercise by shortening TARP; and (3) subjective improvement in the quality of life by the adaptation of the AV delay during exercise.[17]

Conflicting data have been reported regarding the programming of hemodynamically optimal AV delays in recipients of CRT systems during effort, probably reflecting heterogeneous patient characteristics, including degree and type of dyssynchrony, lead positions, and underlying heart disease.[18] The current recommendation is to deactivate the rate-adaptive AV delay in the absence of AV conduction disorder.

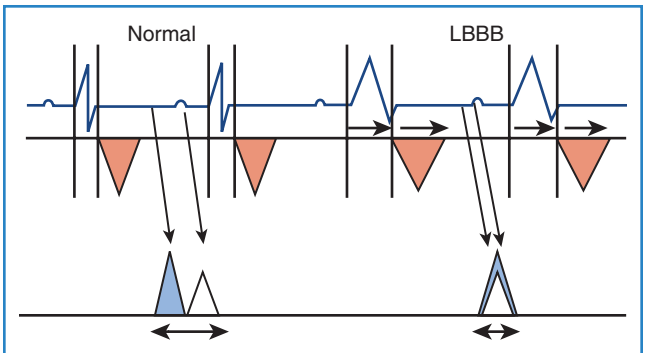

FIGURE 35-8 Effect of left bundle branch block (*LBBB*) on AV synchrony. Left ventricular outflow tract (*orange triangles*) and mitral Doppler (*blue triangle,* E wave; *white triangle,* A wave) are shown during the cardiac cycle. LBBB is responsible for an increased systolic and decreased diastolic interval (see also Figure 35-15) with fusion of A and E waves. The P-R interval is unchanged. *(Modified from Cazeau S, Gras D, Lazarus A, et al: Multisite stimulation for correction of cardiac asynchrony,* Heart *84:579–581, 2000.)*

Ventricular Conduction Delay and Atrioventricular Synchrony

An additional delay is inserted between left atrial and LV activation in cases of marked slowing of intraventricular or VV conduction with left bundle branch block morphology, most often observed in the context of advanced heart disease. Despite the absence of PR interval abnormality of surface ECG (Figure 35-7), unequivocal left AV mechanical dyssynchrony is present on ultrasound Doppler examination (Figure 35-8). Although conventional DDD pacing with a short AV delay can correct LV filling (transmitral Doppler), it should not be programmed in patients with HF because of the potential adverse effects of RV pacing. Moreover, this pacing increases only left heart filling, whereas biventricular stimulation restores AV synchrony on both sides of the heart (see Figure 35-17) as well as intraventricular synchrony and improves clinical outcomes.

Atrioventricular Optimization in DDD/DDDR Pacing

The purpose of an optimal AV delay is to guarantee (1) the maximal contribution of the atrium to the diastolic LV filling, (2) a long diastolic filling period, (3) a short isovolumetric contraction period, and (4) the maximal SV. Empirical programming is suboptimal because of the wide variability among patients in optimal AV delay, caused by marked interindividual differences in electrical and electromechanical intervals in the atria (intra-atrial and inter-atrial conduction times) and ventricles (VV conduction delay, in particular). In case of an excessively long AV delay, LV contraction occurs well after atrial systole, while the mitral valve is passively semi-closed, causing (1) fusion of E and

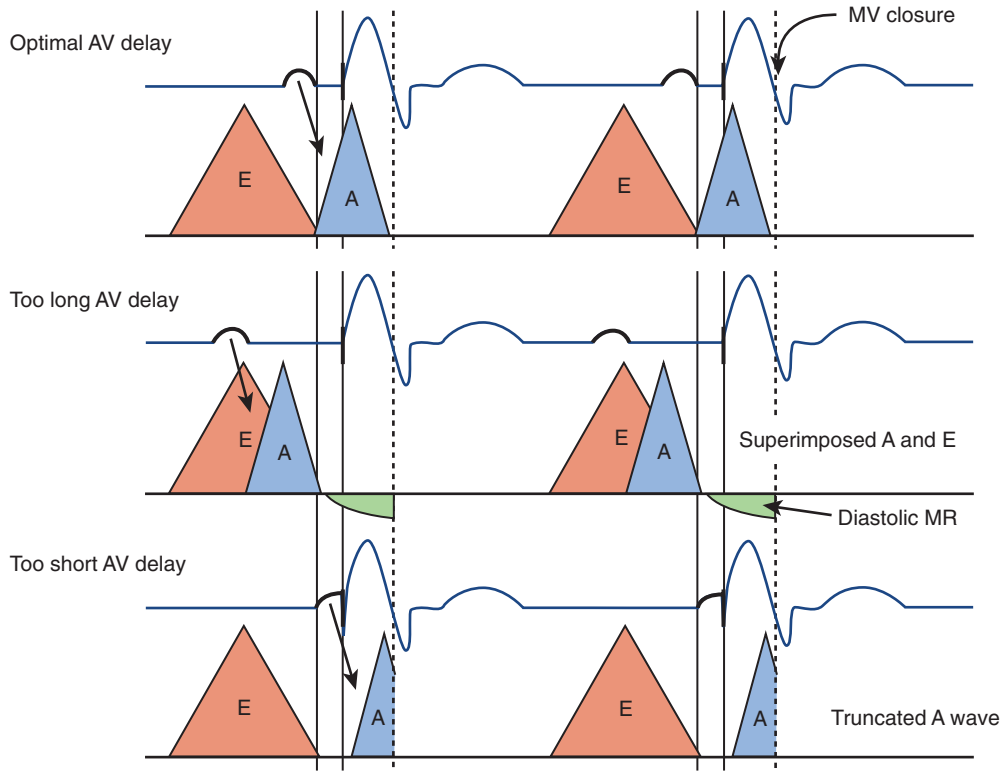

FIGURE 35-9 Effects of changes in AV delay on mitral inflow. *AV,* Atrioventricular; *MV,* mitral valve; *MR,* mitral regurgitation. *(From Barold B, Ilercil A, Herweg B: Echocardiographic optimization of the atrioventricular and interventricular intervals during cardiac resynchronization,* Europace *10:iii88–iii95, 2008.)*

A waves of the filling transmitral Doppler flow and (2) diastolic mitral regurgitation (Figure 35-9). An excessively short AV delay causes the LV contraction to close the mitral valve before the end of ventricular filling (truncated A wave). AV delay is optimized mostly in recipients of CRT systems, whereas in dual-chamber pacing, it is reserved for the rare patients presenting with symptoms attributed to AV dyssynchrony. Several methods are applicable, depending on the choices and practices of the various centers (Table 35-1). Echocardiography and programming algorithms are most often used because of their wide availability, ease of use, and low cost. Other methods are mostly investigative and will not be discussed in detail in this chapter (see Table 35-1).

Atrioventricular Optimization Methods

Ritter described an AV delay optimization formula applicable to recipients of DDD pacemakers presenting without LV dysfunction and complete AV block.[19] This method allows the calculation of AV interval with a ventricular contraction immediately following the deceleration phase of atrial contraction. Its advantages are its simplicity and expeditious application (see Table 35-1). However, its use should be avoided in patients with preserved AV conduction. In recipients of the CRT system, Ritter's formula was shown to produce hemodynamic results that were inferior to those obtained with optimization of AV delay using aortic or mitral velocity-time integral (VTI).[20] Meluzin et al have also described a simple method for patients undergoing CRT.[21] It requires the presence of mitral regurgitation and estimates an optimal AV delay that is closely correlated with CO.

Optimizing AV delay on the basis of aortic VTI, mitral VTI, or the iterative method (see Table 35-1, Figure 35-10) showed immediate increases in CO or LV dP/dt (first derivative of pressure measured over time) in recipients of CRT systems. However, these methods are time consuming and poorly reproducible. In a comparison of mitral VTI with diastolic filling time, aortic VTI, or Ritter's formula, Jansen et al found that the maximal mitral VTI produced the greatest increase in LV contractility, measured by dP/dt.[22]

Endocardial ECG analysis by algorithms also allows the calculation of AV-sensed and -paced optimal AV and VV delays. Studies employing the Expert Ease algorithm (Boston Scientific, Natick, MA), which uses QRS width and spontaneous AV delay to calculate optimal delays, found a close correlation between calculated AV delay and maximal dP/dt (dP/dt_{max}), and in one study, the algorithm yielded results superior to Ritter's method and aortic VTI. QuickOpt (St. Jude Medical, St. Paul, MN) calculates optimal delays as a function of the intervals measured between atrial and ventricular leads. In most studies, a close correlation was observed between the AV and VV delays calculated by QuickOpt and those obtained by echocardiographic optimization. SonR (Sorin Group, Milan, Italy) is a method based on peak endocardial acceleration sensed by a micro-accelerometer embedded at the tip of an RV lead. In this method, a high correlation was observed between optimal AV and VV delays identified by peak endocardial acceleration and by echocardiography, at rest

Table 35-1 AV Optimization Methods

METHODS	DESCRIPTION
ECHOCARDIOGRAPHY	
Optimization of Left Ventricular Filling	
Ritter's formula	Avopt = long AV – short QA + long QA
Iterative: mitral Doppler morphology	Start with long AV, then shortening by 20 ms until truncated A wave, then lengthening every 10 ms to avoid truncated A wave
Mitral VTI	Vopt: associated with maximal mitral VTI
Meluzin	Vopt = long AV – (Interval from end of A wave to beginning of systolic mitral regurgitation)
Diastolic filling time	Target: >40% of cardiac cycle length
Optimization of Left Ventricular Systole	
Aortic velocity-time integral	Vopt: associated with maximal aortic outflow tract VTI
dP/dt	Vopt: maximal dP/dt on mitral regurgitation
Myocardial performance index	Vopt: associated with maximal index
OTHERS	
Electrogram-based algorithm	
Impedance cardiography	
Right heart catheterization	
Finger plethysmography	
Radionuclide ventriculography	

Vopt, *Optimal AV delay;* AV, *AV delay;* long QA, *interval between Q of the electrocardiogram to end of mitral Doppler A wave with long AV delay;* short QA, *interval between Q of the electrocardiogram to end of mitral Doppler A wave with short AV delay;* VTI, *velocity-time integral.*

and during exercise, in normal subjects and in patients with structural heart disease. However, reliable data confirming the clinical advantages conferred by these various algorithms are still lacking.

Limitations of Atrioventricular Optimization

Several limitations have been identified in the optimization of AV delay. First, it varies among methods used, particularly between methods using optimization of ventricular filling and optimization of systolic function. Second, the conditions in which AV delay is usually optimized (at rest, in the decubitus position) do not reflect the real-life conditions of patients who have maintained some level of physical activity. Furthermore, despite several single-center studies reporting hemodynamic benefits conferred by optimization of AV delay, the evidence that it improves the clinical outcomes of the recipients of CRT systems is slim. In a single-center, randomized study of AV delay optimization, in which aortic VTI was used 3 months after implantation of the CRT system, Sawhney et al observed a more than 1-point decrease in New York Heart Association (NYHA) HF functional class in 75% of patients who underwent the optimization procedure compared with 45% of patients who did not undergo the procedure.[23]

It is, however, noteworthy that many of the clinical and echocardiographic benefits observed in patients who underwent CRT were attributable to improvements in the ventricular activation sequence and not in the AV activation sequence. Optimization of AV delay remains, nevertheless, an important step in the initial and long-term management of CRT recipients, since a suboptimal AV delay is likely to deprive them of the expected maximum clinical benefit.

Another challenge in the optimization of AV delay are the prominent variations during long-term follow-up, in particular because of the changes in loading conditions caused by LV reverse remodeling.[24] No definitive consensus has been reached with respect to the preferred time of optimization or the long-term schedule of re-evaluations. A systematic initial optimization as

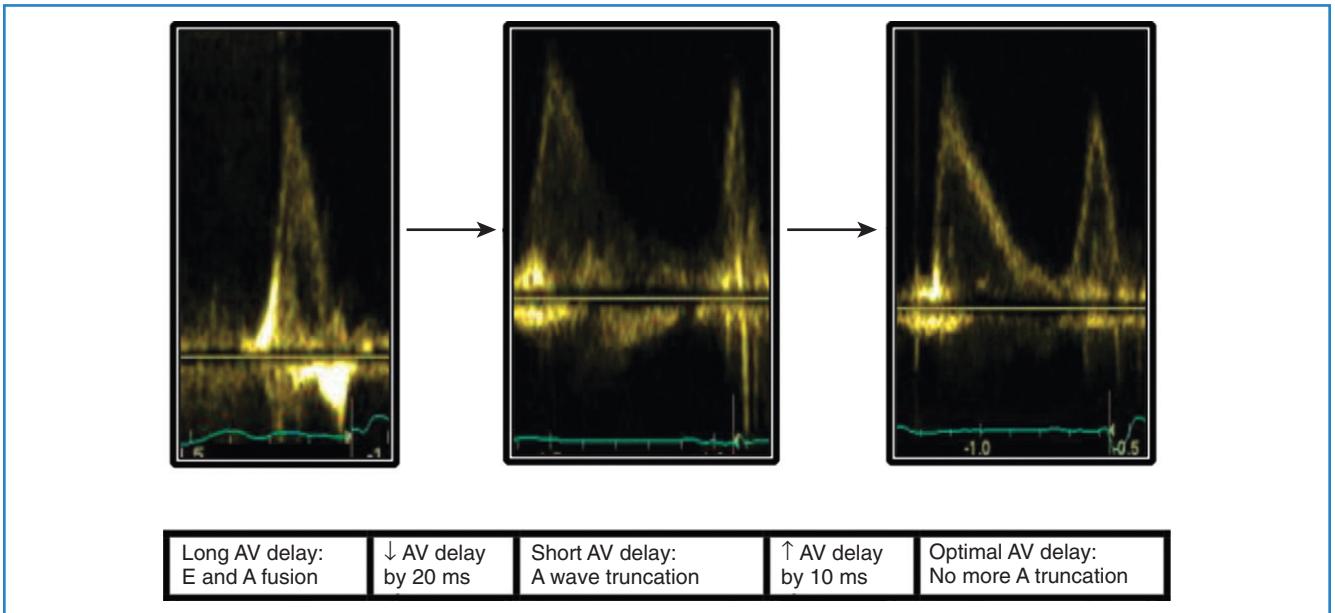

FIGURE 35-10 Iterative echocardiographic optimization of atrioventricular (*AV*) delay. *(Courtesy Dr. E. Donal, University Hospital of Rennes, France.)*

well as repeated procedures, while desirable, are often time consuming and hence precluded in clinical practice. A quick initial evaluation of the morphology of the transmitral flow on Doppler ultrasound is an alternative method of confirming the absence of prominent AV dyssynchrony.[25] AV delay must, nevertheless, be optimized in all nonresponders to CRT.

Optimization of Ventricular Function: Role of the Ventricular Pacing Site

Right Ventricular Apical Stimulation

Hemodynamic Consequences

Acute Effects

The RV apex is the most often chosen pacing site for ease of lead placement, its stability, and predictably low capture threshold. It is, however, the cause of a left bundle branch block–like ventricular activation sequence and electrical and structural remodeling. In 1925, Wiggers et al found that RV apical pacing decreased LV dP/dt and caused cardiac dyssynchrony. They proposed a slowing of intramyocardial conduction, compared with normal propagation through the His-Purkinje system. Since then, multiple studies have confirmed the immediate adverse hemodynamic effects of apical pacing, with or without preservation of AV synchrony.[26] After cessation of ventricular pacing, abnormalities of repolarization (cardiac memory) persist for several days. The incompletely understood mechanisms implicate short-term changes in ionic channels and protein phophorylation and longer-term changes in gene expression and protein synthesis. Abnormal myocardial relaxation and a transient decrease in LVEF accompany these abnormalities of repolarization for a few hours or days after cessation of apical pacing.

Permanent Pacing

In the long term, apical RV pacing may cause major structural changes (Table 35-2), including ventricular dilation and asymmetric hypertrophy. SV and LV dP/dt are decreased, and the pressure–volume curve is shifted to the right. The LV volume is increased by both dilation and hypertrophy, and its performance depends on the Frank-Starling law to a greater extent. Short-term and long-term follow-up studies have shown an approximately 10% decrease in LVEF. Furthermore, shortening of the ventricular filling time and maximal rate of fall of LV pressure (–dP/dt) are manifestations of diastolic dysfunction. Mitral regurgitation sometimes develops or worsens, probably due to a decrease in the transmitral gradient (forces of valve closure) and in the synchrony of papillary muscles contraction.[27] Asymmetric hypertrophy may become visible in the late-activated zones, reflecting inhomogeneous myocardial work and a greater parietal tension at those sites at the onset of ventricular systole. A redistribution of myocardial sympathetic innervation during RV pacing is another cause of asymmetric hypertrophy caused by the focal release of catecholamines. On histologic examination of these zones, myocytes appear hypertrophied and disarrayed, without any increase in capillary density, which results in a decreased coronary reserve. Dilation and hypertrophy further increase ventricular dyssynchrony and decrease LV systolic function, thereby initiating a vicious circle.

Table 35-2 Adverse Effects of Abnormal Ventricular Activation During Right Ventricular Apical Pacing

Hemodynamic function	Depressed left ventricular systolic and diastolic functions Reduced cardiac output Increased filling pressure
Ventricular dyssynchrony	Interventricular dyssynchrony Intraventricular dyssynchrony
Remodeling	Asymmetric hypertrophy Left ventricular dilation
Valvular function	Functional mitral regurgitation
Myocardial perfusion	Changes in regional myocardial perfusion and demand
Autonomic nervous system	Changes in regional innervation

Ventricular Pacing and Clinical Outcomes

Risk of Heart Failure

In patients free from structural heart disease, the prevalence of ventricular dyssynchrony induced by RV apical pacing is between 30% and 60% and is associated with alterations of systolic and diastolic functions. Dyssynchrony due to apical pacing may persist after its cessation.[28] The decrease in LVEF is often modest[29]; only a fraction of patients develop more prominent ventricular dysfunction and overt, long-term HF, rarely (3% to 10%) before at least 3 years of permanent pacing.[30] The prevalence, however, increases over time. After a mean follow-up of nearly 8 years, Zhang et al observed the development of new-onset HF in 26% of patients permanently paced for AV block.[31]

Among several persistent questions, one that still needs to be answered is why some patients free from heart disease develop acute dyssynchrony during pacing and some do not. The lead position with respect to the His-Purkinje system may be a reason. It is similarly unclear why LV function deteriorates in only a very small number of patients. Without new and reliable data, it is hard to predict who, among this patient population, will develop HF.

The risk of developing HF is considerably higher and its onset earlier in patients whose LVEF is already depressed or who have a history of HF or myocardial infarction. This risk is probably caused by slower propagation of the electrical wavefront and more prevalent and more prominent ventricular dyssynchrony in these patients than in those without heart disease.[32] Studies of the relationship between dyssynchrony apparent shortly after device implantation and long-term outcomes are in progress.

Pacing Mode and Clinical Outcomes

Several pacing characteristics and their consequences, including percentage and duration of ventricular pacing, pacing mode with respect to conduction abnormalities, site of ventricular stimulation, and duration of the paced QRS, also determine the development of HF.[33] An increase in the paced QRS duration in patients with SND or AV block is associated with an increased likelihood of development of HF.[34] This association may be explained by a more prominent mechanical ventricular dyssynchrony at some pacing sites, though it might also be a manifestation of more severe myocardial and conduction system disease.

Choosing the right pacing mode is crucial. In the DAVID trial, which enrolled patients presenting with severe LV dysfunction

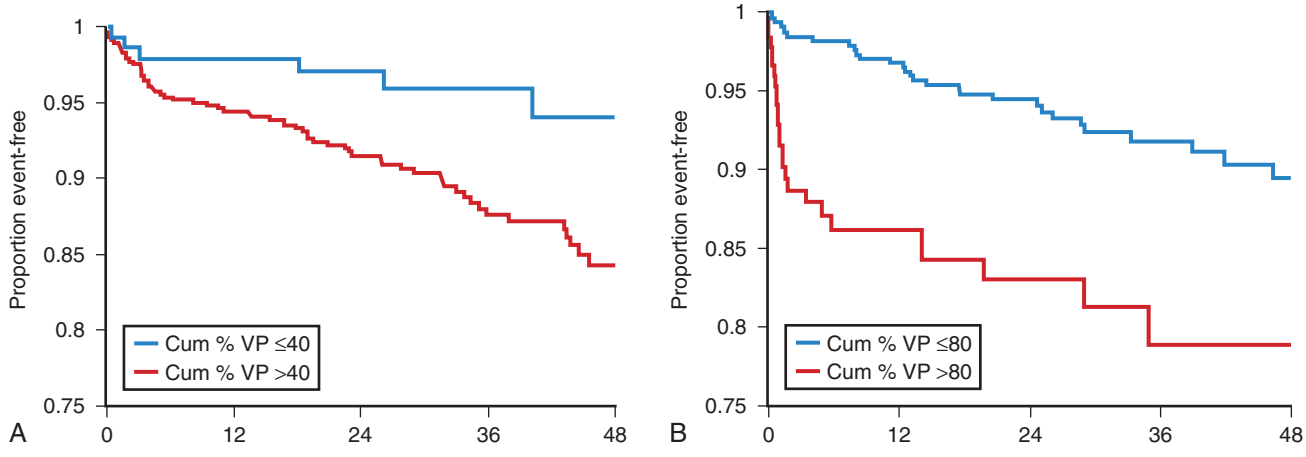

FIGURE 35-11 Cumulative survival free from first hospitalization for management of heart failure according to percent of ventricular pacing during the first 30 days in patients with sick sinus syndrome. **A**, DDDR mode. **B**, VVIR mode. (timeline in months). *(From Sweeney MO, Hellkamp AS, Ellenbogen KA, et al: Mode Selection Trial Investigators: 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 *107:2932–2937, 2003.)*

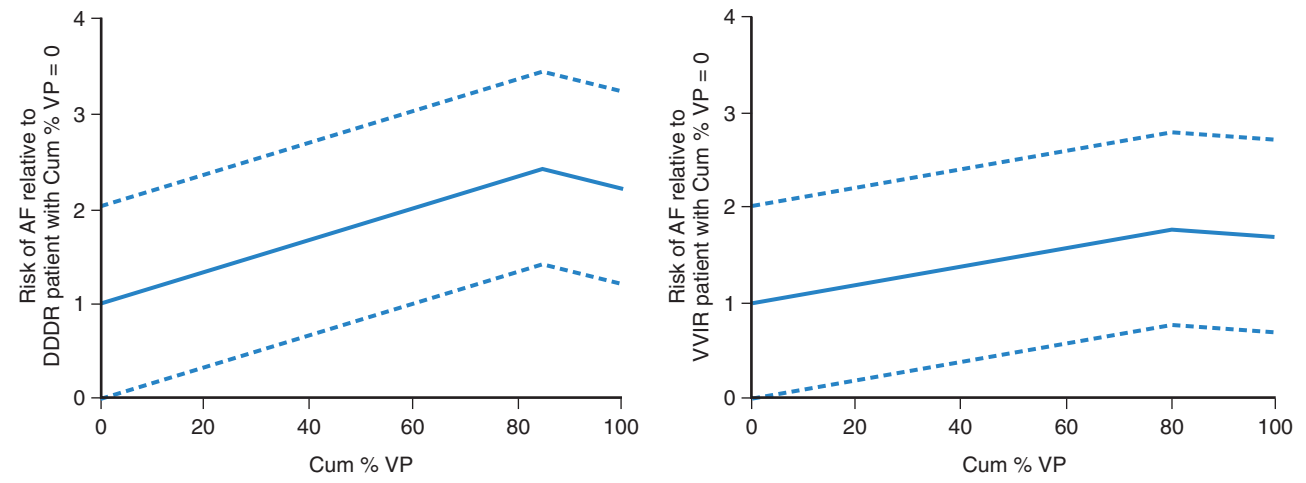

FIGURE 35-12 Relation between risk of atrial fibrillation (*AF*) and cumulative percent ventricular pacing (Cum % VP) estimated by Cox model in a patient with sick sinus syndrome. *Dashed lines* represent 95% confidence intervals for point-by-point estimates of the hazard ratio for a 1% change in Cum % VP. *Left,* DDDR. *Right,* VVIR. *(From Sweeney MO, Hellkamp AS, Ellenbogen KA, et al: Mode Selection Trial Investigators: 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 *107:2932–2937, 2003.)*

and a dual-chamber implantable cardioverter defibrillator (ICD), the incidence of hospitalizations for management of HF was higher among those paced in the DDDR mode, at a basic pacing rate of 70 beats/min with a short AV delay, than in patients paced in the VVI mode, at a backup rate of 40 beats/min, which was associated with a higher percentage of ventricular pacing in the former group.[35]

Furthermore, a post hoc analysis of the Mode Selection Trial (MOST) (Figures 35-11 and 35-12) revealed that in patients paced in DDDR or VVIR for SND, both the rates of atrial fibrillation and hospitalizations for HF increased proportionally to the percentage of ventricular pacing.[36,37] This underscored the importance of limiting RV apical pacing and the risk of loss of benefits conferred by pacing modes that preserve AV synchrony.

Cardiac Pacing and Obstructive Hypertrophic Cardiomyopathy

The benefit conferred by RV apical stimulation in obstructive hypertrophic cardiomyopathy (OHCM) is mediated by ensuing changes in the contraction sequence of the various LV segments, the septum in particular. This mitigates the intraventricular gradient, the Venturi effect inside the LV outflow tract, and the systolic anterior motion of the mitral valve. The hemodynamic benefit depends on complete RV capture and proper AV synchronization. While a short AV delay facilitates the former, it may hamper the latter, particularly in the presence of a long inter-atrial delay, which may worsen the clinical status of these patients, whose hemodynamic function depends prominently on ventricular filling. By lengthening AV nodal conduction time, pharmaceuticals such as

β-adrenergic blockers and calcium antagonists may enable the programming of a longer AV delay while maintaining complete RV capture. Should drug therapy be unsuccessful, radiofrequency ablation or modulation of the AV node is another option.

Despite its attractive premise, RV apical stimulation for OHCM has yielded mixed results. The PIC trial observed a 50% decrease in left intraventricular gradient and a 20% increase in exercise capacity, though the alleviation of dyspnea and chest pain was similar in DDD and AAI modes, suggesting a placebo effect.[38] Except in a subgroup of patients older than 65 years, the Multicenter Pacing Therapy (M-PATHY) trial found neither subjective nor objective differences in exercise capacity between RV-paced patients versus non–RV-paced patients.[39] In the absence of more convincing evidence—and given the availability of other, more effective treatments, including surgery or even alcohol ablation of the septum—the role played by cardiac stimulation in OHCM is currently limited (class IIb recommendation in professional guidelines).[40]

Preventing Unnecessary Ventricular Stimulation

Pacing Mode Selection

A pacing mode that would, similar to AAI, completely eliminate ventricular stimulation would be ideal for patients presenting with SND and intrinsic conduction. However, the risk of new AV conduction disorders mandates standby ventricular pacing. Different technical solutions have been proposed to favor natural AV conduction. In the DDD(R) mode, the percentage of ventricular pacing is not effectively decreased by the programming of a fixed, long AV delay because of the physiological variability of AV nodal conduction. The AV hysteresis algorithm enables a search for intrinsic conduction by the extension of the AV interval and further promotes normal ventricular depolarization, though its performance is limited. Algorithms such as AAIsafeR, managed ventricular pacing, and reverse mode switch, which automatically switch the pacing mode from AAI(R) to DDD(R) in the event of a blocked P wave or critical lengthening of the P-R interval, have been designed. An advantage of AAIsafeR is the programmability of the pacing mode switch criteria. The disadvantages of these algorithms involve mostly patients presenting with prolonged spontaneous AV delay. In the presence of values greater than 300 ms, the upper responsive rate must be limited, and a risk exists of AV dyssynchrony as the HR increases.

The influence of RV pacing minimization algorithms on clinical outcome is still controversial. The randomized INTRINSIC RV study, which included recipients of ICDs, programmed either in the VVIR mode with a backup rate set at 40 beats/min or in the DDDR mode with the AV hysteresis algorithm, found no difference in clinical outcomes between the two groups.[41] The SAVE PACe study, which enrolled patients with SND paced in the DDDR mode with or without an algorithm of RV pacing minimization, found a 9.1% median percentage of ventricular pacing with the algorithm compared with 99% without the algorithm. While a 40% decrease in relative risk in the incidence of persistent AF was observed, the rates of death and hospitalizations related to HF were similar in both groups.[42]

Alternative Right Ventricular Pacing Sites

When permanent ventricular capture is needed, the use of alternative RV pacing sites should be considered to prevent the adverse effects of RV apical pacing and improve ventricular function. The technical feasibility and safety of implanting the RV lead onto the septum have been confirmed in several studies. The short-term to intermediate-term capture threshold, impedance, and sensing characteristics of leads implanted in the apical, septal, or RV outflow tract (RVOT) positions are similar.[43,44] The mean procedural times, complication rates, and risks of lead dislodgment are also similar. The risk of perforation seems low, and the extraction procedures are of similar complexity. The results of studies that compared the short-term and long-term hemodynamic benefits conferred by alternative RV pacing sites versus apical pacing are conflicting for various reasons, including the imprecise definition of the site of lead implant (RVOT versus septum), heterogeneous patient populations and evaluation methods, and, sometimes, insufficient duration of follow-up.[45]

1. *RVOT pacing:* Victor et al studied 16 patients who presented with chronic atrial tachyarrhythmias and AV block and were randomly assigned to RVOT versus RV apical pacing, each for 3 months, 4 months after pacemaker implantations. No differences were found in clinical and functional endpoints, including NYHA functional class, LVEF, exercise duration, and maximal oxygen uptake.[43] The Right Ventricular Outflow Versus Apical Pacing (ROVA) trial randomly assigned 103 pacemaker recipients who presented with HF, an LVEF of 40% or less, and chronic atrial fibrillation to RVOT, RV apical pacing, or dual-site RV pacing in a crossover design.[46] Compared with RV apical pacing, RVOT and dual-site RV pacing both shortened QRS duration, though they did not significantly improve quality of life or other clinical indices at 3 months of follow-up.

2. *Septal pacing:* A small, randomized crossover study compared septal and apical RV pacing in patients with AF.[47] After 3 months, in contrast to apical pacing, RV septal pacing preserved LVEF in patients whose baseline LVEF was 45% or less. No increase in peak oxygen uptake was observed in either group. Tse et al evaluated LV performance and functional capacity, before device replacement and 18 months thereafter in (1) 12 patients who underwent RV septal pacing after being previously paced at the RV apex, and (2) 12 control patients continuously paced at the RV apex.[48] Change to RV septal pacing, but not continuous apical pacing, improved LV systolic function and diastolic function as well as functional capacity. Despite these encouraging observations, septal pacing remains controversial because of the small number of patients enrolled in the studies and the short follow-up of completed studies.[47-51] Larger randomized trials are ongoing.[52]

3. *Direct His bundle or para-Hisian pacing:* This is theoretically the most physiological pacing, producing a normal ventricular activation, narrow QRS, and no ventricular dyssynchrony. It was found superior to RV apical pacing in measurements of CO or in the estimation of NYHA functional class and maximal O_2 consumption in patients presenting with LV dysfunction. It is contraindicated, however, in patients with distal conduction defects. It is rarely performed because of greater procedural complexity and duration and the distinctly higher risk of lead dislodgment and failure to sense or capture, mandating, at least for the time being, the implantation of a backup apical lead.

Right Ventricular Upgrade

CRT has been used as an upgrade for patients presenting with severe LV dysfunction and worsening HF due to RV pacing.

Several small controlled studies have documented improvements in invasively measured hemodynamic function conferred by CRT upgrades, as well as the alleviation of ventricular dyssynchrony and mitigation of LV remodeling (decrease in ED and ES diameters), increase in LVEF, and decrease in NYHA functional class and increase in distance covered during 6-min walk.[53,54] The effects on survival remain unknown, and long-term clinical results have been mixed. Several multicenter studies are ongoing to further address these uncertainties.[55]

Left Ventricular and Biventricular Stimulation

Optimal Left Ventricular Stimulation Site

Theoretically, the optimal ventricular stimulation site yielding the greatest mitigation of dyssynchrony by CRT is the LV region activated last. Several short-term studies have shown prominent hemodynamic improvement by stimulation of that region, as determined by (1) the electrical delay between the QRS onset and the LV-sensed ECG, (2) three-dimensional endocardial mapping, (3) echocardiography (tissue Doppler, strain or speckle tracking), or (4) by magnetic resonance imaging. This site of stimulation is also associated with improvements in functional performance, in reverse remodeling, and in a longer adverse event–free survival. Poor placement of the LV lead could explain nonresponse to therapy in a significant proportion of patients. While it is rational to implant the LV lead in a lateral or posterolateral position, Ansalone et al observed that it corresponds to the zone of latest activation in fewer than 60% of cases. This is further complicated by (1) anatomic variations, (2) technical limitations such as diaphragmatic stimulation or unacceptably high capture threshold, or (3) the presence of scarred myocardium precluding the placement of the LV lead at the preferred site. The targeted hemodynamic and clinical improvements are, nevertheless, of prime importance; preoperative investigations, including echocardiography, magnetic resonance imaging (MRI), and computed tomography (CT) are likely to allow the identification of the best negotiated LV stimulation site, despite the clinical complexity that it might represent.

In contrast to the implantation of the previously described LV lead, optimal placement of the RV lead in biventricular stimulation is poorly understood. Lecoq et al have analyzed the various electrical characteristics associated with CRT.[56] The placement of the RV lead was modified to obtain the thinnest QRS after the implantation of the LV lead. A midseptal position was chosen in the majority of cases. Only the shortening of the QRS (not the baseline QRS duration) predicted the response to CRT. However, the predictive value of QRS shortening remains controversial, and more detailed information regarding the placement of the RV lead is awaited.[57]

Left Ventricular Epicardial Stimulation Versus Endocardial Stimulation

The original intent to stimulate the LV endocardial surface was based on the normal endocardium-to-epicardium electrical activation sequence, which is associated with a speedy and synchronous ventricular depolarization (Figure 35-13). Van Deursen et al found, in an animal model, a shorter ventricular depolarization and less dispersion of repolarization with endocardial stimulation than with epicardial biventricular stimulation.[58] They also observed an acute hemodynamic benefit (Figure 35-14), which seemed less dependent on site or timing than with epicardial

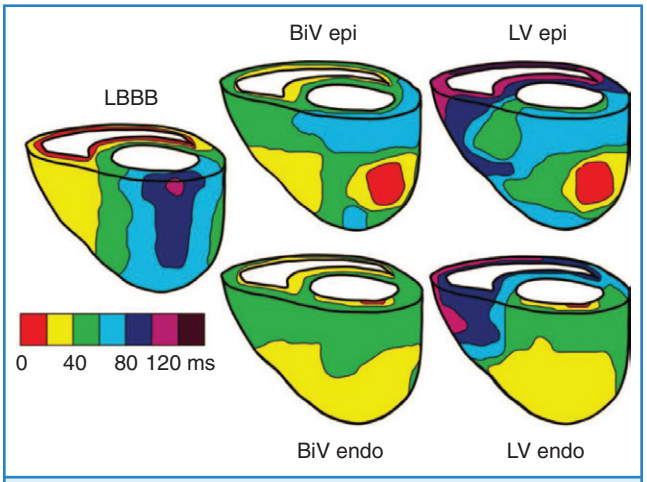

FIGURE 35-13 Three-dimensional reconstruction of electrical activation times in ventricles measured with epicardial and endocardial electrodes in canine heart with experimental left bundle branch block. First activation/pacing sites are in *red* (color bar indicates time scale in milliseconds). Endocardial biventricular pacing induces greater shortening of the total activation time more than epicardial biventricular pacing does. Endocardial biventricular pacing is associated with more synchronous LV activation than epicardial biventricular pacing. *LBBB,* Left bundle branch block; *BiV,* biventricular; *epi,* epicardial; *LV,* left ventricular; *endo,* endocardial. *(From Van Deursen C, van Geldorp IE, Rademakers LM, et al: Left ventricular endocardial pacing improves resynchronization therapy in canine left bundle-branch hearts,* Circ Arrhythm Electrophysiol *2:580–587, 2009.)*

stimulation. Derval et al compared invasive and noninvasive acute hemodynamic measurements made in 35 patients presenting with nonischemic, dilated cardiomyopathies during stimulation from 10 endocardial and 1 epicardial LV sites and found wide interindividual variability in the hemodynamically optimal stimulation site.[59] Stimulating at the optimal site increased LV dP/dt significantly, compared with (1) standard LV epicardial stimulation via the coronary venous system, (2) lateral LV endocardial wall stimulation, or (3) stimulation at the latest site of LV activation ascertained echocardiographically. Stimulation of the endocardial site immediately opposite to the transvenously identified epicardial site had no significant effects on either dP/dt_{max} or LVES pressure. However, compared with epicardial stimulation, endocardial stimulation improved LV diastolic function, as ascertained by measurements of LV – dP/dt.

Trans-aortic, trans-septal, and trans-apical approaches have been described for permanent LV endocardial stimulation in humans. The first feasibility study was carried out by atrial transseptal lead implantation, by Jais et al.[60] In several studies of small numbers of typical CRT system recipients, biventricular endocardial stimulation lowered NYHA functional class and increased LVEF. These data, based on small numbers of observations, need additional studies to clarify the risk/benefit ratio from the perspectives of long-term anticoagulation and complications associated with the various lead implantation techniques.

Single Left Ventricular Stimulation

CRT using a single LV lead is based on the expectation of fusion between stimulated LV and spontaneous RV depolarizations, resulting in a synchronous biventricular activation sequence (see

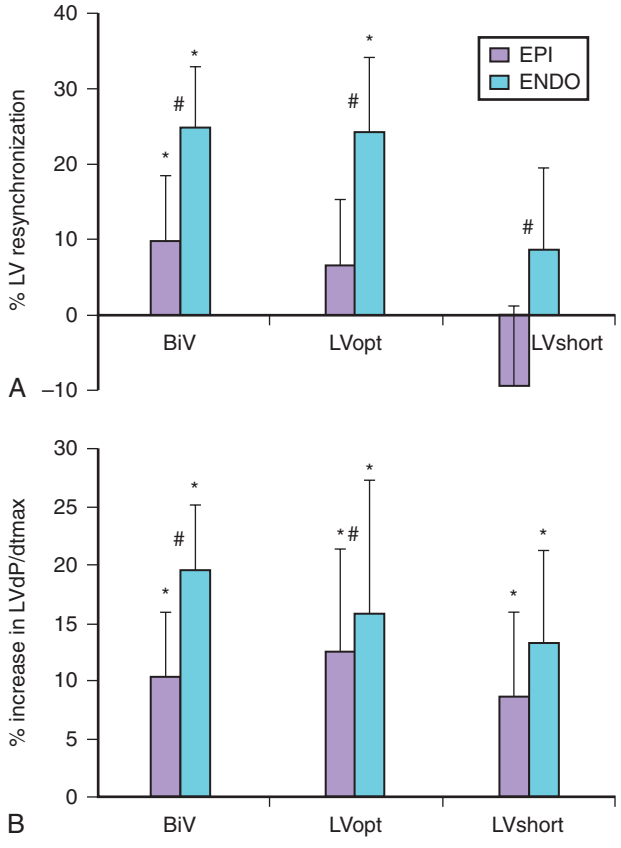

FIGURE 35-14 A, Percent shortening of ventricular activation time. **B,** LV dP/dt_{max} during endocardial and epicardial biventricular (*BiV*) pacing compared with baseline atrial pacing in the presence of left bundle branch block. A larger and significant increase in LV dP/dt_{max} is seen during endocardial pacing than during epicardial pacing and during both biventricular and left ventricular pacing. *Lvshort,* Short AV delay. **P* < .05 versus baseline; *#P* < .05 endocardial (*ENDO*) versus epicardial (*EPI*) (mean values and standard deviations of 48 paired measurements). *(From Van Deursen C, van Geldorp IE, Rademakers LM, et al: Left ventricular endocardial pacing improves resynchronization therapy in canine left bundle-branch hearts,* Circ Arrhythm Electrophysiol *2:580–587, 2009.)*

Figure 35-20). Immediate hemodynamic and clinical improvements were observed in typical candidates for CRT. Furthermore, a fused QRS seemed to be associated with a higher LV dP/dt_{max}. Device Evaluation of CONTAK RENEWAL 2 and EASYTRACK 2: Assessment of Safety and Effectiveness in Heart Failure (DECREASE-HF), a randomized study, compared the 6-month echocardiographic outcomes in patients who underwent (1) synchronous biventricular, (2) sequential biventricular, or (3) single-site LV stimulation.[61] A trend toward a greater decrease in LV dimensions with biventricular LV stimulation than with single-site LV stimulation was observed. In addition, mitral regurgitation worsened in 18% of patients who underwent single-site LV stimulation, perhaps because of greater LV dilation and less complete resynchronization, since ventricular fusion complexes were not required in that study. Furthermore, this means of stimulation is not applicable to ICD recipients or pacemaker-dependent patients, who need an RV lead, because of the notorious instability of the LV epicardial leads and the high capture threshold often associated with them. Finally, despite the availability of a dynamic AV delay function, the programming of synchronous LV-RV activation during spontaneous variations in AV conduction may be challenging, for example, during exercise.

Multiple-Site Left Ventricular Stimulation

CRT using a single LV lead may be insufficient to produce optimal ventricular resynchronization, particularly in the presence of prominent LV dilation. It has been hypothesized that stimulating the LV at two or more distant sites would further improve LV performance and increase the rate of response to CRT. While the feasibility and safety of this strategy has been confirmed, it requires longer procedures and fluoroscopic exposure. In experienced hands, the procedural success rate approaches 85%. In short-term hemodynamic studies in patients with HF, Pappone et al found that dual-site LV stimulation increases LV dP/dt and shortens QRS duration compared with single-site stimulation.[62] In contrast, Padeletti et al observed no further hemodynamic improvement conferred by CRT delivered via dual-site LV stimulation compared with single-site LV stimulation.[63] The multicenter, single-blind, crossover TRIP HF trial included 40 patients who had indications for both CRT and for ventricular pacing because of atrial fibrillation and slow ventricular response.[64] After 3 months of biventricular stimulation, the patients were randomly assigned to biventricular stimulation versus triple-site ventricular stimulation; then they crossed over to the alternative assignment for three additional months. While no difference was observed in clinical outcomes between the two groups, a significantly greater decrease in LVED diameter and increase in LVEF were observed during triple-site ventricular stimulation. Furthermore, 40% of nonresponders to biventricular stimulation (ascertained on the basis of LVES diameter) became responders during dual-site LV stimulation.

Cardiac Resynchronization Therapy

Rationale and Mechanisms

Abnormal intraventricular conduction, usually of left bundle branch block morphology, is present in 30% of patients presenting with severe LV systolic dysfunction. This causes asynchronous LV contraction, a decrease in SV, and ventricular remodeling. Ventricular activation propagates from the right ventricle to the septum and then to the LV free wall. The duration of contraction and isovolumetric relaxation are lengthened, and the ventricular diastolic filling time is shortened proportionally to the degree of ventricular dyssynchrony and QRS duration (Figure 35-15).[65] CRT simultaneously stimulates the LV free wall and the right ventricle during ventricular systole, fusing the two activation wavefronts, improving electrical (narrow QRS) and mechanical (synchronous segmental contraction) synchrony, according to the rapid electromechanical coupling of the myocardium.

Short-Term Hemodynamic Effects

In patients presenting with HF and left bundle branch block, Leclercq et al observed an immediate hemodynamic improvement during biventricular stimulation compared with spontaneous conduction or DDD RV apical pacing (Figure 35-16).[66] Instead of an increase in ventricular preload, the increase in CO was

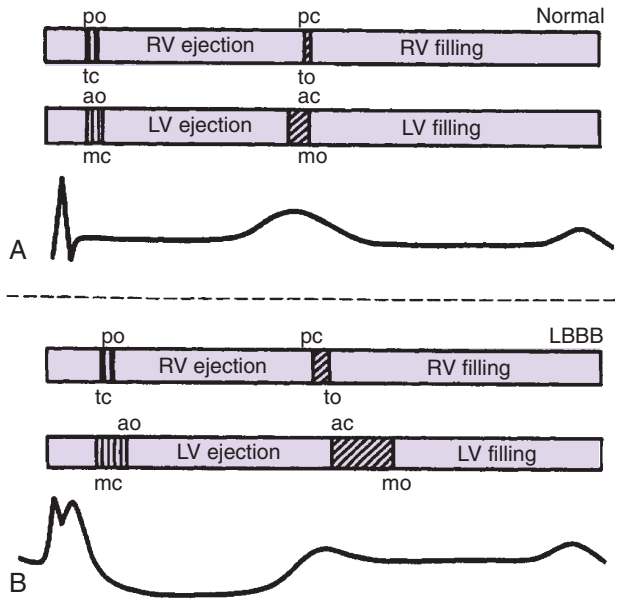

FIGURE 35-15 Left- and right-sided timing events in a patient with left bundle branch block (*LBBB*) and a patient without intraventricular conduction abnormality. In the presence of LBBB, the left-sided events follow the right-sided events. The isovolumetric contraction and relaxation times are longer and the left ventricular (*LV*) filling time is shorter. *p*, Pulmonary; *m*, mitral; *a*, aortic; *t*, tricuspid; *o*, opening; *c*, closure. *(From Grines CL, Bashore TM, Boudoulas H, et al: Functional abnormalities in isolated left bundle branch block. The effect of interventricular asynchrony,* Circulation *79:845–853, 1989.)*

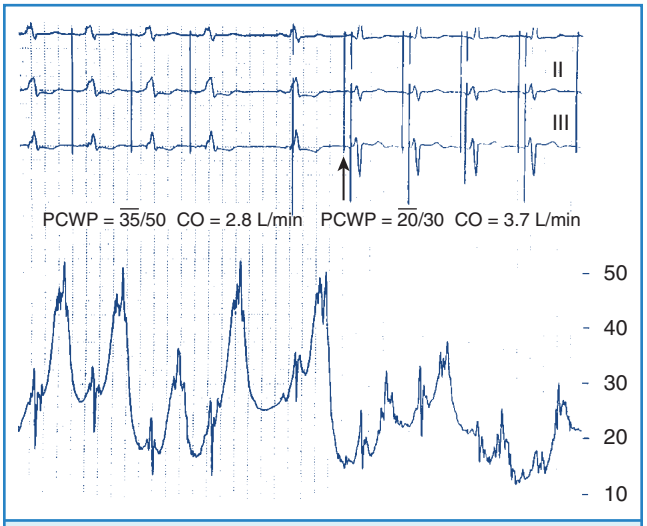

FIGURE 35-16 Instantaneous decrease in pulmonary capillary wedge pressure (*PCWP*) and 32% increase in cardiac output (*CO*) by switch from A-A interval to biventricular DDD stimulation at fixed rate in a patient with ischemic cardiomyopathy. QRS duration is decreased by 35%. *(From Leclercq C, Cazeau S, Le Breton H, et al: Acute hemodynamic effects of biventricular DDD pacing in patients with end-stage heart failure,* J Am Coll Cardiol *32:1825–1831, 1998.)*

caused by an increase in myocardial contractility, since the filling pressures had decreased during CRT. Other studies confirmed improvements in hemodynamic function, which manifested as increases in LV dP/dt_{max}, LVEF, and pulse pressure, and in LV diastolic function, which manifested as a longer ventricular filling time, higher $-dP/dt$, and lower filling pressures.

Multiple mechanisms are behind these hemodynamic benefits. On the one hand, CRT resynchronizes at the AV, VV, and intraventricular levels, with the main hemodynamic benefit brought about by the correction of LV activation and resynchronization of segmental contraction. On the other hand, as Nelson et al observed, a greater efficiency of the cardiac pump is achieved by LV stimulation, which decreases to a modest extent the myocardial consumption of energy.[67] Improvement in VV coupling is another hemodynamically favorable and immediate mechanism of CRT (Figure 35-17).[68] LV activation and onset of diastole are expedited and do not limit LV filling by the space occupied by the right ventricle inside the pericardium when the filling pressures are high.[69]

Long-Term Hemodynamic Effects

The hemodynamic benefits described earlier persist over the long term as well. Furthermore, as a result of improvements in LV pump function and lower filling pressures during CRT, the heart works with lower LV volumes (Figure 35-18).[70] The decrease in wall tension limits the concomitant neurohumoral activation. These combined effects promote reverse remodeling (Figure 35-19), most reliably manifesting as a decrease in LVED diameter. The resynchronized contraction of the subvalvular apparatus and the smaller LV dimensions also facilitate the regression of functional mitral regurgitation. Yu et al observed the persistence of LV reverse remodeling for up to 1 month after the interruption of CRT.[71]

Both the morbidity and the survival benefits conferred by CRT are important. However, currently no evidence indicates that a hemodynamic improvement observed in the short term predicts a favorable long-term outcome. Mullens et al found that biventricular stimulation continues to acutely improve hemodynamic function in the failing heart in most patients, including those in whom cardiac remodeling has progressed during CRT and who are hospitalized for the management of HF.[72] Mullens et al suggested that the progression of disease is not attributable to a diminishing hemodynamic benefit contributed by successful resynchronization. A decrease in LVES diameter is the marker of remodeling that best predicts long-term outcome, though this marker is imperfect since, among CRT recipients whose LVES diameter has decreased by more than 10%, approximately 30% do not derive any survival benefit. Finally, the absence of correlation between (1) functional characteristics such as NYHA functional class and quality of life and (2) survival or ventricular remodeling continues to complicate the identification of potential responders to CRT.[73]

Optimization of Ventricular Timing

While the therapeutic benefits conferred by CRT are distinctly related to the site of ventricular stimulation, the precise placement of the LV lead(s) is limited by a highly variable anatomy of the coronary sinus and its tributaries, by myocardial scars that are unexcitable, or by intolerable phrenic nerve stimulation. Several electrical and mechanical methods of optimization of ventricular activation have been developed in an attempt to vary the RV or

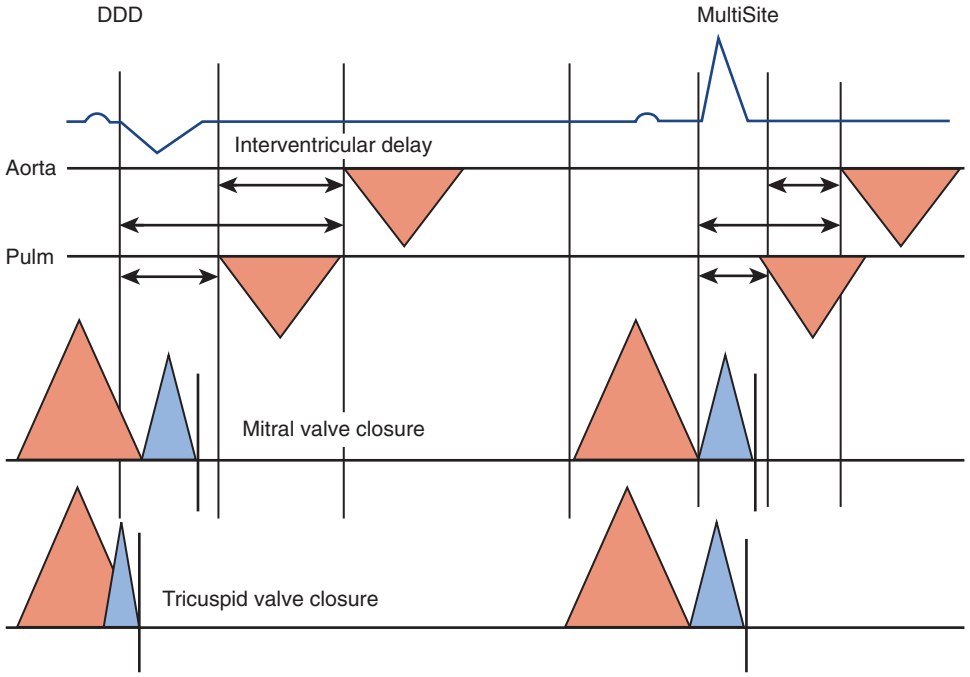

FIGURE 35-17 Correction of interventricular delay with biventricular pacing compared with left bundle branch block or conventional right ventricular apical pacing. Early left ventricular activation during biventricular pacing shortens the left pre-ejection time, shortening the contraction of both ventricles and that of systole. Ventricular filling is improved with biventricular pacing without the need to set a very short atrioventricular delay, as in conventional pacing. *Pulm,* Pulmonary. *(From Cazeau S, Gras D, Lazarus A, et al: Multisite stimulation for correction of cardiac asynchrony,* Heart *84:579–581, 2000.)*

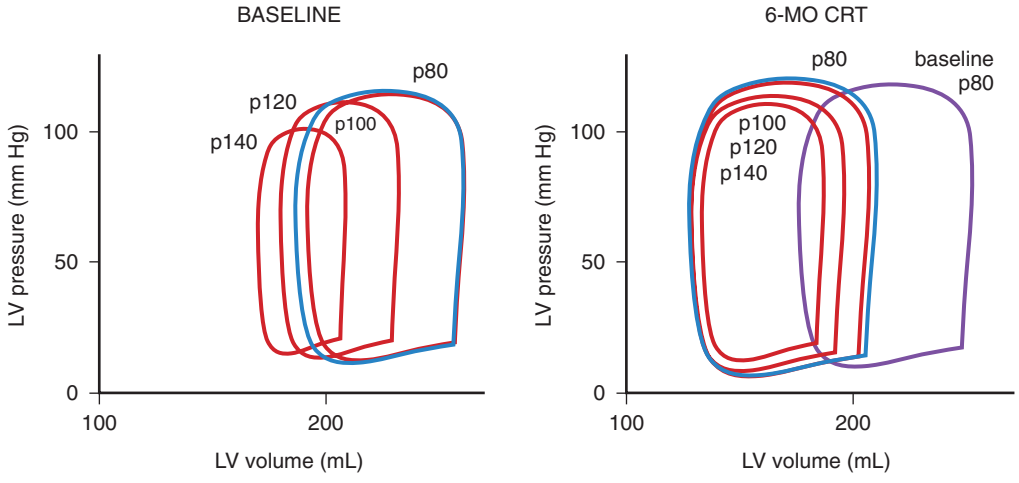

FIGURE 35-18 Hemodynamic effects of long-term cardiac resynchronization therapy (*CRT*). *Left,* Baseline pressure-volume curve at different heart rates; the large left ventricular (*LV*) volume reflects a dilated heart and high filling pressure. *Right,* Effects after 6 months of CRT. Prominent decrease in LV volume without decrease in LV contractility. *(From Steendijk P, Tulner S, Bax JJ, et al: Hemodynamic effects of long-term cardiac resynchronization therapy: Analysis by pressure-volume loops,* Circulation *113:1295–1304, 2006.)*

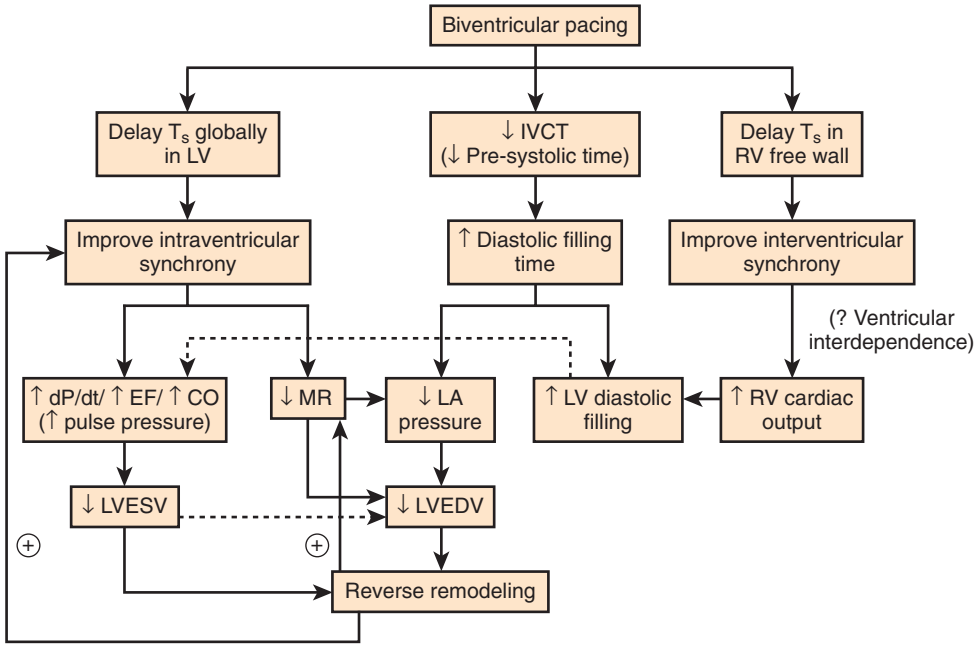

FIGURE 35-19 Proposed mechanisms of benefits conferred by biventricular pacing. The main mechanism is a greater intraventricular synchrony, measured in this study as fewer differences in time to peak sustained systolic contraction, among the left ventricular segments. A second mechanism is shortening of the isovolumetric contraction time with prolongation of the diastolic filling time, which occurs when atrioventricular synchrony is preserved. A third minor mechanism is mediated by ventricular interdependence. Greater synchrony increases the right ventricular cardiac output, which promotes left ventricular filling. *MR*, Mitral regurgitation; *EF*, ejection fraction; *CO*, cardiac output; *ESV*, end-systolic volume; *EDV*, end-diastolic volume; *IVCT*, isovolumetric contraction time; *LA*, left atrial; *LV*, left ventricular; *RV*, right ventricular; T_s, systolic contraction. *(From Yu CM, Chau E, Sanderson JE, et al: Tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure,* Circulation *105:438–445, 2002.)*

LV leads positions, the stimulation vector, and the LV-RV stimulation interval.

Electrical Optimization

Attempts in some studies to obtain the thinnest QRS during CRT by changing the lead(s) position(s) has been associated with higher rates of therapeutic response, though this is still debated. This strategy is clearly limited by the presence of zones of slow conduction situated near the stimulation site, which might conceal components of the QRS, rendering them isoelectric and spuriously shortening the duration of the complex. The morphology of fusion complexes may also help in assessing the effects of CRT. A QRS identical to that produced with left-sided or right-sided stimulation raises the suspicion of conduction delays and latency of capture at the right-sided and left-sided leads, respectively. The programming of sequential LV-RV stimulation may allow a more synchronous activation of the ventricles (Figure 35-20). A change in the bipolar, extended bipolar, or inverted bipolar LV stimulation vector is effective in cases of high capture threshold or phrenic stimulation. The clinical merits of such programming remains to be shown.

Echocardiographic Optimization

In advanced heart disease, intraventricular and interventricular conduction delays are sometimes markedly lengthened, and a sequential activation of the ventricles may be necessary to achieve the best resynchronization. Echocardiography is the most commonly applied method of VV delay optimization, mostly based on aortic VTI as a surrogate measurement of LVEF. It is an iterative method, which consists of changing AV delay while searching for the highest VTI. Despite immediate improvements in LV dP/dt, SVEF, and LVEF conferred by optimization of VV delay, the multicenter Insync III Marquis (Medtronic, Minneapolis, MN), DECREASE-HF, and Resynchronization for Hemodynamic Treatment for Heart Failure Management II (RHYTHM II) ICD trials did not find clear clinical benefits compared with simultaneous biventricular stimulation.[61,74,75] In clinical practice, in the absence of a proven clinical advantage, the systematic optimization of the VV interval is not recommended after implantation of CRT systems.

Several questions remain, therefore, unanswered and are being further investigated, including (1) the putative benefit of VV optimization by algorithms based on electrical intervals, (2) the role played by ultrasound evaluations of intraventricular delays, using tissue Doppler, strain, speckle tracking, or three-dimensional echocardiography as a means of ventricular delays optimization, and (3) long-term clinical benefits conferred by new VV delay optimization methods.

Conclusion

A deeper understanding of the hemodynamic effects of cardiac pacing has unveiled its risks and benefits and has helped in

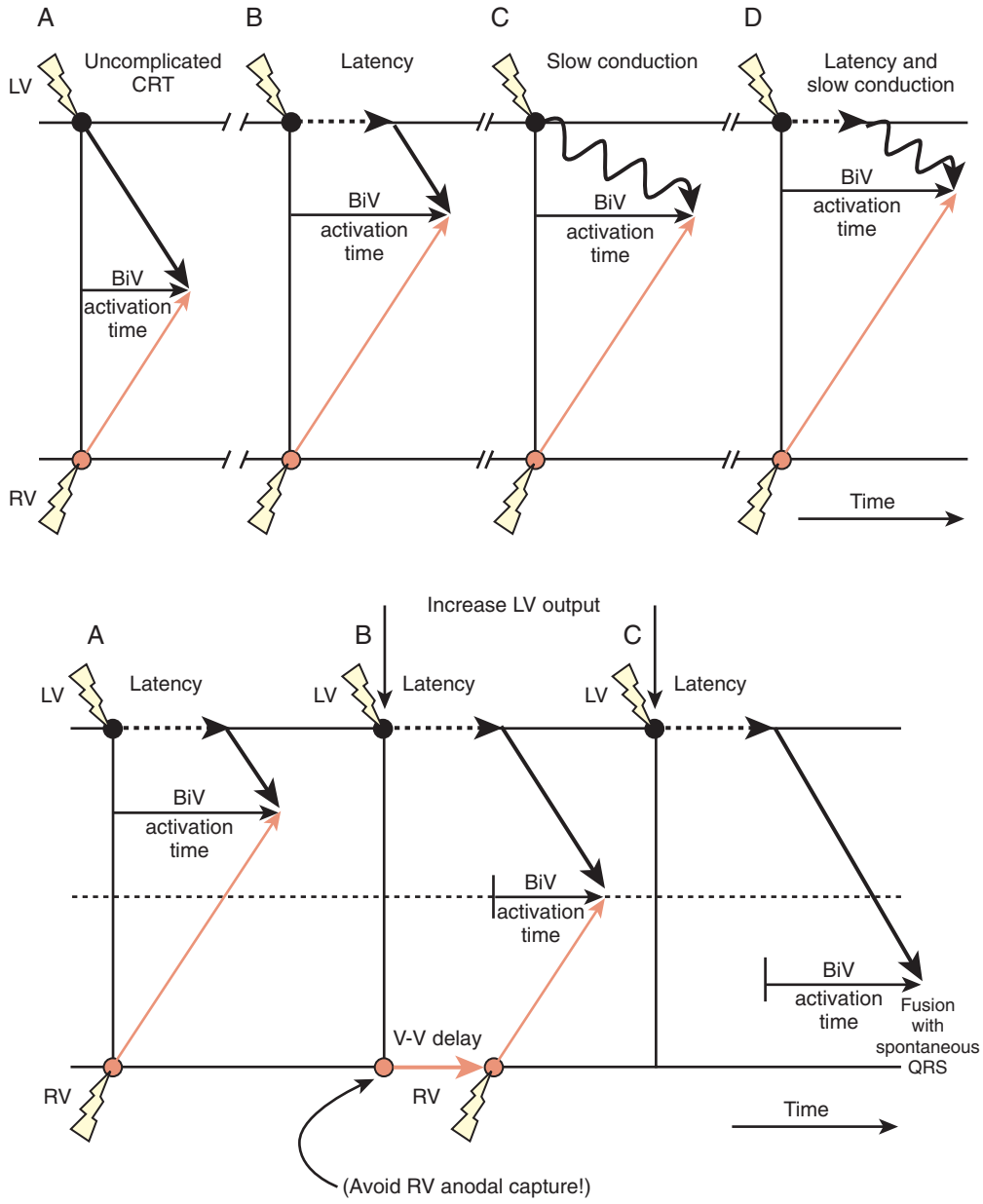

FIGURE 35-20 *Top,* Simultaneous biventricular (*BiV*) pacing showing the effect of ventricular latency or slow conduction due to myocardial scar; the left ventricular (*LV*) depolarization wavefront is delayed. Major portions of the left ventricle are depolarized by the right ventricular (*RV*) wavefront with prolongation of the biventricular activation time. *Bottom,* Interventricular delay programmed with LV pre-excitation to compensate for the LV latency, shortening the BiV activation time. In the case of single-site LV pacing, the degree of fusion with spontaneous conduction on the right side of the heart depends on the programmed atrioventricular delay. This might improve hemodynamic function in patients with a markedly prolonged LV latency, which cannot be overcome by programming maximum interventricular intervals to pre-excite the left ventricle. *LV,* Left ventricle; *RV,* right ventricle; *CRT,* cardiac revascularization therapy; *BiV,* biventricular. *(From Barold B, Ilercil A, Herweg B: Echocardiographic optimization of the atrioventricular and interventricular intervals during cardiac resynchronization,* Europace *10:iii88–iii95, 2008.)*

developing more physiological means of delivery. The complexity and variety of heart disorders and the therapeutic devices available call for the design of tailored cardiac stimulation. Each patient must be treated individually by choosing the best pacing mode, by determining the optimal number and position of leads, and by the activation of carefully chosen algorithms from among the many available ones. The intense research and rapid development of new pacing technology, particularly as it applies to HF, continues to be based on hemodynamic principles and will perhaps provide the keys to yet unsolved problems.

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CHAPTER 36

Electrocardiography of Cardiac Pacing

Shakeeb Razak, Raymond Yee, Andrew D. Krahn, Allan C. Skanes, Lorne J. Gula, George J. Klein, and Peter Leong-Sit

Although the evaluation of permanent pacemakers (PPMs) and implantable cardioverter defibrillators (ICDs) relies greatly on information derived directly from device interrogation, abundant useful information can be gained from careful analysis of surface electrocardiogram (ECG) recording, whether it be a single-lead rhythm strip, multiple-channel ambulatory recording, or the 12-lead ECG.[1-4] ECG recordings are usually the initial (and sometimes the only) diagnostic information available, since access to programmer hardware for device interrogation is limited. Indeed, the proper evaluation of a patient with an implanted device should start with a methodical analysis of ECG information before analysis of the stored device interrogation data.[3-14] The aim of this chapter is to provide the clinician with an overview of the common ECG findings associated with single, dual, and cardiac resynchronization pacing systems and modern pacemaker algorithms. Given the number of different pacing modes and features from various pacemaker manufacturers, a thorough description of all the possible ECG manifestations is not possible, so this review will be confined to describing some of the fundamental aspects of the topic.

Electrocardiographic Recording System Considerations

ECG recording systems typically possess band-pass filters within the range of 0.05 to 150 hertz (Hz) to capture the main components of the signal of interest while minimizing electromagnetic noise and respiratory or motion artifact.[15-17] However, pacing stimulus artifacts (*pacing spikes*) of implanted devices have a pulse width of less than 1 ms and amplitudes of 1 to 8 V, so the frequency content is much higher.[15-17] Despite this, a sufficient component of the pacing stimulus signal can be captured on analog paper recordings, but an accurate representation of the stimulus amplitude may be challenging.

Digital ECG recording systems may distort pacemaker spikes or even completely fail to render the pacing spike because of sampling rate characteristics relative to the narrow pulse width of the pacing spikes. To make pacing spikes more obvious, some ECG systems enhance the pacemaker spikes for display when high-frequency signals meeting manufacturer-specific criteria are detected.[15-18] Limitations in their accuracy can result in overdetection with digitally enhanced "phantom" pacemaker spikes being displayed when no pacing has actually occurred, leading to errors of interpretation.[15,19] Some ECG manufacturers have implemented software solutions to improve the sensitivity of pacemaker stimulus detection but at the risk of overdetection.[16,17,20] This issue is fairly well documented in the biomedical engineering literature, but clinical reports have been rare. In addition, computer algorithms for automated ECG interpretation involving electronic pacemakers have limited accuracy.[21]

Implanted Device Considerations

Myocardial stimulation requires electrical current to pass between two electrodes, with at least one intracardiac electrode contacting the myocardium. A unipolar pacing configuration consists of one intracardiac electrode, and the second electrode is provided by the device generator housing. Bipolar pacing has two intracardiac electrodes, both of which contact the myocardium and are capable of stimulating it. Unipolar pacing generates large pacing spikes visible in all ECG leads, even at low pacing output amplitudes (Figure 36-1, *A*). In contrast, the closely spaced tip and ring electrodes of bipolar pacing leads result in diminutive pacing spikes that may only be readily seen in a few ECG leads (Figure 36-1, *B*). In bipolar pacing, the negative electrode (cathode) usually stimulates the myocardium, but anodal stimulation can occur at higher pacing outputs because of the higher stimulation threshold partly attributable to the greater anode surface area. Any difference between cathodal and anodal stimulations may only be evident on the ECG where the two electrodes are widely separated and the differences in myocardial activation pattern become obvious, such as with some biventricular pacing (cardiac resynchronization pacing therapy, or CRT) (Figure 36-2).

Pacing Stimuli and the Evoked Response

Modern pacing systems perform two fundamental functions: (1) They emit pacing pulses when required by the device software, and (2) they must also detect or sense when intrinsic cardiac activity has occurred so that the device can respond in accordance with device software. As a general rule, pacing stimuli should be seen whenever intrinsic cardiac activity is slower in the paced cardiac chamber than the programmed pacing rate, whereas the occurrence of intrinsic electrical activity in a specific chamber should inhibit pacing output in that chamber (except during asynchronous pacing).

A single-chamber device will emit only one type of pacing spike that evokes myocardial depolarization. The morphology of the evoked P or QRS complexes (followed by a T wave) reflects the location of the stimulating electrodes and myocardial activation conducting away from the pacing site. Paced P waves may be very difficult to discern because of the small amplitude. Dual-chamber devices can emit up to two types of pacing stimuli (atrial and ventricular). CRT pacing systems incorporate separate leads

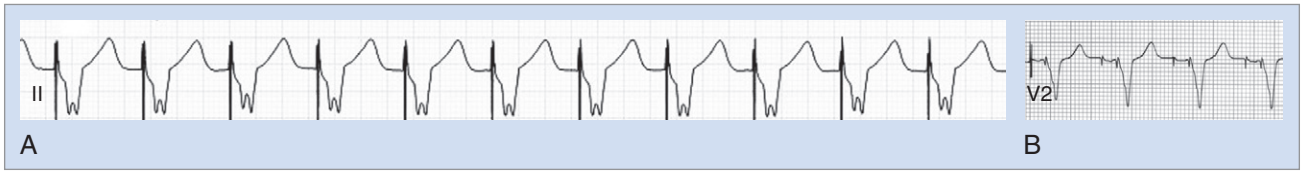

FIGURE 36-1 **A,** Large unipolar pacing spikes seen on a lead II rhythm strip in a patient with a single-chamber ventricular pacemaker. **B,** Surface lead V2 showing small bipolar pacing spikes in a patient with a dual-chamber permanent pacemaker.

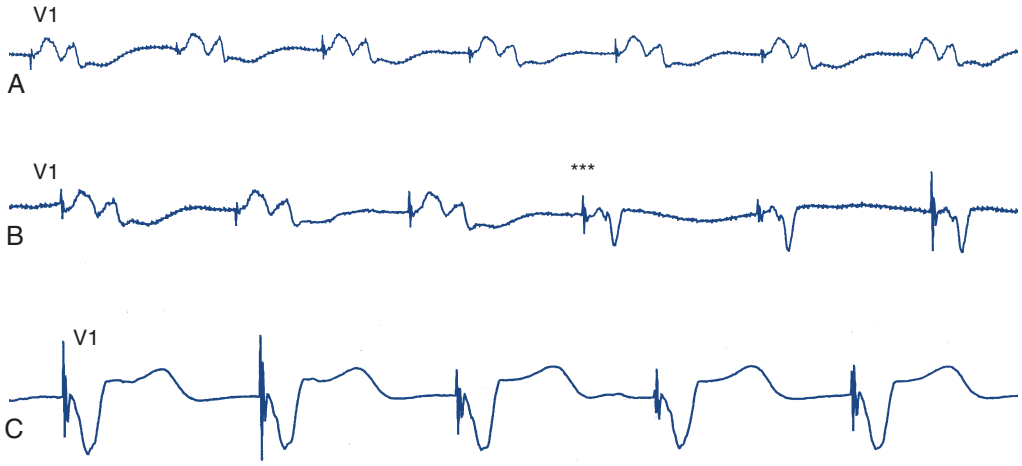

FIGURE 36-2 Continuous rhythm strip of electrocardiographic lead V1 obtained from a patient with a biventricular pacing system in which the left ventricular (LV) tip electrode (cathode) was connected to the right ventricular ring (anode). **A,** LV cathodal stimulation with expected right bundle branch block–like QRS morphology. **B,** As the ventricular output is gradually increased from 2.5 V to 5.0 V, there is transition from cathodal to anodal stimulation at the *asterisks*. **C,** Predominantly anodal stimulation with the expected left bundle branch–like QRS morphology.

for right and left ventricular stimulations, but most of their pacing functions are identical to those of dual-chamber devices. In newer CRT devices, right and left ventricular pacing output timing can be separated, and it may be possible to discern two discrete ventricular pacing spikes.

Absence of Paced Complexes

The absence of paced P or QRS complexes when expected has two general causes: (1) failure of the device system to deliver pacing output and (2) pacing output being delivered but failing to stimulate the myocardium. Failure of pacing output is recognized by the absence of expected pacing spikes, whereas failure to capture is associated with the presence of pacing spikes that fail to capture the myocardium. True failure to capture must also be distinguished from apparent capture failure, in which the evoked response is of small amplitude, such as with atrial pacing. If the paced QRS amplitude is small, myocardial capture can be confirmed by reviewing multiple ECG leads or looking for the accompanying T wave. Failure to capture the myocardium could result from sub-threshold pacing output or circumstances, in which pacing occurs during the refractory period of the chamber (Figure 36-3).

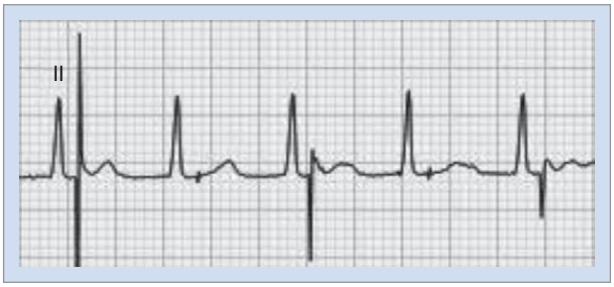

FIGURE 36-3 Rhythm strip showing ventricular pacing spikes with failure of ventricular capture because pacing occurred within the ventricular refractory period.

Fused and Pseudo-Fused Pacing Complexes

The phenomena of fusion and pseudo-fusion, which are best appreciated in the context of ventricular pacing, result from differences between the surface QRS recording and the signal processed by an implanted device. The paced QRS complex of the ECG reflects global ventricular activation recorded from surface leads. However, the pacemaker's sensing circuitry and pacing output use the local electrogram (EGM) at the pacing electrodes. In turn, local EGM timing relative to global ventricular activation will depend on the precise location of the ventricular electrode(s). With ventricular demand pacing (VVI mode), intrinsic beats should inhibit pacing output, but if the local EGM is relatively late, an intrinsic beat might generate a large part of the QRS complex before local ventricular activation can inhibit ventricular pacing output. A relatively early pacing spike may contribute to

some portion of ventricular depolarization, and the resulting hybrid QRS complex will reflect fusion of both activation wavefronts (true fusion). If the pacing spike is late, pacing may not contribute to ventricular activation so that the QRS complex is identical to the intrinsic rhythm (pseudo-fusion) (Figure 36-4). Pseudo-fusion must be distinguished from device undersensing issues. A phenomenon termed *pseudo-pseudo-fusion* also occurs, during which noise artifacts resembling pacing stimuli are superimposed on an intrinsic QRS complex and give the appearance of pseudo-fusion (Figure 36-5).

Atrial Pacing

The conventional site of atrial pacing has been the right atrial (RA) appendage. The resulting paced P wave is positive in leads I, II, III, and aVF and is negative in aVR. In lead V1, the P-wave pattern is quite similar to sinus rhythm with a terminal negative deflection. Pacing from various alternative atrial sites is being actively explored.[22] Pacing from the coronary sinus ostium or the low inter-atrial septum typically results in a biphasic or negative P wave in leads II, III, and aVF and a biphasic (initially positive and then negative deflection) P wave in lead V1.[23] The RA endocardium adjacent to Bachmann's bundle at the confluence of the RA roof and the inter-atrial septum yields a positive P wave in leads I, II, and III; it starts immediately with the pacing spike, and the P-wave width may be noticeably shortened.[22-25]

Right Ventricular Pacing

In describing ECG patterns observed with right ventricular (RV) pacing from various sites, one has to note some degree of variability caused by inter-individual differences in underlying cardiac pathology and by imprecision in the definition of various RV regions and in the confirmation of lead location. In reality, the RV septum, free wall, outflow tract, and apex are fairly large regions (rather than circumscribed points) that merge seamlessly into one another, and their boundaries are ill defined radiographically. Within those limitations, RV pacing generates certain basic QRS patterns.

RV pacing almost always produces a QRS pattern resembling left bundle branch block (LBBB) with predominantly negative QS complex in leads V1 and V2, and left ventricular (LV) stimulation will result in a right bundle branch block (RBBB) pattern.[1-15] By altering the pattern of ventricular depolarization, ventricular pacing alters ventricular repolarization so that the T-wave vector is opposite to the QRS complex; diffuse T-wave inversion that can be mistaken for other causes of repolarization abnormalities is also seen.

The RV apex has traditionally been the site of ventricular pacing, and the electrodes are commonly placed along the diaphragmatic wall. The resulting superior QRS vector (mean frontal axis more commonly to the left superior quadrant) produces negative QRS complexes in the inferior leads (Figure 36-6). Uncomplicated RV apical pacing can produce RBBB-like QRS morphology in lead V1 in 8% to 10% of patients and can be manufactured by malposition of leads V1 and V2 electrodes at the level of the second or third intercostal space (Table 36-1).[2] When seen, R-wave regression is the rule so that the presence of tall R waves in V3 and V4 is suggestive of an LV pacing site once fusion with intrinsic beats has been excluded.[1,2,6,7] The pacing lead is likely in the RV apex or distal septum if moving the V1 and V2 electrodes down to the fifth intercostal space restores the expected the QRS morphology. However, a dominant R wave may not always be eliminated by this maneuver if RV pacing originates from the midseptal region.[2]

Pacing alternate RV sites, predominantly in the right ventricular outflow tract (RVOT) or midseptum as a way of avoiding detrimental effects on LV performance has created interest, although the optimal RV pacing site remains to be defined.[26-32] RVOT pacing shifts the frontal plane QRS axis to the left inferior quadrant so that the QRS is positive in the inferior leads 1-10 (see Figure 36-6).[33] As pacing moves superiorly toward the pulmonic valve, the QRS axis shifts rightward.[1,2] In general, QRS duration with septal pacing is shorter compared with apical pacing.[1-3,6-12]

Left Ventricular Endocardial and Epicardial Pacing

The QRS complex during LV pacing will show an RBBB-like pattern in lead V1, and this persists when leads V1 and V2 are recorded one intercostal space lower. The frontal plane axis will vary, depending on the precise LV site. A lead could be inadvertently placed into the LV cavity if the lead passes through a patent foramen ovale or atrial septal defect, perforates the interventricular septum, or is mistakenly inserted into a subclavian artery. The

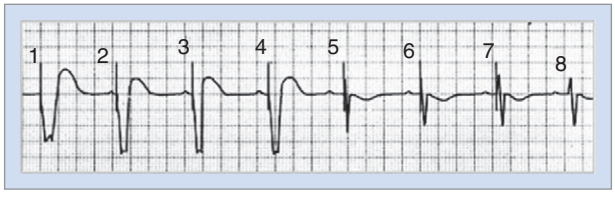

FIGURE 36-4 Rhythm strip showing ventricular paced beats with varying degrees of ventricular fusion. Note the changing morphology of the beats; beat 1 is fully paced, beats 2 through 4 show fusion beats, beats 5 through 7 show pseudo-fusion beats, and beat 8 shows intrinsic sinus rhythm.

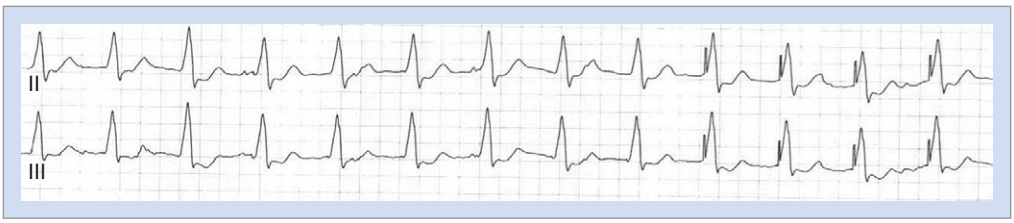

FIGURE 36-5 Pseudo-pacemaker stimuli (pseudo-pseudo-fusion) seen on the last four beats on multiple-lead rhythm strip in a patient with no existing pacing system.

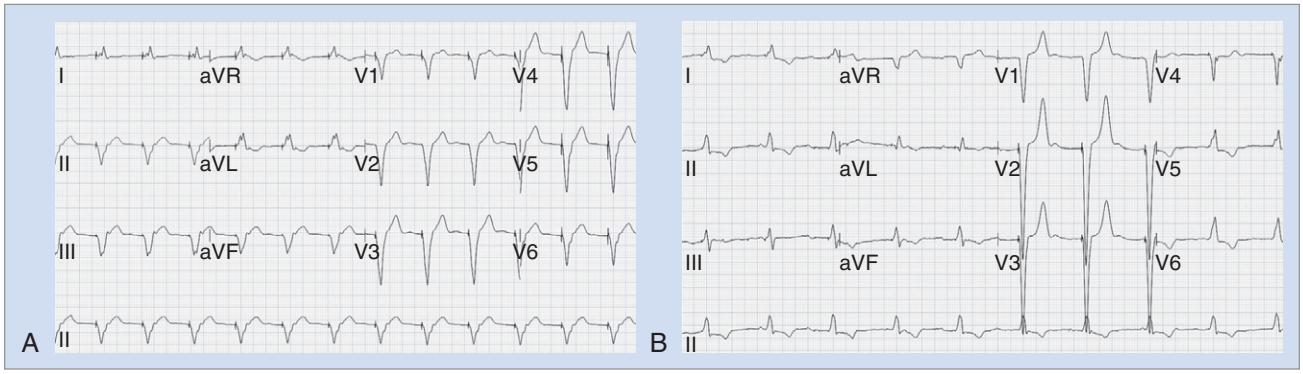

FIGURE 36-6 A, Twelve-lead ECG showing typical features of right ventricular apical pacing with LBBB-like morphology in lead V1 and predominantly negative QS complex in lead V1 and in the inferior leads (II, III, and aVF). Atrial pacing is also present. **B,** Twelve-lead ECG showing typical features of right ventricular septal pacing with LBBB-like QRS morphology in lead V1, predominantly negative QS complex in lead V1, and positive QRS complexes in the inferior leads (II, III, and aVF).

Table 36-1 Causes of a Predominant R Wave in Lead V1 During Ventricular Pacing

- Ventricular fusion with spontaneous beats conducted with an RBBB pattern
- Paced beat in myocardial relative refractory period resulting in aberrant conduction with RBBB morphology
- Coronary sinus left ventricular pacing
- Left ventricular endocardial or epicardial pacing
- Lead perforation of the right ventricular free wall or ventricular septum, with left ventricular stimulation and change on electrocardiogram from LBBB to RBBB pattern
- Uncomplicated right ventricular pacing (lead V1 recorded too high or in the incorrect place)

RBBB, *Right bundle branch block;* LBBB, *left bundle branch block.*
Modified from Barold SS, Guidici JM, Herweg B, et al: Diagnostic value of the 12-lead electrocardiogram during conventional and biventricular pacing for cardiac resynchronisation, Cardiol Clin *24:471–490, 2006.*

diagnosis of a malpositioned lead into the LV chamber is easily missed on a single-lead ECG.[1-3,6-12] However, it is difficult to differentiate between endocardial and epicardial LV pacing.[1-3,6-12] LV epicardial pacing can be achieved by accessing the LV coronary venous tributaries via the coronary sinus or by direct epicardial lead placement through a thoracotomy. The main venous branches used for LV pacing are the middle cardiac, posterolateral, lateral, and anterior interventricular veins. However, there is considerable anatomic variability.[1,2,6,7,12,14] Pacing from branches intermediate in location produces a QRS morphology that can be deduced from the patterns typical with pacing from the main veins (Figure 36-7).

Pacing from the middle cardiac vein results in a superior QRS vector, with sharp negative deflection in leads II, III, and aVF and varying degrees of R wave. Lead I may be isoelectric or positive, depending on how septal the pacing site is. Pacing from the rightward branches of the middle cardiac vein could capture the RV myocardium, producing an LBBB-like pattern in lead V1 and a sharply negative deflection in lead III.

As the LV pacing site shifts to veins that are more lateral, the QRS complexes in lead I become increasingly more negative and those in lead III become positive. Pacing from the anterior interventricular vein produces an inferiorly directed QRS vector with predominant R waves in the inferior leads. If the leads reside in a vein that overrides the septum and paces the RV epimyocardium, an LBBB pattern may be seen.[14] With apical locations in the target vein, leads V4, V5, and V6 are typically negative, and lead aVR is positive; the converse is true with more basal locations.[14]

Biventricular Pacing

With biventricular or CRT pacing, the final QRS morphology reflects a composite of paced left and right ventricular activation as well as any contribution from intrinsic activation, since such patients usually have intact atrioventricular (AV) nodal conduction (with sinus rhythm or atrial fibrillation) or premature ventricular contraction (PVCs).[1,2,6,7,9,12,14] Maximizing the potential benefit of resynchronization pacing therapy requires careful inspection of the QRS morphology while adjusting the AV interval to minimize intrinsic activation. Furthermore, contemporary CRT devices allow independent programming of right and left ventricular pacing output timing to optimize LV hemodynamics.[1,2,6,7,9,12,14] These factors will necessarily dictate the final paced QRS morphology. If RV and LV pacing spikes are sufficiently separated in time, careful inspection of surface ECG may identify up to three pacing spikes (RA, RV, and LV) (Figure 36-8). The QRS complex during biventricular pacing should be compared with pacing from individual sites. The close similarity of QRS vector and morphology to either RV or LV pacing alone suggests unbalanced contribution to global activation and might warrant adjustment of the pacing parameters.[14,34]

QRS duration is typically, but not always, shortened compared with pacing any single ventricular site. Paced QRS duration remains stable over time unless LV lead dislodgement occurs. Importantly, a very narrow paced QRS complex may reflect an undesirable contribution by intrinsic activation rather than optimal resynchronization pacing. Thus, studies have shown a poor correlation between the degree of shortening of paced QRS duration and the clinical response to resynchronization pacing therapy.[1,2,6,7,9,12,14] In contrast, Ricci and colleagues suggested that variation of the intrinsic QRS duration over time might be useful if correlated with remodeling of the ventricles by echocardiography.[35] They have suggested periodic review of the intrinsic QRS complex to confirm the continued presence of intraventricular conduction abnormalities.

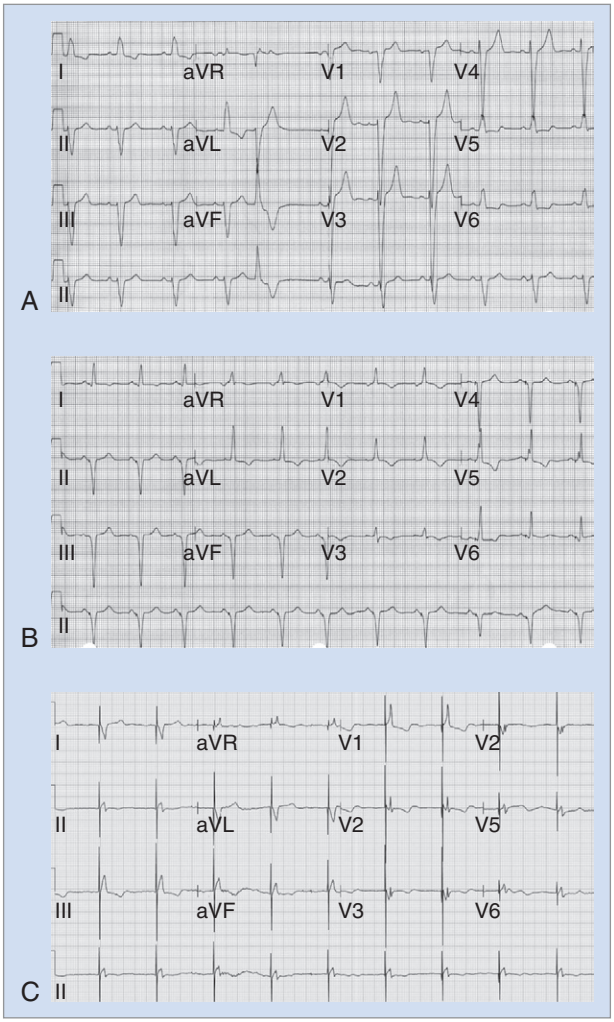

FIGURE 36-7 A, Twelve-lead electrocardiogram (ECG) showing sinus rhythm with left bundle branch block (QRS ~150 ms) and a single premature ventricular contraction in a patient with symptomatic heart failure (NYHA class III functional class) and ejection fraction of 20% on recent imaging. **B,** Twelve-lead ECG in same patient, after insertion of a cardiac resynchronization pacing therapy (CRT)–implantable cardioverter defibrillator (ICD) with the left ventricular lead placed in a posterolateral vein. Note the dominant R wave in V1, negative QRS complexes in the inferior leads (II, III, and aVF), and qR complexes in leads I and V6. **C,** Twelve-lead ECG in a patient with a CRT-ICD showing the left ventricular lead in the anterolateral branch of the coronary sinus. Unipolar pacing spikes are seen with dominant R wave in V1, positive QRS complexes in the inferior leads (II, III, and aVF), and negative QRS complexes in leads I and aVL.

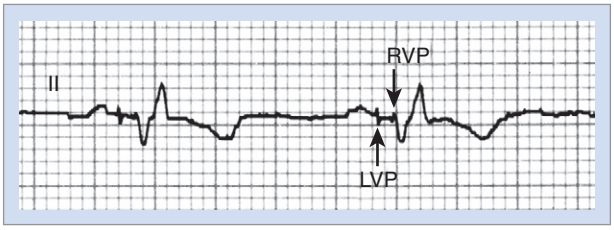

FIGURE 36-8 Surface electrocardiogram lead II showing two different ventricular pacing stimuli artifacts (left ventricular pacing stimulus [*LVP*] and right ventricular pacing stimulus [*RVP*]) in a patient with a cardiac resynchronisation therapy–implantable cardioverter defibrillator. This difference was noted when the interventricular pacing output timing (V-V timing) was programmed so that the LV pacing stimulus preceded RV pacing output by 50 ms. When the V-V interval was 0 ms, only a single ventricular pacing stimulus was seen.

In older CRT systems, the unipolar LV lead (cathode) could be coupled with the RV ring anode for LV pacing. At lower pacing outputs, cathodal stimulation would capture the LV myocardium; however, at higher pacing outputs, anodal stimulation could result in simultaneous RV capture. Detection of anodal stimulation requires awareness of the possibility and careful inspection of multiple surface ECG leads for potentially subtle changes in QRS morphology as the pacing output is varied[1,2,6,7,9,12,14,36] (see Figure 36-2). Currently, biventricular ICDs restrict the coupling of the unipolar LV lead with the RV defibrillation coil electrode, whose larger surface area reduces the likelihood of anodal stimulation. This and the increased reliance on bipolar LV leads have decreased the incidence of anodal stimulation. CRT pacemakers lack a coil electrode, so anodal stimulation is still possible.

Acute Myocardial Infarction in Patients with Permanent Pacemakers

ECG changes seen with ventricular pacing can mimic or mask acute myocardial ischemia and infarction. Certain ECG changes are suggestive of an acute myocardial infarction during ventricular pacing (Sgarbossa criteria): ST-segment elevation 5 mm or more discordant with the paced ventricular complex; ST-segment elevation more than 1 mm concordant with the QRS complex; and ST-segment depression more than 1 mm in leads V1, V2 or V3.[36-40] These findings are associated with a sensitivity of 18% to 53% and a specificity of 88% to 94%. Correlation of ECG findings with suggestive symptoms is important.

Another method that can be used to assess for repolarization changes is to temporarily inhibit ventricular pacing and examine the QRS morphology of the intrinsic rhythm.[1-3,6,7,10,12] Any attendant repolarization changes seen during the intrinsic rhythm must be cautiously interpreted because of a phenomenon called *T-wave memory* or *cardiac memory*.[41-44] *Cardiac memory* refers to persistent ST- and T-wave abnormalities that occur with a sudden transition from one stable ventricular activation pattern to another. T-wave inversion is usually localized to precordial and inferior ECG leads and may persist for a long period after ventricular pacing is discontinued.[41-44] Diagnostic criteria to differentiate between ischemic T-wave inversion and postpacing T-wave inversion using vector direction analysis have also been described.[42,44] The mechanisms responsible for cardiac memory are complex and incompletely understood.[41,43]

Basic Device Operation and Electrocardiogram Manifestations

A systematic approach to analyzing the ECG recording is central to determining the type of pacing device present, its functional pacing mode, and whether pacing function is normal or abnormal.[8] By carefully examining all ECG leads, one should determine the

number of different pacing stimuli and the chamber paced by each, the evoked P-wave or QRS and T-wave morphologies, comparing them with intrinsic rhythm, the timing and relationship of the different pacing spikes, the device response to any intrinsic heart activity, and any instances of apparent pacing and sensing abnormalities. The clinician can then posit an explanation of the device's pacing mode, programmed pacing rates (lower rate, upper rate, or both) and a differential diagnosis to explain any pacing or sensing abnormalities observed (the differential diagnosis should include considerations of specialized pacing algorithm or device malfunction), which can be refined after device interrogation.

A Brief Overview of Pacing Modes

Modern pacing systems have two basic functions: (1) pacing a specific cardiac chamber and (2) sensing intrinsic activity emanating from that chamber and responding in the manner dictated by programming. These basic functions are termed the *pacing mode of the device* and are summarized in a universal four-letter NASPE/BPEG lexicon. The letter in the first position signifies the chamber being paced; the second letter describes the chamber being sensed; the third letter describes how the device responds to sensed signals; and the fourth letter ("R") is often included when a device sensor modulates the pacing rate. A fifth letter can also be added to denote the device's anti-tachyarrhythmia function capability, but this is rarely invoked.

The simplest pacing system encountered in clinical practice is the single-chamber device functioning in demand mode, VVI or AAI, depending on the location of the pacing lead (generically referred to as *SSI*). With SSI, a single type of pacing spike is present, and any intrinsic beats above the device's lower programmed rate should inhibit pacing output. The "escape interval" (between the last intrinsic beat and the ensuing paced beat) should always equal the interval between two consecutive paced beats unless special pacing algorithms are activated. The rate-adaptive pacing mode (SSIR) functions in the same way as the SSI mode except that the pacing rate varies.

The principles that underlie the functions of single-chamber and dual-chamber devices are the same, but ECG analysis is more challenging because atrial and ventricular chamber timing and their interactions need to be considered. In demand dual-chamber pacing (DDD/DDDR), the occurrence of intrinsic atrial electrical activity inhibits output in the atrial chamber; however, since AV synchrony must be maintained, intrinsic atrial beats must also initiate ventricular pacing output (atrial tracking) after a suitable A–V interval unless a spontaneous ventricular beat is sensed. VDD/VDDR pacing modes are minor variants of DDD/DDDR, differing only in that no atrial pacing is present. DDI or DDIR pacing mode is frequently programmed for patients with a history of atrial fibrillation because ventricular tracking of high atrial rates is prevented, but dual-chamber bradycardia pacing support with AV synchrony is maintained during any bradycardia.[45-48] At atrial rates below the lower programmed rate, the device paces both the atrium and the ventricle (unless intrinsic ventricular events are sensed). Sensed atrial events above the programmed lower rate inhibit atrial pacing and are not tracked (i.e., they do not trigger ventricular pacing as in the VDD or DDD mode), whereas the ventricular chamber senses and paces in much the same way as the VVI or VVIR mode.

Asynchronous or fixed pacing (SOO or DOO pacing mode) involves constant pacing output while ignoring intrinsic beats. In the absence of any intrinsic activity, the SSI or DDD mode cannot be distinguished from the SOO or DOO mode. The SOO or DOO mode is useful for avoiding situations where sensing of electromagnetic interference or other noise (for example, surgical cautery or radiofrequency energy) might inhibit pacing output. A PPM also temporarily assumes the SOO mode when it enters a magnetic field of sufficient strength (magnet mode). In the magnet mode, the pacing rate depends on manufacturer, model, and residual battery energy level. In contrast to PPMs, the ICD pacing mode is usually unaffected by magnet application.

Apparent and Real Pacemaker Malfunction

One important step in analyzing the ECG in a patient with a device is to determine whether apparent abnormalities on surface ECG truly represent device malfunction or are the result of some active pacing algorithms.[1-13,49] The discussion is organized according to the types of ECG manifestation that might be encountered. Finally, whenever apparent ECG abnormalities are encountered, recording or noise artifacts should always be considered and excluded.

1. *Pacing failure to capture:* The occurrence of a pacing spike should almost always capture the myocardium. Failure to do so raises two issues: (a) If, for any reason, pacing output occurs during the refractory period of the chamber paced, the pacing output may be insufficient to elicit a response (see Figure 36-3). (b) Pacing spikes outside of the refractoriness should capture the myocardium, and failure to do so indicates that the pacing

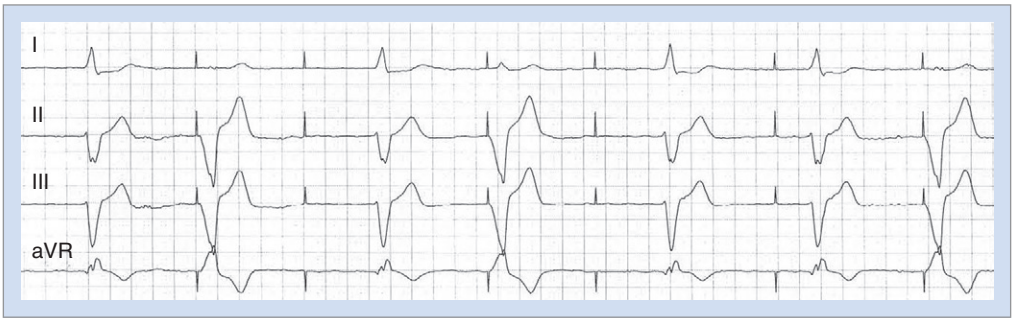

FIGURE 36-9 Multiple-lead rhythm strip obtained from a patient with a single-chamber (VVI) pacing system showing intermittent failure to capture secondary with right ventricular pacing lead dislodgment.

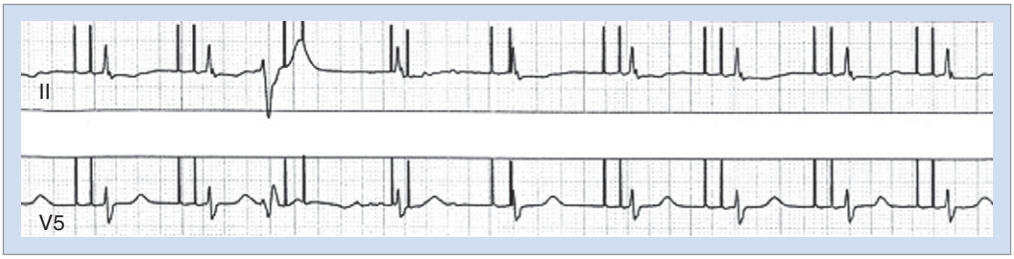

FIGURE 36-10 Rhythm strip demonstrating atrial and ventricular lead failure to capture, with concomitant undersensing in both chambers. This patient had a chronic dual-chamber permanent pacemaker and subsequently developed severe aortic stenosis and mitral regurgitation, which necessitated aortic and mitral valve replacement surgery. During open-heart surgery, both leads were accidentally transected, which resulted in pacemaker malfunction.

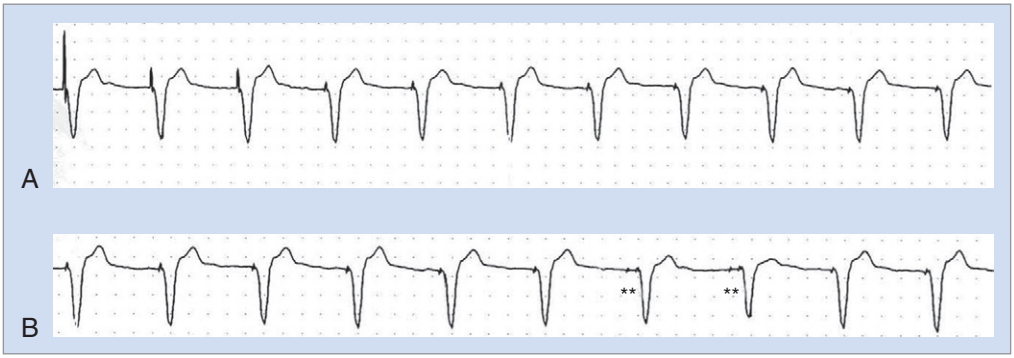

FIGURE 36-11 **A** and **B,** Continuous rhythm strip demonstrating the AutoCapture algorithm with Beat-by-Beat Capture Confirmation (St. Jude Medical, Little Canada, MN) in action. This is a threshold-tracking algorithm that confirms beat-by beat capture of each pacemaker stimulation. It initially starts with a high energy output at the start of **A**. Automatic capture verification monitors every beat for the presence of an evoked response. Automatic reduction in energy output occurs, as seen in **A,** with gradual reduction in the height of the pacing stimulus. Loss of capture seen in **B** in the areas marked by *asterisks* triggers an automatic backup safety pulse (two closely spaced pacing spikes) to ensure capture in the absence of an evoked response. The automatic output regulation sets the output just above the measured threshold in the next two beats. This feature ensures the lowest energy output required for capture and helps optimize device longevity.

output is sub-threshold and should be adjusted (Figures 36-9 and 36-10). Most modern pacemakers and ICDs contain automated pacing threshold functions that periodically measure the pacing threshold, so a single instance of capture failure may not indicate pacemaker malfunction. Each manufacturer's device has a characteristic ECG signature that can be recognized once one becomes aware of such algorithms (Figure 36-11).

2. *Absent or delayed pacing output:* The absence of a pacing spike when it is expected to occur indicates failure of pacing output (Figure 36-12). Failure of pacing output can result from two fundamental causes: pacemaker inhibition by sensed physiologic/nonphysiologic signals and pacemaker algorithms. Since the VVI or DDD mode is intended to withhold pacing output when an intrinsic cardiac event is sensed, the failure to pace could be caused by pacemaker inhibition by sensed physiological or nonphysiological signals. Nonphysiological signals, or "noise," could arise external to the patient (such as electromagnetic interference caused by electrical equipment) or internal to the patient (for example, noise artifact generated by a fractured lead conductor wire). Extrinsic noise will frequently be recorded on surface ECG simultaneously with failure of pacing output, whereas noise emanating from within the device system would not. Physiological signals sensed by the pacemaker and mistaken for myocardial activation include repolarization potentials (T waves), far-field depolarization signals from another cardiac chamber (far-field P-wave or R-wave oversensing), or, rarely, sensing of multiple components of the local EGM (Figure 36-13). Apparent failure of pacing output can also result from certain pacing algorithms. In single-chamber devices, rate hysteresis reduces the amount of pacing by allowing the intrinsic heart rate needed to initiate pacing to be lower than the actual lower pacing rate (Figure 36-14). Various manufacturers also have functions that allow the nocturnal pacing rate or the rest pacing rate to be less than the diurnal pacing rate. Both features are intended to decrease the pacing burden and conserve battery energy.[1-13]

3. *Faster or earlier-than-expected pacing output:* If over-sensing of noise or physiological signals can lead to inhibition of pacing output, it follows that undersensing of intrinsic beats can result in pacing spikes occurring earlier than expected or when they should be inhibited. This would occur with the magnet or VOO mode. Unexpected pacing output can also occur secondary to a pacemaker safety feature. Many modern devices are equipped with a function that converts the pacing mode to VOO or DOO if high rate signals are detected. This avoids the

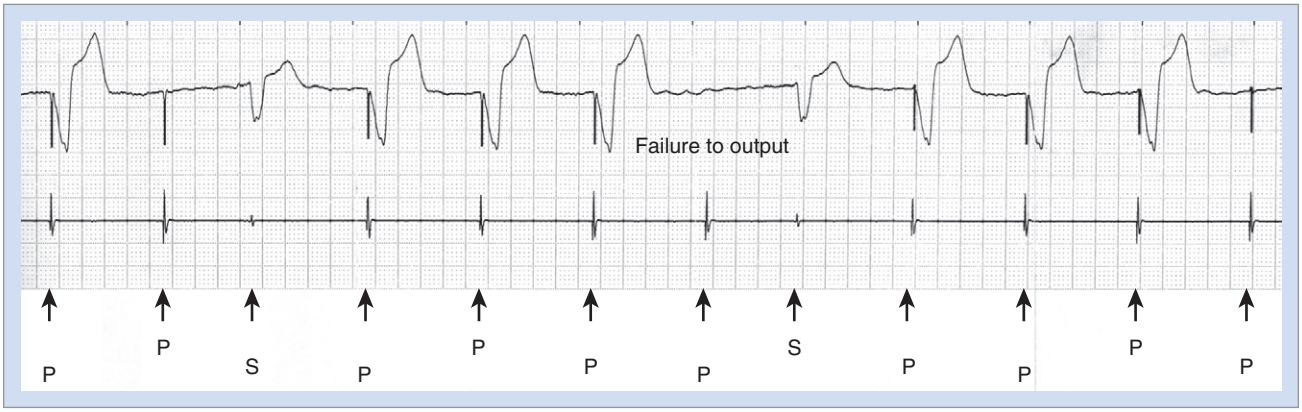

FIGURE 36-12 Multiple-channel recording that includes surface lead II (*top*), intracardiac electrogram (*middle*) and marker channel (*bottom*) obtained from a patient with a 10-year-old VVI pacemaker generator. The electrocardiogram lead shows intermittent pacing failure, with absence of paced QRS complexes on two occasions. On the first occasion, a pacing spike failed to capture, and the second episode was associated with absence of any pacing spike. The marker channel and intracardiac electrogram channels, however, indicate that the device was delivering pacing output on both occasions. *P*, Paced event; *S*, sensed event.

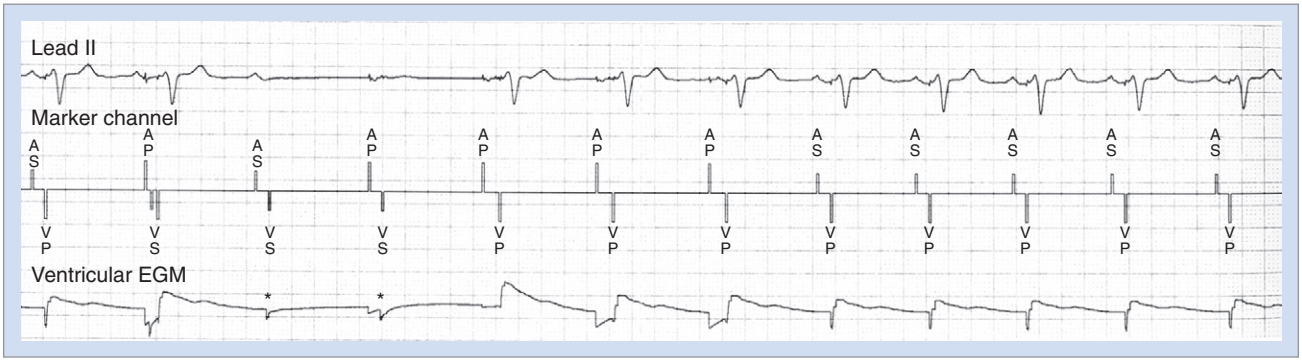

FIGURE 36-13 Strip showing surface lead II, marker channel annotation, and ventricular electrograms obtained from a 71-year-old man with a DDD pacemaker implanted 8 years ago for complete atrioventricular block. The patient presented with intermittent syncope. The first two complexes showed atrial sensing with ventricular pacing, and atrial pacing with ventricular sensing. What followed was an intrinsic atrial beat that was appropriately sensed (no atrial pacing spike) but failed to elicit any obvious ventricular pacing output. Review of the marker channel annotation and ventricular electrograms (*EGM*) confirmed intermittent atrial undersensing and revealed that inhibition of ventricular pacing output was due to some sensed ventricular signal, the origin of which needed to be determined (*asterisk*). The differential diagnosis of no apparent ventricular pacing output included failure of the generator to emit pacing output, ventricular oversensing inhibiting pacing output, and a pacing algorithm.

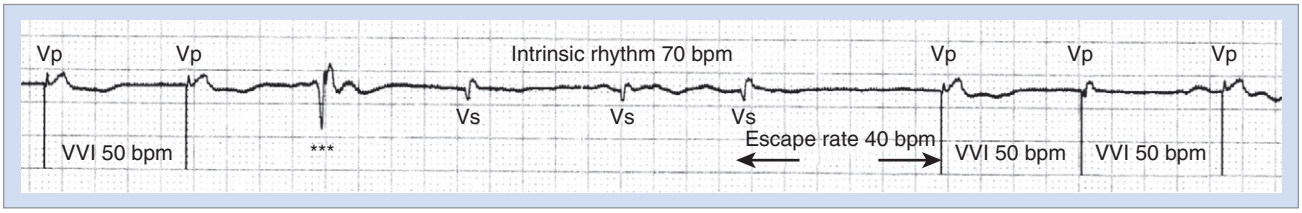

FIGURE 36-14 Lead II rhythm strip demonstrating ventricular rate hysteresis in a patient with a VVI pacemaker. The first two beats represent ventricular pacing at 50 beats/min (*bpm*). Intrinsic beats at roughly 70 beats/min inhibit subsequent pacing, beginning at the beat marked by *asterisks*. Because the hysteresis rate is 40 beats/min, ventricular pacing cannot begin again until the heart rate drops below this threshold. Once pacing output is initiated, the pacing rate resumes at 50 beats/min. *Vp*, Paced ventricular rhythm; *Vs*, sensing of intrinsic ventricular rhythm.

possible situation where sustained nonphysiological "noise," which could be mistaken for intrinsic rhythm, could inhibit pacing output. This would be potentially dangerous for any pacemaker-dependent patient. If the noise originates external to the patient, the ECG would be expected to show a combination of noise artifacts and asynchronous pacing spikes.

Issues Specific to Dual-Chamber Devices

Dual-chamber devices have added pacing algorithms that increase the types of possible apparent and real ECG abnormalities.

1. *Changes in AV interval:* Dual-chamber devices permit the A-V interval of atrial-paced events to be programmed differently from that of atrial-sensed events. Paced A-V intervals are usually programmed 30 ms to 50 ms longer to compensate for stimulus latency. Pacing algorithms that incrementally shorten A-V intervals as pacing rate increases mimic the physiological P-R interval shortening secondary to autonomic tone. Another cause for an unusually short AV interval is a pacing algorithm that forces ventricular pacing output if a ventricular event is sensed shortly after an atrial-paced event. This algorithm avoids the possibility of ventricular oversensing or cross-talk inhibiting ventricular output. Cross-talk occurs when the pacing output in one chamber (chiefly the atrial chamber) is detected by the sensing circuitry of the other chamber and is mistaken for an intrinsic event (chiefly the ventricle). Pacemaker manufacturers have developed pacing algorithms that force ventricular pacing output whenever a ventricular-sensed event occurs very shortly after an atrial-paced event. A PVC fortuitously occurring shortly after delivery of an atrial pacing spike could trigger a similar response.

   Some pacing algorithms also dynamically extend the A-V interval to encourage intrinsic AV conduction with the intent to decrease ventricular pacing in patients with intact AV conduction. When activated, the algorithm periodically extends AV delay by a programmable amount, allowing intrinsic conduction to result in ventricular-sensed events that inhibit ventricular pacing.[50] Because the specifics of algorithms differ among manufacturers, the ECG features that identify the operation of an algorithm as the cause of A-V interval variation will vary by manufacturer; it is therefore important to appreciate the details of algorithm operation for each device.

   Some devices may shorten the AV delay to when a threshold amount of ventricular-sensed events is exceeded. This feature, termed *negative AV hysteresis*, was originally designed for dual-chamber pacemakers but is now predominantly used in CRT.[51] This function will manifest as a shorter-than-expected AV delay not explained by other causes. It may also result in varying QRS morphology caused by varying degrees of fusion with the intrinsically conducted complexes.

2. *Failure of ventricular pacing output:* In addition to the previously mentioned causes of failed ventricular pacing output, dual-chamber devices have some unique causes. The increasingly encountered causes are pacing algorithms designed specifically to minimize the amount of RV pacing. One of these is the Managed Ventricular Pacing algorithm (MVP, Medtronic Inc, Minneapolis, MN) (Figure 36-15). This algorithm is an atrial-based pacing mode, which essentially operates in the AAI/R mode, with ventricular backup when needed. When enabled, the device behaves initially as if in DDD pacing mode, with ventricular pacing following each atrial-paced or -sensed event. The algorithm performs an AV conduction check by inhibiting ventricular pacing output for a single cycle. Lack of a ventricular-sensed event (indicative of AV block) would be followed by a backup ventricular pacing output at the lower escape interval. Ventricular pacing after each atrial event resumes until the next scheduled conduction check. In the event that AV conduction is intact and an intrinsic ventricular beat is detected, ventricular pacing output is withheld, and the device effectively functions in the AAI or AAIR mode as long as ventricular-sensed events continue to follow every atrial event. The signature ECG features identifying this algorithm as the cause of the failed ventricular pacing output is shown in Figure 36-15. Additional confusion may also occur at the time of device implantation. After attaching the leads to a device with this feature enabled, the implanter will note DDD pacing behavior at a nominal AV delay instead of the expected AAIR pacing. This is caused by the fallback mode of DDD until system integrity is confirmed via performance of several internal checks. After this period, which may take up to 30 minutes, the pacemaker will revert to the MVP pacing algorithm. This initially confusing behavior can be manually overridden with the help of a programmer.

3. *Failure to capture:* In addition to the previously described causes of real and apparent capture failure, certain dual-chamber pacing algorithms can lead to intermittent failure to capture and are not indicative of device malfunction. Modern pacemakers are able to automatically measure atrial and ventricular pacing thresholds through the course of a day (see Figure 36-11).

   Such a feature has even been introduced to assess the LV lead in CRT devices.[52] Different manufacturers have developed their own approaches, so recognizing these on ECG requires detailed knowledge of the specific algorithm; however, the principle underlying each is the same. These algorithms comprise four fully automatic pacemaker functions: (1) capture confirmation, (2) threshold search, (3) output regulation, and (4) backup high-voltage pulse in case of loss of capture. Capture confirmation is achieved by the ability to detect the presence or absence of an evoked response by the sensing circuitry. An automatic threshold search is initiated when certain prespecified conditions are met. Pacing output is gradually reduced in the chamber being assessed until capture is lost. Patient safety is ensured by the delivery of a high-voltage backup pulse after the sub-threshold test pulse has failed to capture. After determination of the threshold, the device adjusts pacing output in that chamber to a value sufficient to provide a safety margin. These capture-threshold assessment algorithms are a common cause of concern in monitored patients, since it can be difficult to distinguish intermittent loss of pacing capture. The manufacturer-specific algorithm creates an ECG signature that can be readily recognized once one becomes familiar with it.

4. *Rapid atrial or ventricular pacing:* In the DDD or DDDR mode, a device is expected to track sensed atrial activity and pace the ventricle to maintain AV synchrony up to the programmed upper tracking rate (Figure 36-16). In abnormal circumstances, ventricular pacing occurs at or near the upper tracking rate, but it is not expected. Theoretically, any cause of sustained atrial oversensing could result in ventricular tracking unless the atrial rate exceeds the mode-switching rate

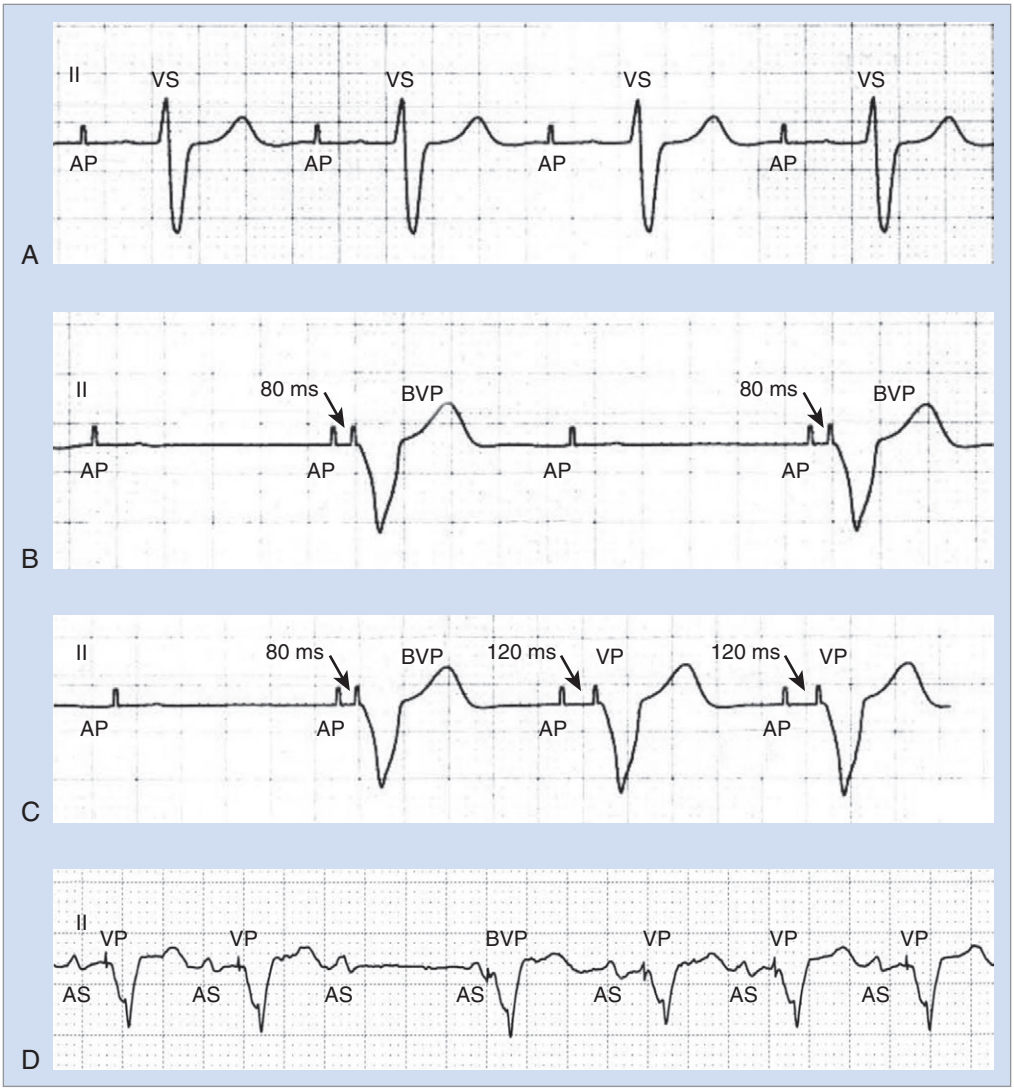

FIGURE 36-15 Normal function of two aspects of the Managed Ventricular Pacing (MVP Algorithm, Medtronic, Minneapolis, MN) in a patient with an Adapta dual-chamber permanent pacemaker (Medtronic). **A,** The device is functioning in AAI(R) mode with atrial pacing while allowing for intrinsic atrioventricular (AV) conduction. **B,** Transient loss of AV conduction with backup ventricular pacing (*BVP*). The occurrence of consecutive A-A intervals without a ventricular-sensed event triggers a BVP 80 ms after the scheduled atrial pace (if pacing is occurring in the chamber) or after the inhibited atrial pace (i.e., 80 ms after the escape A-A interval). **C,** When loss of AV conduction occurs twice within a window of four consecutive A-A intervals, the device reverts to the DDD(R) mode. The paced AV delay is 120 ms in this example. After switching to DDD(R) operation, the device will perform the scheduled "conduction checks" to determine whether intrinsic AV conduction has resumed and if the device can return to the AAI(R) mode. **D,** If no conducted VS occurs, the device continues to operate in DDD(R). Failure to recognize the signature electrocardiogram features of the algorithm can result in the misdiagnosis of pacemaker malfunction. *AP*, Atrial-paced event; *VS*, ventricular-sensed event; *VP*, Ventricular-paced event.

(automatically switches the device out of the DDD or DDDR mode), but certain causes are worth special mention.

a. *Algorithm for atrial fibrillation prevention*[45-48,53]: Several pacing algorithms that are currently available attempt to reduce the burden of atrial tachycardia or fibrillation by addressing potential triggers such as premature atrial contractions (PACs); bradycardia, including sinus pauses; and bradycardia immediately on conversion to sinus rhythm. One such algorithm attempts to suppress atrial ectopy by overdrive atrial pace at a specified rate above the intrinsic sinus rate (Atrial Pacing Preference, Guidant Corp., Indianapolis, IN; Atrial Dynamic Overdrive, St. Jude Medical, Little Canada, MN). Other algorithms interrupt the post-extrasystolic pause after a detected PAC or the bradycardia after spontaneous conversion of atrial fibrillation with a period of relatively rapid atrial pacing which then gradually decelerates toward the baseline. These algorithms are frequently responsible for atrial pacing at relatively high rates that would otherwise be unexplained.

b. *Management of neurally mediated syncope:* Another algorithm that increases the pacing rate was developed to help manage vasovagal syncope. The condition may be associated with a marked decrease in heart rate early in the episode that may contribute to hypotension and syncope.

The pacing algorithm is triggered by a sudden decline in the sensed atrial rate and initiates dual-chamber pacing at a prespecified higher rate (Figure 36-17). This feature is usually intended to combat the cardio-inhibitory response of vasovagal episodes and can manifest as sudden increases in pacing rate not explained by patient activity. The response is nonspecific so that any situation associated with sudden marked decreases in atrial rate can trigger the algorithm.

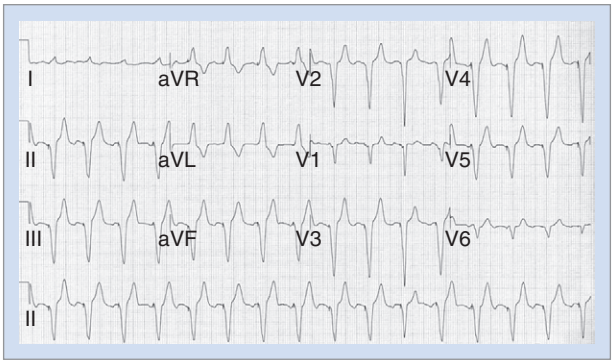

FIGURE 36-16 Twelve-lead electrocardiogram demonstrating pacemaker upper rate behavior in a patient with a dual-chamber permanent pacemaker and paroxysmal atrial fibrillation. The upper rate behavior is due to tracking of the atrial rate during a bout of atrial fibrillation.

c. *Ventricular regularization:* Some devices contain pacing algorithms that reduce the ventricular rate changes associated with atrial fibrillation and ventricular extrasystoles. Ventricular pacing interrupts long diastolic pauses and then gradually decelerates toward a target determined by the particular algorithm unless intrinsic beats intervene. Some pacing algorithms pace the ventricle during atrial fibrillation (AF) at higher rates than expected. These rate stabilization pacing algorithms are designed to reduce the irregular ventricular response that is the hallmark of AF by pacing at a rate approximating the mean ventricular rate of conducted AF. In so doing, they narrow the range of heart rates by eliminating the most extreme long and short R-R intervals. During AF, because of their faster-than-expected and intermittent pacing characteristics, ventricular rate–stabilization algorithms can be confused with intermittent undersensing of AF and failure to mode-switch.

d. *Maximization of resynchronization pacing:* While minimizing RV apical pacing is beneficial for those with dual-chamber pacemakers, maximizing biventricular pacing is the aim of CRT. Maximizing biventricular pacing is especially difficult in patients with AF who have frequent conducted beats or when ventricular ectopic beats occur frequently because such sensed ventricular events would ordinarily inhibit ventricular pacing output. To address this, CRT algorithms that force immediate delivery of LV pacing output on sensing of an RV event within a certain rate range (Figure 36-18) have been introduced.[9,51,54] Other algorithms

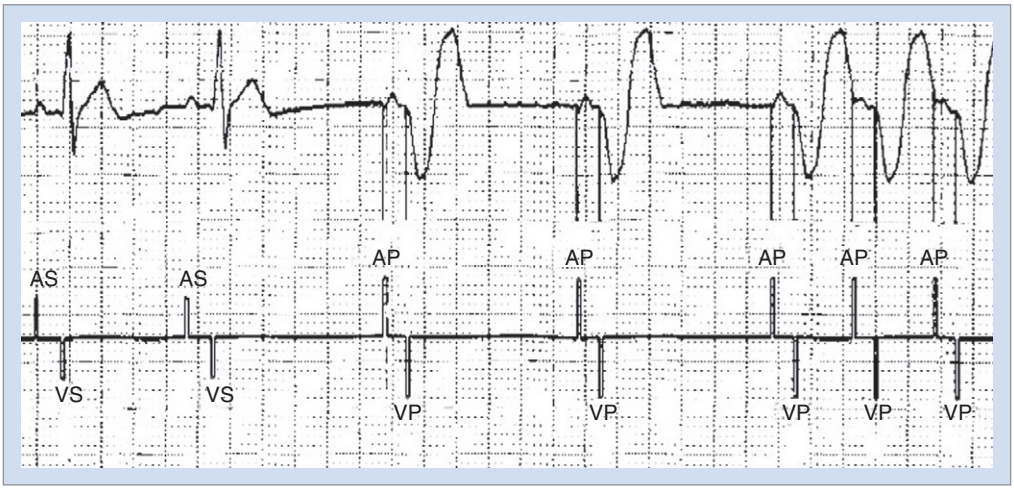

FIGURE 36-17 Recording (lead II and marker channel annotations) demonstrating the initiation of rate drop response. The first two intrinsic beats are at a rate of 65 beats/min followed by an abrupt decrease in rate that triggers 2 beats of backup dual-chamber pacing at the lower rate of 50 beats/min. This sudden drop in heart rate is sufficient to trigger the rate drop response, which results in dual-chamber pacing at the prespecified rate of 120 beats/min. *(Courtesy Frann Hill, Medtronic Canada Inc., Mississauga, ON, Canada.)*

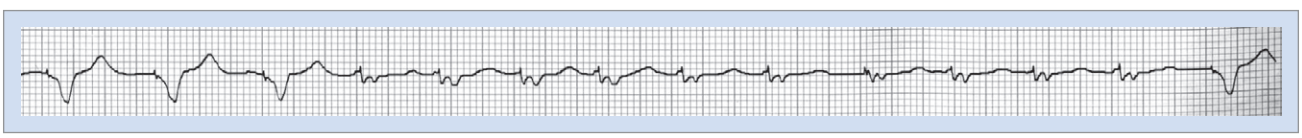

FIGURE 36-18 Rhythm strip (lead II) obtained from a patient with atrial fibrillation and a cardiac resynchronisation therapy–implantable cardioverter defibrillator device. The first three beats reflect biventricular pacing; this is followed by intrinsic conduction for the next 10 beats, which is sensed by the right ventricular sensing circuitry and triggers synchronous left ventricular pacing and return to biventricular pacing on the final beat.

attempt to maximize resynchronization therapy by increasing base pacing rates in response to ventricular-sensed events during AF. The ECG manifestations of these algorithms are pacing stimuli delivered at times when the ventricular complex on telemetry would have been expected to be sensed by the ventricular lead. It is therefore frequently confused with ventricular undersensing.

Conclusion

In spite of its well-recognized limitations, the standard ECG is a valuable tool in the assessment of patients with implanted arrhythmia management devices, as it is capable of providing a great deal of useful information when scrutinized carefully. It may not provide the definitive answer about the nature of any pacing issue, but it certainly can provide sufficient information to narrow the range of likely possibilities.

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CHAPTER 37

Pacemaker Follow-up

Paul Knops and Luc Jordaens

Introduction

Since the implantation of the first human pacemaker in 1958, electrical myocardial stimulation against various types of rhythm disorders of the heart has become available. Pacemakers were initially introduced for the treatment of heart block and later on for sinus node disease. Currently, they are used for a variety of conditions, including tri-fascicular block and syncope related to a variety of pathologic reflexes. This implies that pacemakers now have an important role as lifesaving devices.[1] They are important tools for improving quality of life in several of the cited conditions; thus pacemaker therapy has become one of the most effective medical treatments. The recent innovation of cardiac resynchronization added another dimension to pacing because combined left and right ventricular stimulation is a useful tool in improving heart function by restoring synchronous ventricular activation and contraction.

The international revised North American Society of Pacing and Electrophysiology and the British Pacing and Electrophysiology Group (NASPE/BPEG) generic (NBG) pacemaker code (Table 37-1) is generally used to address the pacing chamber, the chambers sensed, and the response to sensing as well as to determine if rate modulation and multi-site pacing have been activated.[2] Figure 37-1 shows electrocardiograms (ECGs) with the three most often used methods of cardiac stimulation. In Figure 37-2, a photograph and the x-ray image of a pacemaker with the most important components are shown. These are the connectors for the electrodes leading to the heart; the pulse generator itself comprises the power source and the electronic circuit that controls the timing, the impulses, and a variety of programmable features. The pacemaker is connected to one or more pacemaker electrodes (epicardiac or endocardiac), which allow conduction of the stimulus from the pulse generator to the myocardium (Figure 37-3). Pacemaker electrodes can be implanted in the right atrium, the right ventricle, and the coronary sinus for left-sided stimulation by venous access or inserted surgically for epicardial access. Electrodes can be unipolar or bipolar.

The third part of the pacemaker system (beside the pacemaker itself and the electrodes) is the pacemaker programmer (Figure 37-4), which usually is not considered as critical for pacemaker operation. However, this tool is used to check the integrity of the pacemaker system and control the functioning of the pacemaker. Nowadays, these programmers have evolved into dedicated computers, which have made possible extensive programming of pacemakers and advanced interrogation of pacemaker diagnostics. This chapter focuses on the essential elements and developments of modern pacemaker follow-up.

Goals of Pacemaker Follow-up

The first goal of the pacemaker clinic is to monitor the patient's status and verify that the applied pacemaker therapy still meets the needs of the patient. The second goal is to verify that no problems occurred with the implanted device. The third goal is to monitor the battery status of the device and schedule a device replacement in time.

Organization of the Pacemaker Clinic

In the early pacemaker era, follow-up largely was intended to monitor the proper technical operation of the electronic device itself. Over time, pacemakers have evolved into a stable and trustable technology, and they are now equipped with multiple diagnostic tools. Although the proper technical functioning of the pacemaker still is the most critical part of therapy, a shift from pure technical device checkup to clinical rhythm control is often necessary. Therefore modern pacemaker follow-up takes place in a highly specialized, multi-disciplinary environment. There is general consensus about the various aspects of monitoring cardiovascular implantable electronic devices (CIEDs).[3] The essential elements of a well-organized pacemaker clinic are summarized below.

Staff and Assisting Personnel

A well-organized pacemaker clinic can depend on personnel from multiple disciplines. The pacemaker follow-up clinic is under the supervision of the cardiologist and an allied professional with a technical background such as a medical engineer or a skilled nurse or dedicated nurse practitioner. Both physicians and allied professionals should have internationally accepted competencies.[4,5] The pacemaker clinic is typically integrated into a general cardiology facility, which facilitates easy access to administrative and other supporting personnel. Involvement of a dedicated psychologist and pediatric cardiologists may be required.

Equipment

Routine pacemaker follow-up is often performed in a dedicated pacemaker control room (Figure 37-5), which allows efficient, high-quality device follow-up. This room should be equipped with an examination table, an electrocardiogram (ECG) recorder, pacemaker programmers with appropriate and updated device software, advanced life support material such as external defibrillator

Table 37-1 The Revised NASPE/BPEG Generic (NBG) Code for Antibradycardia, Adaptive-Rate, and Multi-site Pacing

POSITION:	I	II	III	IV	V
Category	Chamber(s) paced	Chamber(s) sensed	Response(s) to sensing	Rate modulation	Multi-site pacing
	O = None A = Atrium V = Ventricle D = Dual (A+V)	O = None A = Atrium V = Ventricle D = Dual (A+V)	O = None T = Triggered I = Inhibited D = Dual (T+I)	O = None R = Rate modulation	O = None A = Atrium V = Ventricle D = Dual (A+V)
Manufacturers' designation only	S = Single (A or V)	S = Single (A or V)	*Note*: Positions I through III are used exclusively for antibradyarrhythmia function.		

From 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 *25:260–264, 2002.*

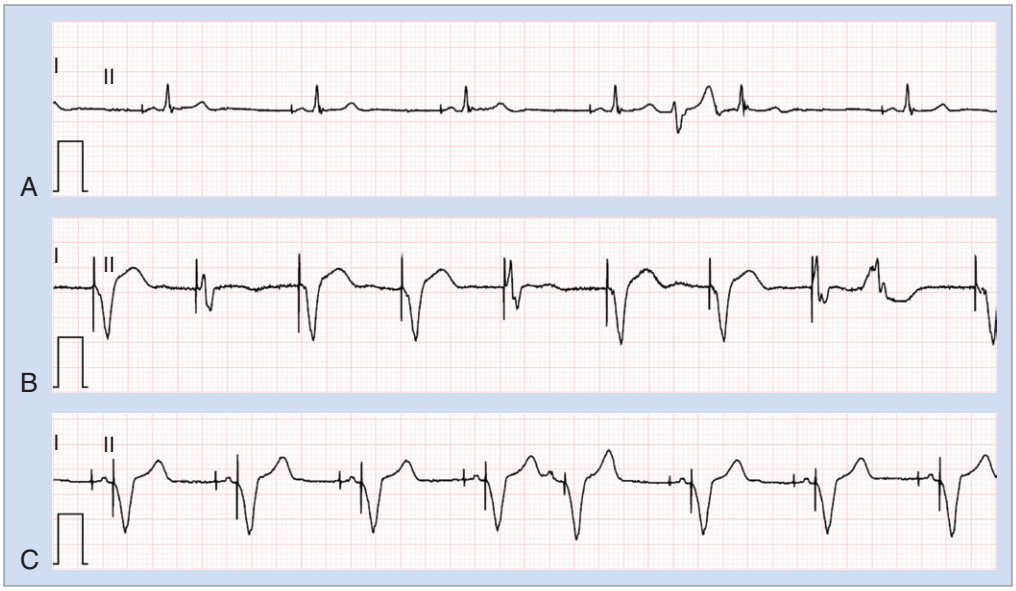

FIGURE 37-1 Electrocardiograms (ECGs) of the three most commonly used methods of cardiac stimulation. ECG strip A shows AAI pacing, with the pacing spike before the P wave. Note that the pacemaker does not inhibit during ventricular or nodal extrasystoles (beat 5). ECG strip B shows VVI pacing. In beats 2, 5, and 8, pacemaker activity fuses with simultaneous intrinsic or ectopic heartbeats, whereas the pacemaker inhibits on an early ventricular extrasystole (beat 9). ECG strip C shows DDD pacing. The pacemaker behavior in beat 5 clearly demonstrates the advantage of DDD pacing: ventricular synchronized pacing (tracking) on a premature atrial beat. All the other atrial complexes are preceded by a spike.

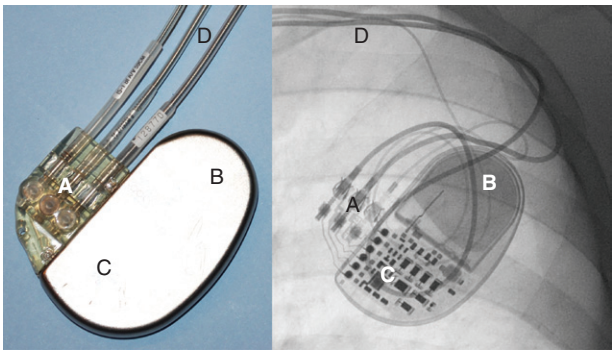

FIGURE 37-2 Photograph and radiographic image of a biventricular pacemaker. **A,** Connector block for the electrodes. **B** and **C,** Sealed housing containing battery or power source (**B**) and electronic circuit board (**C**). **D,** Conductors (electrodes) leading to the endocardium.

with trans-cutaneous pacing capabilities and resuscitation materials, technical documentation, and specifications of pacemakers in use. Computers connected to the hospital network and the Internet, with online access to electronic patient records, the pacemaker database, and remote follow-up web pages, should be available.

Access to Other Facilities

Easy access to the departments of radiology and neurology, the clinical laboratory, and other cardiology units with all facilities (ECG, exercise test, Holter, echocardiogram) should be possible.

Remote Monitoring and Remote Control

New technology (discussed in other chapters) is now simplifying follow-up of pacemakers. Remote monitoring makes checkup of the system integrity, the actual pacemaker settings,

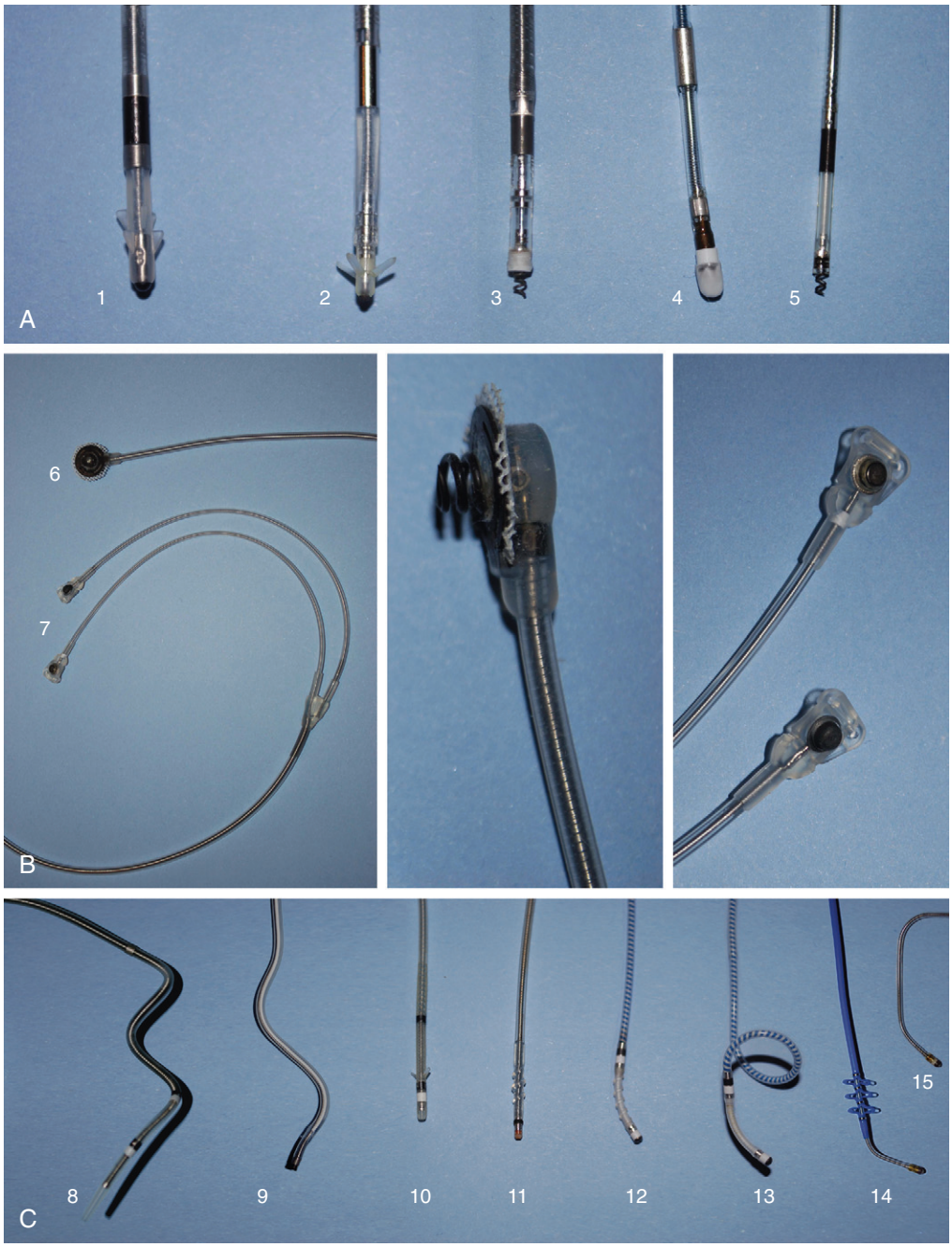

FIGURE 37-3 Pacemaker electrodes. **A,** Straight endocardiac passive fixation (tined) electrodes (*1, 2*) and active fixation (screw-in) electrodes (*3, 4, 5*). One (nonretractable) screw-in lead is covered with a dissolvable coating (*4*). **B,** Epicardiac bipolar electrodes. Screw-in electrode (*6*) and suture-on electrode (*7*). *Middle*, Close-up (side view) of a screw-in electrode (*6*). *Right*, close-up of a suture-on electrode (*7*). **C,** A variety of passive fixation coronary sinus electrodes. Fixation can be achieved by wedging the preshaped distal tip of the electrodes (*8, 9, 13, 15*) or the small silicone fins or lobes (*10, 11, 12*) into the vein. Electrode 14 shows an electrode that combines a preshaped tip with deployable lobes.

and pacemaker diagnostics accessible via cellular telephones or landlines. Integration with the Internet allows physicians and hospitals to perform technical follow-up for most of the available features; serious problems can thus be identified at an early stage. Remote monitoring should become an integral part of the modern pacemaker clinic. Because the remote data are presented by secured Internet sites, remote monitoring only requires a personal computer with network capabilities and can be performed anywhere. For remote follow-up, online access to electronic patient records and the pacemaker database is still necessary, such as to review the patient's medical history. When the decision is made to contact or call in the patient on the basis of the remote pacemaker data, the electronic patient record can provide actual address and telephone information. As the patient is not physically present, the other previously mentioned equipment is not needed.

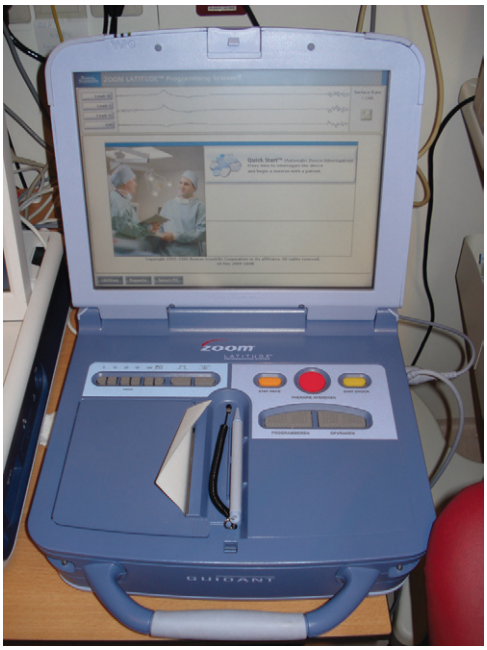

FIGURE 379-4 Combined pacemaker and implantable cardioverter defibrillator (ICD) programmer from Boston Scientific Corp. On a programmer device, the following generic key components can be seen: telemetry wand for wireless contact with the pacemaker, electrocardiogram cable, touch screen with pencil, buttons for emergency therapy and to abort therapy, buttons for interrogation and (re)programming, and paper strip printer with print buttons.

FIGURE 37-5 Dedicated pacemaker follow-up room with a variety of programmers. This picture shows how a dedicated pacemaker follow-up room can be arranged. Some essential equipment can be seen: emergency alarm system and telephone, computer and printer facilities connected to the Internet, multiple programmers of different pacemaker manufacturers, defibrillator, fitted with external pacing capabilities, ECG recording system, and patient examination table.

Normal Routine Pacemaker Follow-up

Postimplantation and Predischarge Follow-up

Proper pacemaker functioning and connection of the electrodes must be confirmed in the peri-operative and immediate postoperative periods. After the implantation of a pacemaker system, pacemaker follow-up should be performed on a regular basis to confirm the efficacy of the applied therapy.[3,6,7] The first follow-up should be performed before hospital discharge.

First Outpatient Clinical Follow-up

Immediately after implantation, special attention should be given to the wound to confirm normal wound healing. The pocket should be inspected during the first outpatient clinical follow-up, normally at 8 to 10 days after implantation, at which time stitches can be removed if subcutaneous resorbable suture material was not used. Otherwise, suture removal can be done by a general practitioner or a nurse. Also, the programmed parameters should be carefully reviewed and a first fine-tuning of the device performed. This can be performed on the basis of the first limited pacemaker Holter readings. From then on, regular long-term ambulatory device follow-up can be maintained.

Long-Term Device Follow-up

A technical control was normally required 3 months after implantation to verify the output of the pacemaker and to fine-tune the stimulation as the threshold (which varies the most in the first few months because of the endocardiac healing process) returns to the baseline. The output could be optimized at this point in time. If an automatic capture control function is available, checked at the time of discharge, and activated, the first control can be delayed.[8]

Checkup can be done nowadays on a less-frequent basis than in the past (e.g., every 12 months) depending on the clinical indication and the battery status. However, a physical checkup once a year is mandatory for reimbursement in some health care systems; it can also be useful to maintain contact with the patient. Furthermore, it should be kept in mind that during control, other items besides the output and the sensing should also be verified. Regular control should be streamlined in such a way that a routine is followed and the goals of the pacemaker clinic are achieved.

Remote Follow-up

If remote monitoring is available, it can modify the character and the frequency of the face-to-face controls in outpatient clinics. Remote monitoring, especially with systems that provide automatic warnings when a patient's rhythm or pacemaker therapy gets destabilized, offers chances to overcome any (possible) problems at an early stage, often even before the patient notices it or the possible problem is clinically detectable or becomes urgent. A strategy to review and examine only events and warnings can be followed. Even then, remote monitoring is potentially better than regular long-term device follow-up because these warnings will be reported immediately at the moment of destabilization. With normal regular ambulatory pacemaker control intervals, at worst, this destabilization will be seen only at the next follow-up, perhaps as late as 6 months after it happens or when the patient is admitted to the hospital.

Contents of Routine Ambulatory Pacemaker Follow-up

To achieve the goals of the pacemaker clinic, routine pacemaker follow-up should be performed in a structured way. Box 37-1 summarizes all the elements of a methodical, routine, more advanced control (as needed).

Patient History and Physical Examination

Along with pacemaker functioning, the patient's physical and general well-being should also be checked. During this examination, the patient should be questioned about symptoms such as syncope, dizziness, shortness of breath, reduced chronotropic competence, palpitations, precordial pain, and any pacemaker-related complaints such as pectoral or diaphragmatic muscle stimulation. Pectoral muscle stimulation is more common in unipolar programmed settings because in this setting the pacemaker is functioning as the anode of the system. An isolation defect of a conductor in this region can also generate this phenomenon.

During inspection of the scar, any signs of impending infection and all other issues should be easily identified by simple inspection of the pocket, a step that should never be skipped. Also, the first signs of necrosis caused by pressure of the pacemaker can or a pacemaker lead can be revealed during this inspection. When the skin is still intact and infection of the pacemaker pocket does not seem present, a relocation or expansion of the pocket can be sufficient; this helps prevent total removal of the pacemaker system when infection does occur. Patient reports of device movement can be verified by further examination.

A routine ECG will show whether the patient has pacing or no pacing in his or her daily life and is often useful to understand data from the programmer.[9] Also, the ECG will reveal many other features at the atrial and ventricular levels. This is highly important for cardiac resynchronization therapy (CRT) because QRS width and axis can be proof of biventricular pacing versus right or left ventricular stimulation alone and because the axis, in general, tells something about the pacing site (Figure 37-6).[10]

Technical Pacemaker Control

Checkup of the technical integrity is another routine that may be dealt with simply by interrogating the device and printing out or reading a completely automated report. This typically shows the actual battery voltage, the impedance over the system and the leads, and data on pacing and sensing, which are often expressed as histograms or tables (Figure 37-7). At the impending end of (battery) life (EOL, end-of-life, or EOS, end-of-service) an early warning is reported, called the *elective replacement index* (ERI). At this time, the appointment for elective replacement should be scheduled within a reasonable time, according to the specifications of the device. When the battery is almost completely depleted, the device often reverts to a backup mode, simply delivering single-chamber synchronous pacing and later reverting to asynchronous pacing until no more output is possible (Figure 37-8). The behavior of current lithium iodine batteries is adequately predictable, so when a normal (remote) follow-up scheme is followed, premature battery depletion or asynchronous EOL behavior should no longer appear on pacemaker follow-up. To prolong the generator life, several precautions can be taken during control. One is to use automatic capture; if this is not available, the output should be programmed at a level that ensures safety (usually two to three times the measured threshold), without depleting the energy of the battery.[8,11] Several systems now have an automatic threshold function, a system to verify automatically the sensing the various levels of the pacemaker and automatic sensor optimization capabilities. This may lead to reprogramming, if possible. Otherwise, automatic adjustments may have

Box 37-1 Follow-up Procedures at the Pacemaker Clinic

HISTORY

Patient Condition and Medical Problems

Syncope, dizziness
Precordial pain or angina
Shortness of breath
Reduced exercise capacity
Palpitations, pauses, and low heart rate
Adjustment of medication

Potential Pacing-Related Complaints

Pectoral or diaphragmatic muscle stimulation
Position-dependent or motion-dependent palpitations
Chronotropic incompetence
Fatigue

Other Medical Problems

Radiation

PHYSICAL EXAMINATION

Inspection of the Pocket

Redness
Venous ectasy
Signs of thrombosis
Decreased skin integrity (erosion)
Infection
Palpation of the pocket

TECHNICAL EXAMINATION

Battery Status

Checkup of technical integrity of pacemaker and leads
Threshold, sensing levels, impedences, intracardiac electrogram
Other available measurements, if needed

Device Statistics

Histograms, counters, Holter monitoring, events, trending

Optimization of Pacemaker Settigns

Mode, output, rate modulation parameters
All rate parameters
Atrioventricular delay parameters
Blanking and refractory parameters
Additional features

ADDITIONAL TESTS

Radiography

Blood tests (leukocytes, BSE, CRP, BNP, etc.)
Exercise test
Holter monitoring
Echocardiography
Pocket, body, and arm positions and movements
Forced muscle contractions

GENERAL PATIENT ADVICE

Routine Advice

Electrical equipment, magnetic fields
Disease, exercise and sport
Counseling, psychological support when necessary

BSE, *Blood selenium;* CRP, *C-reactive protein;* BNP, *brain natriuretic peptide*

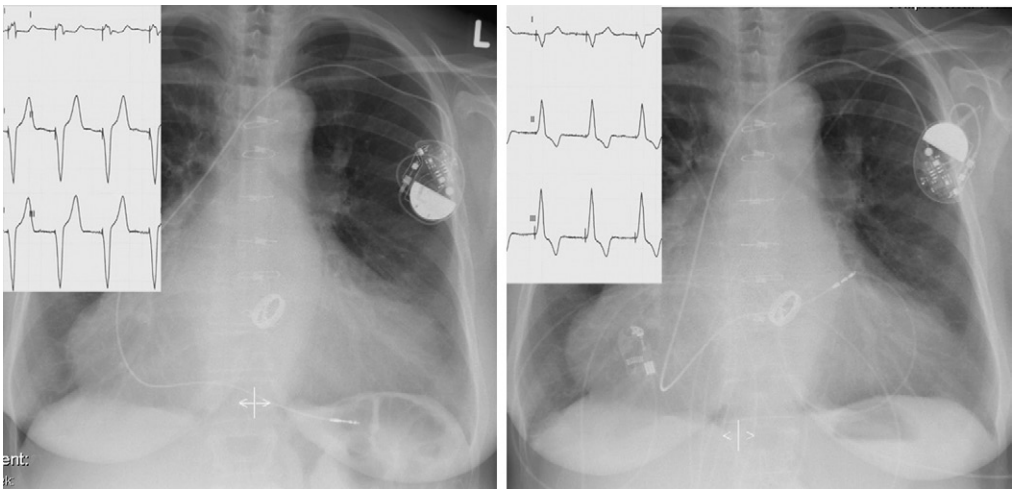

FIGURE 37-6 Relationship between the surface electrocardiogram (ECG) and the pacing site on an x-ray. *Left*, VVI pacemaker with lead in the right ventricular apex in a patient with a mitral valve prosthesis. The ECG shows a positive QRS complex in lead I and negative complexes in leads II and III. *Right*, The ventricular lead is located in the right ventricular outflow tract. Note the opposite ventricular activation on the corresponding surface ECG (negative QRS complexes in lead I and positive complexes in leads II and III).

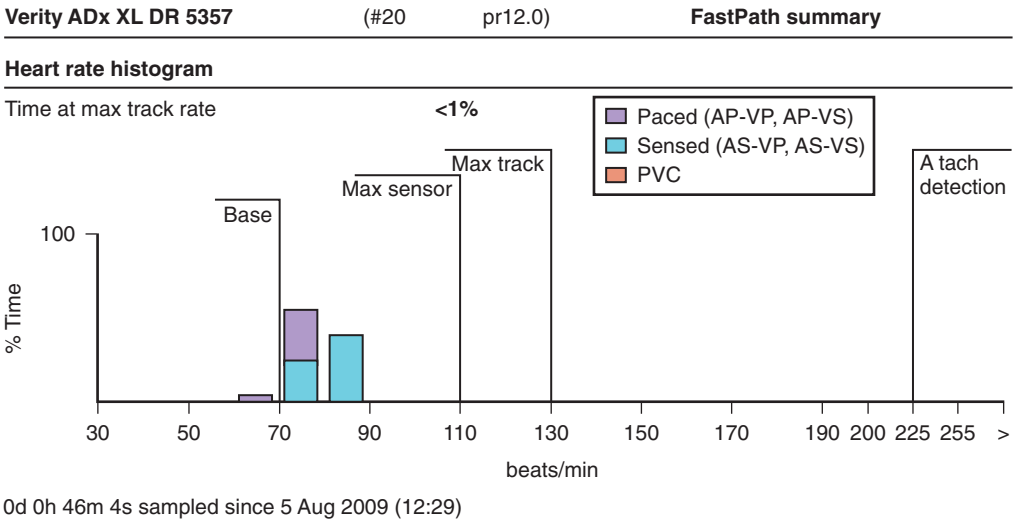

FIGURE 37-7 Pacemaker data expressed as histograms. Example of stored pacemaker data. This histogram from a rate-responsive dual-chamber pacemaker (St. Jude Medical, St Paul, MN) describes the paced and sensed rate distribution and the main programmed pacemaker frequencies in beats per minute. Note the limited variation in frequency between 60 and 90 beats/min. *Purple* indicates when atrial pacing occurs; *blue* indicates when atrial sensing is present. AP, *Atrial paced*; VP, *ventricle paced*; AS, *atrial sensed*; VS, *ventricle sensed*; PVC, *premature ventricular contraction*; tach, *tachycardia*.

occurred all the time, and a printout of this function will be generated. It is generally supposed that activation of the automatic features simplifies follow-up without problems for selected patients.[12] These automatic features can always be checked manually, if preferred, during routine follow-up.

The integrity of the conductors should also be examined by observing the intracardiac electrogram (IEGM). When diagnostics are available, more appropriate programming of the device can be performed to avoid the unnecessary features. Alternatively, new features can be included to provide more comfort for the patient. In general, it is wise to start the pacemaker therapy by simply providing basic functions, depending on the patient's indications for a pacemaker. Features such as rest rate or night drop and flywheel or rate smoothing (Figure 37-9) can be activated later, on the basis of the collected pacemaker diagnostics and Holter or histogram information.[13] These features should be activated only when adequate lower and upper rates are programmed and after correct steepness of the sensor response has been studied, such as by exercise testing or a 6-minute walk test.[14] Furthermore, as it is known, right ventricular apical pacing should

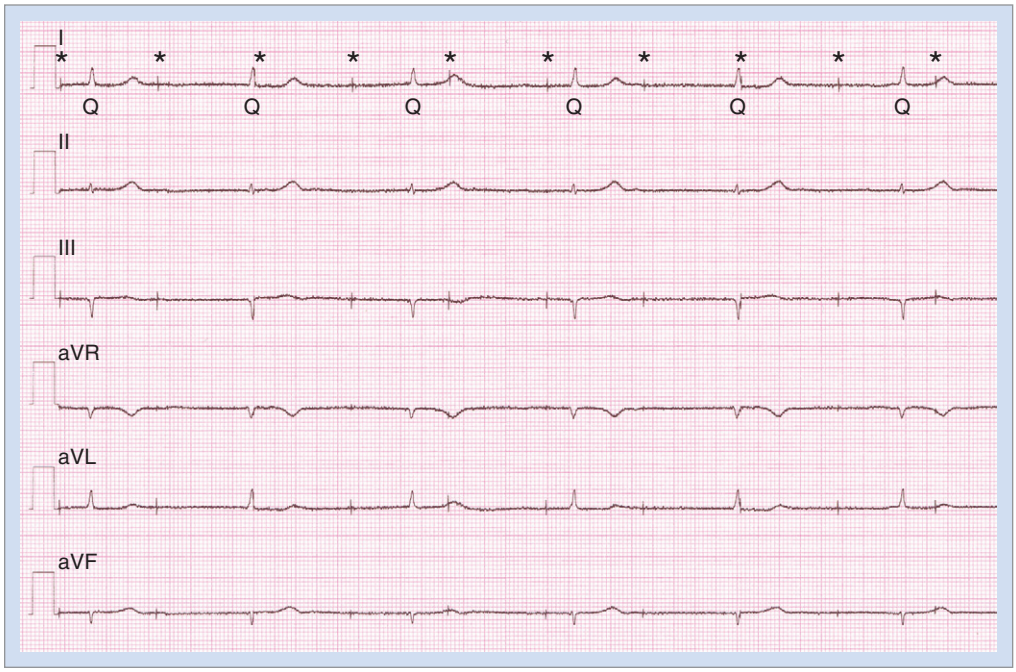

FIGURE 37-8 Subthreshold asynchronous pacemaker stimulation at the end of battery life. The figure shows the asynchronous fixed-rate pacing behavior at the end of life of the battery. The asynchronous fixed-rate pacing without capture can be clearly seen; the pacing spikes (*asterisks*) on the electrocardiogram do not cause any QRS complexes and show no relation to the underlying intrinsic heart activity (*Q*).

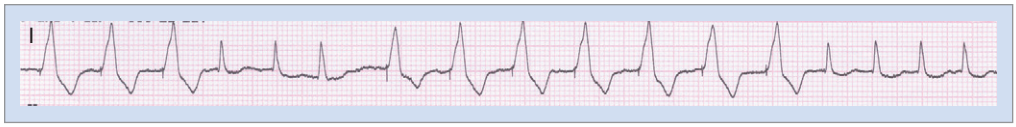

FIGURE 37-9 Rate smoothing during atrial fibrillation. On this electrocardiogram strip, a ventricular pacemaker system can be seen to adapt the programmed lower pacing rate (*asterisk*) to the intermittent fast conduction during atrial fibrillation. This rate-smoothing algorithm prevents the occurrence of long cycles in heart rate and improves the stability of heart rate.

be avoided.[15] This can be ensured with programming the pacemaker modus into AAI, a low backup rate in VVI, DDI with a low rate if an atrial lead is necessary, or ventricular lead implantation on alternative sites such as the right ventricular septum or the outflow tract.[16] The alternatives are automatic mode switching algorithms from AAI to DDD or automatic adjustment of the AV delay if the pacemaker system allows it.[17] However, if ventricular pacing is needed, correct programming in DDD mode with adapted AV delay is necessary.[18,19]

More Advanced Control and Troubleshooting

More advanced fine-tuning of the pacemaker may be necessary; it is often done unexpectedly or may occur when a patient is admitted to the hospital. The reason for such an event might be syncope or a surgical or medical event such as myocardial infarction, which requires reprogramming or renewed programming. It is almost impossible to describe general rules to solve the diverse problems related to pacemakers; each patient deserves an independent, individualized, and tailored approach. For example, pacemaker fine-tuning is required for persistent atrial fibrillation and atrioventricular block in an older adult who is wheelchair dependent rather than for paroxysmal atrial fibrillation and rate-dependent AV block (Figure 37-10) in a young cyclist, even when a comparable pacemaker system could have been implanted.[20]

Troubleshooting for the pacemaker system is not always easy. A routine ECG or the reading of the programmer may reveal the reasons for the (potential) dysfunction of the pacemaker system. Box 37-2 lists several potential complications and problems that should be solved with more expert knowledge and systematic analysis of the electrograms and surface ECG.

Various IEGM recordings that display noise, high frequency, or other noncardiac signals can help discover interference that may be caused by cellular phones or magnetic fields. Because of improved signal filtering and detection algorithms, pacemaker malfunction caused by such phenomena seems to have become relatively rare.[21,22]

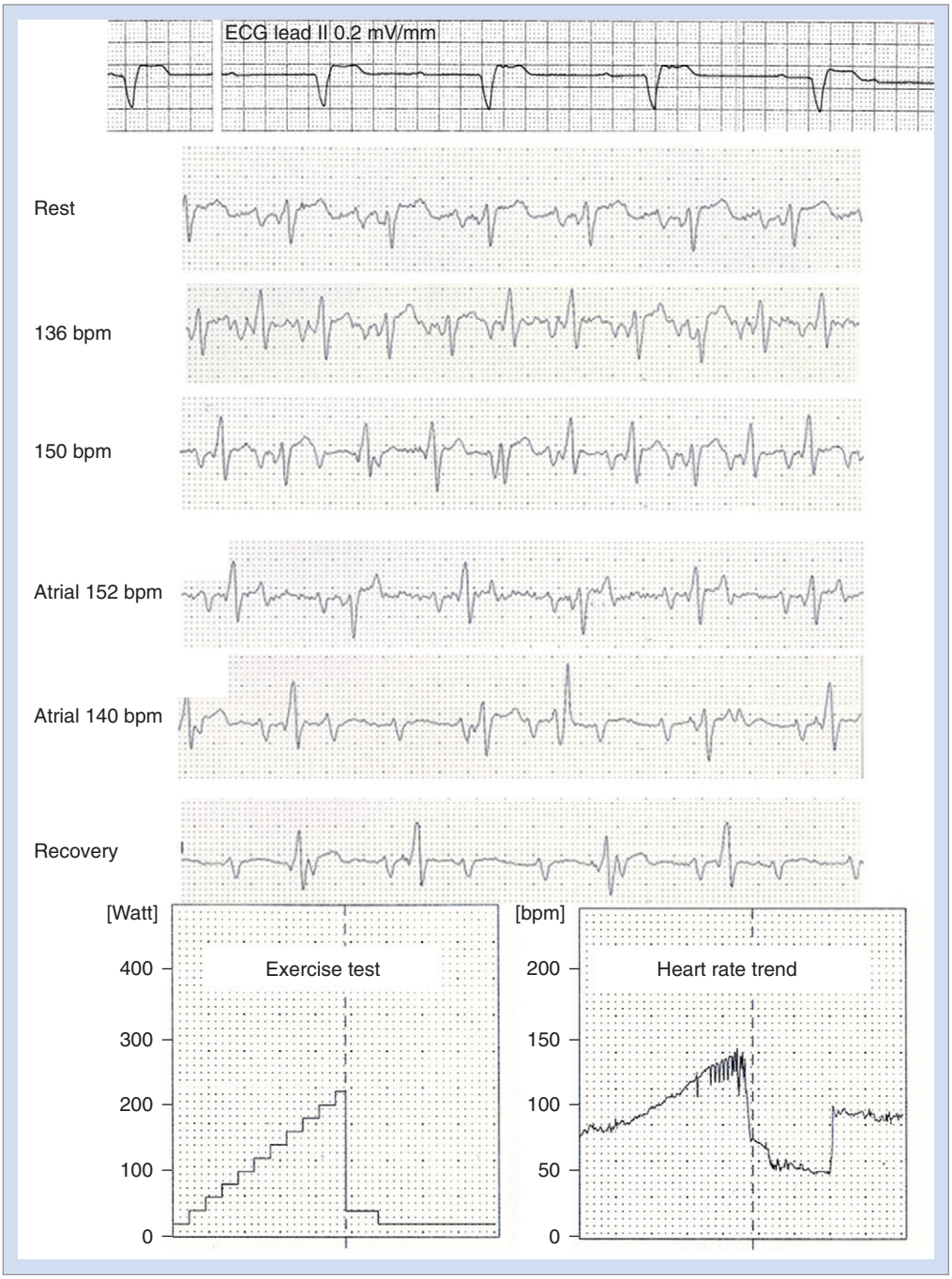

FIGURE 37-10 Exercise test revealing rate-dependent atrioventricular (AV) block. The patient with complete heart block (*upper strip*) was submitted to exercise testing after having palpitations with a VDD pacemaker. After initial correct tracking, a Wenckebach phenomenon was observed, with 2:1 AV tracking from 150 beats/min on; during recovery, poor sensing explains the low pacing rate in the ventricle. The lower strip shows the heart rate trend (*at right*).

Specific problems such as pacemaker-mediated tachycardia (Figure 37-11) require some understanding of the normal conduction behavior of the heart and of the particular pacemaker algorithms designed to avoid them.[23] Some maneuvers may be necessary to provoke or reproduce complaints associated with pacemaker-mediated tachycardia. Pacemaker syndrome is another problem typically associated with (but not limited to) ventricular pacing and retrograde conduction.

Complaints associated with far-field R-wave sensing or undersensing of supraventricular activity can be resolved by individual adjustment of blanking and refractory periods.[24] Marker annotations combined with IEGMs help interpret these problems.

Pectoral and diaphragmatic stimulations require special attention. They can be reproduced during the consultation by asking the patient to recreate the conditions that caused them. They may

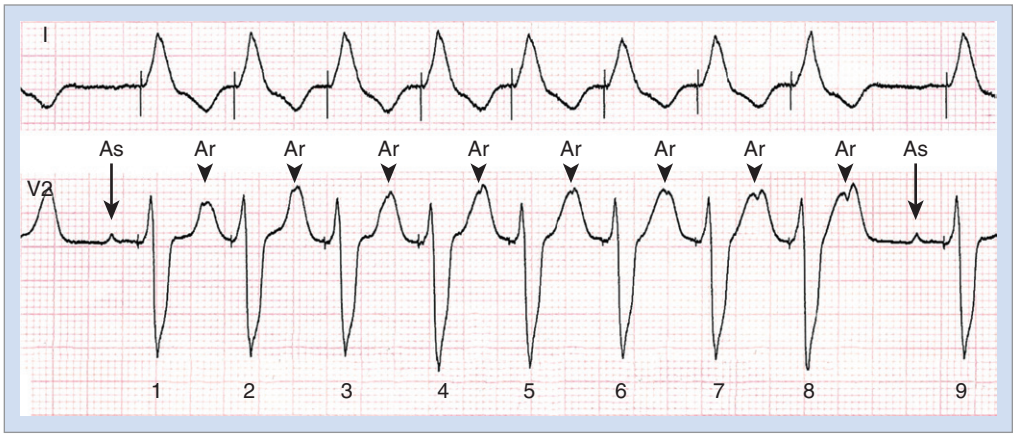

FIGURE 37-11 Pacemaker-mediated tachycardia (PMT). After a normally sensed and tracked atrial complex (*As, beat 1*), retrograde conduction from the ventricle to the atrium occurs (*Ar*), which is sensed and tracked again and causes PMT. A dedicated algorithm will terminate the PMT (after beat 8), which causes the second pause that in turn, allows a normal atrial complex.

Box 37-2 Pacemaker Dysfunction

1. Malpacing in variable degrees
   - Intermittent capture
   - No capture
   - No output
2. Malsensing
   - Oversensing
   - Undersensing
3. Malprogramming
   - Pacemaker syndrome
   - Pacemaker-mediated tachycardia
4. Malfunction of the programmer

be solved with reprogramming, or replacement of the unipolar electrode with a bipolar one may be required.

Additional Tests

Other diagnostic tools or additional tests, such as radiographs, Holter monitoring, exercise testing, and echocardiography, are often used to understand or clarify certain pacing-related problems.

Radiographic examination of the chest or the pacemaker pocket can be performed to reveal dislocation, fracture, or crush of a pacemaker lead. The incidence of a lead crush is higher in systems in which the lead is implanted via a subclavian venous access, in which the risk of crush between the clavicular bone and the first rib is higher compared with a cephalic venous access. Although lead impedance can reveal a lead fracture, it is difficult and sometimes impossible to confirm lead fractures by radiography because of the bipolar spiral construction of the leads. Insulation defects or lead fractures sometimes cause unpredictable problems because of intermittent conductor contact or leakage current. These phenomena can present as unexpected attacks of dizziness or syncope. IEGMs are often informative, as they might display noise. Radiographs are useful to identify an unknown implanted device. Focused pictures can show the screws in the connector.

Holter studies can be performed when the patient's complaints cannot be verified with pacemaker diagnostics or when stored pacemaker electrograms are not available.

Exercise tests are useful to evaluate the behavior of the pacemaker if a patient reports difficulty during effort. Also, the effects of reprogramming can be identified and correct pacemaker programming easily confirmed.

Hemodynamic fine-tuning can be done using echocardiography to adjust the A-V interval, the V-V interval (for resynchronization devices), and the intraventricular interval.[15,25] Optimization of cardiac resynchronization devices requires more attention than described here and is discussed in other chapters in this text.

Avoiding Surgery

Some pacemaker-related problems can be resolved by simply reprogramming the pacemaker, but some need invasive procedures. Almost every reprogrammable pacemaker parameter can contribute to a noninvasive resolution of a pacing-related problem. Reprogramming is sometimes effective only in combination with adjustment of the pharmacologic therapy (e.g., class Ic antiarrhythmic drugs increase the pacing threshold). However, on other occasions, invasive procedures may be necessary to understand and solve a pacing-related problem.

Medical Conditions Requiring Adjustment of Pacing

Although a patient may have an indication for pacemaker therapy, it does not mean that the indication will not change over time. Because of several circumstances such as progress of the clinical picture or a new development in the disease, adjustments in the pacemaker therapy may be necessary. Some of the typical factors or effects that necessitate adjustment of the pacemaker therapy are drug therapy, electrolyte disturbances, and cardiac conditions such as angina pectoris, atrial fibrillation, and heart failure.

General Advice to the Patient

Sometimes, the law requires that a patient not drive during the first weeks after implantation or replacement of a pacemaker. The risks involved in driving should therefore be explained. Some physical activities should be restricted for a short time until the wound heals and until the electrodes are fixed in their intended positions. Educational materials for the patient can be helpful in such situations.

Reporting

All the actions taken during the pacemaker checkup should be reported and stored, such as on a dedicated computer or the hospital database. An electronic patient record system would help make the latest follow-up results directly available to the physician. Furthermore, a letter should be sent to the patient's physician and a new appointment made.

Device Advisories and Safety Alerts

Good databases also allow taking fast action when a device or lead advisory is issued. The affected devices or leads can be easily queried from the database. Alert notifications as well as specific device advisory information from the manufacturer should be added to the concerned patient's files. The patient should be given clear information from both the manufacturer and the physician. Finally, all the essential technical and clinical information from the device or the lead and information about patients involved in safety advisories should be reported to, or shared with, the relevant government authorities, manufacturers, and other physicians.[26,27] With these efforts, remote monitoring will be of significant assistance.[28,29]

Summary

Good clinical care of a patient with a pacemaker demands a well-structured, regular, and methodical long-term follow-up program. The increased pacemaker memory capabilities allow storage of multiple technical and clinical events. A clear understanding of both technical and clinical issues related to pacemaker therapy is necessary. Successful pacemaker follow-up is changing more and more from a pure technical system control to an integrated clinical consultation. IEGM, pacemaker diagnostics, pacemaker Holter information, and real-time measurements should all be analyzed to determine the integrity of the pacemaker system and the efficacy of the applied therapy. Subsequent reprogramming should overcome pacemaker-related problems and contribute to optimal patient care.

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CHAPTER 38

Electrical Therapy for Bradycardia: Future Directions

Fred Kusumoto and Nora Goldschlager

Since its introduction more than a half century ago, progressive improvements in technology have led to the dramatic evolution of cardiac pacing therapy. The changing demographics of the United States have led to an increase in the pacemaker implantation rate from 37 per 100,000 person years 30 years ago to 99 per 100,000 patient years during the first decade of the twenty-first century.[1] The technology implemented in cardiac resynchronization devices and implantable cardiac defibrillators has received more widespread attention, but it should not be forgotten that technological improvements for cardiac pacemakers continue to evolve at a rapid pace. Even more importantly, the maturity and relative constancy of the basic indications for cardiac pacemaker therapy have helped clarify the shortcomings of current devices and identify areas for future basic and clinical research. For example, more widespread use of magnetic resonance imaging (MRI) for diagnostic purposes has provided the incentive for manufacturers to develop pacemakers using materials that will not be affected by the magnetic and electrical fields generated by scanners.

Remote Follow-up of Cardiac Pacing Devices

No other emerging technology associated with implantable cardiac devices has the widespread ramifications that are associated with remote follow-up techniques. Traditionally, information from implanted cardiac devices has been available only to physicians specializing in cardiac devices. Improved technology allows one to think of devices as "health monitors" that can acquire and transfer information from the device itself to an accessible centralized location that could be used by all health care providers and, importantly, by the patient.

Currently, all commercially available cardiac pacemakers have some type of remote monitoring system.[2] Information stored in the memory of the pacemaker can be downloaded wirelessly to a receiver located in the patient's home. Both patient-activated downloads and automatic downloads are possible, depending on the manufacturer. Information is transmitted via cell phone or over landlines to a central server that is maintained by the pacemaker manufacturer. This downloaded information can then be accessed via the Internet in a "two-way" manner, initiated by the physician as well as automatically, with automatic alerts sent from the server to the physician. Initial studies have suggested that remote monitoring can identify potential problems more quickly than can in-office or clinic visits.[2,3] In one study of patients with implantable defibrillators, remote monitoring identified lead failure (conductor wire break or insulation breach) 2 months earlier than can standard monitoring; consequently, lead failure–related inappropriate shocks were experienced by only 27% of patients with remote monitoring compared with 53% of patients with traditional follow-up.[4]

Identification of atrial arrhythmias in patients with bradycardia has been shown to provide important prognostic information. In a nested cohort of 312 patients from the Mode Selection Trial (MOST), the presence of a 5-minute or longer episode of atrial tachycardia was associated with an increased risk of death (heart rate [HR], 2.48; confidence interval [CI], 1.25 to 4.91) and development of atrial fibrillation (HR, 5.93; CI, 2.88 to 12.2).[5] The usefulness of early identification of atrial arrhythmias by remote monitoring in improving clinical outcomes is the subject of several large multicenter trials. Preliminary results from the TRENDS study suggest that atrial fibrillation "burden" (>5.5 arrhythmia hours per day) is associated with a higher thromboembolic rate (2.4% per year) compared with that in patients without atrial arrhythmias identified by the device (1.1%).[6] Another multicenter study, Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT), has completed its enrollment and will also evaluate whether atrial arrhythmias identified by and stored in the device can identify a group of patients at higher risk for stroke. Coupled with remote follow-up, early documentation of atrial arrhythmias may be beneficial in reducing the incidence of stroke by identifying patients who would benefit from anticoagulant therapy. Figure 38-1 shows an example of a patient with atrial fibrillation and an implanted pacemaker. Interrogation of the pacemaker after ablation of the atrial fibrillation confirms successful elimination of detected episodes of this arrhythmia.

Early studies have provided interesting data indicating that device-based hemodynamic monitoring may be beneficial in patients with heart failure. Devices currently in use can estimate patient activity via motion sensors and specific respiratory parameters and can estimate pulmonary venous congestion via intrathoracic impedance measurements.[7] Fluid accumulation within pulmonary spaces decreases intrathoracic impedance, since fluid offers less resistance to electrical current than does air. In a small clinical study of 33 patients, a decrease in thoracic impedance was observed approximately 2 weeks before hospitalizations for heart failure. An example of the clinical use of intrathoracic impedance is shown in Figure 38-2. In the study, after remote monitoring was initiated, decreased impedance was used along with clinical variables to increase the diuretic dose of a patient with severe systolic dysfunction, which may have prevented rehospitalization.

Indirect estimates of volume status using technologies such as intrathoracic impedance can be incorporated into any

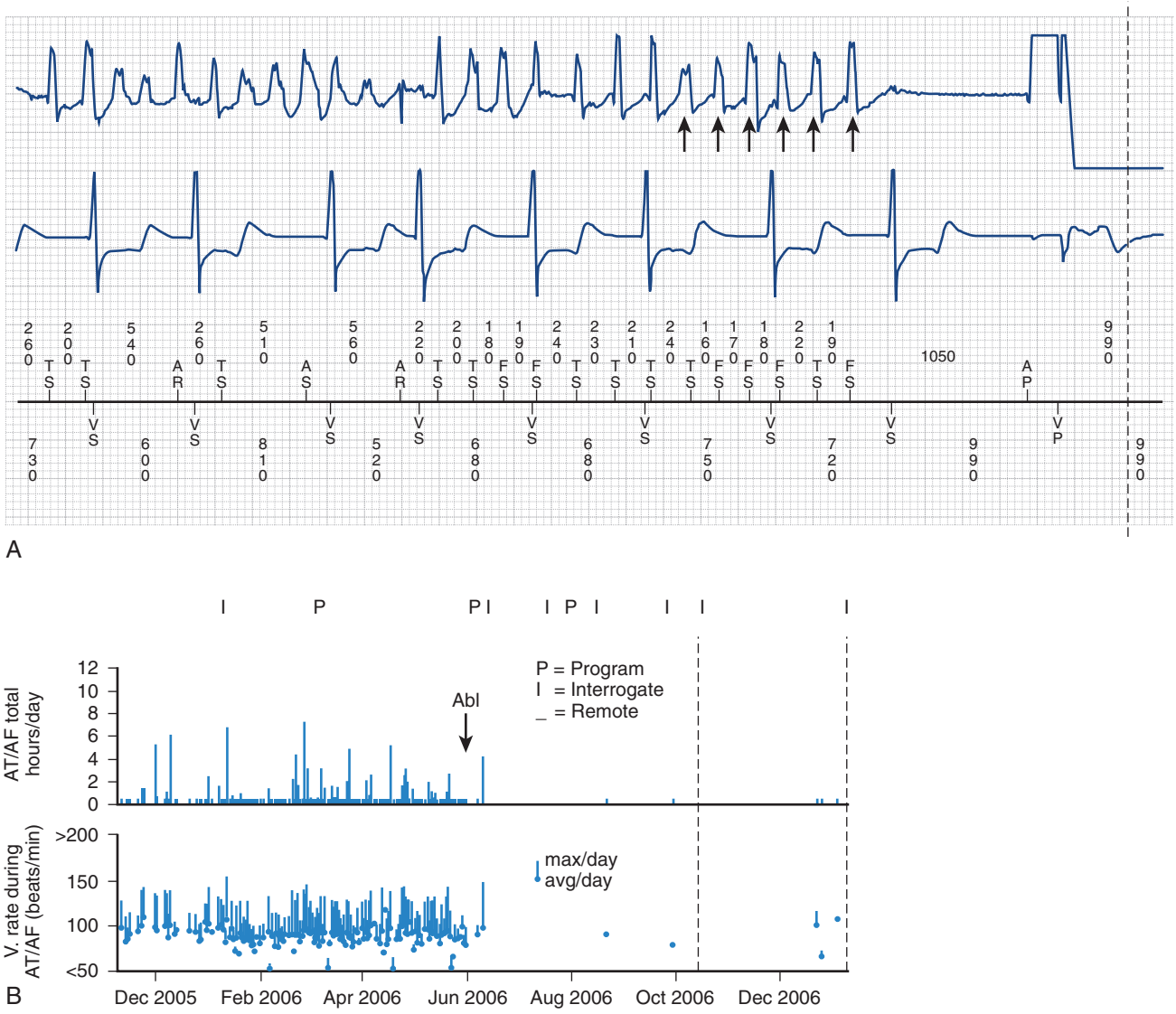

FIGURE 38-1 **A**, Electrograms from a patient with episodes of atrial fibrillation. Atrial electrograms reveal rapid and irregular activity (*arrows*) consistent with atrial fibrillation that terminates at the end of the strip. **B**, Long-term continuous monitoring from the device confirms elimination of atrial arrhythmias after radiofrequency catheter ablation. *AT/AF,* Atrial tachycardia/atrial fibrillation; *Abl,* ablation. *(From Kusumoto FM, Goldschlager: Remote monitoring of cardiac devices,* Clin Cardiol *25(2):89–90, 2009.)*

lead-device system, but direct pressure measurements using specialized investigational leads may provide theoretical or real advantages. One lead system uses a specially designed pressure transducer that is placed in the right ventricular outflow tract; the transducer directly measures right ventricular pressure and uses an algorithm to estimate pulmonary artery diastolic pressure (Figure 38-3). Pulmonary artery diastolic pressure, as a correlate of pulmonary capillary wedge pressure, can be used as an estimate of left ventricular preload to guide heart failure management. In addition, the pressure monitor may also be useful in confirming the presence of ventricular arrhythmias by identifying accompanying hemodynamic compromise (Figure 38-4). In the largest study to date, the Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure (COMPASS-HF) trial, 274 patients with class III or IV heart failure were randomized to two groups: one in which information was available to clinicians and the other in which clinicians were blinded to hemodynamic data. After a 6-month follow-up, clinical use of a hemodynamic monitor resulted in a nonsignificant 21% reduction in heart failure–related events.[8] Another specialized lead system under clinical investigation uses a pressure tip placed at the inter-atrial septum to directly measure left atrial pressure.

In addition to intracardiac pressures, new technologies that monitor other non-heart rate–related parameters such as ST-segment deviation and systemic blood pressure are being developed.[8-11] ST-segment changes can be monitored by analyzing the intracardiac electrogram from a tip electrode located in the right ventricle and the device "can." The device continuously monitors the relationship between the ST segment and the P-Q

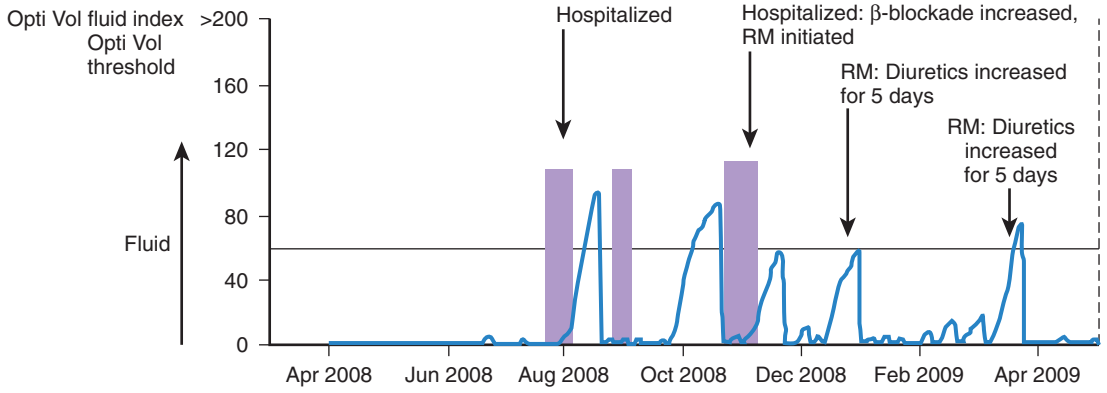

FIGURE 38-2 Intrathoracic impedance monitoring in a patient with severe systolic dysfunction. After several hospitalizations for heart failure, remote monitoring (*RM*) was initiated. During follow-up, decreased intrathoracic impedance was detected via an algorithm as an increase in the "fluid index" during remote monitoring. The patient was contacted by telephone, and after a discussion with the patient, the diuretic dose was increased for 3 days and the fluid index returned to baseline. *(Modified from Kusumoto FM, Goldschlager: Remote monitoring of cardiac devices,* Clin Cardiol *25[2]:89–90, 2009.)*

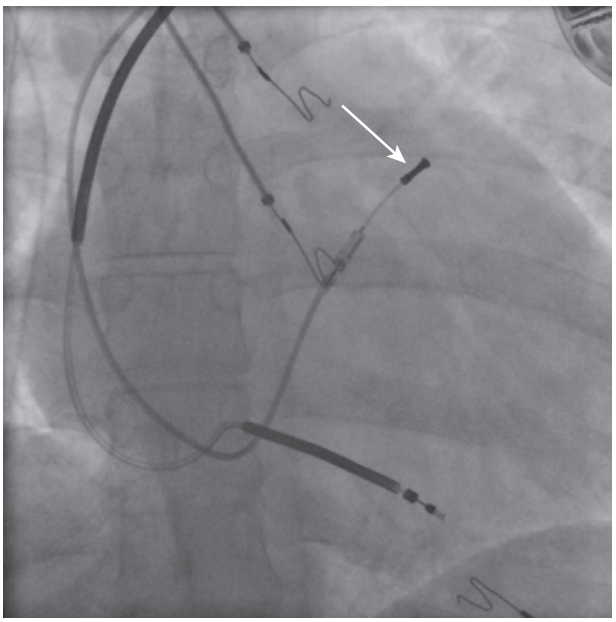

FIGURE 38-3 Fluoroscopy of a patient with an investigational single-chamber implantable cardiac device that uses a second lead (*arrow*) placed in the right ventricular outflow tract; the second lead uses a special sensor, which directly measures right ventricular pressure.

segment. If a significant shift between the ST segment and the P-Q segment persists for a programmed number of beats, the device can either vibrate or provide an audio alert. In an animal study, changes in the ST segment recorded by implanted leads occurred earlier than in those recorded from surface electrocardiogram (ECG) leads; these changes therefore confer an ability to quickly detect myocardial ischemia in any of the three major coronary arteries. Initial data from experimental studies suggest that systemic blood pressure changes can be estimated by measuring bioimpedance between two electrodes placed in the subcutaneous tissue. Incorporation of this technology into implanted devices may provide a method for monitoring antihypertensive therapy.

It is hoped that freer and more widespread access to medical information by medical providers will improve healthcare outcomes and reduce costs. Implantation of devices will likely be the first clinical field where this information revolution will take place. Current devices provide simple audible alerts when the implanted device detects a potential problem, but it is an easy leap to imagine providing patients with access to information in a simplified and understandable format. In this way, implanted devices coupled with remote follow-up can initiate a major paradigm shift, with patients taking a more active role in their medical care, based on actual data rather than symptoms alone.[12]

Newer Cardiac Pacing System Algorithms

The development of specialized and complex algorithms for cardiac pacing systems has had a significant impact on pacemaker programming and thus on the delivery of more appropriate pacing therapy. Large randomized studies performed in the last decade of the twentieth century identified the deleterious effects of right ventricular pacing, especially if performed from the right ventricular apex.[13,14] Importantly, this deleterious effect occurs even when only moderate ventricular pacing is present. In a post hoc analysis of MOST, cumulative ventricular pacing greater than 40% of the time was associated with a 2.6-fold increased risk of hospitalization for heart failure.[15]

Several studies have shown that right ventricular pacing is also associated with an increased likelihood of developing persistent atrial fibrillation. For example, in MOST, a linear dose-response relationship was noted between ventricular pacing and the likelihood of developing atrial fibrillation, with a 20% increase in the likelihood of developing atrial fibrillation with each 10% increase in cumulative ventricular pacing.[15] More recently, it has become

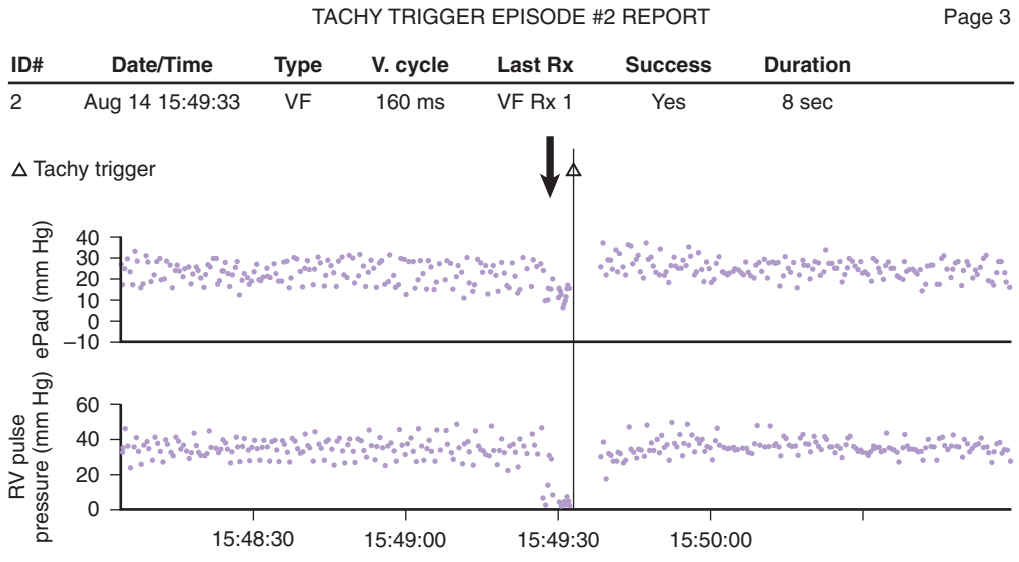

FIGURE 38-4 A significant drop in right ventricular (*RV*) pulse pressure (RV systolic – RV diastolic) readings during an episode of ventricular fibrillation (*VF*) (*arrow*) that confirms loss of RV pulse pressure caused by hemodynamic compromise during the event.

apparent that specific algorithms that minimize right ventricular pacing can reduce the likelihood of atrial fibrillation in patients with sinus node dysfunction. In the Search AV Extension and Managed Ventricular Pacing for Promoting Atrioventricular Conduction (SAVE PACe) trial, 1065 patients with sinus node dysfunction and normal AV conduction were randomized either to an algorithm specifically designed to minimize ventricular pacing or to conventional dual-chamber pacing without this function.[16] The algorithm resulted in a significant reduction in ventricular pacing (minimizing ventricular pacing algorithm: 9%; conventional programming: 99%) and after an almost 2-year follow-up, minimizing right ventricular pacing was associated with a 40% reduction in the relative risk for persistent atrial fibrillation (conventional DDD pacing: 12.7% versus minimizing pacing algorithm: 7.9%). The MINimizE Right Ventricular Pacing to Prevent Atrial Fibrillation and Heart Failure (MINERVA) trial is currently under way to evaluate whether algorithms that minimize ventricular pacing will reduce the burden of atrial fibrillation in those patients who already have an established diagnosis of atrial arrhythmias.[17]

The clinical benefits of other complex algorithms appear to have limited benefit in the aggregate; it is quite certain that these complex algorithms can be useful in selected individual patients.[18] In the Advanced Elements of Pacing Randomized Controlled Trial (ADEPT), 872 patients who had a blunted heart rate response to exercise (chronotropic incompetence) were randomized to standard dual-chamber pacing or to dual-chamber pacing that modulated heart rate on the basis of input from an accelerometer and a minute ventilation sensor (rate adaptation).[18] Although the use of rate-adaptation algorithms was associated with an increased heart rate in response to exercise, this did not translate into significant differences in quality-of-life and activity indices between the two groups. Initial unblinded trials had suggested that specialized pacing algorithms that provided higher pacing rates in response to sudden changes in heart rate could be useful for patients with severely symptomatic vasovagal syncope.[19] However, a subsequent double-blind trial did not show any clinical benefit of pacing using specialized algorithms in patients with vasovagal syncope.[20]

It is expected that in the next 5 years, pacemakers will be characterized by increased automatic functions. Automated algorithms for adjusting pacing output to minimize energy requirements and extend battery life have already been developed for atrial and ventricular pacing (e.g., the "autocapture" feature, St. Jude, Sylmar, CA).[21,22] In a multicenter randomized trial of 910 patients who underwent implantation of a dual-chamber pacing system, automatic threshold evaluation of ventricular capture was found to be reliable and comparable with manual threshold evaluation and led to a projected 16% increase in longevity from 8.9 to 10.3 years.[23] Large registry studies (ULTRA and Automaticity, both sponsored by Boston Scientific, St. Paul, MN) are currently under way to evaluate whether automatic algorithms will increase pacemaker longevity and reduce the use of health care resources.

Site Selection

In anti-bradycardia devices, ventricular leads have traditionally been placed in the right ventricular apex and atrial leads in the right atrial appendage. These sites were chosen because they provided stable positions for the available leads, which used passive fixation to stabilize the stimulating electrode on the endocardial surface of the heart. With the development of leads that use active fixation mechanisms, implanters are now able to place leads anywhere in the ventricular endocardial surface. Large studies that will provide information on optimal pacing sites in patients with bradycardia are now under way; however, it has become clear that site selection requires individualization.

It has been known for more than 40 years that pacing from the right ventricular apex alters the ventricular contraction pattern by producing functional left bundle branch block; this, in turn, can be associated with adverse acute hemodynamic effects

and long-term structural, metabolic, and functional effects.[24] The realization that techniques to "resynchronize" ventricular activation patterns could improve outcomes in patients with systolic left ventricular dysfunction and increased QRS duration has brought this issue to the forefront. It has been proposed that pacing from the right ventricular septum could allow for more physiological ventricular activation in patients with atrioventricular block. Small acute hemodynamic studies and chronic studies with short-term follow-up have yielded mixed results with regard to the benefits of septal pacing.[25,26] Three large studies—Optimize RV Selective Site Pacing Clinical Trial (Optimize RV), Right Ventricular Apical and High Septal Pacing to Preserve Left Ventricular Function (Protect Pace) Trial, and Right Ventricular Apical versus Septal Pacing (RASP) Trial—with left ventricular ejection fraction as the primary endpoint and planned long-term follow-up (24 to 36 months)—are currently under way. Short-term hemodynamic data suggest that biventricular pacing may have beneficial effects in patients with reduced left ventricular function and a normal QRS duration (<0.12 seconds) who will require a significant percent of ventricular pacing.[27] Similarly, in the Multicenter Automatic Defibrillator Implant Trial–Cardiac Resynchronization Therapy (MADIT-CRT) trial, biventricular pacing was associated with a 41% reduction in heart failure events in patients with reduced left ventricular function (ejection fraction [EF] <30%) and mild heart failure symptoms (NYHA classes I and II).[28]

Certain atrial pacing sites may have some beneficial effect with regard to the development of atrial arrhythmias. Early small prospective studies have suggested that pacing from sites along the inter-atrial septum, including the coronary sinus os and Bachmann's bundle, may be associated with a decreased incidence of atrial fibrillation and other atrial arrhythmias.[29,30] However, subsequent moderately sized trials have suggested that the benefits of atrial pacing from selected sites such as the atrial septum are not uniform, with either no benefit or only modest benefit (30% reduction in atrial fibrillation burden).[31,32] The Septal Pacing for Atrial Fibrillation Suppression Evaluation (SAFE) trial has been designed as a large multicenter trial to evaluate the association of septal pacing with a decrease in the development of persistent (>7 days) atrial fibrillation. Early studies have suggested that multiple-site atrial pacing (usually from a lateral right atrial site and a second atrial site at the coronary sinus os or within the coronary sinus), in addition to using specific atrial sites, results in a more normal atrial activation sequence with an accompanying improvement in the contribution of atrial contraction.[33,34] Finally, multiple-site atrial pacing may reduce atrial vulnerability to induction of atrial fibrillation.[33]

Power Sources

Lithium iodine has been the traditional source of battery power for the past three decades because of its stable and predictable characteristics. Currently available batteries can have a lifetime of 8 to 12 years, depending on use and programmed output. Pulse generator replacement is associated with a twofold increased risk of pocket infection compared with initial pacemaker implants. Therefore, the development of reliable leads, and thus devices with longer battery life, would be extremely beneficial and result in a significant reduction in the use of health care resources.[2] Lithium carbon monofluoride batteries that may offer higher energy density, thus allowing for longer service life, are being developed. It should be noted that the longest-lasting pacemaker reported in the medical literature is a nuclear-powered pacemaker that was implanted in 1973 and was still operating in 2007.[35] Although they are long-lasting, nuclear pacemakers are no longer available because of high initial costs and the rapid evolution of lithium iodine power sources in the 1970s. However, engineers are evaluating the feasibility of using newer-generation nuclear batteries in implantable medical devices. Another avenue for improving cardiac longevity has been the development of energy-efficient circuit components (e.g., capacitors) that use unusual materials such as wet tantalum. Finally, theories on the possibility of "harvesting and storing" the kinetic energy of heart motion and using it to power a pacemaker have been proposed.

Lead Design, Lead Reliability, and "Leadless" Pacing

Significant improvements in lead design have taken place in the past 10 years. Manufacturers have developed high-impedance electrodes that reduce the amount of current required for myocardial stimulation. In one small clinical study of 40 patients, high-impedance electrodes were shown to reduce by 50% the current required for pacing, but unfortunately this did not lead to a longer time to pulse generator replacement, perhaps partly because of the small number of patients (24 of 40) who had complete follow-up.[36]

The focus of modern lead design has shifted to increasing reliability, since the pacing lead remains the most common cause of device failure. Recent studies have suggested that the lead failure rate is approximately 20% to 30% in the first 10 years and that attrition of lead integrity continues thereafter.[37,38] Manufacturers are investigating new lead designs that employ cables rather than coils and multiple layers of insulation to improve lead longevity. Several novel technologies incorporating a remote "receiver" that is placed within the heart and is coupled wirelessly to a "transmitter" located in the shoulder area are being developed.[39-41] Ultrasound bursts from a transmitter on the chest have resulted in successful ventricular pacing in animal models and during acute hemodynamic studies in humans (Figure 38-5).[39,40] More recently, pacing has been achieved in an experimental model by using magnetic fields to generate the power required for cardiac stimulation.[41]

Biologic Pacing

Over the past decade, interest has been growing in developing a biologic pacemaker. Several approaches to developing such a device exist.[42-45] The first method is to change the function of existing cardiac myocytes by increasing β-adrenergic receptor expression or by encouraging the development of diastolic depolarization; the latter can be achieved by blocking the background potassium (K^+) currents responsible for the resting membrane potential or by enhancing diastolic currents (I_f).[42,43] The second general strategy is to use cell therapy approaches to differentiate stem cells into cardiac myocytes with pacing characteristics.[44] In canine models, a "tandem system" that uses both a biologic pacing system and an electronic system has been implanted.[45] The biologic system functions most of the time and responds appropriately to catecholamine challenge. When the biologic system slows, the electronic system takes over. As this technology matures, it is likely that pacemakers using hybrid biology hardware architecture or perhaps even a stand-alone biologic design will become commercially available for clinical use.

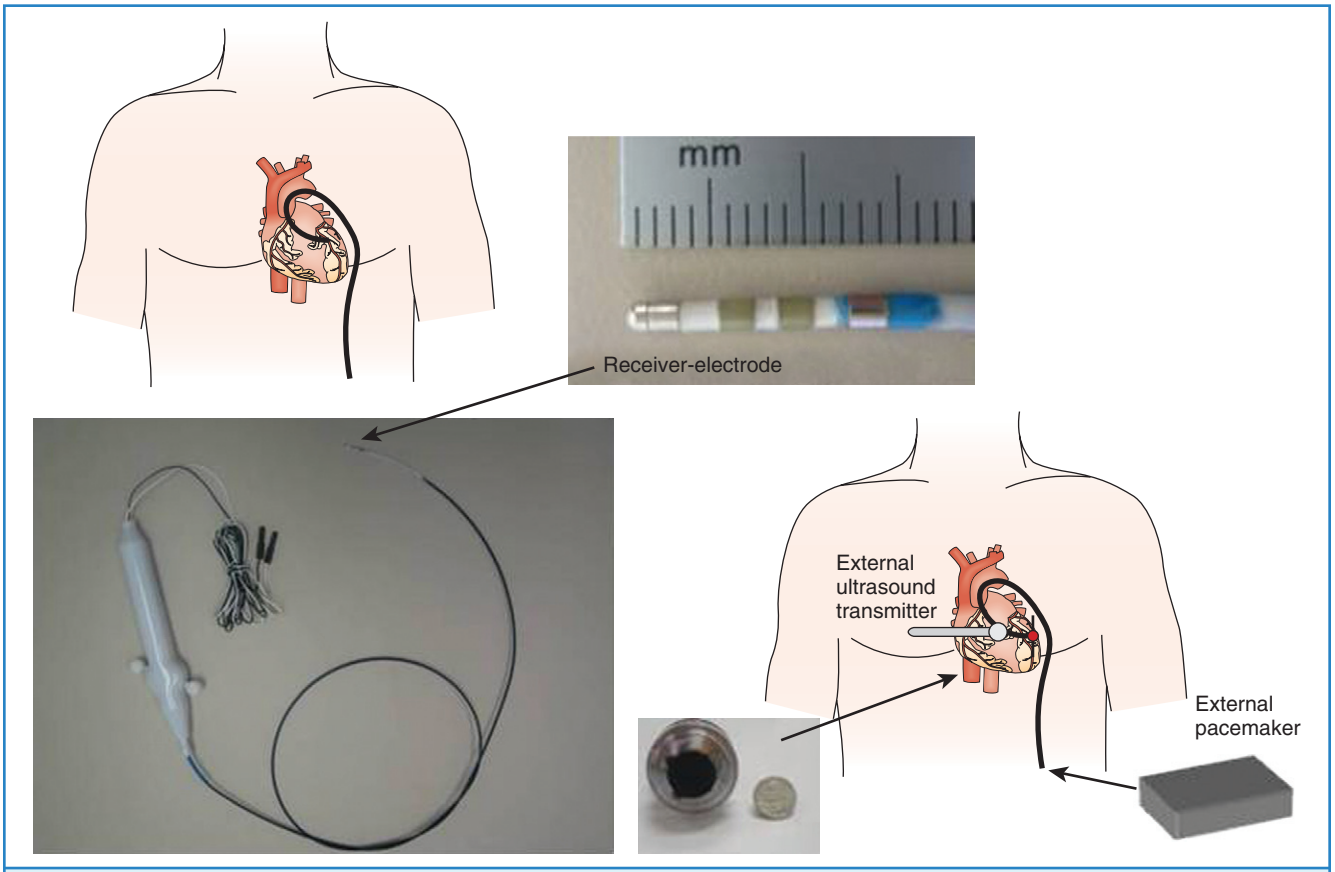

FIGURE 38-5 Catheter used for ultrasound leadless pacing. The catheter tip contains a receiving transducer and a circuitry that converts ultrasound energy to electrical energy, which is transmitted to the myocardium via the distal electrodes. *(Courtesy Debra Echt, EBR Systems, Sunnyvale, CA.)*

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CHAPTER 39

Sinus Node Dysfunction

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In the early 1900s, Keith and Flack identified the sinus node as the region responsible for the activation of the heart.[1] Laslett first suggested sinus node dysfunction as a cause of bradycardia in 1909, and during the 1950s and 1960s, Short, Ferrer, Lown, and others described the clinical spectrum of sinus node dysfunction commonly called *sick sinus syndrome resting sinus bradycardia*.[2-5] Sinus node dysfunction can have multiple electrocardiographic manifestations, including sinus pauses, bradycardia-tachycardia syndrome, and inappropriate sinus node response to exercise (chronotropic incompetence).

Epidemiology

It can be difficult to differentiate sinus node dysfunction from physiological sinus bradycardia in a specific population. In a study of 50 young adult males, 24-hour ambulatory electrocardiographic monitoring revealed that 24% of the study group had transient heart rates less than 40 beats/min, pauses up to 1.7 seconds while awake, and 2.1-second pauses while asleep.[6] Similarly, in a study of 50 young adult women, pauses from 1.6 to 1.9 seconds were observed.[7] In older asymptomatic individuals, transient heart rates less than 40 beats/min and pauses of 1.5 to 2.0 seconds were observed in less than 2%.[8] The decreased incidence of nocturnal bradycardia in this normal older adult population is probably caused by decrease in vagal tone that occurs with increasing age.

Sinus node dysfunction should be suspected when a patient describes symptoms of fatigue, syncope or presyncope, or exercise intolerance and is noted to have sinus bradycardia or pauses on the 12-lead electrocardiogram (ECG) or during Holter monitoring. In general, symptomatic sinus node dysfunction increases with age, with the incidence doubling between the fifth and sixth decades of life. In one study of approximately 9000 patients visiting a regional cardiac center in Belgium, Kulbertus et al estimated that the incidence of sinus node dysfunction is less than 5 per 3000 people older than 50 years of age.[9] However, sinus node dysfunction is more commonly identified today because of an increased older adult population and increased physician awareness. In recent epidemiologic studies, sinus node dysfunction accounted for approximately 50% of the 300,000 new pacemakers implanted in the United States and 20% to 30% of the 900,000 new pacemakers implanted in Europe.[10-12]

Although more common in older adult patients, it is important to note that several specific younger patient groups can also have sinus node dysfunction. First, patients with congenital heart disease can have sinus node dysfunction. In 39 patients younger than 40 years of age who underwent pacemaker implantation for sinus node dysfunction at the Mayo Clinic, 64% had associated congenital heart disease.[13] The most common condition was transposition of the great arteries corrected by a Mustard operation, since this procedure requires extensive atriotomies. Second, sinus node dysfunction is commonly observed after heart transplantation. Third, several familial forms of sinus node dysfunction have been identified and account for approximately 2% of patients who present with sinus node dysfunction.[14-16] Bharati et al described a family with congenital absence of sinus rhythm. Several other investigators have described different forms of sinus node dysfunction that appeared to be genetically transmitted.[14] Finally, sinus node dysfunction is observed in approximately 4% of patients after cardiac transplantation.[17,18] Some, but not all, studies have found that a heart from a donor older than 40 years of age is associated with a higher incidence of sinus node dysfunction, necessitating permanent cardiac pacing.[17,18] It appears that the incidence of permanent pacing after transplantation has decreased significantly with the widespread use of bicaval anastomoses rather than bi-atrial anastomoses.[19]

Anatomy

As described by Keith and Flack, the sinus node was shown to be lying in the terminal groove (sulcus terminalis), in the lateral part of the junction between the superior caval vein and the right atrium. This lateral position was endorsed by Koch and by most subsequent investigators.[1,20-23] The horseshoe-shaped arrangement, with the node situated anteriorly and draped over the crest of the atrial appendage, as described by Hudson, is found in approximately 10% of hearts (Figure 39-1).[24,25]

The shape of the node, most commonly, is like that of a tadpole, with the head section situated anterosuperiorly and the tapering tail extending for a variable distance inferiorly toward the entrance of the inferior vena cava.[25,26] The fatty tissues of the terminal groove serve as the epicardial landmark, whereas the terminal crest (crista terminalis) in the anterolateral quadrant of the entrance of the superior vena cava is the endocardial landmark for the nodal head. In the adult heart, the nodal body is approximately 1 to 2 cm long, but the tail portion can extend considerably longer. In the subepicardium, the long axis of the node is parallel to the terminal groove, but the body and tail then gradually penetrate intramyocardially toward the subendocardium when traced inferiorly. Thus, while the nodal head is in the subepicardium of the terminal crest, the tail portion is close to the subendocardium.[26]

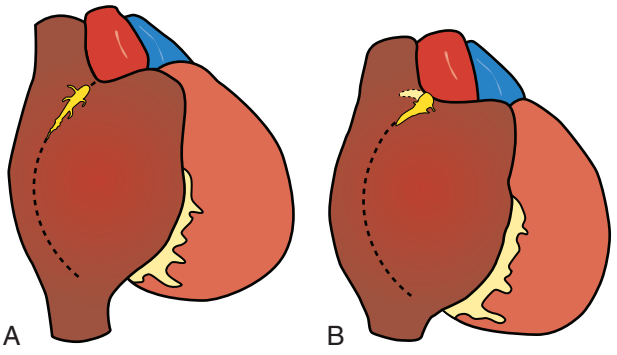


FIGURE 39-1 Hearts viewed from the right show the typical location of the sinus node in the terminal groove (**A**) and the horseshoe variant (**B**).

On histology, the node appears as a dense aggregation. The nodal cells are specialized myocytes that are histologically distinct from the ordinary myocardium of the atrial walls (Figure 39-2). They are small interlacing cells, less darkly stained, and with fewer myofibrils than in the neighboring ordinary myocytes. The specialized cells are associated with a fibrous tissue matrix. Ordinary myocardial cells are sometimes found scattered within the node. The nodal margins may be discrete, with fibrous separation from the atrial myocardium, or interdigitate through a short transitional zone. In the latter, tongues of nodal and transitional cells extend into the atrial myocardium. Prongs radiating from the nodal body are common. An anatomic study demonstrated 1 to 10 tongues of nodal tissue radiating mostly from the nodal body.[26] The radiations penetrated the terminal crest in all directions, and some even extended into the muscular sleeve around the superior caval vein (see Figure 39-2). Another interesting observation from this study was the fragmentation of the tail portion of the node. In nearly two thirds of the nodes examined, the distal tail was traced to islands of nodal tissues among the fibro-fatty tissues and atrial myocytes in the subendocardium.

Innervation

The sinus node is the most densely innervated component of the cardiac conduction system.[27,28] In the epicardium and in the environs of the node are collections of ganglion cells, which contribute vagal postganglionated nerve fibers to the node. The central part of the node is more densely populated with nerve fibers and bundles than are the peripheral regions.[27]

Arterial Supply

The artery supplying the node is a branch from the right coronary artery in 55% of hearts and from the left coronary artery in the remainder (Figure 39-3).[29] When arising from the right coronary artery, it is usually the first atrial artery and ascends in the interatrial groove. Rarely, the artery arises near the acute margin from the lateral atrial artery to ascend the lateral wall of the right atrial appendage. The nodal artery is often a branch of the left anterior atrial artery when it arises from the left coronary system. In some hearts, it is a branch of the left lateral atrial artery. In both settings, it traverses the anterior wall of the left atrium and crosses the anterosuperior wall to reach the sinus node. The nodal artery approaches the node from an anterior direction in the majority of hearts but can also approach from a posterior direction or form an arterial circle around the cavoatrial junction.[29] Typically, a prominent nodal artery passes centrally through the length of the nodal body and gives rise to small side branches along the way. In some hearts, the nodal artery branches as it approaches the node and several branches penetrate the nodal body. Occasionally, the artery passes along the side of the node and sends branches into the node. When the node is supplied by an arterial circle, the arteries enter the node at both ends.

Age-Related Changes

The sinus node displays marked histologic differences in infancy and in adulthood. In infants and in children, nodal cells predominate and the node appears relatively large compared with the bulk of the terminal crest. In the young individual, the node comprises nodal cells and fibrous tissue in nearly equal proportions.[30] From about 30 years of age, fibrous tissue becomes more prominent, and the node appears smaller (see Figure 39-2).[31] In the older adult, nodal cells decline, with increase in fibrosis. From 70 years onward, nodal cells may make up only 10% of the sinus node in patients who were in sinus rhythm up to death.[31] However, as Shirashi and colleagues noted, the average volume of nodal cells in adults is 2.4 times more than in infants.[32] This is mainly due to cellular hypertrophy. The same group found a 7.4 times increase in the volume of interstitial connective tissue in adult sinus nodes compared with that in infants. Another study using stains that are more specific for collagen tissue found an increase in collagen from infancy to adulthood, but the amount remains constant throughout adulthood.[33] Contrary to general concepts, a detailed study has found that the loss of nodal cells is independent of the degree of arteriosclerosis.[34] Fibrosis causing loss of continuity with the neighboring myocardium and increased fibrosis in the nodal approaches and internodal myocardium occur with increasing age. Using semi-quantitative assessment, Chow et al found dominance of sympathetic nerves initially in infancy, which gradually changed to co-dominance of sympathetic and parasympathetic nerves with increasing age.[28]

Sinus Node in Congenital Heart Malformations

The majority of malformed hearts have the atrial chambers in their usual positions and the sinus node in its regular position. Abnormal positions of the sinus node have been found to occur in hearts with juxtaposition of the right appendage and in hearts with an atrial arrangement other than the usual type (Figure 39-4). Left juxtaposition exists when both atrial appendages lie to the left side of the arterial trunks rather than to either side at the base of the heart. In this malformation, the right appendage passes between the front of the atrial chambers and the great arteries. While the orifice of the superior vena cava remains in its usual position, the terminal crest is distorted, and the location of the sinus node is deviated. A study of six hearts with left juxtaposition showed a variable displacement of the node anteriorly (see Figure 39-4).[35]

Other malformations with abnormal positions of the sinus node are those that affect the arrangement of the atrial chambers. When atrial chambers are arranged in mirror-image fashion, the morphologically right atrium containing the sinus node is in the left-sided position. When bilateral right atrial appendages are present, as in right atrial isomerism, the sinus node is duplicated and is situated in both right and left positions.[36,37] By contrast,

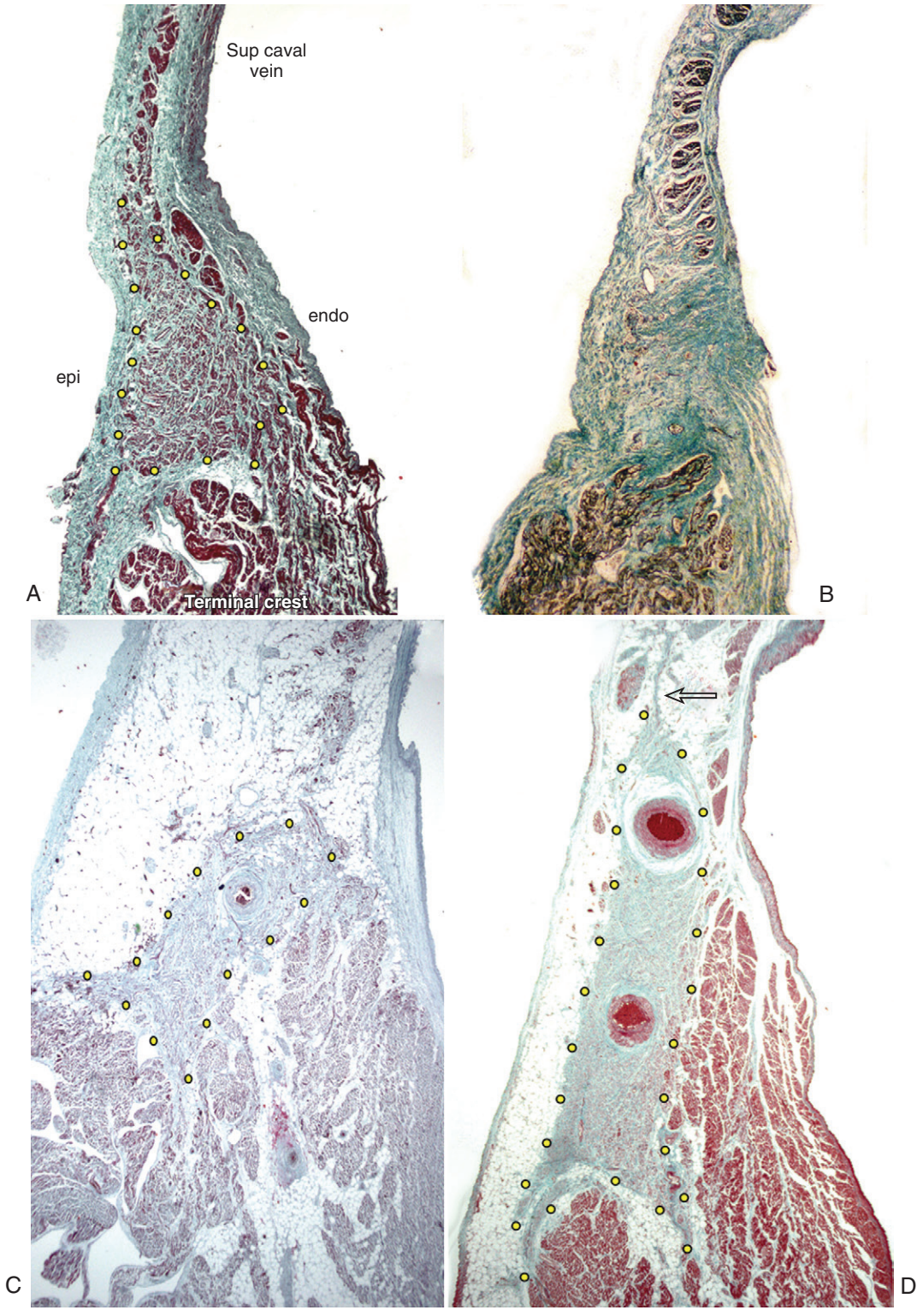


FIGURE 39-2 Longitudinal sections through the cavoatrial junction showing the variations in structure of the sinus node (*within yellow dots*) in four cases. The stain (Masson's trichrome) colors the fibrous tissue green and the myocardium red. The normal sinus node from the infant or child (**A**) is relatively large and has abundant specialized myocytes. In contrast, the sinus node is absent and the area replaced with fibrous tissue (**B**) in **D,** an infant with congenital heart block. **C,** The sinus node is relatively small in this section from a 16-year-old. **D,** A normal sinus node from an adult showing increased fibrous tissue and nodal extensions. The superior extension (*arrow*) penetrates into the musculature of the superior vena cava. *epi*, Epicardium; *endo*, endocardium; *Sup*, superior.

when both atrial chambers are of left morphology, as in left atrial isomerism, the terminal crests are absent.[37] Although, in this group, bilateral superior venae cavae can be present, the sinus node is not found in its usual position relative to either vena cava. When present, it is inferiorly displaced and smaller than usual. In some hearts, a remnant of specialized tissue is found in the posterior atrial wall near the atrioventricular (AV) junction, and in other hearts no nodal tissue can be identified.

Pathology

Many factors have been implicated in the etiology of sinus node dysfunction. Amyloid deposition within the sinus node and adjacent musculature is well recognized, as are anatomic findings of diffuse fibrosis or fibro-fatty replacement. Senile amyloidosis in older adults affects the atrial myocardium, including the approaches to the sinus node and the node itself. Marked loss of nodal cells associated with increased fibrosis or fatty changes of the atrial myocardium has been reported in sick sinus syndrome.[33,38] Although usually seen in the older patient, these changes can also be seen in the young. Hypoplastic or atrophic sinus node may exist as a congenital anomaly that, with age-related loss of specialized cells, may progress to nodal dysfunction in later life or may be present in infancy (see Figure 39-2).[39-41]

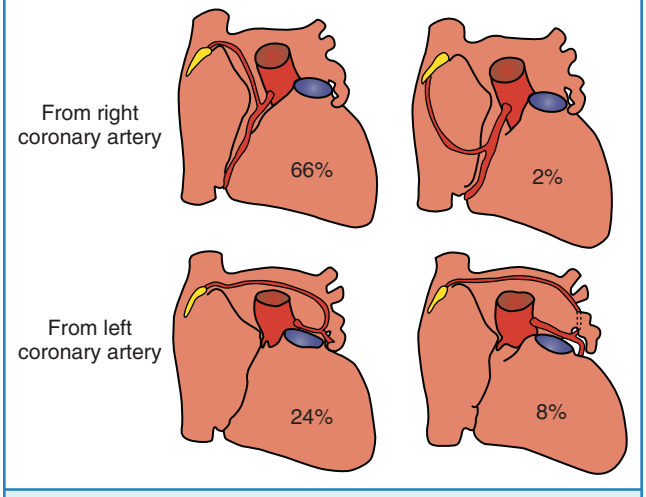


FIGURE 39-3 Variations in the course taken by the sinus node artery.

Basic Electrophysiology of the Sinus Node

The structural and functional organization of the sinus node is quite complex, and significant differences are seen in the organization of the sinus node among species.[42,43] The most extensive studies of the sinus node have been performed in rabbits. The rabbit node contains prototypical, small, structurally primitive pacemaker cells that are concentrated in the center; larger transitional latent pacemaker cells that are concentrated more peripherally; and intermingled, nonpacing atrial cells extending into the node from the atrial margins of the node in strands that are more prominent in the periphery. The cells within the node are relatively poorly coupled by gap junctions, and substantial interstitial tissue is interspersed among the fascicles of nodal cells.[44] The resultant relatively poor intercellular communication slows the propagation of impulses from the central pacemaking regions toward the periphery of the node. In addition, the coupling of the transitional cells near the margins of the node with atrial myocardial cells is not a smooth continuum but consists of irregular junctions of interweaving strands of transitional cells and atrial cells extending into the interior of the node. Mapping of electrograms in and around the node has disclosed an apparent "multicentric" initiation of activation that likely represents irregular

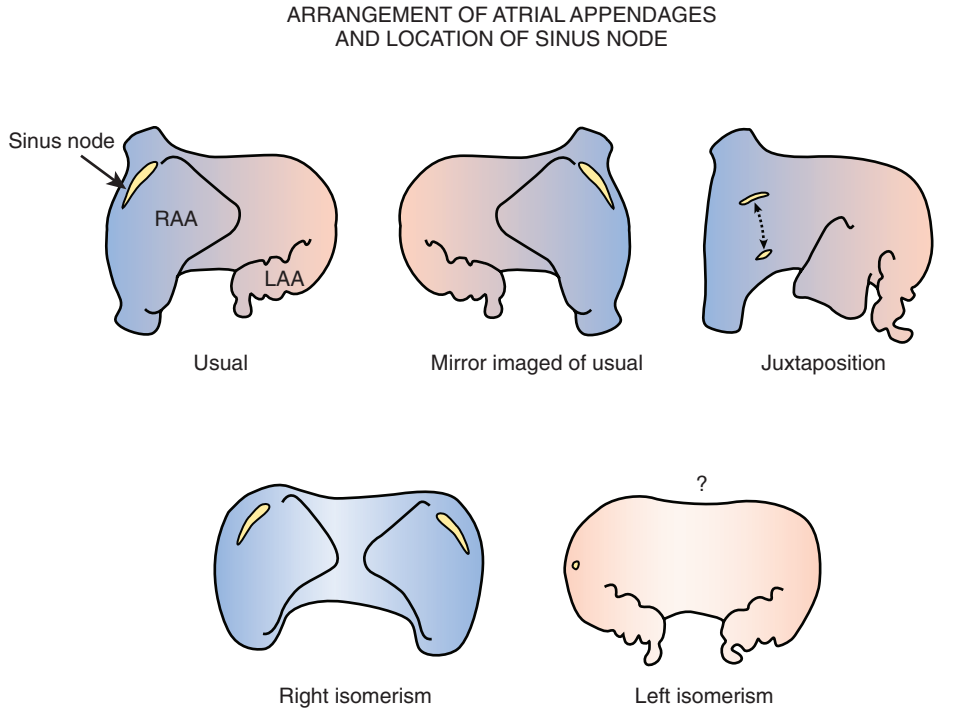


FIGURE 39-4 Sinus node showing variations in location according to the atrial malformation. *RAA*, Right atrial appendage; *LAA*, left atrial appendage.

propagation to the atrial myocardium rather than simultaneous generation of impulses at separate sites. The node preferentially connects to the atrium in the superior aspects of the crista terminalis, and conduction block seems to exit the node in the direction of the atrial septum.

A dense representation of sympathetic and parasympathetic nerves and ganglia in the node ensures a sensitive autonomic responsiveness.[45] With increasing vagal influence, the primary pacemaking site near the superior aspect of the node tends to migrate inferiorly, whereas an increasing adrenergic influence produces return to the primary dominant pacemaker sites in the superior region of the node. Detailed and sensitive analyses of P wave morphology and mapping of the sinus node indicate a dynamic shifting of pacemaker sites as well as changes in heart rate.

Action Potentials

Small, primitive pacemaker cells in the interior of the node generate the dominant pacemaker potentials and show the least polarized maximum diastolic potentials (–60 to –40 mV), the most rapid rates of diastolic depolarization with smooth transition from end-diastole to the upstroke, and the slowest upstroke velocities (≈1 to 10 V/sec) (Figure 39-5).[46] Latent pacemakers are concentrated more peripherally in the node. These cells are more polarized and show less rapid diastolic depolarization, a more abrupt transition from diastole to upstroke, and more rapid upstrokes. A continuous gradation of the properties of transitional cells—from the characteristics of primary pacemaker cells to the properties of highly polarized surrounding atrial cells with stable resting potentials close to –80 mV and upstroke velocities approaching 100 V/sec—can be seen. This gradation of properties is conditioned by cell coupling and electrotonic interaction as well as by the differing intrinsic properties of the myocytes within the node. Because of the electrotonic influence of atrial cells, the pacemaker capabilities of transitional cells are muted, whereas the more remotely connected interior cells are shielded from nonpacing atrial myocytes, allowing them to maintain pacemaker dominance.[47] Separation of latent pacemaker cells near the atrial margins from the atrium and from the centrally located dominant pacemakers results in a faster intrinsic rate in latent pacemakers freed from the influence of nonpacemaking atrial cells. Cells in other parts of the atrium can also act as backup pacemakers, especially those in the inferior portions of the node near the coronary sinus. These pacemaker cells can respond appropriately to autonomic influence and, under abnormal conditions, can usurp control of the heart. The electrophysiological properties of these subsidiary pacemakers have not been as well characterized as those of the sinus node.

Recent studies indicate an influence of the fibroblasts within the node on pacemaker function and conduction.[48] Inexcitable fibroblasts can couple with sinus node cells through gap junctions and depolarize the cells, reduce the rate of pacemaking, and impair conduction. Loss of sinus node myocytes associated with an increase in fibroblasts, collagen, and elastin has been implicated in sinus slowing and increased incidence of sinus node dysfunction and sinus node block with aging.

Detailed mapping by electrical and optical methods suggests that the sinus node is functionally connected to the atrial myocardium in discrete, relatively narrow sites, rather than diffusely along the margins of the node.[49,50] At these sites, the propagating wavefront encounters a larger mass of the myocardium and source–sink mismatch that diminishes the safety factor for conduction. With certain conditions, including aging, that cause fibrosis or reduction of excitatory current, sinus node block may occur.

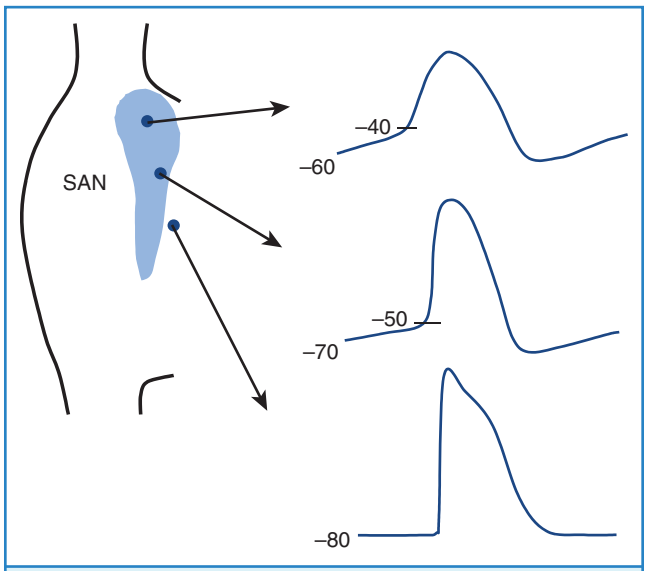


FIGURE 39-5 Samples of action potentials recorded from different regions of the sinus node (*SAN*) from the center to the periphery of the node.

Currents

Sinus node pacemaker cells are relatively depolarized because of an absence or paucity of channels for the I_{K1} current.[51,52] These channels are plentiful and open at negative membrane potentials in atrial and ventricular myocytes. They establish a dominance of K^+ permeability in the resting state, thereby determining a resting potential approximating the K^+ equilibrium potential (≈ –90 mV). The absence of these channels is most complete in the small, central pacemaker cells operating at diastolic potentials between –60 mV and –30 mV. In larger, more polarized transitional cells, I_{K1} may be present but reduced to varying degrees. The low upstroke velocities of these cells are related to a lack of operating sodium (Na^+) channels, those channels that transmit the intense excitatory Na^+ current in atrial and ventricular cells.[52] The absence or paucity of this excitatory current is caused by a deficiency of the channels in individual myocytes and the depolarization of the myocytes during diastole to levels of membrane potential at which Na^+ channels, if present, would be inactivated. The smallest cells may lack Na^+ channels entirely. Larger transitional cells may contain Na^+ channels and may operate at diastolic potentials at which Na^+ channels can be activated to provide some excitatory Na^+ current and more rapid upstrokes. The slow and diminutive upstrokes in the primary pacemaker cells are generated by the L-type Ca^{2+} current (I_{CaL}), which serves as the trigger for release of Ca^{2+} by the sarcoplasmic reticulum and therefore the trigger for contraction in all cardiac cells but is the primary excitatory current in depolarized sinus nodal cells. This current is slower and far less intense than the Na^+ current, accounting for the poor

upstrokes and slow conduction within the node. The currents producing diastolic depolarization, which is the fundamental pacemaker potential, comprise a multitude of candidates, but no uniform consensus about this exists at present.[53-57] The "funny" current I_f, encoded by *HCN4*, is a nonspecific cation current that is mainly an inward Na^+ current activating relatively slowly at negative membrane potentials in the range of diastolic potentials.[58] It becomes more intense at more negative membrane potentials. This current is well expressed in sinus nodal cells, responds appropriately to adrenergic and cholinergic stimulation, and thus is a plausible candidate to be an important pacemaker current. However, some studies have shown activation at more negative levels than the diastolic potentials of the primary pacemakers (below –60 mV) and a greater representation in peripheral latent pacemakers.

The I_f current is enhanced in the diastolic potential range of sinus node cells by activation of adenylate cyclase, for example, with adrenergic (sympathetic) stimulation, increasing cyclic adenosine monophosphate (cAMP) in the cytosol. Binding of cAMP to the channel increases the probability of the channel opening in the voltage range of –40 mV to –100 mV. Cholinergic (vagal) stimulation reduces cAMP, the I_f current, and the rate of pacemaking. Downregulation of *HCN4* and I_f with prolonged atrial tachycardia may account for the impairment of sinus node function in atrial fibrillation and tachycardia.[59,60]

The importance of I_f in pacemaking in human sinus node had been validated by recent discoveries. Mutations in *HCN4* impair sinus node pacemaking.[56,61] Selective blockers of I_f have been demonstrated to slow sinus rate in human subjects.[58] I_f has been demonstrated in sinus node cells from excised human sinus node.[62]

In the absence of I_{K1}, the delayed rectifier K^+ currents I_{Kr} and I_{Ks}, which are activated during the action potential, can play a role in the attainment of the maximum diastolic potential by providing the K^+ permeability that would bring the transmembrane potential close to the K^+ equilibrium potential at the end of the action potential when they are fully activated. As these currents deactivate in diastole, the membrane potential would drift toward the more positive equilibrium potentials of other major ions such a Na^+, Ca^{2+}, and Cl^-. It has been argued that one or another of the delayed rectifier currents is the major pacemaker current.[54] However, although I_{Ks} has an appropriate autonomic sensitivity, I_{Kr} does not. I_{Ks} is not prominent in the sinus nodes of all species.

Ca^{2+} currents, both I_{CaL} and the T-type Ca^{2+} current (I_{CaT}), have also been implicated in pacemaker function. I_{CaL}, which has an activation threshold that is more positive than –40 mV in most cardiac cells, could be active toward the end of diastolic depolarization in the depolarized primary pacemaker cells, whereas I_{CaT}, with an activation threshold that is more negative, might be active in earlier phases of diastolic depolarization and in latent pacemaker cells. I_{CaL} responds to autonomic influence in a manner similar to that of the sinus node, and recent studies have suggested that the activation threshold may be more negative in sinus nodal cells.

It has recently been proposed that inward Na^+/Ca^{2+} exchange current (NCX) activated by spontaneous release of Ca^{2+} from sarcoplasmic reticulum is a major depolarizing current in late diastole in sinus node cells. This postulated "internal Ca^{2+} clock" is driven by high levels of phosphorylation of Ca^{2+}-cycling proteins, modulated by adrenergic and cholinergic stimulation.[57]

Pacemaker activity can be notably influenced by the acetylcholine-activated K^+ current, $I_{K,Ach}$, which markedly increases K^+ permeability throughout the cycle, speeding repolarization, hyperpolarizing the cell, and reducing the rate of diastolic depolarization. This current appears to be less sensitive to acetylcholine than the I_f current in the sinus node. The complexities of pacemaker function have yet to be fully clarified. Contemporary molecular biologic techniques will be powerful tools to clarify the locations and functions of channels in the sinus node and their roles in sinoatrial (SA) nodal pacemaking.

Etiology

Sinus node dysfunction results from various conditions that have in common the capability to depress automaticity in and electrical conduction from the sinus node and perinodal and atrial tissues. These conditions can be intrinsic, resulting from structural damage to the sinus node, or extrinsic, caused by medications or systemic illnesses. The clinical and electrocardiographic manifestation of sinus node dysfunction is inappropriate sinus or atrial bradycardia.[63-66] Some patients may also experience episodes of supraventricular tachycardias (tachycardia-bradycardia syndrome). Because the clinical manifestations of sinus node dysfunction can mimic normal physiological conditions (bradycardia) or can be caused by diseases that do not affect the sinus node (supraventricular tachycardias), the assessment and management of patients with suspected sinus node dysfunction can be challenging.[67-69]

Extrinsic Causes of Sinus Node Dysfunction

Sinus bradycardia can be caused by medications that suppress automaticity; these include β-blockers, some calcium channel blockers (diltiazem and verapamil), digoxin (especially in the presence of high vagal tone), class I and III antiarrhythmic medications, ivabradine (currently available in Europe), and sympatholytic drugs such as clonidine. Sinus bradycardia in these cases is frequently transient and reversible once the offending agent is withdrawn.

Sinus bradycardias can also be a manifestation of systemic illnesses or other extrinsic conditions such as hypothyroidism; hypoxemia caused by sleep apnea; increased intracranial pressure; or increased vagal tone that occurs, for example, during endotracheal suctioning, vomiting, and the Valsalva maneuver. These conditions are important to diagnose, since their appropriate treatment often results in resumption of normal sinus node function.

Intrinsic Causes of Sinus Node Dysfunction

Intrinsic sinus node dysfunction is usually caused by degenerative processes involving the sinus node and the sinus node area. The syndrome is usually acquired but can rarely be familial.[8] Sinus node dysfunction is present when inappropriate sinus bradycardia, pauses in sinus rhythm (sinus arrest), sinus node block, or a combination of these exist.[70] The degenerative process and associated fibrosis may also involve the AV node and intraventricular conduction system; as many as 17% of patients with sick sinus syndrome have evidence of AV block and bundle branch block.[71]

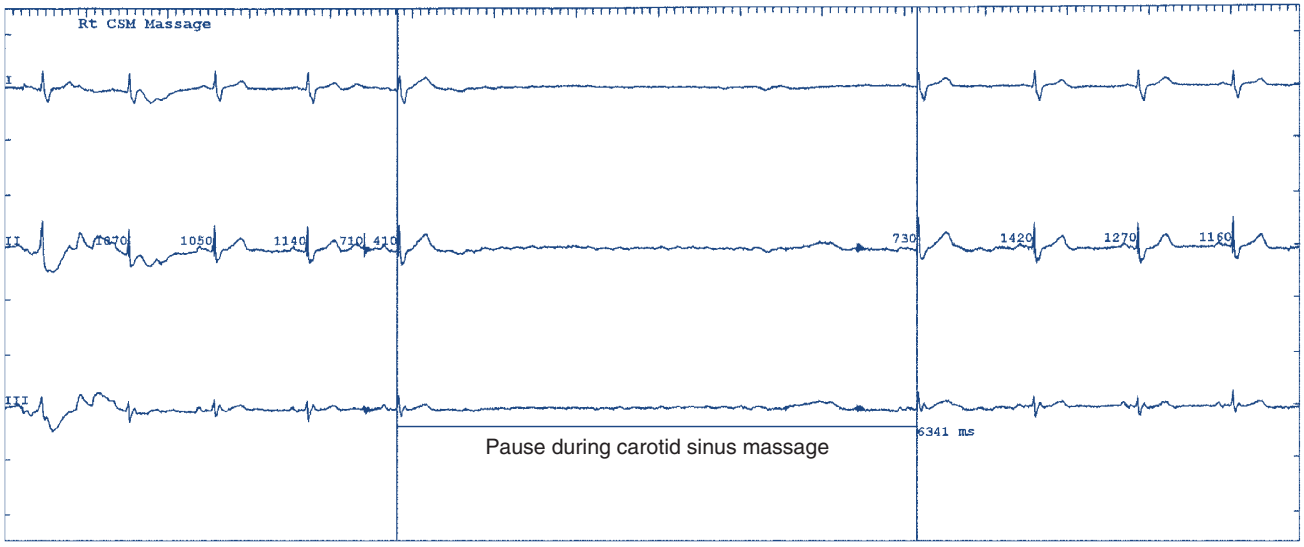


FIGURE 39-6 Sinus arrest during right carotid massage in a female older adult with recurrent syncope, as seen on simultaneous three-lead electrocardiogram (ECG) rhythm strip. Note that the pause exceeds 6 seconds and persists beyond the duration of the massage. Numbers on ECG leads II and III indicate duration of intervals in milliseconds (*ms*).

Natural History

The natural history of sick sinus syndrome is one of spontaneous clinical improvement alternating with periods of clinical deterioration. Patients generally seek medical attention when they are symptomatic from bradycardia. In the majority of cases, the heart rate spontaneously increases, and symptoms diminish.[72-74] However, the clinical course is not predictable. Even patients with more severe symptoms such as syncope may remain free of symptom recurrence for years, and slightly more than half do not experience another syncopal episode over a 4-year follow-up.[74] No clear explanation exists for this erratic course of the syndrome. The autonomic nervous system may play an important role in the genesis of symptoms, especially in the trigger of syncope.[74] The prevalence of abnormal responses to carotid sinus massage (pauses exceeding 3 seconds) and tilt table testing is significantly higher in patients who experience syncope than in those who do not, highlighting the contribution of abnormal neural reflexes in the pathophysiology (Figure 39-6).[74,75]

Although symptoms are common in patients with sick sinus syndrome, survival is usually not affected, even in patients who develop syncope.[76] Death related directly to dysfunction of the sinus node occurs in less than 2% of patients over 6 to 7 years of follow-up.[77,78] However, patients with sick sinus syndrome often have comorbid conditions that can shorten their lifespan. Coronary atherosclerosis is the most prevalent among these conditions, although myocardial ischemia and infarction, congestive heart failure, and advanced age are also common.[79,80] In one report, patients with sick sinus syndrome had a 4% to 5% excess annual mortality in the first 5 years of follow-up compared with an age-matched and sex-matched population.[81] However, the mortality in patients without other coexisting diseases at the time of diagnosis of sinus node dysfunction did not differ significantly from that observed in controls. Thus, although medical intervention and permanent cardiac pacing may be required to improve symptoms, no data exist supporting the claim that these management strategies improve survival.

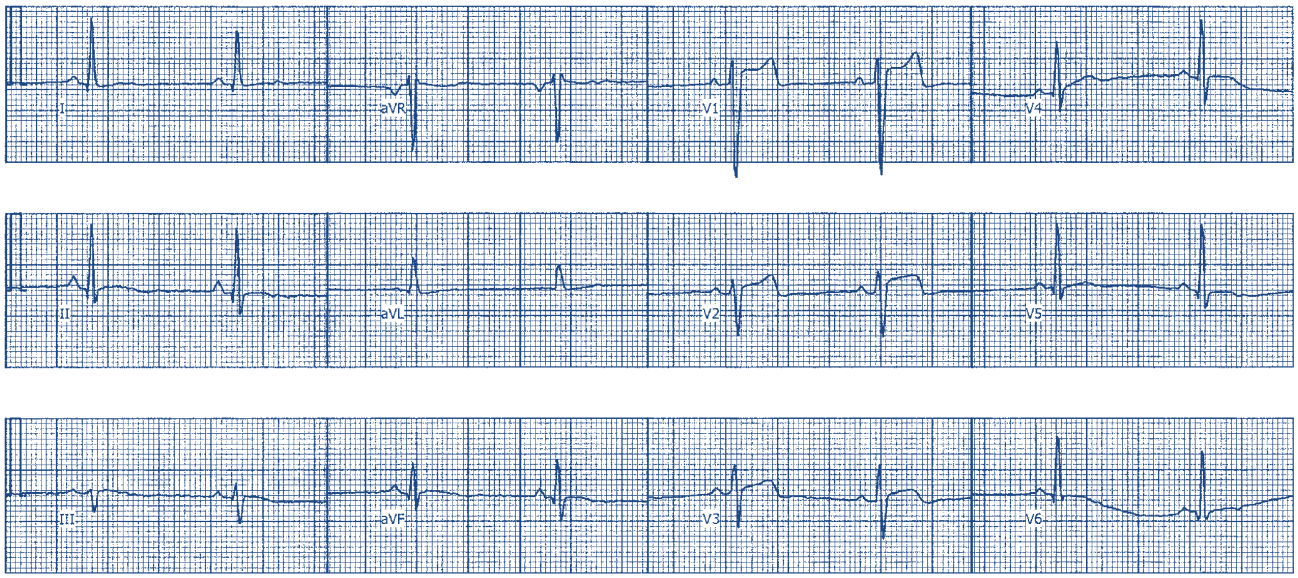
Clinical Manifestations

The clinical manifestations of sick sinus syndrome are caused by both bradycardia and tachycardia. In bradycardia-tachycardia syndrome, patients experience paroxysmal episodes of supraventricular tachycardia, which can be atrial tachycardia, atrial flutter or fibrillation, or re-entry tachycardia (Figure 39-7). More than one type of tachycardia may occur in the same patient. Episodes of rapid heart rate can lead to palpitations, angina, and syncope. Conversely, slowing of the heart rate without a compensatory increase in stroke volume leads to a reduction in cardiac output, which results in fatigue, weakness, lightheadedness, and dizziness.

Failure of the heart rate to increase appropriately with exercise (chronotropic incompetence) is a manifestation of sinus node dysfunction. Proposed definitions for chronotropic incompetence include failure to reach 85% of age-predicted maximum heart rate at peak exercise, failure to achieve a heart rate above 100 beats/min, or a maximal heart rate during exercise greater than two standard deviations below that of a control population.[82-84] In patients with chronotropic incompetence, symptoms may be present only during activity.

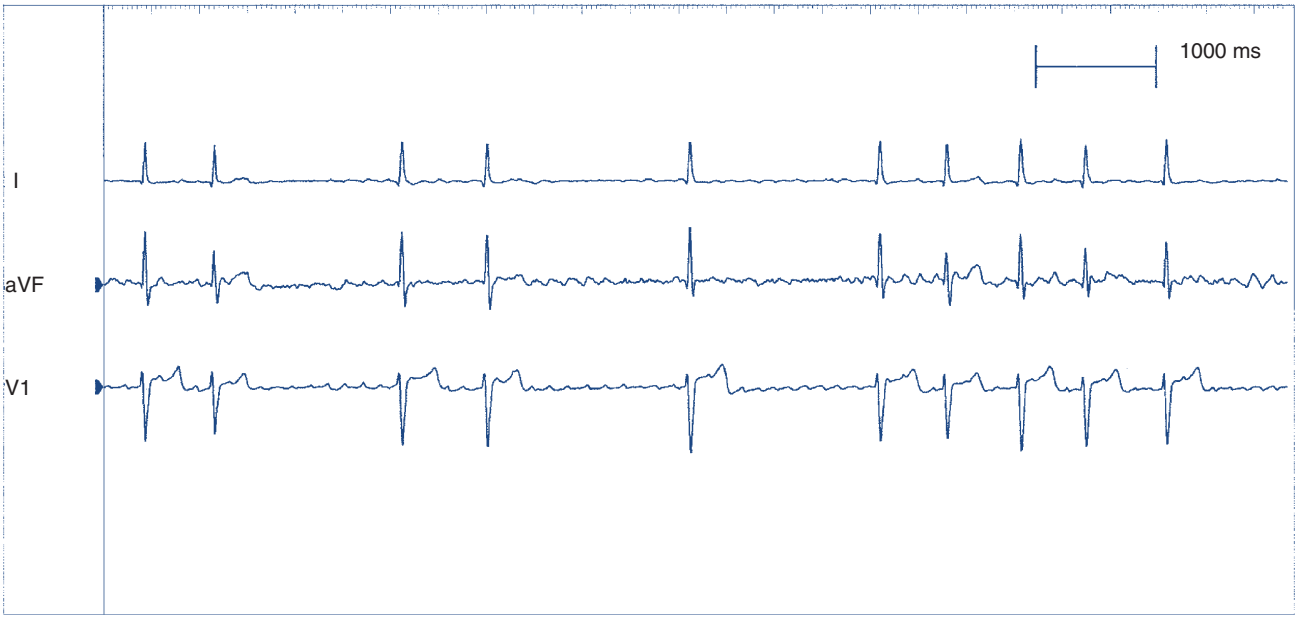
In about 17% of patients with sick sinus syndrome, overt congestive heart failure may develop, which may be related or contributed to by the slow heart rate, loss of the atrial contribution to left ventricular filling in patients who develop atrial fibrillation, or loss of AV synchrony in patients with implanted ventricular pacing systems.[73]

Syncope or severe presyncope is one of the classical manifestations of sick sinus syndrome and occurs in about 25% of patients. In one prospective trial, the actuarial rates of syncope were 16% and 31% after 1 and 4 years of follow-up, respectively.[73,74] Syncope is usually caused by excessive slowing of or transient pauses in sinus rhythm or by sinus exit block with an inadequate escape rhythm (Figure 39-8). In patients with bradycardia-tachycardia syndrome, overdrive suppression of the sinus node may occur when the tachycardia terminates, resulting in prolonged pauses and syncope. Use of antiarrhythmic medications in these patients,



Sinus bradycardia

A



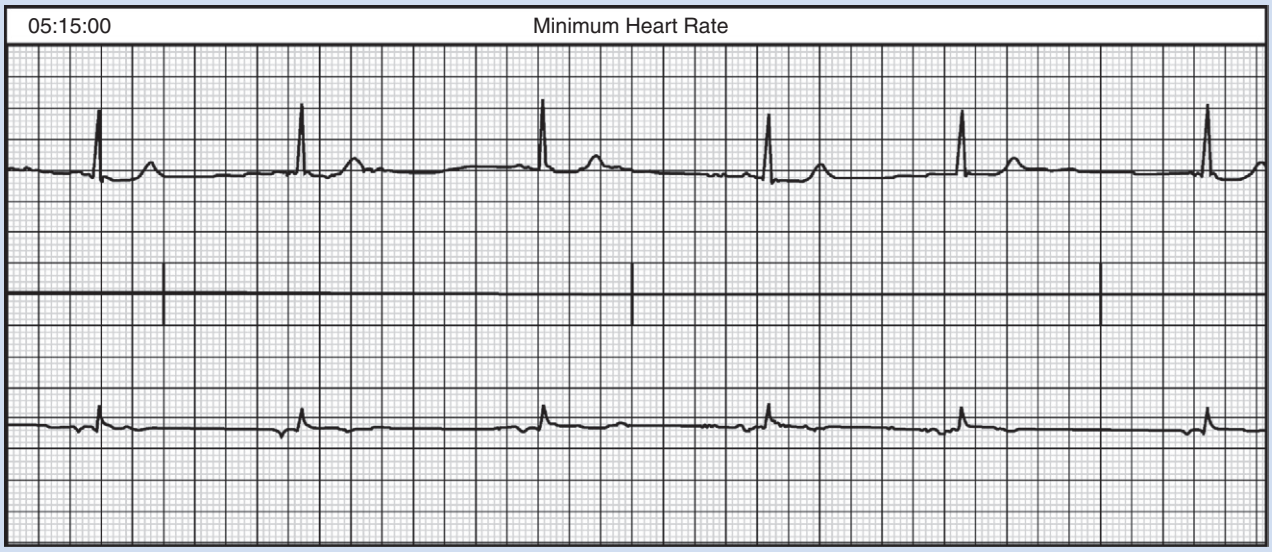
Bradycardia-tachycardia syndrome

B

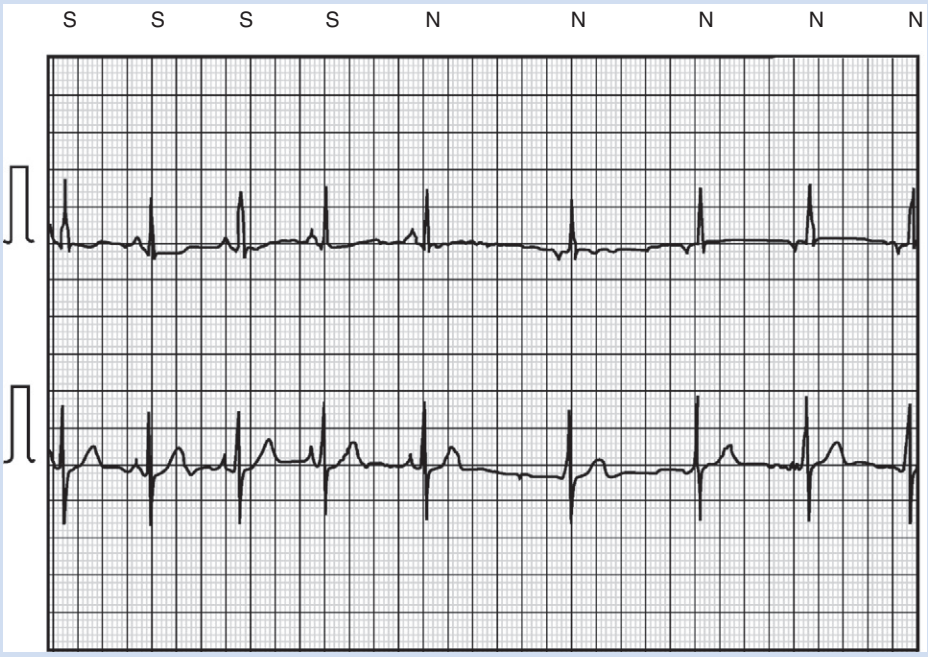
FIGURE 39-7 **A,** Twelve-lead electrocardiogram during sinus bradycardia in a patient with bradycardia-tachycardia syndrome. **B,** Tachycardia in the same patient in **A** with rapid and slow atrioventricular conduction, as seen on a three-lead rhythm strip. The patient is in coarse atrial fibrillation, which is paroxysmal in nature in this individual.

while successful in controlling the tachycardia, frequently leads to worsening of the bradycardia episodes with exacerbation of symptoms, and permanent cardiac pacing is required for rate support.

About one third to one half of patients with sick sinus syndrome experience episodes of supraventricular tachycardia.[73,78] Published reports indicate that chronic atrial fibrillation occurs in about 11% of cases after a mean follow-up of 19 months, increases to 16% at 5 years, and to 28% at 10 years.[73,74,84] Variables that have been associated with the development of chronic atrial fibrillation are age; left ventricular end-diastolic diameter; presence of valvular heart disease; and ventricular, rather than physiological, atrial or dual-chamber, pacing.[84-86] Chronic atrial fibrillation is also more common in patients with tachycardia-bradycardia



A



B

FIGURE 39-8 A, Sinus bradycardia in a young patient with primary electrical disease and syncope, as seen on a dual-channel Holter monitor recording. **B,** Sinus pause in the same patient as in **A** with an escape low atrial or junctional rhythm on another dual-channel Holter recording conducted on a different occasion. Escape rhythms may have a rate slow enough to cause symptoms of cerebral hypoperfusion.

syndrome who have had paroxysmal atrial fibrillation. When atrial fibrillation develops, many patients previously symptomatic from bradyarrhythmia experience a substantial improvement, likely due to the increase in ventricular rate.[87]

Thromboembolic events, which occur in 3% to 9% of patients, may be a manifestation of sick sinus syndrome.[73,74] In patients with bradycardia-tachycardia syndrome, the incidence increases to 24%.[56] Ventricular pacing (as opposed to atrial or dual-chamber pacing) and the presence of pre-existing cerebrovascular disease are also associated with a higher thromboembolic event rate during follow-up.[84-86] High-risk patients should be carefully identified and placed on long-term anticoagulation therapy. However, not all cerebrovascular accidents in these patients are caused by embolic events. Older adults with atherosclerotic cerebrovascular disease may have transient ischemic attacks or frank cerebral infarction if bradyarrhythmia or tachyarrhythmia is associated with a fall in cardiac output and reduction in cerebrovascular perfusion.

Atrioventricular Conduction in Sinus Node Dysfunction

At the time of diagnosis, up to 17% of patients with sick sinus syndrome have evidence of AV conduction system disease; although high-degree AV block is unusual, it is reported in only 5% to 10% of cases.[88] The presence of AV conduction disease will affect therapeutic decisions, for example, those related to safety of concomitant antiarrhythmic drug use and pacemaker mode choice. Electrocardiographic and electrophysiological findings suggestive of significant AV conduction system involvement include a P-R interval greater than 240 ms, complete bundle branch block, development of type I second-degree AV block during atrial pacing at rates of 120 beats/min or less, H-V interval prolongation, and second-degree or third-degree AV block. During follow-up, AV conduction in patients with sick sinus syndrome usually remains stable.[89-91] In one literature survey of 28 studies of atrial pacing, an annual incidence of second-degree and third-degree AV blocks of 0.6% per year was reported.[89] A similarly low incidence (4 of 110 patients) was reported in a prospective trial of atrial versus ventricular pacing in patients with sick sinus syndrome (including those 70 years of age or younger with P-Q intervals ≤220 ms and those older than 70 years of age with P-Q intervals ≤260 ms); in addition, all patients had normal AV conduction at an atrial pacing rate of 100 beats/min at pacemaker implantation.[86]

The progression of AV conduction disease is thus usually slow and can be detected by careful clinical and electrocardiographic monitoring of these patients. Extrinsic influences such as exposure to antiarrhythmic agents or drugs that can block conduction in the AV node are more frequently responsible for worsening of AV conduction than is progressive degeneration within the conduction system.[92-94]

Sinus Node Dysfunction in Acute Myocardial Infarction

Sinus bradycardia occurs commonly in patients with acute myocardial infarction, especially those with inferior and posterior infarctions.[95,96] The bradycardia is usually due to stimulation of the afferent vagus nerve terminals, which are more common in the inferior and posterior ventricular walls. This vagal response can be potentiated by pain and by the use of vagotonic medications such as morphine sulfate and can be associated with a vasodepressor response resulting in systemic hypotension. Intravenous atropine usually reverses the vagal effects associated with myocardial infarction.

In addition to autonomic nervous system influences, sinus bradycardia may also be caused by ischemia of the sinus node or atrial tissue, although this diagnosis is rarely made clinically. Sinus node ischemia is also more common in inferior wall myocardial infarction, since the sinus node is usually supplied by the right coronary artery. The clinical manifestations are sinus bradycardia in the majority of cases; however, bradycardia alternating with episodes of supraventricular tachycardia has been reported in up to 35% of patients.[97] In the majority of cases, the sinus node dysfunction is temporary, and normal sinus rhythm returns during the hospitalization.[97,98] Pacemaker implantation is rarely indicated. However, patients who experience alternation of bradycardia and tachycardia occasionally may require long-term antiarrhythmic therapy.[97]

Both noninvasive and invasive means of diagnosing sinus nodal dysfunction are available. Generally, the noninvasive methods of electrocardiographic monitoring, exercise testing, and autonomic testing are used first. However, if symptoms are infrequent, invasive electrophysiological testing may be needed.

Diagnostic Evaluation

Noninvasive Testing

The diagnosis of sinus nodal dysfunction is rarely made from a random ECG. If symptoms suggestive of sinus node dysfunction are frequent, Holter monitoring may be useful.[77,99,100] It is important to have the patient wear a Holter monitor and document the symptoms in a diary for correlation of symptoms with the heart rhythm recorded at the time. In many cases, a Holter monitor can exclude sinus nodal dysfunction as the cause of symptoms if normal sinus rhythm is documented during dizziness, presyncope, or syncope. However, sinus bradycardia and sinus pauses may be recorded in asymptomatic individuals, reducing the specificity of these findings for the diagnosis.[6,101]

Event recorders are more useful than Holter monitors in patients with infrequent symptoms. Patient-activated models exist but are limited to patients who have symptoms prolonged enough to record the rhythm during an event. For patients who have little to no warning, a loop recorder event monitor can be used. These recorders can be activated as soon as symptoms occur or after the fact, since the last 45 seconds of ECG recording are "frozen." Newer models that can be automatically triggered by bradycardia or tachycardia are useful in some patients. One study has demonstrated mobile cardiac outpatient telemetry (MCOT) to be even more useful than external event loop recorders in making an arrhythmic diagnosis.[102] When an ECG diagnosis cannot be recorded by less invasive means, implantable loop recorders are useful in patients with recurrent symptoms suggestive of a bradyarrhythmia.

Exercise testing is of limited value in diagnosing sinus node dysfunction.[70] However, it is useful in differentiating patients with chronotropic incompetence from those with resting bradycardia who are able to demonstrate a normal heart rate increase with exercise. Patients with sinus nodal dysfunction and chronotropic incompetence exhibit abnormal heart rate responses to exercise. The increase in heart rate at each stage of exercise may be less than normal, with a plateau seen below the maximum age-predicted heart rate. Other patients may achieve an appropriate peak heart rate during exercise but have slow heart rate acceleration in the initial stage of exercise or a rapid deceleration of heart rate in the recovery stage. These abnormal chronotropic responses can help identify the cause of exercise intolerance in some patients with sinus nodal dysfunction and help determine their pacemaker prescription.[103]

Autonomic testing of the sinus node includes various pharmacologic interventions and maneuvers to test reflex responses. An abnormal response to carotid sinus massage (pause greater than 3 seconds) indicates carotid sinus hypersensitivity and may suggest the presence of carotid sinus syndrome. This response may also occur in asymptomatic older adults.[104] Heart rate response to the Valsalva maneuver (normally decreased) or upright tilt (normally increased) can also be used to verify that the autonomic nervous system is itself intact.

The most commonly used pharmacologic intervention in the evaluation of sinus node dysfunction is the determination of the intrinsic heart rate.[105] A low intrinsic heart rate is consistent with abnormal intrinsic sinus nodal function. A normal intrinsic heart rate in a patient with known clinical sinus nodal dysfunction suggests abnormal autonomic regulation.

Invasive Testing

Sinus nodal function can be evaluated invasively with an electrophysiological study. This type of testing is usually reserved for symptomatic patients in whom sinus nodal dysfunction is suspected but cannot be documented in association with symptoms by noninvasive means. The pacing tests most commonly used are the sinus nodal recovery time and sinus node conduction time.

Pacing the atrium at rates faster than the inherent sinus rate is used to record the sinus node recovery time. A delay in the return of spontaneous pacemaker activity (overdrive suppression) is a normal finding immediately after cessation of rapid atrial pacing. In patients with sinus nodal dysfunction, however, the sinus node generally takes longer to recover. A better measurement is the corrected sinus nodal recovery time, which is obtained by subtracting the spontaneous sinus cycle length before pacing from the sinus nodal recovery time. Thus, a patient with an abnormally long sinus nodal recovery time could have a normal corrected sinus nodal recovery time if the resting heart rate is slow.[106] The indirect measurement of the corrected sinus nodal recovery time reflects both sinus node conduction time and sinus automaticity and thus has some limitations. Indirect sinus nodal recovery time measurements can be confounded by sinus nodal entrance block during rapid atrial pacing with resultant shortening of the sinus nodal recovery time and by sinus nodal exit block after pacing, thereby prolonging the measured sinus nodal recovery time. An abnormal sinus nodal recovery time is not found in all patients with sinus nodal dysfunction, partly because of sinus nodal dysfunction not being a homogenous entity from the standpoint of pathology. Despite these limitations, the indirect corrected sinus nodal recovery time is employed frequently in the evaluation of sinus nodal function.

The sinus node conduction time, another commonly used invasive pacing test, is traditionally measured indirectly from the high right atrium.[107,108] Several assumptions are used in the calculation, including sinus nodal automaticity not being affected by the premature beat, conduction in and out of the sinus node being equal, and the premature atrial beat not causing a shift in the principal pacemaker site. An additional limitation of the sinus node conduction time test is the need for a regular cycle length in sinus rhythm. Sinus arrhythmia may make the calculation of the sinus node conduction time by this method impossible.

Evidence-Based Therapy

In the course of the first decade of this century, the importance of making clinical decisions on the basis of evidence from clinical trials has been emphasized in clinical medicine. This section reviews the available information from clinical trials on the efficacy of pacing therapy and the effects of pacing mode selection in patients with sinus node dysfunction.

Effectiveness of Pacing Therapy

Only a single published study, the THEOPACE (theophylline and permanent pacemaker) study, has evaluated the effectiveness of pacing therapy versus no therapy or pharmacologic therapy for preventing symptoms in patients with sinus node dysfunction. In this study, 107 patients with presumed sinus node dysfunction (>45 years of age, with a mean resting sinus rate <50 beats/min or intermittent sinus node block, or both, noted on diurnal ECG on two separate occasions, and symptoms thought to be secondary to sinus node dysfunction) were randomized to no treatment, oral theophylline, or dual-chamber rate-adaptive pacing.[72] Patients with severe sinus node dysfunction, defined as symptomatic heart rates less than 30 beats/min or sinus pauses greater than 3 seconds, were excluded. After an average 18-month follow-up, syncope had occurred in 6% of patients who received pacing therapy and 17% and 23% in the theophylline and control arms, respectively. In all three groups, the incidence of atrial tachycardias was similar (26% to 28%). The THEOPACE study demonstrated that pacing therapy provides symptomatic benefit in patients with sinus node dysfunction. However, it is unlikely that pacing therapy confers a survival benefit, since natural history studies suggest that sinus node dysfunction by itself does not appear to be associated with an increased risk of death.[76]

Pacing Mode Choice

In patients with sinus node dysfunction, bradycardia can be prevented by single-chamber ventricular pacing (VVI mode), single-chamber atrial pacing (AAI mode), or dual-chamber pacing (DDD mode). Several randomized studies have evaluated the effects of pacing mode in patients with sinus node dysfunction. The first prospective study, initially published in 1994 with follow-up data presented in 1997 and 1998, evaluated 225 patients with sinus node dysfunction, who were randomized to single-chamber atrial pacing or single-chamber ventricular pacing.[86] After a mean follow-up of 3.3 years, atrial pacing was associated with a significant decrease in thromboembolic events (atrial pacing: 5.5%; ventricular pacing: 17.4%) and a nonsignificant reduction in atrial fibrillation (atrial pacing: 14%; ventricular pacing: 23%). In addition, progression of heart failure symptoms was observed in 9% of patients in the atrial pacing group and 31% of the ventricular pacing group. In the Pacemaker Selection in the Elderly (PASE) trial 407 older adults (mean age, 76 years) were randomized to either the VVIR mode or the DDDR pacing mode, with a mean follow-up of 30 months.[109] In 175 patients with sinus node dysfunction, the DDDR pacing mode was associated with improved cardiovascular functional status and better quality-of-life scores in the role physical, role emotional, and social function categories of the SF-36 questionnaire. The DDDR pacing mode was associated with insignificant reductions in mortality (DDDR, 12%; VVIR, 20%) and incidence of atrial fibrillation (DDDR, 19%; VVIR, 28%). Of the entire study group, 26% of patients crossed over from the VVIR pacing mode to the DDDR pacing mode because of symptoms related to pacemaker syndrome.

The Canadian Trial of Physiologic Pacing (CTOPP) evaluated the effects of pacing mode choice in patients with symptomatic bradycardia.[110] The 2568 patients in the study were randomized to single-chamber ventricular pacing or a "physiologic" pacing mode that preserved AV synchrony (AAI mode or DDD mode). While no

significant differences in the annual rate of stroke or death were detected (ventricular pacing, 5.5%; physiological pacing, 4.9%), the annual rate of atrial fibrillation was significantly lower in the physiological pacing group (ventricular pacing, 6.6%; physiological pacing, 5.3%). The reduction in atrial fibrillation became more apparent 2 years after initial randomization. Subgroup analysis suggested that the indication for permanent pacing (sinus node dysfunction or AV block) did not have a significant effect on the annual rate of stroke or death. An important caveat with regard to this study is that after 5 years of follow-up, 95% of patients randomized to ventricular pacing were still programmed to ventricular pacing, whereas only 75% of patients randomized to physiological pacing were actually still in a physiological pacing mode.

In the latest large randomized study, the Mode Selection Trial (MOST), 2010 patients with sinus node dysfunction were randomized to dual-chamber pacing or single-chamber ventricular pacing.[111] After a 5-year follow-up, no differences in mortality or stroke were detected, but a marked reduction in progression to atrial fibrillation was noted, particularly in patients without a prior history of the arrhythmia; however, the rate of crossover to dual-chamber pacing because of symptoms of pacemaker syndrome was 31%, and dual-chamber pacing was associated with improved quality of life.

Recently, a large meta-analysis that combined data from all of the large prospective trials with a total of 35,000 patient years of follow-up was published.[112] Atrial-based pacing was not associated with improved survival or reduction in cardiovascular death or heart failure. However, atrial-based pacing was associated with a modest 20% reduction in atrial fibrillation and stroke. No subgroup appeared to receive special benefit from atrial pacing.

Thus, available data suggest that pacing modes that preserve AV synchrony are associated with a reduced incidence of atrial fibrillation, particularly after several years. In addition, preservation of AV synchrony is associated with improved quality of life and a reduction in the incidence of pacemaker syndrome.

Management

The first step in the evaluation and management of patients with sinus node dysfunction is to exclude physiological sinus bradycardia caused by extrinsic conditions affecting the sinus node or sinus node tissue. β-Blockers, some calcium channel blockers (verapamil and diltiazem), digoxin, and other medications having sympatholytic activity can result in sinus node dysfunction. It is therefore important to carefully review all medications taken by patients, since withdrawal of the offending agents usually results in restoration of normal sinus function. Other causes of extrinsic sinus node dysfunction should be investigated and excluded; these include hypothyroidism, sleep apnea, and other systemic diseases. The specific situation in which the bradycardia occurs should be analyzed in order to document bradycardia triggered by an increase in vagal tone that occurs, for example, during suctioning or vomiting. Whenever possible, treatment should be directed toward correcting the extrinsic condition causing the bradycardia.

Guidelines for Management of Patients with Intrinsic Sinus Node Dysfunction

When intrinsic sinus node dysfunction is suspected, it is important to try to correlate the symptoms with documentation of the arrhythmia, since sinus node dysfunction is common, especially in older adults, and may not cause symptoms. The intermittency of symptoms and ECG features characteristic of the syndrome may make it difficult to establish a cause/effect relationship. A Holter monitor, event recorder, or implantable loop recorder may be useful to establish the diagnosis, and prolonged monitoring may be required. In selected cases, it is best to use the implantable loop recorder that continuously acquires electrocardiographic signals.[111]

Krahn et al placed implantable loop recorders in 16 patients with syncope and negative electrophysiological and tilt table tests. Of the 16 patients, 15 had recurrent syncope, and sinus arrest was documented in 5 patients.[111] As indicated above, invasive electrophysiological studies are usually not required to specifically evaluate sinus node function, as they have significant limitations.

Therapy is aimed at improving symptoms, as no evidence that medical therapy or pacemaker implantation improves survival exists; this is partly because of the low mortality rate related to bradyarrhythmia per se. However, it is important to acknowledge the possibility of other causes besides bradycardia for a patient's symptoms. In a post hoc analysis of 177 patients from the MOST study with an ejection fraction of 35% or less, the 4-year sudden cardiac death rate was 15.5%, or 3.9% annually.[113]

Indications for Permanent Pacing

Pharmacologic therapy for bradycardia caused by sinus node dysfunction is generally ineffective; pacemaker implantation is therefore the optimal therapy. In the United States, sinus node dysfunction is the most common indication for pacemaker implantation.[10] The benefit to be expected from permanent pacing depends largely on the appropriateness of the indication.

Guidelines for pacemaker implantation in sinus node dysfunction have been published.[114] Indications for permanent pacing in sinus node disease are summarized in Table 39-1. The guidelines emphasize the importance of correlating symptoms and bradycardia, whenever possible. The principal benefits of pacing therapy are prevention of syncope, improvement of symptoms caused by poor tissue perfusion, and prevention of congestive heart failure caused by decreased cardiac output, which, in turn, is caused by slow heart rates. In a 1970s observational series of severely symptomatic patients, pacemaker therapy was shown to improve symptoms of fatigue, lightheadedness, and near-syncope.[115] In a randomized trial from the 1990s, which was conducted to assess the efficacy of pacemakers in patients with sick sinus syndrome, the occurrence of syncope was lower in the paced group over a mean follow-up duration of 18 months (6% in the pacemaker group vs. 23% in controls; $P = .02$).[72] Heart failure also occurred less often in patients assigned to pacemaker therapy (3% vs. 17%; $P = .05$), whereas the incidence of sustained paroxysmal tachyarrhythmias, chronic atrial fibrillation, and thromboembolic events was not different between the groups. Compared with observational series and retrospective studies, pacemaker implantation in this randomized trial did not demonstrate different effects on "minor" symptoms such as fatigue, dizziness, palpitation, and New York Heart Association class in the pacemaker group compared with the "no treatment" group; this was due to subjective improvement occurring in the placebo group as early as 3 months following randomization.[72]

In some patients, bradycardia may be iatrogenic and exacerbated by medications used to treat supraventricular tachycardias. If these medications constitute the only alternative for the

Table 39-1 Indications for Permanent Pacing in Sinus Node Dysfunction

CLASS	INDICATIONS
Class I	Sinus node dysfunction with documented symptomatic bradycardia, including frequent sinus pauses that produce symptoms. In some patients, bradycardia is iatrogenic and will occur as a consequence of essential long-term drug therapy of a type and dose for which there are no acceptable alternatives.
	Symptomatic chronotropic incompetence
Class IIa	Sinus node dysfunction occurring spontaneously or as a result of necessary drug therapy with a heart rate <40 beats/min when a clear association between symptoms consistent with bradycardia and actual presence of bradycardia has not been documented
	Syncope of unexplained origin when major abnormalities of sinus node function are discovered or provoked in electrophysiological studies
Class IIb	Minimally symptomatic patients, chronic heart rate <40 beats/min while awake
Class III	Sinus node dysfunction in asymptomatic patients, including those in whom substantial sinus bradycardia (heart rate <40 beats/min) is a consequence of long-term drug treatment
	Sinus node dysfunction in patients with symptoms suggestive of bradycardia that are clearly documented as not associated with a slow heart rate
	Sinus node dysfunction with symptomatic bradycardia due to nonessential drug therapy

Class I: *Conditions for which there is evidence or general agreement, or both, that a given procedure or treatment is beneficial, useful, and effective.*
Class II: *Conditions for which there is conflicting evidence or a divergence of opinion, or both, about the usefulness/efficacy of a procedure or treatment.*
Class IIa: *Weight of evidence/opinion is in favor of usefulness/efficacy.*
Class IIb: *Usefulness/efficacy is less well established by evidence/opinion.*
Class III: *Conditions for which there is evidence or general agreement, or both, that a procedure/treatment is not useful/effective and, in some cases, may be harmful.*
(From 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 *117: e350–e408, 2008.)*

management of tachycardia, and if the patients are symptomatic from bradycardia, they should receive permanent pacing. However, if bradycardia does not produce symptoms, the rhythm per se is not an indication for pacing.

The published guidelines also take into consideration the erratic course of the disease and the difficulty in establishing the cause/effect relationship between symptoms and arrhythmia.[114] Accordingly, pacing is considered useful in patients with heart rates less than 40 beats/min in whom symptoms are consistent with bradycardia but the correlation between the two cannot be clearly established. Pacing is not indicated in asymptomatic patients, in patients with bradycardia caused by nonessential medical therapy, and when symptoms are clearly documented to be not caused by bradycardia.

Permanent pacing is indicated in patients with chronotropic incompetence and who become symptomatic during activity because of inability to increase heart rate and cardiac output. These patients experience an improvement in symptoms and exercise tolerance with rate-responsive pacing.[9,116]

Pacing Mode Selection

Single-chamber atrial pacemakers, single-chamber ventricular pacemakers, and dual-chamber pacemakers will all prevent bradycardia in the patient with sinus node disease. Each pacemaker type is associated with inherent advantages and disadvantages. Single-chamber atrial pacemakers are simple, relatively inexpensive (approximately $3000 to $4000), and maintain AV synchrony. However, they will not prevent ventricular bradycardia if AV block develops. Up to 20% of patients will have abnormal AV conduction at the time of diagnosis of sinus node dysfunction; these patients are not candidates for single-chamber atrial pacing.[71] In a prospective study of 225 patients with 1:1 conduction at heart rates less than 100 beats/min. Andersen et al found that AV conduction was unchanged from initial evaluation after a mean 5.5-year follow-up.[90] The annual incidence of second-degree and third-degree AV block that required implantation of a dual-chamber pacing system was only 0.6% per year.[90]

Single-chamber ventricular pacemakers are also simple and inexpensive. They prevent bradycardia in the presence of AV block but do not maintain AV synchrony. Loss of AV synchrony is associated with a 20% to 30% decrease in cardiac output and is associated with *pacemaker syndrome*.[117] Pacemaker syndrome is a constellation of symptoms that can include dizziness, chest pain, weakness, effort intolerance, presyncope, and syncope. The mechanism of pacemaker syndrome is complex but appears to be caused by decreased cardiac output from loss of AV contraction and retrograde conduction through the His-Purkinje-AV node axis. Reduced cardiac output leads to reflex sympathetic activation. Atrial contraction when the mitral and tricuspid valves are closed also leads to an increase in atrial pressure and release of atrial natriuretic peptide and peripheral venous and arterial dilation. The reported incidence of pacemaker syndrome has varied widely among studies (1% to 80%), which probably reflects variability in definition rather than a true variability in incidence.[118,119] In large randomized trials such as PASE and MOST, crossover from single-chamber ventricular pacing to dual-chamber pacing because of pacemaker syndrome was approximately 25% to 30%.[110,120,121]

Dual-chamber pacemakers maintain AV synchrony and prevent bradycardia from all causes. However, dual-chamber

pacemakers are more complex and relatively expensive ($5000 to $7000). In addition, since two intracardiac leads are required, the incidence of lead dislodgment is higher with dual-chamber systems (dual-chamber, 6%; single-chamber, 2%). Dual-chamber pacing requires specific programming in patients with sinus node dysfunction to avoid ventricular pacing, which can be hemodynamically detrimental in many patients. In the SAVE PACe (Search AV Extension and Managed Ventricular Pacing for Promoting Atrioventricular Conduction) trial, 1065 patients with sinus node dysfunction were randomized to standard dual-chamber pacing or to use of a pacing algorithm that minimizes ventricular pacing.[122] The risk of developing persistent atrial fibrillation was significantly reduced by 40% by minimizing ventricular pacing (conventional, 12.7% vs. special algorithm to minimize ventricular pacing, 7.9%).

Currently available pacing systems have a rate-adaptation feature. When rate adaptation is programmed "on," the pacing system employs a sensor such as body motion, minute ventilation, Q-T interval changes, measures of myocardial contractility, or combinations of these to estimate metabolic need. The pacemaker will change the pacing rate on the basis of input from the sensor. This feature is particularly useful for patients with sinus node dysfunction associated with chronotropic incompetence. However, in the randomized, controlled Advanced Elements of Pacing Trial Trial (ADEPT), 872 patients with a blunted heart rate response (<80% maximum predicted heart rate) were randomized to rate adaptive pacing "on" or "off."[123] Rate adaption was not associated with improved exercise capacity or improved quality of life.

Pacemakers have monitoring capabilities that allow the clinician to evaluate the range of heart rates a patient has over a specific period. If a blunted range of atrial rates is recorded, the presence of chronotropic incompetence should be suspected. Monitoring also allows the clinician to confirm that pacemaker programming is minimizing ventricular pacing. Finally, sinus node dysfunction is commonly associated with atrial fibrillation that can be minimally symptomatic. Continuous monitoring can be used to identify patients who may benefit from anticoagulation therapy.

Sinus Node Dysfunction in Specific Conditions

Acute Myocardial Infarction

Sinus bradycardia is common in acute myocardial infarction, especially in inferior and posterior wall infarction, where it is usually caused by increased vagal tone or ischemia of the sinus node tissue.[17,18] Increased vagal tone may also result in transient AV block and hypotension from peripheral vasodilation. This arrhythmia usually does not require treatment unless the patient is symptomatic (hypotension, ischemia, or bradycardia-related ventricular arrhythmia). It usually responds well to intravenous atropine. In symptomatic patients who are unresponsive to atropine or who have recurrences requiring multiple doses of atropine, temporary transvenous pacing may be required. Pacing is usually performed from the right ventricular apex; however, where it is important to maintain AV synchrony (such as refractory hypotension), an additional J-shaped electrode can be placed in the right atrial appendage for dual-chamber pacing. Alternatively, atrial pacing can be achieved using a temporary electrode positioned in the proximal coronary sinus. Sinus node dysfunction occurring during acute myocardial infarction is usually temporary, and permanent pacing is rarely required.

Carotid Sinus Hypersensitivity and Carotid Sinus Syndrome

An abnormal response to carotid sinus massage (>3 seconds of asystole) may occur in asymptomatic patients and does not constitute an indication for therapy; correlation with symptoms is essential (Table 39-2). Up to 64% of patients with syncope caused by carotid sinus syndrome can remain asymptomatic during follow-up; therapy should be reserved for patients with recurrent presyncope or syncope.[124] Drugs that can enhance the hypersensitive response to carotid sinus massage, such as digoxin and sympatholytic agents (clonidine, methyldopa), should be discontinued, if possible.

The type of therapy (pacing vs. pharmacologic) and success are based on the mechanism of syncope. Pacing is efficacious in the cardio-inhibitory response to carotid sinus massage.[125-128] In patients with a predominant vasodepressor response, neither pacing nor anticholinergic therapy prevents the fall in blood pressure, since this is caused by inhibition of sympathetic vasoconstrictor nerves as well as by activation of cholinergic sympathetic vasodilator fibers.[128] Elastic support stockings and volume expansion with sodium-retaining drugs may be useful in alleviating the symptoms.

Initial data suggested that unexplained falls in older adults might be caused by carotid sinus hypersensitivity and that, in some cases, pacing therapy may be beneficial.[129] A selected group

Table 39-2 Indications for Permanent Pacing In Hypersensitive Carotid Syndrome

CLASS	INDICATIONS
Class I	Recurrent syncope caused by carotid sinus stimulation; minimal carotid sinus pressure induces ventricular asystole of >3 seconds' duration
Class IIa	Syncope without clear, provocative events and with a hypersensitive cardio-inhibitory response
Class IIb	Significantly symptomatic neurocardiogenic syncope associated with bradycardia documented spontaneously or at the time of tilt table testing
Class III	Hypersensitive cardio-inhibitory response to carotid sinus stimulation without symptoms or with vague symptoms
	Recurrent syncope, lightheadedness, or dizziness in the absence of a hyperactive cardio-inhibitory response

Class I: *Conditions for which there is evidence or general agreement, or both, that a given procedure or treatment is beneficial, useful, and effective.*
Class II: *Conditions for which there is conflicting evidence or a divergence of opinion, or both, about the usefulness/efficacy of a procedure or treatment.*
Class IIa: *Weight of evidence/opinion is in favor of usefulness/efficacy.*
Class IIb: *Usefulness/efficacy is less well established by evidence/opinion.*
Class III: *Conditions for which there is evidence or general agreement, or both, that a procedure/treatment is not useful/effective and, in some cases, may be harmful. (From 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 *117:e350–e408, 2008.)*

of 175 patients with a history of nonaccidental falls and significant bradycardia (asystole >3 seconds) in response to carotid sinus massage were randomized into pacing therapy and no pacing therapy groups; after a 1-year follow-up, injurious events were reduced by 70% in the pacing therapy group. However, in a recently published double-blind, placebo-controlled, crossover trial, pacing therapy did not reduce the number of falls in a cohort of older patients with carotid sinus hypersensitivity.[130]

The indications for permanent pacing in carotid sinus syndrome are summarized in Table 41-2. Single-chamber atrial pacing is contraindicated, since vagal activation frequently results in AV block and absence of a ventricular escape rhythm. Although single-chamber ventricular pacing prevents bradycardia, it can potentially exacerbate symptoms caused by neurohormonal effects associated with pacemaker syndrome. Dual-chamber pacing is therefore preferred, since it maintains AV synchrony regardless of the cause of bradycardia. In addition, the current generation of dual-chamber pacing systems allows programming of different heart rates after sensed and paced ventricular beats. By programming a pacemaker to pace at a relatively fast rate on initiation of pacing, symptoms associated with carotid sinus syndrome can be ameliorated even in the presence of a significant vasodepressor response.[131]

Vasovagal Syncope

Vasovagal syncope is the most common cause of syncope in young people. In 1932, Lewis used the term *vasovagal* to emphasize the combination of arterial vasodilation and bradycardia associated with this syndrome.[132] While the exact mechanism of vasovagal syncope is not known, it does appear that activation of cardiac mechanoreceptors leads to activation of higher neural centers and reflex withdrawal of sympathetic tone and increased vagal tone.

The most common cause for bradycardia in vasovagal syncope is sinus bradycardia or sinus arrest. For this reason, although pacemakers do not affect the vasodepressor component of this syndrome, they have been used to treat the subset of patients with particularly severe symptoms unresponsive to drug therapy. Two relatively large randomized but unblinded studies have evaluated the efficacy of pacing therapy for the treatment of vasovagal syncope. In the North American Vasovagal Pacemaker Study (VPS-I), 54 patients with severe vasovagal syncope and relative bradycardia (trough heart rate <60 beats/min during tilt table testing) were randomized to pacing or no pacing.[133] The study was terminated after 2 years when analysis showed that pacing was associated with an 85% decrease in syncopal episodes. Similarly, in the Vasovagal Syncope International Study (VASIS-I), 42 patients with severe drug-refractory vasovagal syncope were randomized to pacing or no pacing.[134] Only one patient in the pacing group experienced syncope, while 14 patients in the no-pacing group experienced syncope during a mean 3.7-year follow-up. More recently, the first randomized, double-blind trial (VPS-II) found a nonsignificant 30% risk reduction in time to syncope with DDD pacing (P = .14), which was considerably lower than in previous studies.[135-138] Significant procedural complications, including lead dislodgement, venous thrombosis, infection, and pericardial tamponade, occurred in 10% of patients. Given the limited efficacy of pacing therapy, pacing should be reserved only for severe drug-refractory cases of vasovagal syncope that are associated with a prominent bradycardia component. Patients who require pacing therapy for drug-resistant vasovagal syncope should receive a dual-chamber pacemaker because transient AV block can be observed during bradycardia episodes. Special programming features that provide an initial higher pacing rate when pacing is initiated have been developed to optimize pacing therapy for patients with vasovagal syncope.[136,139]

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CHAPTER 40

Atrioventricular Block

Epidemiology: Nora Goldschlager
Anatomy: Siew Yen Ho
Basic Electrophysiology: Ralph Lazzara
Diagnostic Techniques: Gerald Naccarelli
Evidence-Based Therapy: Fred Kusumoto and Nora Goldschlager

In 1852, Stannius noted that placing a ligature between the atria and the ventricles could cause bradycardia in a frog's heart.[1] In the late 1800s, Tawara and His identified the atrioventricular (AV) node and His bundle as the normal conduction axis between the atria and the ventricles in humans, and Wenckebach suggested blocked AV conduction as a cause for slow and irregular pulses.[2-4]

Epidemiology of Atrioventricular Block

Transient AV block can be observed in children and young adults during sleep[5]; persistent AV block is unusual. This type of AV block is usually caused by increased vagal tone and is often a normal finding. In a continuous monitoring study of 100 healthy teenaged boys, transient first-degree AV block was observed in 12% and second-degree AV block in 11%.[5] In young adults the incidence of transient AV block decreases to about 4% in women and 6% in men.[6,7] In the normal older adult population, transient type I (Wenckebach) second-degree AV block is seen only rarely (1%), and higher-grade AV block is not observed.[8]

Persistent first-degree AV block is rarely seen in young adults. Review of more than 70,000 electrocardiograms (ECGs) from young men entering the Canadian and U.S. military demonstrated a prevalence of first-degree AV block of less than 1%.[9,10] Electrocardiographic studies have shown increased P-R intervals and an increased incidence of first-degree AV block with aging.[9-14] While approximately 2% of adults older than 20 years of age have first-degree AV block, the incidence increases to more than 5% in people older than 50 years of age.[11,13] With increasing age, the development of AV conduction disorders is more common; in one epidemiologic study of 1500 patients older than 65 years of age, AV conduction and intraventricular conduction defects were identified in 30% of patients.[14] Using high-resolution electrocardiographic techniques, the increased P-R interval associated with aging was found to be caused by delay in conduction in the AV node or the proximal portion of the His bundle.[11] In people younger than 60 years of age, it is uncommon (4%) for persistent first-degree AV block to progress to second-degree or higher-grade AV block in the absence of associated disease.[13]

Acquired persistent second-degree and third-degree AV blocks are almost never observed in normal populations regardless of age. The incidence of symptomatic high-grade AV block is currently estimated to be 200 per million per year.[15]

Isolated congenital complete (third-degree) AV block is a well-described problem that occurs in approximately 1 in every 20,000 live births.[16] Congenital complete AV block is the most common manifestation of neonatal lupus erythematosus and appears to be associated with the development of autoantibodies in the maternal circulation. Other hereditary conditions associated with AV block are the Kearns-Sayre syndrome (ophthalmoplegia, retinitis pigmentosa) and myotonic dystrophy.[17]

Anatomy

Anatomy and Blood Supply

The AV system of specialized myocytes is the only muscular bridge through the insulating fibro-fatty tissue plane that separates the atrial myocardial masses from the ventricular myocardial masses. The AV system begins with the atrioventricular node at its atrial end. The compact node is recognizable, when seen in cross-sections, as a half-oval shaped structure adjacent to the central fibrous body in the young (Figure 40-1, *A*).[18] With increasing age, the shape changes to become spindle-like.[19] When traced inferiorly, toward the base of Koch's triangle, the compact area diverges into two prongs, usually with the artery supplying the node running in between. The extent of the prongs varies from heart to heart; the right extension increases with age.[20] Interposing between the compact node and the working atrial myocardium is a zone of transitional cells. These cells are histologically distinct from the cells of the compact node as well as the working cells but are not insulated from the surrounding myocardium. They approach the compact node superiorly, inferiorly, and from the left and right sides of the atrial septum. In the vestibular area of the right atrium, an overlay of ordinary myocytes is present in the subendocardium from the atrial wall in front of the oval fossa that streams over the zone of transitional cells. The transitional cells, therefore, provide the crucial proximal bridge between the ordinary and the specialized myocardium. Fibro-fatty tissue increases with age in this region, and the transitional cell zone becomes wider.[19] When the conduction system is traced into the penetrating bundle of His, little difference is seen in the cellular composition of the two areas (see Figure 40-1, *B*). The specialized myocardial cells themselves, however, become aligned in a more parallel fashion distally into the AV conduction bundle. The AV node, therefore, is an integral part of the atrial musculature (see Figure 40-1, *A*), in contrast to the atrioventricular bundle, which,

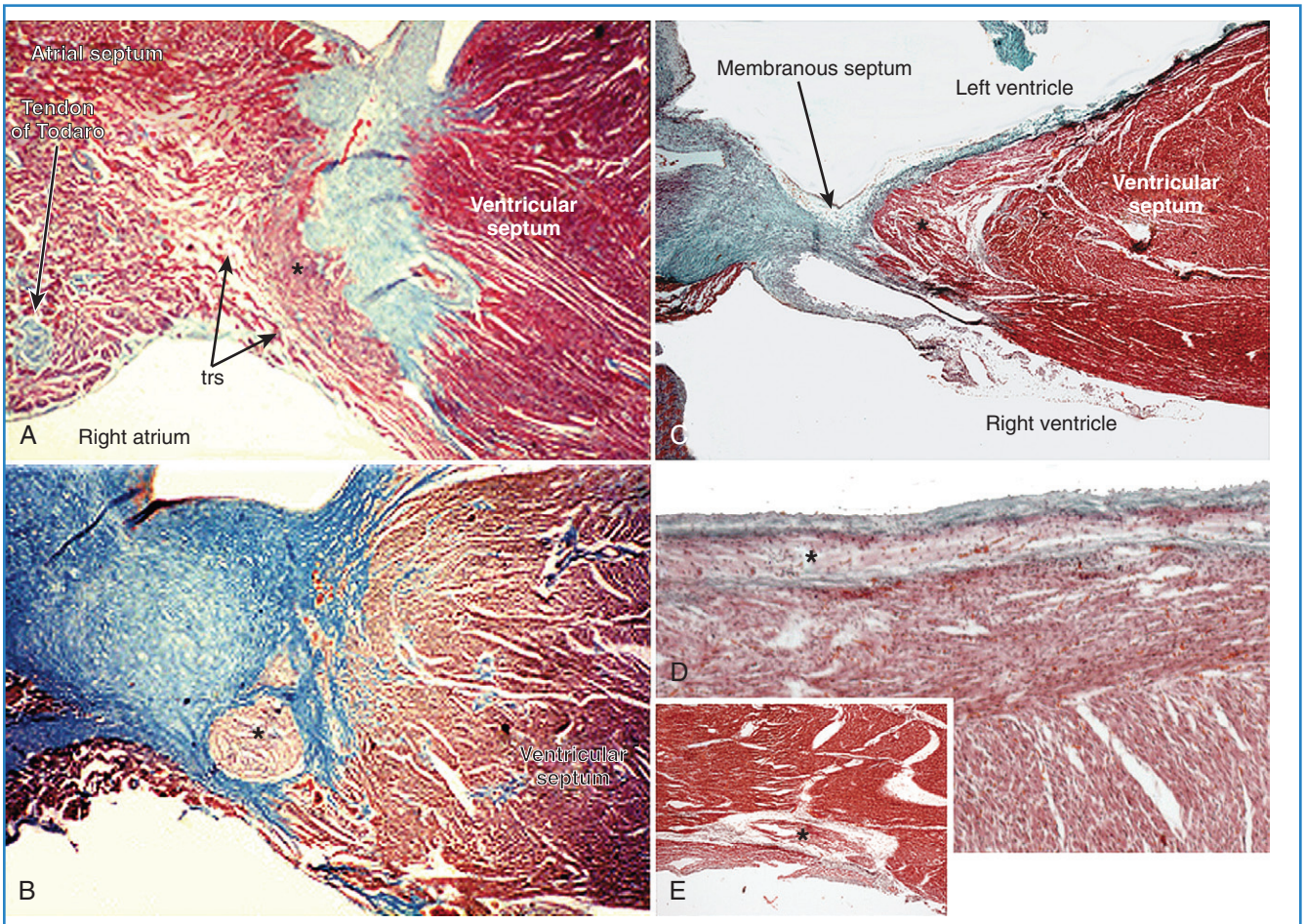

FIGURE 40-1 Histologic sections from children showing the normal configuration of the atrioventricular (AV) node (**A**), penetrating bundle of His (**B**), branching AV bundle (**C**), left bundle branch (**D**), and right bundle branch (**E**). All the sections are perpendicular to the plane of the cardiac septum with the left heart displayed superiorly and right heart inferiorly. *Asterisks* mark the conduction tissues. *trs*, Zone of transitional cells (trichrome stain: myocardium in red; fibrous tissue in green-blue).

in passing through the central fibrous body, is insulated from the adjacent myocardium (see Figure 40-1, *B*). The His bundle, approximately 2 mm in cross-sectional diameter, is the only bridge of myocardial continuity between the atria and the ventricles. The common AV bundle and its continuation, the branching bundle, and bundle branches are also ensheathed in fibrous tissue. In the normal heart, the AV-branching bundle is sandwiched between the membranous septum and the muscular ventricular septum, usually a little to the left of the septal crest, giving origin to the left and right bundle branches (see Figures 40-1, *C* to *E*). The AV bundle lies in the subendocardium of the left ventricle beneath the commissure between the right-coronary and noncoronary leaflets of the aortic valve. In most hearts, the right bundle branch passes through the septal crest to emerge subendocardially in the septal aspect of the right ventricle (see Figure 40-1, *E*). Distally, the bundle branches divide into increasingly finer branches. Eventually, they ramify into the so-called *Purkinje network* and lose the fibrous sheaths at the interface with the ordinary ventricular myocardium.[18]

Most frequently, the arterial supply to the AV node is a branch from the right coronary artery, whereas it is a branch from the circumflex artery in nearly 20%. When the dominant right coronary artery extends beyond the cardiac crux, the nodal artery originates distal to the U loop of the dominant artery.[20,21] In most hearts, the penetrating bundle and AV conduction bundle are supplied by a branch from the posterior descending coronary artery. The right bundle branch is supplied by the first septal perforating artery arising from the anterior descending coronary artery, which also supplies the AV conduction bundle in some hearts.[22,23]

Congenital Complete Atrioventricular Block

Congenital complete heart block can occur in congenitally malformed hearts or in otherwise normal hearts.[24] Complete AV block associated with a cardiac defect is most frequently seen in the anomaly of congenitally corrected transposition, in isomeric arrangement of the atrial appendages, and in some AV septal defects. Although complete AV block may be present at birth, it is more usual for the arrhythmia to be progressive.

When occurring in an otherwise structurally normal heart, the pattern of the cardiac conduction system can take one of three

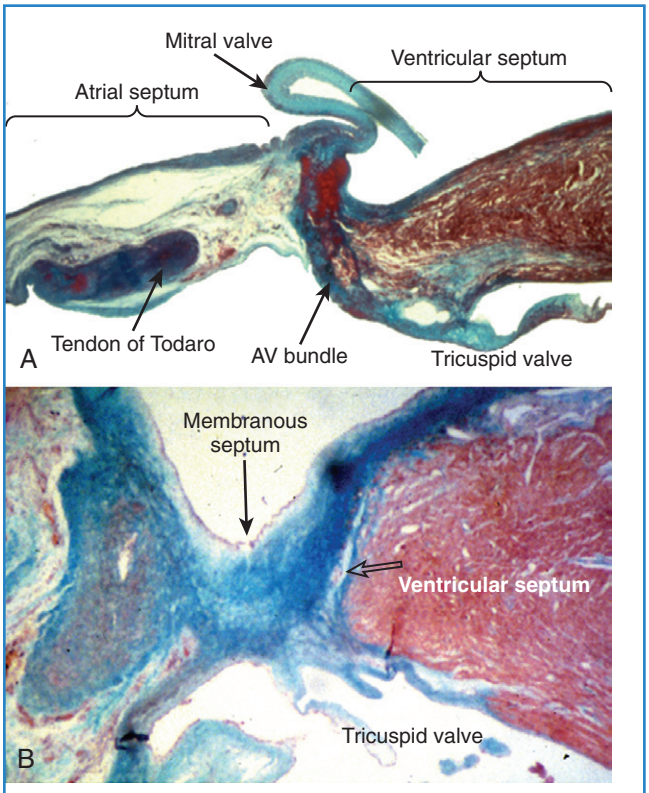

FIGURE 40-2 Histologic sections from two infants with congenital complete heart block cut in similar planes as those shown in Figure 40-1. **A**, An extreme case of atrial-axis discontinuity. The atrial septum totally lacks the myocardium in the region of the atrioventricular node and the node is missing. **B**, An example of intraventricular discontinuity. Only a small island of the branching bundle buried in the fibrous tissue remains (*open arrow*) (trichrome stain: myocardium in red; fibrous tissue in green-blue).

anatomic forms according to the location of the interruption: (1) atrial-axis discontinuity, (2) nodal-ventricular discontinuity, or (3) intraventricular discontinuity.[25-27] The last form is extremely rare.[28] The AV node is deficient or even absent in the most common form, which is described as atrial-axis discontinuity.[25,29] The block is proximal to the His bundle. In the extreme form, the area that is normally occupied by the compact AV node and the zone of transitional cells is replaced by fibrous tissue or fibro-fatty tissue (Figure 40-2, *A*). In others, variable remnants of the nodal tissues appear as islands in the fibrous or fibro-fatty tissues.

Nodal-ventricular discontinuity is less common. The AV node and its atrial approaches are normally formed, but the conduction bundle is interrupted or markedly fragmented at the penetrating portion. Conduction tissues may be totally absent in the central fibrous body. The common and branching AV bundle may be normal or may be deficient to some degree. Depending on the extent of interruption of the conduction bundle, this form may give rise to a narrow or wide QRS complex.

The rarest form, intraventricular discontinuity of the conduction bundle, may occur in families.[28] The branching bundle or the proximal parts of the bundle branches are replaced by fat or fibrous tissue (see Figure 40-2, *B*).

The association of congenital complete heart block with maternal connective tissue disease is well documented.[30-32] The presence of anti-Ro(SS-A) antigen in maternal serum is a marker for isolated congenital heart block.[32] A study of hearts from 8 afflicted children has shown the lack of an AV node in 7, whose maternal sera were anti-Ro positive, and nodal-ventricular discontinuity in the remaining 1, whose maternal serum was anti-Ro negative.[33] However, Chow et al described two cases with a combination of nodal-ventricular and intraventricular discontinuities demonstrating that morphologic patterns are not always clear cut.[34] Furthermore, anti-Ro antibodies were not exclusively associated with atrial-axis discontinuity, since maternal serum was anti-Ro positive in one of these two cases.

Another study compared the anatomic substrate producing complete heart block in normally structured hearts and in hearts with isomerism of the atrial appendages.[35] The pattern of AV block in the cases with left isomerism was nodal-ventricular discontinuity, whereas all but one of the normally structured hearts showed atrial-axis discontinuity with the anticipated nodal area filled with fibro-fatty tissue. The remaining normally structured heart showed the rarest substrate—intraventricular discontinuity. Interestingly, associated fibrosis of several of the sinus nodes was present, suggesting some sort of target mechanism or deficiency specific to the conduction tissues.

The association of complete AV block with congenitally corrected transposition of the great arteries is well recognized.[36] The block may be congenital because of deficiency of the AV node or bundle. More commonly, AV block is progressive in adults. When congenitally corrected transposition occurs with usual arrangement of the atria, the AV conduction system is abnormally located. The AV node is displaced anteriorly, and the AV conduction bundle courses anterosuperiorly, in the trigonal region of fibrous continuity between the pulmonary and mitral valves, related to the anterocephalad border of the left ventricular outflow tract before entering the ventricular septum. The long bundle renders it particularly vulnerable to fibrotic changes with increasing age, eventually resulting in interruption.

Acquired Complete Atrioventricular Block

Complete AV block can be categorized into four major pathologic groups and a further group with miscellaneous conditions.[37] An autopsy series of hearts from 200 patients who had AV block of more than 1-month duration found idiopathic bilateral bundle branch fibrosis in 38%, coronary artery disease in 17.5%, cardiomyopathy in 13%, calcific AV block in 11%, and other causes in 20.5%.[37]

Idiopathic Bilateral Bundle Branch Fibrosis

The crest of the muscular ventricular septum undergoes degenerative changes, including fibrosis, fatty infiltration, and focal microscopic dystrophic calcification with advancing age. The normal aging process begins in the fourth decade of life but may be accelerated by coronary artery disease, diabetes mellitus, and hypertensive heart disease. Since the branching AV bundle and the beginning of the main bundle branches are located in this area, they are susceptible to being disrupted (Figure 40-3). Two forms of bundle branch fibrosis, focal and diffuse—dubbed Lev disease and Lenègres disease, respectively—are recognized, but they probably represent extreme ends of a pathologic spectrum.[38,39] In both groups the mean ages are reported to be in the

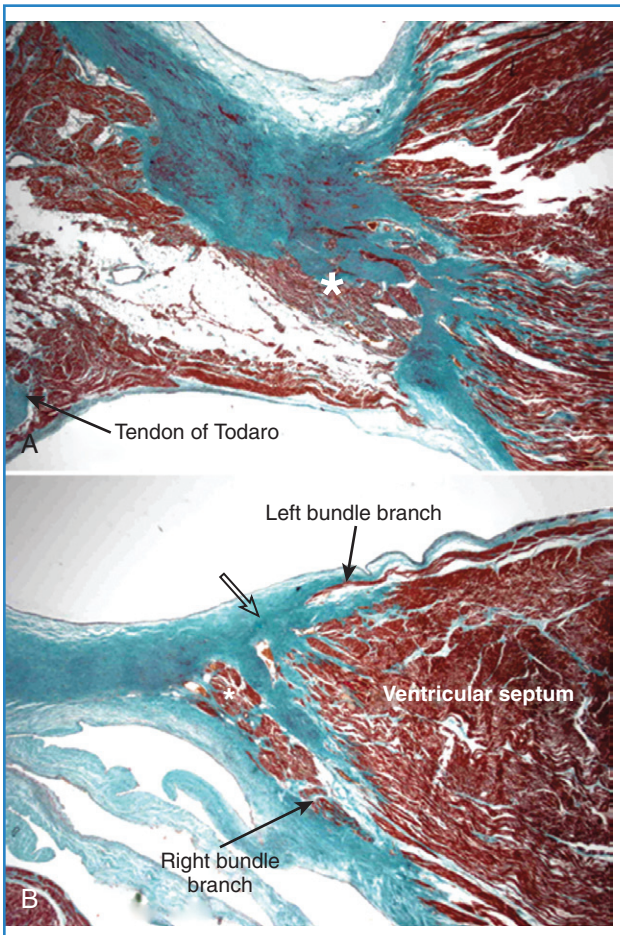

FIGURE 40-3 Histologic sections from a young adult showing loss of more conduction tissues than anticipated. **A**, Deficient atrial input to the atrioventricular node (*asterisk*). **B**, A narrow origin of the left bundle branch and loss of continuity (*open arrow*) with the branching bundle [trichrome stain: myocardium in red; fibrous tissue in green-blue].

sixth and seventh decades. Damage to the distal branches is minimal in the focal form, whereas damage in the diffuse form can extend to the middle and distal portions of both left and right bundle branches.

Coronary Artery Disease

Complete AV block can occur in acute or chronic coronary artery disease. Since different segments of the proximal portion of the AV conduction system are supplied by the right or the left coronary systems, the site of infarction related to coronary occlusion is important. When AV block complicates acute posteroseptal myocardial infarction, the occluded coronary artery is always the artery that ultimately gives origin to the AV nodal artery. Most cases reveal only small focal areas of necrosis in the node, the AV bundle, or both. Massive necrosis of the AV node and its approaches, inflammatory cell infiltration, or occlusion of the nodal artery is rare. In some cases, no obvious pathologic changes are seen in conduction tissues. By contrast, anteroseptal infarction associated with occlusion of the anterior descending coronary artery is more extensive and causes necrotic damage to the branching and bundle branches. The AV node may or may not be spared, although careful studies have shown no arterial lesions in the supply to the AV node.[40]

Chronic coronary insufficiency, with or without previous myocardial infarction, can affect various parts of the AV conduction system. The damage predominantly to the bundle branches may, over time, progress to cause complete AV block. The most common pattern in autopsy series is destruction of both bundle branches.[39,41] Pathologic studies suggest that the majority of patients with chronic AV block do not have more coronary atherosclerosis than do normal patients without AV block.[41,42] Some cases may be associated with small vessel disease.

Cardiomyopathy

Nonischemic cardiomyopathy with left ventricular dilatation and thin wall is commonly associated with markedly increased fibrosis, vacuolation of myocytes, and even necrosis of individual cells. Changes in the specialized myocytes mirror those of ordinary contractile myocytes, with loss of cells in the bundle branches and replacement fibrosis. In extreme cases, the conduction cells diminish throughout the distal left bundle branch.

Hypertrophic cardiomyopathy is rarely associated with chronic AV block. Histologic investigations have shown interstitial fibrosis or necrosis in the conduction system, interruption of the His bundle, abnormally small intramural coronary arteries with thick walls, and narrow lumens.[43-45]

Calcific Atrioventricular Block

The calcific mass in calcific AV block is usually large enough to be seen with the naked eye at autopsy. Because of the proximity of the His bundle, the AV and branching bundles to the aortic valve, and the area of aortic-mitral fibrous continuity, the conduction bundles are at risk of destruction or compression when these sites undergo massive calcification, for example, in senile aortic valve calcification, senile mitral ring calcification, or chronic rheumatic valve disease.

Miscellaneous

This heterogeneous group includes amyloidosis, hemochromatosis, connective tissue disease, myocarditis familial cardiomyopathy and skeletal myopathy, infective endocarditis, and tumors involving the conduction system. In amyloidosis, heavy deposits are found in the sinus node with relatively small amounts in the AV node and main conduction bundles. In patients with AV block, deposits are present in the ventricular myocardium, which also shows extensive scarring. Involvement of the small arteries suggest fibrosis and attenuation of the conduction bundles are more related to the scarring process.[41] Myocarditis of any etiology, whether acute or chronic, may cause complete AV block. In the acute phase, inflammatory changes are predominantly in the ventricular myocardium affecting the distal bundle branches. Rarely, the conduction system is more involved than is the surrounding myocardium.[41] When the conduction system is involved, the changes include degeneration, vacuolization, and necrosis of cells of the bundle branches. Infective endocarditis affecting the aortic valve, the mitral valve, or both may extend to the central fibrous body, membranous septum, and crest of the muscular ventricular

septum to involve the AV bundles. Any type of tumor that metastasizes to the heart has the potential to affect the conduction system to varying degrees. Metastatic tumor deposits in the ventricular septum can destroy the bundle branches. One particular benign tumor, a mesothelioma, has an affinity for the AV node and its approaches. It is a slow-growing cystic mass located in this region of the atrial septum, hence also known as *cystic tumor of the AV node*. A female-to-male ratio of approximately 3:1 and a mean age of 38 years at presentation are seen. Some patients may die suddenly without any history of heart problems.[46]

Surgical and Interventional

Complete AV block may be a consequence of interventional procedures to correct congenital heart malformation. Damage may be caused by sutures or incisions into the musculature containing the conduction bundles, AV node, or their arterial supply. Although surgically induced iatrogenic block is rare nowadays, the shift toward trans-catheter device closure for ventricular septal defects has again put the spotlight on the potential risk to the AV conduction system.[47,48] AV block may also be a complication following isolated myectomy or alcohol ablation for hypertrophic obstructive cardiomyopathy.[49,50]

Basic Electrophysiology

It is generally accepted that the AV junction consists of the AV node with its atrial connections of transitional fibers and the bundle of His.[51] In electrophysiological considerations of AV block, it is useful to define the AV junction more broadly, including the atrial connections to the AV node, the AV node, the bundle of His, and the proximal portions of the bundle branches that are insulated from the ventricular myocardium by fibrous matrix. Heart block can occur from interruption of conduction in any of these components of the AV junction as defined broadly. In this array of components, great electrophysiological and histologic diversity is seen (Figure 40-4). The range of conduction velocities, resting and action potential (AP) amplitudes, AP durations, and intercellular conductivity observed within the AV junction is greater than in the remainder of the atrial and ventricular myocardium.

The Compact Atrioventricular Node

Within the central compact node are cells with distinct electrophysiological characteristics. These characteristics of the prototypical AV nodal cells manifested by intracellular recordings in multicellular preparations have been replicated in cells isolated from the AV node, allowing determination of the activities of specific currents, pumps, and exchangers.[52,53] The amplitudes of resting potentials (–60 mV), APs (–85 mV), and upstroke velocities (<10 V/sec) are reduced. These cells manifest diastolic depolarization, a high total transmembrane (input) resistance, and relative insensitivity to changes in extracellular K^+. They have post-repolarization refractoriness; the absolute refractory period outlasts the AP. The relative refractory period, during which relatively diminished, more slowly conducting APs are generated, is prolonged well into diastole. The amplitudes and upstroke velocities of APs and conduction velocity are strongly modulated by autonomic activity, increasing with adrenergic (sympathetic) stimulation and decreasing with cholinergic (vagal) stimulation. The AV junction is richly innervated with vagal and sympathetic fibers, but recent observations with high-resolution staining for neural tissues indicate that innervation of the compact node may be more sparse than that of the transitional fibers or the nodal extensions.[53,54]

Important features of the transmembrane potentials can be explained by the array and activities of specific ionic currents. Like sinoatrial nodal cells, AV nodal cells lack the ionic current I_{K1}. These potassium ion (K^+) channels in atrial and ventricular cells are open at strongly negative membrane potentials, providing the dominant K^+ permeability that maintains the transmembrane potential near the K^+ equilibrium potential. The absence of these channels in AV nodal cells is responsible for the relatively reduced resting potential positive to the K^+ equilibrium potential, the insensitivity to extracellular K^+ concentration, and the high membrane resistance of these cells.

AV nodal cells, like sinoatrial nodal cells, lack sodium (Na^+) channels, which provide the excitatory current for atrial and ventricular cells; some cells may have channels that are inactivated at the low resting potentials.[55,56] The excitatory current for AV nodal cells is I_{CaL}, a calcium current that generates a slow upstroke because it is slower and less intense than the Na^+ current. L-type calcium ion (Ca^{2+}) channels require a relatively long period to recover from inactivation, hence the post-repolarization

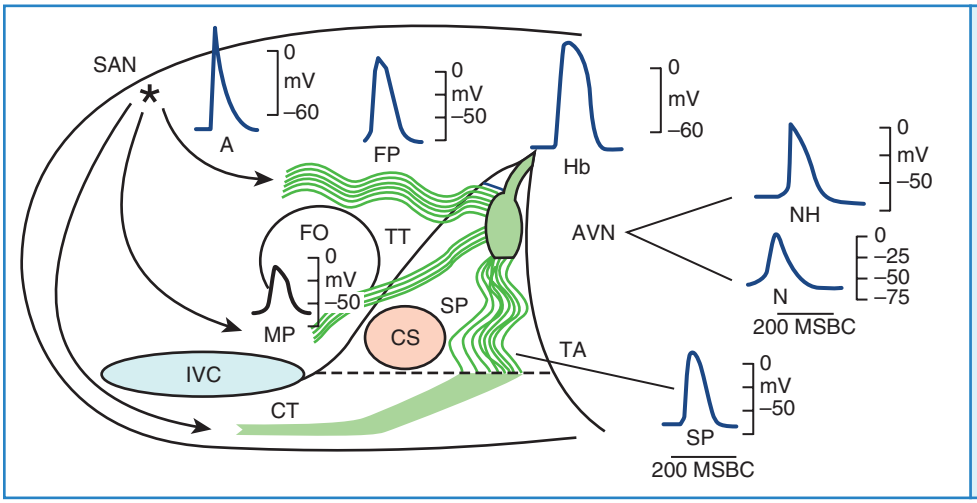

FIGURE 40-4 A representation of the right atrium and action potentials from the atrium and atrioventricular junction. *A*, Atrial potential; *AVN*, AV node; *CS*, coronary sinus; *CT*, crista terminalis; *FO*, fossa ovalis; *FP*, fast pathway and potential; *SP*, slow pathway and potential; *Hb*, His bundle and potential; *IVC*, inferior vena cava; *MP*, mid pathway and potential; *N*, central nodal potential; *NH*, distal nodal potential; *TT*, tendon of Todaro.

refractoriness of the AV node. The potent actions of autonomic stimulation on AV nodal conduction are largely due to the modulation of I_{CaL} by adrenergic and cholinergic stimulation via specific receptors and transduction systems. This current is enhanced, and its kinetics of activation, inactivation, and recovery are accelerated by adrenergic stimulation; it is conversely affected by cholinergic stimulation.

T-type Ca^{2+} current (I_{CaT}) has been shown recently to be important in AV conduction in mice. Genetically modified mice lacking these channels manifest slow conduction within the AV node as well as reduced rates of AV nodal pacemakers.[57] A study has reported congenital heart block and sinus bradycardia in children exposed to maternal antibodies that reduce both L-type and T-type channels, indicating a possible role of T-type channels in human AV nodal conduction.[58]

On the one hand, AV nodal cells contain the pacemaker current I_f, which may contribute to the automaticity of AV nodal cells. On the other hand, the current I_{to}, a rapidly activating and inactivating K^+ current that produces the notch of the AP (phase I) and is prominent in atrial cells, is sparse or absent in AV nodal cells. The repolarizing K^+ current I_{Kr} is present and probably a major factor in the repolarization of AV nodal cells. The repolarizing current I_{Ks}, a contributor to repolarization in atrial, ventricular, and His–Purkinje cells, appears to be absent in AV nodal cells.

Ca^{2+}-activated K^+ channels (K_{Ca}) have been demonstrated in the activation of K_{Ca} in human atrial myocytes and has been shown to increase the rate of AV nodal pacemakers and accelerate repolarization.[59,60]

The K^+ current $I_{Ach,Ado}$ is prominent in sinoatrial nodal cells and atrial cells but not in ventricular cells. It is also present in AV nodal cells. Activation of this current by acetylcholine or adenosine drives the resting potential to more negative values, suppresses automaticity, and diminishes the AP, thus slowing AV conduction.

Gap junctions appear to be sparse and smaller in the central AV node than in the atrial and ventricular myocardium.[61] The gap junctions in the node are composed predominantly of connexin40 rather than connexin43, which is dominant in the ventricular myocardium. The relatively poor intercellular communication in the AV node is probably the result of these gap junction properties as well as a relative increase in the volume of extracellular space surrounding AV nodal cells, compared with the atrial and ventricular myocardium.

Transitional Atrio-Nodal Connections

The transitional fibers connecting the atrium to the AV node aggregate in zones that are functionally relatively discrete, though not insulated from the atrial myocardium. Observations indicate that anisotropy is a major determinant of directional conduction in these pathways.[62] They extend from the node to and beyond the border of Koch's triangle and connect to the node at relatively discrete sites along its margins.

These atrio-nodal connections have APs with characteristics that are intermediate between atrial cells and prototypical cells in the compact node. Like the AV node, these transitional connections may show decremental conduction and Wenckebach type of block. Until recently, functional definitions of these connections distinguished a "fast pathway" located at the anterosuperior aspect of the node and connecting to the atrium anterior to the fossa ovalis and a "slow pathway" connecting to the node inferiorly and posteriorly and extending posterior to the isthmus region inferior to the coronary sinus os. The terms "fast" and "slow" do not necessarily represent different conduction velocities in these pathways but different conduction times determined by the access and length of the pathways, depending on the site of origin of global atrial activation. In humans, the fast pathway is usually but not invariably considered to have a longer refractory period than the slow pathway.

Newer techniques for high-resolution integrated histologic and molecular mapping of the AV junction and its atrial connections in the rabbit heart have disclosed additional complexities of its structure and function.[63] The compact node stains positive for neurofilament, which is expressed in the conduction system but not the atrial or ventricular myocardium, but connexin43 stains weakly in the node. The myocytes in the node are small and dispersed within fibrous tissue. The infero-posterior extension of the node toward the coronary sinus, thought to represent the slow pathway, is also positive for neurofilament and sparse in connexin43 with small dispersed cells like the compact node. Transitional tissue, which joins the node at its inferoposterior end near the coronary sinus and also more anteriorly near the compact node, has connexin43, lacks neurofilament, but has smaller dispersed cells, thus being intermediate between the node and the atrium. The anterior transitional fibers are thought to represent the fast pathway. The node is connected to the atrium at discrete sites with transitional fibers joined to nodal and atrial fibers. The infero-posterior extension may be the primary site for AV nodal pacemakers.[64]

Certain observations indicate that the atrial connections to the node are more complex.[51] A mid-pathway with deep (in relation to the right endocardium) connections to the node in its superior aspect and connections to the atrium in the septum posterior to the fossa ovalis has been described. Left-sided connections have been described in humans.[65] The functional inter-relationships of the pathways in normal AV conduction are not fully elucidated. It is clear that these pathways, the atria, and the AV node can form various configurations of re-entry circuits that cause AV nodal re-entrant tachycardia. Interruption of the atrial connections to the AV node can produce AV block.

Bundle of His and Bundle Branches

The bundle of His and bundle branches, which are insulated by fibrous matrix from the ventricular myocardium, constitute the ventricular aspect of the AV conduction axis. They function to rapidly disseminate activation to the ventricular myocardium in a pattern that optimizes ejection of blood by a synchronized and coordinated apex to base contraction.[66] Conduction in these tissues is the most rapid of all conductions in cardiac tissue, promoting synchronization of activation of distal sites. The architecture of the bundle branches and their proximal insulation promote apex-to-base contraction and septal-free wall synchronization. The APs of these fibers in multicellular preparations manifest very rapid upstrokes, prolonged plateaus and repolarization, and automaticity.

Quantitative measurement of individual currents in isolated Purkinje cells has been relatively limited. The Na^+ current is abundant, accounting, in part, for the fast upstroke and the rapid conduction velocity. The ionic basis for the prolonged plateau has not been determined, but I_{Ks} appears to be less active in Purkinje cells than in ventricular myocardial cells.[67] The T-type Ca^{2+} current is present in Purkinje fibers and may contribute to automaticity and to the excitatory current.[68]

The basis for the automaticity of the His-Purkinje system is debated. Some favor the decay of a K^+ current activated during the AP as the primary basis for automaticity, whereas others favor the current I_f.[69] As in the sinoatrial node and the AV node, multiple ionic determinants of automaticity may be present. The automaticity of the His-Purkinje system is more prominent proximally than distally. Automatic firing of the distal Purkinje system is slow and erratic. As a result, heart block caused by degeneration and fibrosis of the bundle branches is more malignant than is heart block caused by the interruption of conduction in the AV junction proximal to the bundle of His.

Gap junctions are abundant in the Purkinje strands of the bundle branches and their distal ramifications. They are uniformly distributed along the lengths and ends of the fibers and promote good intracellular communication throughout the margins of the cells and rapid conduction. However, the bundle of His fibers appear relatively poorly connected in the transverse dimension, so dissociation within the bundle of His has been observed in experimental animals and in humans.[70]

Diagnostic Techniques

Since the prognosis and treatment for AV block differ, depending on whether block is within the AV node or is infranodal, determining the site of block is important. In many cases, this can be done noninvasively. The QRS duration, P-R intervals, and the ventricular rate on surface ECG can provide important clues in localizing the level of block. Several noninvasive interventions may also prove helpful, such as vagal maneuvers, exercise, or administration of intravenous atropine. These methods take advantage of the differences in autonomic innervation of the AV node and of the His-Purkinje system.[71] While the AV node is richly innervated and highly responsive to both sympathetic and vagal stimuli, the His-Purkinje system is influenced minimally by the autonomic nervous system. Carotid sinus massage increases vagal tone and worsens AV nodal block. Exercise or atropine improves AV nodal conduction due to sympathetic stimulation. In contrast, carotid sinus massage improves infranodal block, while exercise and atropine worsen infranodal block because of the change in the rate of the impulses being conducted through the AV node.

Exercise testing is a useful tool to confirm the level of block that is already suspected in second-degree or third-degree block with a narrow or wide QRS complex. Patients with presumed AV nodal block or congenital complete heart block and a normal QRS complex will usually increase their ventricular rate with exercise. However, patients with acquired complete heart block and a wide QRS complex usually show minimal or no increase in the ventricular rate.

An electrophysiological study is indicated in a patient with suspected high-grade AV block as the cause of syncope or presyncope when documentation cannot be obtained noninvasively.[72,73] In patients with coronary artery disease, it may be unclear whether symptoms are caused by AV block or ventricular tachycardia, and an electrophysiological study can be useful in establishing the diagnosis. Some patients with known second-degree or third-degree block may benefit from an invasive study to localize the site of AV block and to determine therapy or assess prognosis. Once symptoms and AV block are correlated by electrocardiography, further documentation by invasive studies is not typically required. Asymptomatic patients with transient Wenckebach block associated with increased vagal tone should not undergo invasive electrophysiological investigation.

The electrophysiological study allows analysis of the bundle of His ECG as well as the performance of atrial and ventricular pacing to identify conduction abnormalities and inducible ventricular tachycardia. The atrio-His (A-H) and His-ventricle (H-V) intervals are measured from the bundle of His ECG.[74] Atrial pacing techniques are used to define the site of block and assess AV nodal and His-Purkinje conduction. During decremental atrial pacing, the A-H interval normally will gradually lengthen until AV nodal Wenckebach block is noted. The H-V interval will normally remain consistent despite different pacing rates. Abnormal AV nodal conduction is defined as Wenckebach block occurring at slower atrial-paced rates than what is normally seen (i.e., >500 ms). To determine whether AV nodal disease is truly present or just under the influence of excessive vagal tone, atropine alone or autonomic blockade with atropine and propranolol can be given to differentiate inherently abnormal AV nodal conduction from vagally mediated abnormalities. Infranodal block (Mobitz type 2) is present when the atrial deflection is followed by the His ECG, but no ventricular depolarization is seen. Block below the His is abnormal, unless associated with very-short-paced cycle lengths (350 ms or less).[75]

While retrospective studies provide useful information that can often help generate a hypothesis, they frequently exaggerate the benefit of treatment. It is always preferable to base clinical decisions, if possible, on data from prospective randomized trials. However, no prospective randomized trials have evaluated the efficacy of pacing therapy in patients with AV block, as there are no alternatives to pacing therapy for the patient with symptomatic AV block (not because of reversible causes). In addition, it is difficult to assemble large groups of asymptomatic patients with specific types of AV block. Recommendations for permanent pacemaker implantation are based on observational studies on the natural history of AV block. In general, permanent pacemakers are implanted in patients with symptomatic AV block and in patients with asymptomatic AV block caused by His-Purkinje disease.[76]

Pacing Mode Choice

Prospective data on the effects of pacing mode choice in patients with AV block are limited. Both single-chamber ventricular pacing and dual-chamber pacing will prevent bradycardia in patients with AV block. However, only dual-chamber pacing maintains AV synchrony. Dual-chamber pacing also reduces the incidence of pacemaker syndrome. Despite these potential advantages, the importance of dual-chamber pacing in patients with AV block has not been well established, particularly in older adults.

In the Pacemaker Selection in the Elderly (PASE) trial, 407 older adults (mean age 76 years) were randomized to either the rate-adaptive ventricular inhibited (VVIR) or rate-adaptive dual-chamber (AV) inhibited/triggered (DDDR) pacing mode.[77] In the 201 patients who had pacing systems implanted for AV block, no reduction in mortality, stroke, or atrial fibrillation was observed. In contrast to the observation in patients with sinus node dysfunction, dual-chamber pacing was not associated with improvement in quality-of-life indices. In the Canadian Trial of Physiologic Pacing (CTOPP), 2568 patients with symptomatic bradycardia were randomized to single-chamber ventricular pacing or a "physiologic" pacing mode that preserved AV synchrony (single-chamber atrial pacing or dual-chamber pacing).[78] AV block was

the indication for pacing in approximately 60% of the patients. Physiological pacing was not associated with a reduction in stroke or death due to cardiovascular disease, which was the study's primary endpoint. Interestingly, physiological pacing was associated with a reduction in the development of chronic atrial fibrillation even in those patients with pacing systems implanted for AV block.[79] A large prospective study recently examined the importance of pacing mode selection in older adults with AV block.[80] In the United Kingdom, in the Pacing and Clinical Events (UK-PACE) Trial, patients older than 70 years of age with AV block were randomized to the ventricular inhibited (VVI), VVIR, and DDD pacing modes. Patients were followed up for at least 3 years. The primary endpoint was all-cause mortality, although other secondary outcomes such as atrial fibrillation, heart failure, stroke/transient ischemic attack/thromboembolism, pacing system revision, cardiovascular events such as angina or myocardial infarction, exercise capacity, and quality of life were also evaluated. A composite endpoint of all outcomes was also examined. Patient recruitment occurred from 1995 to 1999, and the trial terminated in September 2002 with a median follow-up of 4 years.[80] Of the patients, 504 were randomized to VVI pacing, 505 to VVIR pacing, and 1012 to DDD pacing. Some patients remained in the randomized mode: 96.6% of VVI patients, 96.4% of VVIR patients, and 87.7% of DDD patients. No difference was seen in all-cause mortality or time to atrial fibrillation or other cardiovascular events. An increased stroke risk with VVI pacing (hazard ratio, 1.58) was observed, but no differences were found in any other secondary endpoints or in the composite endpoint. This trial suggests that older patients derive limited and specific benefits and fail to obtain other favorable results compared with younger patients with DDD pacing. This may reflect more advanced atrial and cardiovascular disease status or other variables.

In summary, it is unlikely that any randomized trial will be performed to evaluate the efficacy of pacing therapy in patients with AV block. Although the evidence for the usefulness of dual-chamber pacing in patients with AV block is incomplete at present, most patients with AV block should receive a dual-chamber pacing system.[76,81]

Management of Atrioventricular Block

When AV block is identified, management requires a search for reversible causes, an assessment of hemodynamic stability to determine whether temporary pacing is required, and, finally, a decision on whether permanent pacing will be necessary.

Temporary Pacing

In the hemodynamically unstable patient with AV block, the clinician must identify any rapidly reversible causes. Reversible causes include hyperkalemia, hypoxia, increased vagal tone, and ischemia. While treatment for reversible causes is initiated, it must be decided quickly whether temporary pacing will be required for the hemodynamically unstable patient. Temporary pacing is most quickly initiated by transcutaneous passage of current between two specially designed pads placed on the chest wall. Patch position is the most important factor for determining the effectiveness of transcutaneous pacing. The cathode should be placed on the left chest over the cardiac apex, and the anode placed on the back between the spine and the scapula or anteriorly just above the right nipple. Currents of 20 to 140 mA are usually required to capture and activate the ventricles. Using the correct technique, transcutaneous pacing is effective in more than 90% of cases and associated with very few complications.[82,83] However, transcutaneous pacing cannot be used for prolonged periods because of patient discomfort and the unreliability of capture due to impedance changes.

If temporary pacing must be used for more than 30 minutes, transvenous pacing should be initiated, as it is far more stable and better tolerated. With transvenous pacing, intravascular access is obtained usually through the right internal jugular vein and a pacing catheter is positioned into the right ventricle. The pacing catheter is connected to a pulse generator; ventricular capture can usually be obtained with currents of 1 to 2 mA. Transvenous pacing can be used for long periods with minimal complications (<2% once venous access is achieved).[82]

Permanent Pacing

Once the patient is stabilized, the clinician must assess whether the AV block will be permanent. In several conditions, persistent AV block will gradually resolve. In approximately 10% to 15% of patients with inferior and posterior wall myocardial infarctions, transient second-degree, advanced, or complete AV block will be observed.[84] In almost all cases, AV block will resolve, and permanent pacing is not required. Approximately 8% to 10% of patients with Lyme disease will have transient AV conduction abnormalities caused by myocarditis involving the AV nodal region. AV block usually resolves within several weeks, and permanent pacing is almost never required. Acute rheumatic fever can also present with AV block that is expected to resolve after several weeks.[84]

Indications for Permanent Pacing

Indications for permanent pacing in acquired AV block have been published by a Joint Committee of the American College of Cardiology (ACC) and the American Heart Association (AHA) in 1984, 1991, 1998, and 2002, and in 2008 in collaboration with The Heart Rhythm Society (HRS).[76] The ACC/AHA/HRS 2008 guidelines use the standard three-group classification schema. Class I indications are conditions for which there is evidence or general agreement that a given procedure or treatment is beneficial, useful, and effective. Class II indications are conditions for which there is conflicting evidence or a divergence of opinion about the usefulness/efficacy of a procedure or treatment. Class II has been further divided into class IIa, where the weight of evidence/opinion is in favor of usefulness/efficacy, and class IIb, where usefulness/efficacy is less well established by evidence/opinion. Class III indications are conditions for which there is evidence or general agreement that a procedure/treatment is *not* useful/effective and, in some cases, may be harmful. Despite some shortcomings,[76] the ACC/AHA/HRS guidelines provide a useful framework for management. The indications for permanent pacing in *symptomatic* patients with second-degree or third-degree AV block are often straightforward (Table 40-1). Controversial indications involve mostly asymptomatic patients.[76,85] The decision to implant a pacemaker in *asymptomatic* patients is more difficult and requires knowledge of the pathophysiology and natural history of AV block.[86] As a general rule, since escape rhythms from ventricular tissue are unreliable, a pacemaker should be implanted in asymptomatic patients if AV block occurs in His-Purkinje tissue.

Table 40-1 Indications for Permanent Pacing in Atrioventricular Block

Permanent pacemaker implantation is indicated for third-degree and advanced second-degree atrioventricular (AV) block at any anatomic level associated with the following:

1. Bradycardia with symptoms (including heart failure) or ventricular arrhythmias presumed to be caused by AV block
2. Arrhythmias and other medical conditions that require drug therapy that results in symptomatic bradycardia, in awake, symptom-free patients in sinus rhythm, with documented periods of asystole ≥3.0 seconds) or any escape rate less than 40 beats/min
3. An escape rhythm that is below the AV node, in awake, symptom-free patients with atrial fibrillation and bradycardia with one or more pauses of at least 5 seconds or longer after catheter ablation of the AV junction
4. Postoperative AV block that is not expected to resolve after cardiac surgery

Third-Degree Atrioventricular Block

Symptomatic third-degree AV block is a class I indication for pacing therapy. For asymptomatic patients, the current guidelines use a rate cutoff, with escape ventricular rates less than 40 beats/min designated as a class I indication and ventricular rates greater than 40 beats/min designated as class IIa. Although this distinction may seem reasonable, one must confirm whether the patient is truly asymptomatic; in some cases, symptoms associated with third-degree AV block are subtle. More importantly, prognosis depends on the stability of the escape rate pacemaker rather than the actual rate; escape rhythms from ventricular tissues (wide QRS complexes) are inherently unstable. In practice, acquired third-degree AV block not associated with any reversible causes is usually considered a class I indication for permanent pacing whether symptoms are present or absent.

Second-Degree Atrioventricular Block

Symptomatic second-degree AV block is a class I indication for pacing regardless of type of block. The use of pacing therapy for asymptomatic patients with second-degree AV block is controversial and depends on the type (site) of AV block.

In general, type 1 second-degree AV block associated with a narrow QRS complex (<0.12 seconds) is due to block in the AV node, and the current published guidelines do not recommend pacemaker implantation in the asymptomatic patient. In a study of 56 patients with documented chronic second-degree AV block caused by AV nodal conduction delay, those without associated cardiac disease had a benign course, whereas those with associated cardiac disease had a poor prognosis because of progression of underlying cardiac disease rather than the development of sudden bradycardia.[86] However, in another retrospective study of 214 patients with second-degree AV block, survival and requirement for pacing were not different among patients with type 1 and type 2 heart block, and the presence or absence of bundle branch block did not appear to aid in the prediction of survival.[87] In view of these conflicting data, it is prudent to closely monitor patients with type 1 second-degree AV block and a narrow QRS complex for symptoms and for progression of conduction tissue disease (e.g., development of fascicular block or QRS widening). If type 1 second-degree AV block is associated with a wide QRS complex (>0.12 seconds) AV block will be located in the AV node in 30% to 40% of patients and in the His-Purkinje system in 60% to 70% of cases.[88,89] In these cases, an invasive electrophysiological study is often required to identify the site of block. If intra-Hisian or infra-Hisian block is identified, a pacemaker should be implanted, as these conditions usually progress to complete heart block within 5 years.[90]

Type 2 second-degree AV block generally occurs in His-Purkinje tissue. Asymptomatic patients with type 2 AV block usually do develop symptoms and will require permanent pacing.[79]

In 2:1 second-degree AV block, every other P wave conducts, preventing comparison of consecutive P-R intervals. The QRS complex provides a clue as to the site of block: A narrow QRS complex is associated with His-Purkinje block 30% of the time, and a wide QRS complex is associated with His-Purkinje block approximately 80% of the time.[17,91] In the asymptomatic patient with 2:1 block, maneuvers (such as exercise, atropine, or continuous ECG monitoring) to alter the conduction ratio between the atria and the ventricles may allow localization of the site of block. However, in some cases, electrophysiological evaluation to determine the site of block will be required.

First-Degree Atrioventricular Block

If first-degree AV block is severe, atrial activation and contraction can occur while the ventricles are contracting in response to the previous atrial contraction, which leads to an inappropriate rise in atrial pressures and symptoms similar to pacemaker syndrome. In this situation, symptoms can be significant, even with exercise, as the P-R interval does not shorten appropriately with adrenergic stimulation. The current guidelines classify symptomatic first-degree AV block as a class IIa indication for pacemaker implantation.[76] Asymptomatic first-degree AV block is a class III indication for pacing. The one exception to this recommendation is the asymptomatic patient with first-degree AV block, abnormal QRS axis caused by left anterior or left posterior fascicular block, and neuromuscular disease.[76] Neuromuscular diseases such as myotonic dystrophy and Kearns-Sayre syndrome are associated with progressive AV block; since development of complete heart block can be unpredictable, implantation of a permanent pacemaker is justified.

Pacing Mode Choice

Three pacing modes (DDD, VDD, and VVI) can be used to prevent bradycardia in patients with AV block.

VVI and VVIR Pacing

In the VVI or VVIR pacing mode, bradycardia is prevented, and if rate adaption is programmed to be "on," the heart rate will increase with exercise. However, AV synchrony not present in either of these pacing modes. The importance of AV synchrony is controversial in patients with AV block because the main contribution to increased cardiac output with exercise is heart rate rather than AV synchrony and the incidence of pacemaker syndrome is lower in patients with AV block compared with patients with sinus node dysfunction. However, it seems intuitively reasonable that in the presence of organized atrial activity, the VDD and DDD pacing modes are most appropriate. In fact, since the

early 1990s, the British Pacing and Electrophysiology Group guidelines have stated that the only indication for the VVI and VVIR pacing modes is atrial fibrillation/flutter with AV block or slow ventricular response.[81] The VVI and VVIR pacing modes may also be appropriate in patients who are incapacitated and inactive as well as in those with other medical problems associated with a short life expectancy.

DDD and DDDR Modes

The DDD pacing mode prevents bradycardia and provides AV synchrony in patients with AV block. Although less important for exercise-related increases in cardiac output, several studies have demonstrated that AV synchrony is associated with improved symptoms at baseline levels of activity. The report of a large randomized study (UK-PACE) that compared the VVI and DDD pacing modes in older patients (older than 70 years of age) with second-degree or third-degree AV block has been published.[80] Although the DDD pacing mode is the most complex, most guidelines recommend this pacing mode in patients with AV block, as it maintains AV synchrony regardless of the cause of the bradycardia.

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CHAPTER 41

Paroxysmal Supraventricular Tachycardia and Pre-excitation Syndromes

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Anatomy and Pathology: Saroja Bharati
Electrocardiography: Bruce D. Lindsay
Diagnostic Approach: Samuel Levy

Paroxysmal supraventricular tachycardia (PSVT) has been a well-recognized clinical syndrome and an electrocardiographically defined arrhythmia since the early days of electrocardiography. The clinical syndrome was defined in European literature in the nineteenth century. In 1867, Cotton reported on an "unusually rapid action of the heart," and was followed by further observations by French and German scientists.[1,2] Variously referred to first as *Bouveret's syndrome* and later as *paroxysmal atrial tachycardia*, it was described classically as "a fully unprovoked tachycardia attack, lasting a few seconds or several days, in patients who as a rule have otherwise healthy hearts."[1] It has been electrocardiographically defined in the Tenth Bethesda Conference on Optimal Electrocardiography as "a tachycardia usually characterized by an atrial rate of 140 to 240 beats/min and by an abrupt onset and termination. It may or may not be associated with intact atrioventricular conduction. Specific electrophysiological studies may elicit specific mechanisms such as retrograde and anterograde pathways and sites of re-entry."[3]

In the past 25 years, this has been an intensively studied arrhythmia, with extensive definition of its genesis, presentation, subtypes, and electrophysiology. Pharmacologic therapy and, later, nonpharmacologic therapy have been investigated and refined. This is now a classic story in the evolution of clinical cardiac electrophysiology and forms a fundamental cornerstone in the modern treatment of cardiac arrhythmias.

Epidemiology

The epidemiology of PSVT has not been widely investigated in modern times. Early electrocardiographic reports were useful in arrhythmia detection in patients presenting with sustained palpitations and persistent episodes of supraventricular tachycardias (SVTs) but had little role for this purpose in the large body of patients with brief SVT events terminating before presentation to the physician.[4,5] These efforts were supplemented by the advent of ambulatory electrocardiography, which documented a large number of cardiac arrhythmias in asymptomatic patients. Conversely, it confirmed that many symptoms experienced by patients with or without heart disease that are suggestive of tachyarrhythmias occur when no arrhythmias or simply premature beats are documented on monitoring. Epidemiologic data are extensively colored by the selection criteria and the electrocardiographic documentation mode used in the study. Brodsky et al reported that ambulatory electrocardiographic recordings in 50 male medical students detected atrial premature beats in 56%, but only one had more than 100 beats in 24 hours.[6] The limited period of observation precludes objective assessment of development of SVT events in these subjects. Thus Hinkle et al, in a study of 301 men with a median age of 56 years, detected various supraventricular arrhythmias in 76% of these individuals.[7] However, coronary disease was present in 20% of these patients. Clark et al studied an apparently normal population ranging from 16 to 65 years old and noted a low incidence of supraventricular arrhythmias.[8,9] In contrast, recent longitudinal studies with telemetric monitoring and even implanted cardiac pacemakers document a very high incidence of asymptomatic and symptomatic atrial arrhythmias, particularly atrial fibrillation (AF) in patients with bradyarrhythmias.[10] Thus, it would be appropriate to infer that the true incidence of PSVT in the general population remains unknown because of its evanescent nature and limited methods of detection. It would also be appropriate to surmise that the incidence may be higher than generally believed over a long observation period. Atrial arrhythmias also increase with age.[11] In the Cardiovascular Health Study, short runs of PSVT occurred in 50% of men and 48% of women, doubling in prevalence in octogenarians. PSVT has been shown to occur in 28% of nursing home residents.[11]

More data are available for pre-excitation syndromes, particularly Wolff-Parkinson-White (WPW) syndrome. Electrocardiographic studies of healthy individuals suggest that the incidence of this condition is 3 in 1000 of the general population.[12] Early studies suggested that the morbidity and mortality in WPW syndrome with tachyarrhythmias were greater in adults with ventricular fibrillation (VF) occurring in those with AF and antegrade pre-excitation.[13] However, Klein et al have reported on the natural

history of asymptomatic WPW syndrome; they noted a very low incidence of major morbidity and serious symptomatic arrhythmias, including AF with rapid antegrade conduction and mortality.[14]

Supraventricular arrhythmias are seen at all ages and are particularly common in infants, children, and young adults. The age-related behavior of these rhythms has also been the subject of epidemiologic study. In a study of infants younger than 1 year, Mantakas et al noted that associated congenital heart disease was present in 35%, and 90% developed SVTs with narrow (35%) or wide QRS (45%) complexes.[15] Most patients (90%) improved with growth or remained stable, but patients with congenital heart disease could have refractory arrhythmias. The quality and duration of life in children with WPW syndrome without clinical dysrhythmias have been reported to be normal.

Anatomy and Pathology

Normal Anatomy of the Sinus Node

Tachycardias of sinus node origin have been described. These can present as paroxysmal episodes of SVT or inappropriate sinus tachycardia (IST), which is nonparoxysmal in nature. Postural orthostatic tachycardia syndrome is discussed elsewhere in the text and is associated with sinus tachycardia and orthostasis. Sinoatrial re-entrant tachycardias (SARTs) arise in the region of the sinus node and peri-nodal region. See Chapter 39 for a detailed treatment of the normal anatomy of the sinus node.

Normal Anatomy of the Atrioventricular Junction

To understand the pathologic base for atrioventricular (AV) nodal tachycardia and AV re-entrant tachycardia (AVRT), the normal anatomy of the AV node and its approaches, including the atria and the AV bundle, is briefly reviewed in the following regions of interest: (1) approaches to the AV node including the atrial septum, (2) AV node, and (3) AV node–bundle junction.[16-27]

Approaches to the Atrioventricular Node

Approaches to the AV node include the atrial myocardium located in the anterior, superior, midseptal, and inferior regions as they converge to the AV node. The approaches beneath the coronary sinus area may be called the *posterior* or *inferior* approaches. In addition, approaches also originate from the tricuspid valve. Left-sided approaches include those from the left atrial myocardium and the mitral valve. Superior approaches include the pectinate muscles as they merge from the superior, lateral, and posterior walls of the right atrium toward the AV nodal area, atrial septum, and Todaro's tendon. Approaches to the AV node are formed by different types of myocardial fibers coming from different directions as they merge toward the AV nodal area (Figure 41-1). Histologically, in general, the cells are relatively loosely arranged with lighter-staining, smaller cells. The size and shape of the myocardial fibers vary considerably from one approach to the other in the vicinity of the node. In general, there is increase in the elastic collagen connective tissue intermingling with the cells, fat, and a large amount of nerve fibers. At the electron microscopic level, the mitochondria and myofibrils of the atrial myocardial cells are not as well organized as the ventricular cells, and some of them do not have a transverse tubular system.[16]

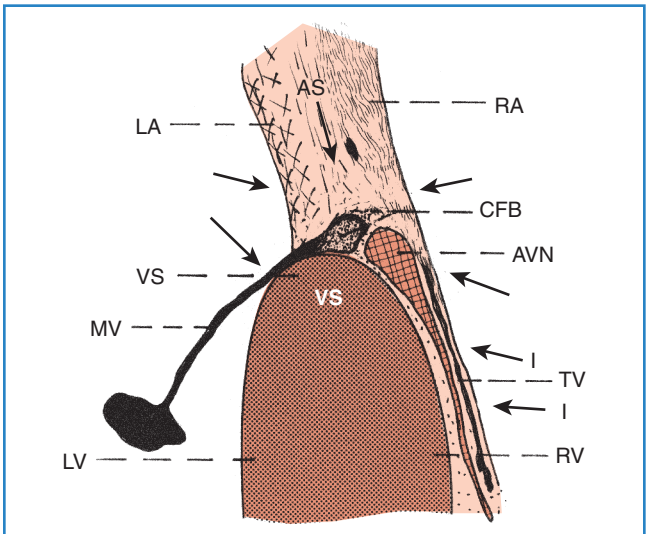


FIGURE 41-1 Schematic representation of the atrioventricular (AV) junction depicting the approaches to the AV node. *Arrows* point to the approaches to the AV node from the tricuspid valve area, right atrial aspect, right ventricular aspect, atrial septal aspect, left atrial aspect, and mitral valvular aspect; *AVN*, AV node; *CFB*, central fibrous body; *LA*, left atrial myocardium–left atrial approaches; *LV*, left ventricular side of the septum; *MV*, approaches from the mitral valve; *RA*, right atrial myocardium–superior approaches; *AS*, atrial septum; *I*, inferior approaches; *RV*, right ventricular side of the septum–right ventricular approaches; *TV*, approaches from the tricuspid valve; *VS*, summit of the ventricular septum. *(From Bharati S, Lev M: The anatomy of the normal conduction system: Disease-related changes and their relationship to arrhythmogenesis. In Podrid PJ, Kowey PR, editors:* Cardiac arrhythmias, mechanism, diagnosis and management, *Baltimore, 1995, Williams & Wilkins.)*

Significance of the Size Variations of the Approaches to the Atrioventricular Node

Atrial myocardial fibers, including collagen, elastic tissue, and nerve elements in the approaches to the AV nodal area, can vary in size, shape, and direction, suggesting that there may be functional differences in the speed of conduction.[16-20] Anatomically, one approach to the AV node may be more dominant than the other. For example, dominant posterior approaches with less prominent superior approaches in humans suggest the possibility of dominant slow pathway conduction. Likewise, dominant superior approaches with practically absent inferior approaches suggest the possibility of the dominance of fast pathway conduction or other alterations in AV nodal conduction. Myocardial fibers in the atria may get entrapped within the central fibrous body and join the AV node. In other instances, approaches to the AV node as well as the AV node may be entrapped within the tricuspid or mitral valve annulus or the base of the aortic valve. During an altered physiologic state, these anomalies may form an anatomic substrate for a re-entry circuit, resulting in various types of supraventricular or junctional arrhythmias.[16-18]

Atrioventricular Node

The AV node is normally in continuity with its atrial approaches.[16-23,26] It is a sizable structure and is usually located near the annulus of the septal leaflet of the tricuspid valve. In the

adult, it measures approximately 5 to 7 mm in length and 2 to 5 mm in width. The node extends closely beneath the endocardium of the right atrium, adjacent to the septal leaflet of the tricuspid valve, and lies very close to the right ventricular aspect of the ventricular septum and the central fibrous body. The size and shape of the node are not uniform in nature and vary considerably from heart to heart. At the light microscopic level, the AV node consists of a meshwork of cells that are approximately the size of atrial cells but are smaller than ventricular cells. Histologically, the AV node may be divided into three layers: (1) superficial, or subendocardial, (2) intermediate, or midzone, and (3) deep, or innermost.[16-18]

Superficial or Subendocardial Layer of the Atrioventricular Node

The approaches that come from various directions merge gradually with the superficial or subendocardial part of the AV node. These fibers are loosely arranged with smaller nodelike cells oriented along the atrial cells, some intermingling with the atrial cells, fat, elastic tissue, collagen, and nerve fibers. A distinct increase in fat occurs with normal aging of the heart.[16-18]

Intermediate or Midlayer of the Atrioventricular Node

AV nodal cells are more or less compact; however, the orientation and arrangement of the cells vary considerably. The collagen and elastic tissue content is less than that seen in the superficial layer with fewer nerve fibers. In the older age group, fat may be present in the intermediate layer of the node.[16-18]

Deep or Innermost Layer of the Node

AV nodal cells are tightly arranged and may be considered compact. However, the arrangement and orientation of these cells also vary considerably. Some amounts of collagen and elastic tissue are present, though somewhat less than in the intermediate and superficial layers. Fat may be seen intermingling with the nodal cells in patients in the older age group. At the light microscopic level, the nodal fibers vary from the periphery toward the central fibrous body.[16-18] At the electron microscopic level, fewer myofibrils and mitochondria are present and are randomly arranged. The cytoplasmic reticulum is poorly developed, and no transverse tubular system exists. It is not known whether the AV node contains more glycogen than the surrounding atrial and ventricular myocardium. The gap junctions are scarce, but desmosomes are frequent. Fascia adherens are more than in the sinoatrial nodal cells but not as frequent as in atrial and ventricular myocardial cells.[16-18]

Blood Supply and Nerve Supply to the Atrioventricular Node

In approximately 90% of hearts, the AV node is supplied by ramus *septi fibrosi*, a branch from the right coronary artery reinforced by branches from the anterior descending coronary artery.[16-23] Copious nerve cells surround the AV node, especially in the atrial septum adjacent to the AV node and nerve fibers within the node. The exact distribution and destination of the nerves in the AV nodal area in humans are still unknown. However, the rich autonomic innervation of the sinoatrial node and AV nodal areas in the canine heart indicates that the sinoatrial node is particularly responsive to parasympathetic adrenergic regulation, whereas the AV nodal conduction is preferentially sensitive to sympathetic adrenergic regulation.

Variations in Size, Shape, and Location of the Atrioventricular Node

The node lies beneath the septal leaflet of the tricuspid valve close to the right ventricular aspect of the ventricular septum and the central fibrous body. The AV node may be draped over the central fibrous body within the atrial septum, or some of the fibers may be partly within the tricuspid valve annulus and may be partly within the central fibrous body. In some cases, the fibers may be situated toward the left atrial aspect or partly within the mitral valve annulus, or they may be situated close to the base of the aortic valve.[16-23] AV node–like cells may also be seen near the tricuspid, mitral, and aortic valve annuli. Some of these nodelike cells may enter the central fibrous body and eventually join the regular posterior AV node. In addition, an accessory AV node may be seen anterosuperiorly in the parietal wall of the right atrium near the annulus of the tricuspid valve.[16] Note that not all the AV nodal cells eventually form the AV bundle; some, such as leftover nodal cells, remain and lie adjacent to the central fibrous body or near the valves.

Mahaim Fibers

Conduction fibers from the AV node, AV bundle, and left bundle branch may join the ventricular myocardium. They have been referred to as *Mahaim fibers*, or *paraspecific fibers of Mahaim*. They may form the substrate for a unique variety of ventricular pre-excitation. The myocardial fibers resemble the cells of the tissue of origin and gradually take over the characteristics of the ventricular myocardial cells. Mahaim fibers may be present from the AV node to the right, left, or middle part of the ventricular septum.[16-23]

Accessory Atrioventricular Bypass Pathways—Fibers of Kent

Accessory AV bypass pathways bypassing the AV node are seen in normal infants up to 6 months of age.[21] The myocardial cells on the atrial side resemble atrial cells, and those on the ventricular aspect resemble ventricular cells.[16-22] In adults, it has been well documented that such pathways cause pre-excitation with varying types of supraventricular arrhythmias.

Atrioventricular Node–Bundle Junction

The AV node penetrates the central fibrous body to become the penetrating part of the AV bundle. The penetrating AV bundle undergoes or assumes different shapes and contours. The orientation of fibers differs significantly. The node-bundle junction is very small, measuring approximately 1 to 1.5 mm in greatest dimension or less in the majority of hearts. The node-bundle junction becomes a part of the AV node and may be considered the most distal part of the AV node or the beginning part of the penetrating AV bundle.[16-18] The AV nodal cells that are close to the tricuspid valve and the posterior approaches are first molded to form the penetrating AV bundle. Conversely, the nodal fibers from the anterosuperior aspect are the last to lose their continuity with the superior approaches as they enter the central fibrous

body to form the AV bundle. Thus, the formation of the AV bundle within the central fibrous body occurs differentially. The posterior part of the AV node penetrates the central fibrous body earlier than the anterior or superior part. The superior part of the AV node includes the nodal fibers closer to the left atrial side, atrial septal, and right atrial aspects.[16-18]

Functional Significance of the Node-Bundle Junction

The variation in sizes of the superior and inferior components of the node, as well as the variations in which they form the AV bundle, may provide a substrate for arrhythmias. Since histologically the node-bundle junction has the characteristics of both the AV node and the AV bundle, its functional properties may be intermediate, having characteristics of both the node and the penetrating AV bundle. Likewise, the atrial myocardial approaches from the mitral valve, tricuspid valve, the right ventricular myocardium, and the atrial septum tend to get entrapped within the central fibrous body and may later join the AV node, the node-bundle junction, or both. The normal variations in morphology of the AV junction have the potential for supporting AV nodal arrhythmias.[16-18] The variation in the morphology of the AV junctional area also probably predisposes to varying types of physiological phenomena, including dual AV nodal pathways and other junctional arrhythmias.[15,16] For example, an anterior AV node in the parietal wall of the atrium or near the tricuspid valve annulus or double AV node may alter its conduction velocity. Dual AV nodal pathways may be normal or abnormal. They may be transient or become permanent.[16-18]

Accessory Atrioventricular Node and Its Relationship to Pre-excitation and Atrioventricular Junctional Tachycardias

Few pathologic studies document an accessory AV node being responsible for pre-excitation or other arrhythmias originating from the AV junction. Figure 41-2 shows a 5-month-old infant with a history of intractable junctional tachycardia. He died suddenly, and postmortem examination demonstrated a displaced coronary sinus relative to the septal leaflet of the tricuspid valve with a double AV node and double AV bundle (see Figure 41-2). In other instances, the AV node has been located partly within the central fibrous body with a left-sided AV bundle, or the right AV node has been completely interrupted by sutures, and a left-sided AV node was connected to the atrial septum. It was recently documented that an accessory AV node located anterior to the AV junction directly communicated with the right atrium and right ventricle in a curved fashion that produced ventricular pre-excitation and formed the retrograde limb of typical AVRT. In

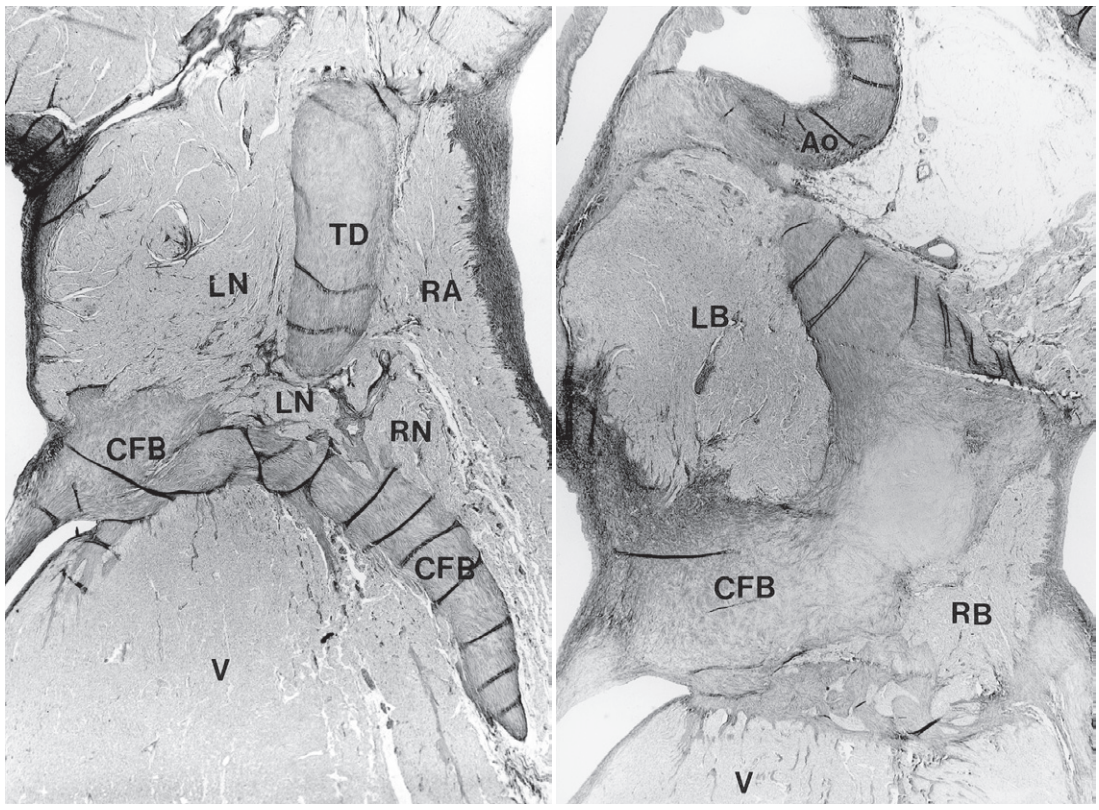


FIGURE 41-2 A 5-month-old infant with a lifelong history of tachycardia had a heart rate of 206 beats/min. He was diagnosed with junctional tachycardia. During cardiac catheterization, he developed ventricular fibrillation and died. **A,** Pathologic examination revealed a double atrioventricular (AV) node within the central fibrous body. **B,** Two AV bundles are seen in this section within the central fibrous body. Weigert-van Gieson stain ×19.5. *RN*, Right-sided AV node; *LN*, left-sided AV node; *CFB*, central fibrous body; *RA*, right atrium; *LB*, large left-sided AV bundle; *RB*, small right-sided AV bundle; *V*, summit of the ventricular septum; *TD*, tendon of Todaro; *Ao*, aorta. *(From Bharati S, Moskowich, Scheinman M, et al: Junctional tachycardias: Anatomic substrate and its significance in ablative procedures,* J Am Coll Cardiol *15:172–186, 1991.)*

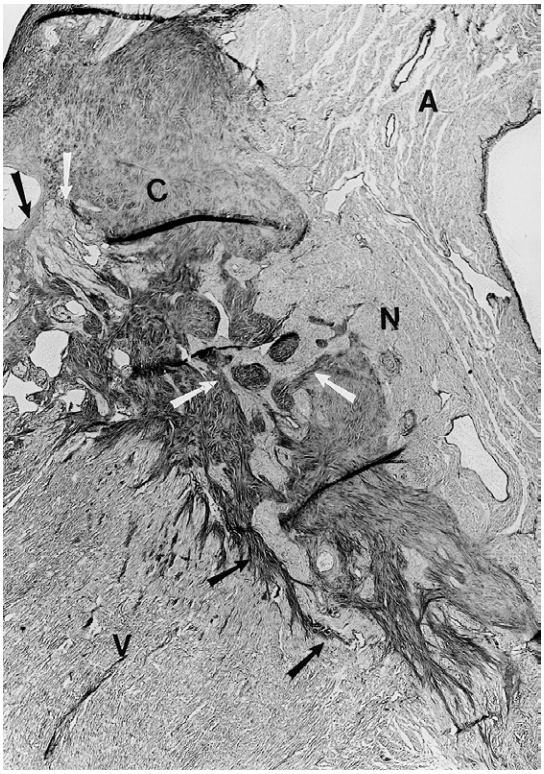


FIGURE 41-3 A 13-month-old child diagnosed with hypertrophic cardiomyopathy and supraventricular tachycardia died suddenly. Photomicrograph demonstrates the Mahaim fibers from the atrioventricular (AV) node (*N*) joining the ventricular septum (*V*). *Black arrows* point to profuse nodo-ventricular fibers from the AV node joining the ventricular septum on the right and left sides. *White arrows* point to loop formation of AV nodal fibers within the central fibrous body. Weigert–van Gieson stain ×30. *A*, Atrial approaches to the AV node; *C*, central fibrous body. *(From Cantor RJ, Gravatt A, Bharati S: Pathologic findings following sudden death in an infant with hypertrophic cardiomyopathy and supraventricular tachycardia,* J Cardiovasc Electrophysiol *8:222–225, 1997.)*

Box 41-1 Classification of Regular Supraventricular Tachycardias with Narrow QRS Complexes

SINUS NODE DISORDERS
Paroxysmal sinus tachycardia
Nonparoxysmal sinoatrial tachycardia

AV NODAL REENTRANT TACHYCARDIAS
Slow-fast (type 1)
Fast-slow (type 2)
Slow-slow (type 3)

RE-ENTRANT AND ECTOPIC ATRIAL TACHYCARDIAS
Intra-atrial reentrant tachycardia
Automatic atrial tachycardia (unifocal or multifocal)

PRE-EXCITATION SYNDROME: WOLFF-PARKINSON-WHITE SYNDROME
Orthodromic AV re-entry
Permanent junctional reciprocating tachycardia
Antidromic AV re-entry
Atrial tachycardia, atrial flutter, or atrial fibrillation, with or without accessory pathway conduction

OTHER PRE-EXCITATION SYNDROMES: MAHAIM CONDUCTION
Nodoventricular and nodofascicular reentry
Atrial tachycardia, AV nodal re-entry, or atrial fibrillation with nodo-ventricular or nodo-fascicular bystander conduction

OTHER PRE-EXCITATION SYNDROMES: LOWN-GANONG-LEVINE SYNDROME
Atrial tachycardia, atrial flutter, or atrial fibrillation with enhanced AV nodal conduction

AUTOMATIC AV JUNCTIONAL TACHYCARDIAS

AV, Atrioventricular.

another patient with typical pre-excitation and recurrent AVRT who died suddenly, no conventional anomalous pathways were present on the right side. Instead, an anterior accessory AV node in the right atrium continued as the infundibular right ventricular myocardium.

These types of abnormalities of the AV junction are seen in children as well as in adults. Pathologic study in a 13-month-old child with hypertrophic cardiomyopathy and paroxysmal SVTs, consistent with AV reciprocating tachycardia using a concealed posterior accessory pathway, revealed that the central fibrous body was abnormally formed with numerous Mahaim fibers (nodo-ventricular) on both sides of the septum with fibrosis of the left bundle branch (Figure 41-3).

Concepts and Classification

The fundamental concepts underlying recurrent PSVT have been elucidated by decades of experimental and clinical electrophysiological investigations. Early experimental studies of Moe et al and the seminal clinical studies of Durrer, Wellens, Castellanos, Rosen, and Denes, among others, helped define the mechanisms and substrates involved in these arrhythmias.[28-31] Extensive pathologic studies, as mentioned earlier, have further enhanced our understanding of the anatomic basis of these arrhythmias. Fundamental to our understanding is the concept that these arrhythmias may be caused by either enhanced automaticity or re-entry. Although the latter may predominate in certain populations and clinical practice, considerable overlap exists in clinical and electrocardiographic features. Automatic arrhythmias may arise from the sinoatrial region and from the working atrial myocardium or the AV junction. Re-entrant rhythms may arise in these structures as well and may also involve accessory AV connections or other variants in the pre-excitation syndrome. Box 41-1 lists the PSVT categories by electrophysiological mechanisms and substrate. A summary of the basic concepts involved in the genesis of these arrhythmias is provided in the following discussion.

Basic Electrophysiology

The anatomic and electrophysiological substrate and physiology of SVTs have been given fresh investigative impetus by the evolution of catheter ablation procedures. Sinus node tachycardias have been simulated in experimental studies using epinephrine injection into the fat pad.[32] (Figure 41-4, *A*).These show evidence of origin either in the sinus node itself or in the superior aspect

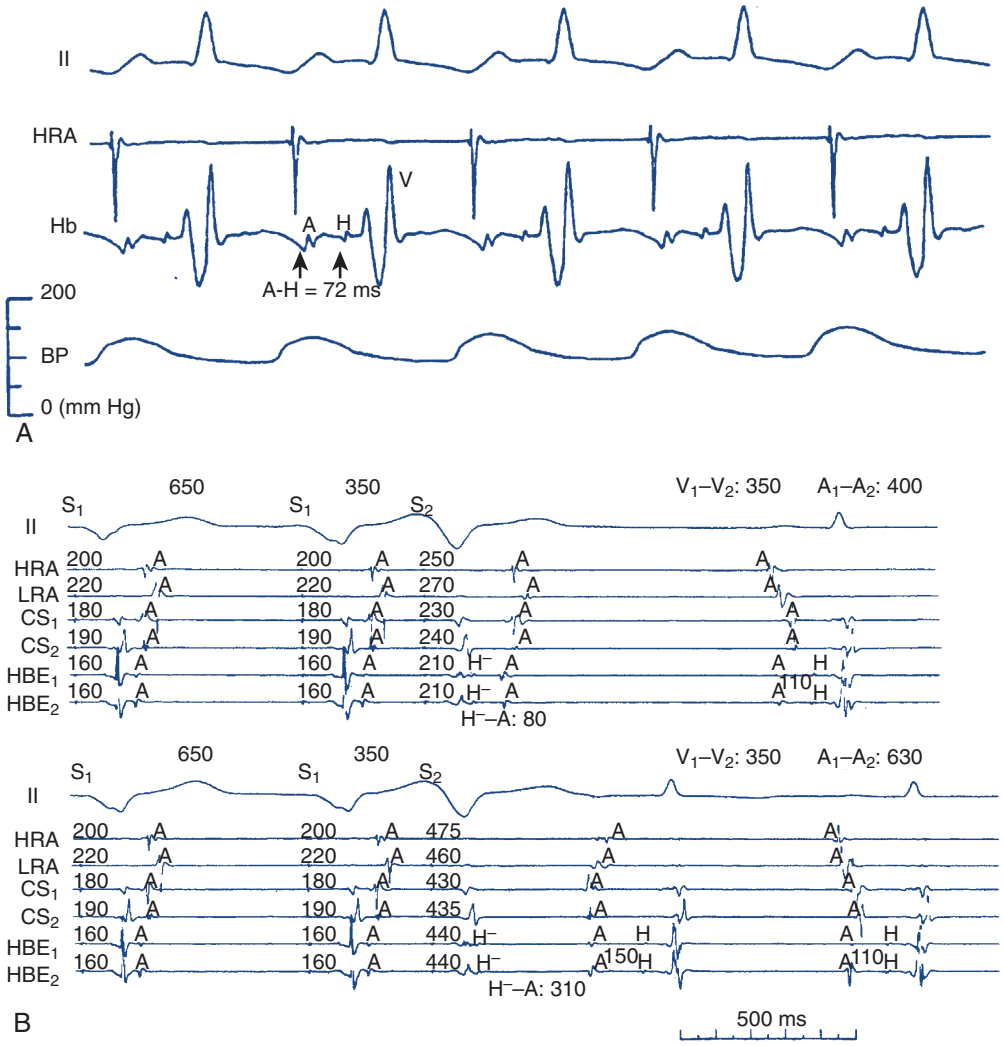


FIGURE 41-4 A, A typical response to the injection of epinephrine into the fat pad. Traces, from *top*: Electrocardiogram (ECG) lead II; electrograms for the high right atrium (*HRA*) and bundle of His (*Hb*) showing atrial (*A*) His bundle (*H*) and ventricular activation (*V*). **A,** During the control state at a sinus rate of 166 per beats/min the A-H interval measured 72 ms and systolic blood pressure (SBP) was 157 mm Hg. **B,** After 0.3 mg of epinephrine was injected into the fat pad, the sinus rate increased to 203 beats/min, but the A-H interval and SBP were relatively unchanged (72 ms and 150 mm Hg, respectively). **B,** Induction of retrograde dual atrioventricular (AV) nodal pathway conduction with ventricular extrastimulation (same patient as in Figure 41-2). *H*, Retrograde bundle of His potentials. Retrograde atrial activation sequence resulting from retrograde fast AV nodal pathway conduction (*A*) is first the low septal right atrium (*SRA*) in the bundle of His electrographic lead (*HBE*), followed by the proximal coronary sinus (*CS1* and *CS2*), high right atrium (*HRA*) and lateral right atrium (*LRA*), whereas that resulting from retrograde slow AV nodal pathway conduction (*B*) is first CS1 and CS2, followed by low SRA, LRA, and HRA. The morphology of the atrial electrogram changes as a result of the shift from retrograde fast to retrograde slow AV nodal pathway conduction. Ventriculoatrial conduction time (S0A interval) is measured from the stimulus to the onset of atrial electrogram at each recording site and is expressed in milliseconds. *(From Sung RJ, Waxman H, Saksena S, et al: Sequence of retrograde atrial activation in patients with dual atrioventricular nodal pathways,* Circulation *64:1053–1060, 1981.)*

of the crista terminalis. These have been ablated by chemical or electrical techniques.

On the basis of anatomic dissections and pathologic study of involved hearts, the accessory bypass tract has been recognized as working myocardial bundles that may cross the AV annulus at any location or bridge elements of the specialized conduction system with the atrial or ventricular working myocardium. The re-entrant circuit in AVRTs has four components—the atrium, the normal AV node, the ventricle, and the accessory pathway. In some instances, the tachycardia is located in the atrium or the AV node and simply uses the accessory pathway for conduction to the ventricles, the so-called *bystander pathway*. In contrast, AV nodal pathways are believed to be located within or in the immediate environs of the AV node. This latter structure has been stratified into transitional regions with the atrium (AN region), compact node (N region), and the bundle of His (NH region). The N region is synonymous with the anatomic descriptions of the compact AV node. The re-entrant circuit in AV nodal re-entry is confined to the AV node and the adjoining atrial myocardium. A concise description of these two substrates and their physiology is used as the basis for defining the specific variants of these arrhythmias.

Atrioventricular Nodal Re-entrant Tachycardias

Pioneering anatomic studies of Tawara and Kent and physiological demonstration of dual AV nodal physiology in dogs by Moe have laid the foundation for our current understanding of this condition.[28,33,34] Tawara and others examined the compact AV node, but more recent studies have focused on the connections of the node. Moe et al first suggested the presence of functionally and spatially distinct pathways with fast and slow conduction properties in the canine AV node.[30] Subsequently, the cellular electrophysiological properties of the node and its environs were studied (see Chapters 4 and 24). The AN and N regions lie in the triangle of Koch framed by Todaro's tendon, the tricuspid annulus, and the ostium of the coronary sinus. This anatomic location is critical to the understanding of the technique of catheter ablation of this arrhythmia. The N region is located at the apex of the triangle, where the NH region in the nonbranching part of the AV bundle penetrates the central fibrous body to become the bundle of His. Considerable uncertainty existed in the understanding of the AN region and the atrial connections of the AV node. Truex and Smythe demonstrated atrial extensions of the compact AV node, with a prominent posterior tail that extended to the ostium of the coronary sinus.[24] Anderson et al defined superficial, deep, and posterior zones in these connections.[35] The superficial zone extended into the anterosuperior part of the node, the posterior zone into the inferoposterior aspect of the compact node, and the deep fibers connected the left atrial septum to the node. Anderson noted that this latter connection joins the distal part of the node, suggesting the possibility of a lesser degree of AV nodal conduction modulation by slow currents and more rapid AV conduction. Definition of these three inputs further refined our clinical techniques of AV nodal modification or ablation. Racker also described discrete superior, medial, and lateral atrio-nodal bundles.[36] The medial and lateral bundles converged into a single proximal AV bundle leading into the compact AV node. These two bundles are believed to form, in part or in entirety, the anterior "fast" and posterior "slow" AV nodal physiological pathways.

Moe et al demonstrated the electrophysiological substrate for AV nodal re-entrant tachycardias (AVNRTs) by developing the concept of dual AV nodal pathways as its basis.[28] They noted a marked prolongation of AV nodal conduction when a premature atrial extrastimulus was delivered at a critical coupling interval. This was often associated with an echo beat, postulated to be caused by two AV nodal pathways—a β-pathway with a faster conduction and long refractoriness and an α-pathway with shorter refractoriness and slower conduction times. At critical coupling intervals, the premature beat shifts conduction from the β-pathway to the α-pathway and re-engages the β-pathway in a retrograde direction to result in an atrial echo beat. More recent, elegant studies on isolated canine and pig hearts by McGuire, de Bakker, and Janse have shown nodal type action potentials in the cells around both mitral and tricuspid valve rings.[37] These cells are separated from atrial cells by a zone of cells with intermediate action potentials. Adenosine reduced the amplitude and upstroke velocity of action potentials in nodal-type cells, but their morphologic characteristics were indistinguishable from those of atrial myocytes. However, they could be distinguished by the absence of connexin43, which was present in the atrium and the ventricle. Posterior AV nodal approaches were dissociated by pacing from the atrium and the AV node, and echo beats used the slow posterior pathway in a retrograde direction and preceded atrial activation. These posterior approaches were not used in fast pathway conduction.

Human Correlates of Experimental Observations

Clinical correlation of these experimental concepts of AV nodal physiology was demonstrated by the early work of Bigger and Goldreyer, as well as by Denes, Rosen, and coworkers.[31,38] The critical role of AV nodal conduction delay in the onset of SVT was recognized. Denes et al demonstrated longitudinal dissociation of the AV nodal conduction in patients with recurrent SVT.[31] The critical link between anatomic and physiological concepts in humans was provided by a landmark study by Sung et al.[39] They demonstrated the posterior input and output of the "slow" AV nodal pathway and the anterior location of the "fast" AV nodal conduction pathway (see Figure 41-4, *B*). Although submerged in controversy for some time, this observation formed the basis for the development of fast and slow pathway ablation for the cure of AV nodal re-entry. Several years later, this study was directly validated in intraoperative studies in humans. McGuire et al mapped Koch's triangle to define the earliest atrial activation during AVNRT in patients during cardiac surgery. A zone of slow conduction was found in the triangle in 64% of patients.[40] Atrial activation patterns confirmed that the fast pathway was connecting at the apex of the triangle near the AV node–bundle of His junction, whereas the slow pathway did so at the orifice of the coronary sinus near the posterior aspect of the AV node. Two types of AVNRT were distinguished: (1) the common type, or type 1, called the "slow-fast" form, which used the slow pathway for anterograde propagation and the fast pathway for retrograde conduction; and (2) the uncommon type, or type 2, called "fast-slow" AVNRT. Contiguous ablation lesions can affect both pathways, confirming their proximity. The presence of multiple "slow" pathways has also been identified, resulting in a third form of re-entry, called "slow-slow," or type 3, AVNRT. These different types and pathways support the concept that these arrhythmias are supported by AV nodal tissue, transitional atrio-nodal inputs, and other peri-nodal tissues, which have varying electrophysiological properties and functionally simulate distinct electrical pathways.

Atrioventricular Re-entrant Tachycardias

The classification of pre-excitation syndromes has evolved since the original eponyms were given to Kent, Mahaim, and James fibers. The long-proposed and accepted classification by the European Study Group is shown in Box 41-2. However, limitations of this classification are being recognized, and correlation with the

Box 41-2 Classification of Pre-excitation Syndromes

1. AV bypass tracts providing direct connections between the atrium and ventricle
2. Nodo-ventricular connections between the AV node and ventricular myocardium
3. Fasciculo-ventricular connections between the fascicles of the specialized conduction system and the ventricular myocardium
4. AV nodal bypass tracts with direct connections between the atrium and the bundle of His

AV, Atrioventricular.

previous eponyms remains occasionally tangential. The major reason for this observation is the recognition that decremental conduction is a property not solely confined to the AV node but also seen with accessory AV connections. Speculation around the embryologic basis of these connections swirls around the original suggestion by Gallagher that these may be displaced AV nodal and specialized conduction system tissues.[41] Decremental conduction has been observed in posteroseptal AV connections in the permanent form of junctional reciprocating tachycardia, as well as in atrio-fascicular bypass tracts, which commonly link the parietal atrial myocardium in the right atrium to the right bundle branch at its distal portion and are detected as Mahaim physiology. The tachycardia propagates in an antegrade direction over the atriofascicular pathway and in a retrograde direction over the normal AV conduction system and involves the atrium and the ventricle as critical elements in the circuit. This is quite distinct from the nodo-ventricular connections originally described by Mahaim. In this latter instance, the tachycardia has a similar propagation sequence but can exist totally without atrial involvement and has been referred to as a "subjunctional tachycardia."

The anatomic basis for AVRT is the accessory AV pathway, a small band of working myocardium bridging the AV annulus. The location of these pathways is most frequent in the left ventricular free wall, followed by posteroseptal and paraseptal locations and, least commonly, in the right atrial free wall and left anterior AV annulus. Multiple AV connections are seen in approximately 15% of patients. Typical dimensions for these locations and such connections have been elucidated by pathologic studies. In cadaver hearts, the posterior septal space was noted to extend from the coronary sinus orifice for 2.3 ± 0.4 cm, and the length of the left ventricular free wall was 5 ± 1 cm. Posteroseptal accessory pathways were located in the proximal 1.5 cm of the coronary sinus in the posterior septum and those between 1.5 and 3 cm could be either in the left free wall or the posterior septal space. Posteroseptal accessory pathways beyond 3 cm were invariably in the free wall.

Basic Electrophysiological Concepts in Pre-excitation Syndromes

AV accessory pathways, as well as AV nodal bypass tracts, generally exhibit "all or none" conduction behavior during electrophysiological evaluation. Rapid nondecremental conduction up to the point of refractoriness is the norm and is exhibited during antegrade and retrograde conduction, especially when competing AV nodal conduction is absent. When decremental conduction in response to progressive premature stimulation is observed, it is usually caused by switching of conduction to the AV node–His axis, though enhanced AV nodal conduction may occur in the same patient. When the accessory pathway conducts in an antegrade direction, the most common manifestation is WPW syndrome with a short P-R interval and δ-wave (caused by ventricular pre-excitation by the pathway) and prolongation of QRS duration (caused by abnormal intraventricular conduction patterns). In some instances, when the antegrade refractoriness of the accessory pathway is particularly long or if the pathway fails to permit such conduction, it may remain concealed and only manifest when retrograde propagation occurs over echo beats or AVRT. Patients with concealed accessory pathways have normal surface electrocardiograms (ECGs). Rarely, decremental conduction is observed in the anomalous pathway. Although this is occasionally caused by nodo-ventricular connections, more often the cause is slowly propagating accessory pathways or other causes of Mahaim physiology. The electrophysiological basis for decremental conduction in accessory pathways has been speculative. Suggestions include impedance mismatch at the interface between the pathway and the atrial or ventricular myocardium or extreme tortuosity of these fibers in some instances, which has been seen pathologically. Investigations suggest that block in such pathways usually occurs at the ventricular connection and may be related to anisotropy, fiber narrowing, or altered intercellular junctions. Age and autonomic state–related changes in electrophysiological properties may lead to intermittent manifestations of pre-excitation syndromes and the arrhythmias supported by them in a patient's lifetime. Incessant tachycardias and manifest pre-excitation of infancy waning during childhood and adolescence or an initial appearance of the condition in young adults is common. Aging generally can impair pathway function, and it is uncommon, though not rare, for the condition to manifest itself for the first time in an older adult.

Supraventricular Tachycardias Caused by Enhanced Automaticity

Nonparoxysmal forms of sinus node tachycardia, often referred to as *inappropriate sinus tachycardia* (IST), show similar ECG patterns but can demonstrate a gradual acceleration (*warm-up phenomenon*), which suggests enhanced automaticity.[32] IST is characterized by an elevated heart rate (HR) at rest and an exaggerated HR response to physical activity or emotional stress. These have been reproduced with isoproterenol.

Accelerated junctional rhythms manifesting as supraventricular tachyarrhythmias have been recorded with particular frequency in the era of extensive digitalis use without blood concentration determinations.[42] They have been noted in postoperative patients, after myocardial infarction (MI) and during electrolyte abnormalities.[42,43] These arrhythmias are believed to be caused by triggered automaticity resulting from delayed afterdepolarizations in most instances. Pacing can enhance the afterdepolarizations, and they can be increased in amplitude by an increase in extracellular calcium concentrations, which can be seen in digitalis toxicity. Ischemia in experimental models can also result in accelerated, triggered automaticity in the coronary sinus region. Hypokalemia can predispose to afterdepolarizations. Acceleration is often seen in triggered rhythms at initiation and can clinically manifest as nonparoxysmal junctional tachycardias on the ECG. The triggered arrhythmias can often be induced by overdrive pacing and do not necessarily resume after pacing ceases, unlike other automatic rhythms. Triggered rhythms have also been induced in human diseased atrial tissues resected at surgery and in coronary sinus cells during experimental studies.

Clinical Presentation

PSVT presents most commonly as sudden onset of palpitations with rates typically ranging from 100 to 260 beats/min and may be associated with chest discomfort, dyspnea, near syncope, and syncope.[1,44] It is of variable duration and may last from seconds to days. Termination is usually sudden as well, although in some forms, gradual disappearance may be noted. Chest discomfort in children and adults without overt heart disease may be related to the perception of rapid heart action; after an episode, it may

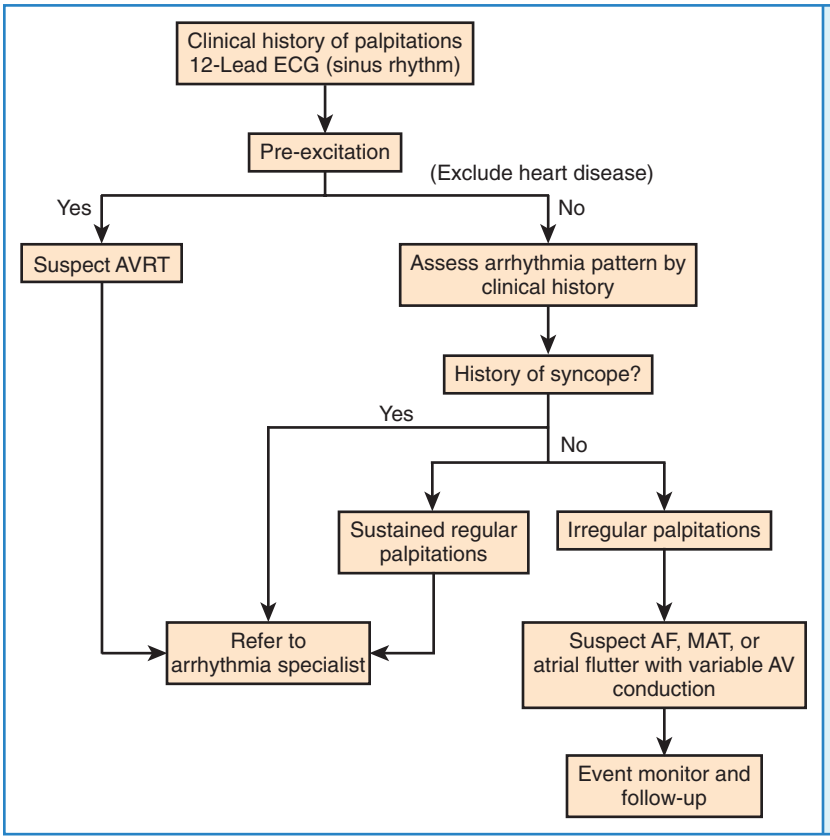


FIGURE 41-5 Initial evaluation of patients with suspected tachycardia. *ECG*, Electrocardiogram; *AVRT*, atrioventricular re-entrant tachycardia; *AF*, atrial fibrillation; *MAT*, multifocal atrial tachycardia; *AV*, atrioventricular. *(From Blomström-Lundqvist C, Scheinman MM, Aliot EM, et al: ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias,* Circulation *108;1871–1909, 2003.)*

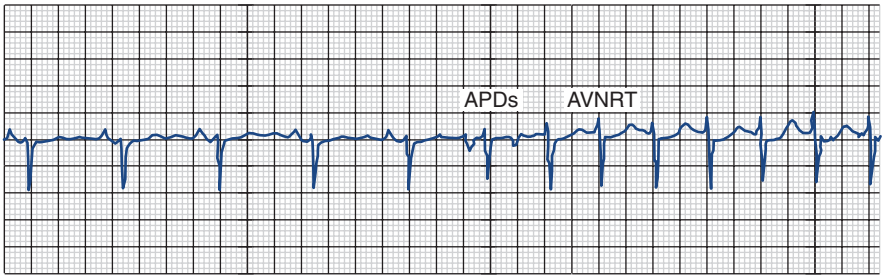
persist in a milder form for a period. In older patients and in the presence of heart disease, this may be related to myocardial ischemia. Dyspnea may be a prominent symptom, often in patients with pre-existing left ventricular dysfunction, when pulmonary congestion may worsen because of poor forward cardiac output. Symptoms suggestive of near-syncope and syncope are seen with extremely rapid PSVT and result from a compromise of cardiac output. In many forms of PSVT, atrial and ventricular activations are not timed sequentially to achieve appropriate ventricular filling.[45] Rapid rates further compromise this, and forward cardiac output can be seriously compromised, especially with heart rates greater than 200 beats/min. In some patients, PSVT can be minimally symptomatic or even asymptomatic. In children and infants, incessant PSVT can lead to a tachycardia-induced cardiomyopathy with symptoms of left ventricular failure, failure to thrive, and syncope. Very rapid or hemodynamically unstable episodes of this arrhythmia have been known to precipitate MI, ventricular tachyarrhythmias, and cardiac arrest. SART is a form of paroxysmal SVT characterized by palpitations, and tachycardia rates slower than AVNRT or AVRT, typically ranging from 100 to 150 beats/min.[46] Gomes reported a history of recurrent palpitations with a significant proportion having syncope or dizzy spells.[46] Most had organic heart disease. IST is a form of PSVT.[47] It is an ill-defined clinical syndrome with diverse clinical symptoms that can range from intermittent palpitations to multi-system complaints.[47,48] A clinical scheme for evaluation of symptomatic PSVT from the American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) practice guidelines is shown in Figure 41-5.[49]

Electrocardiography

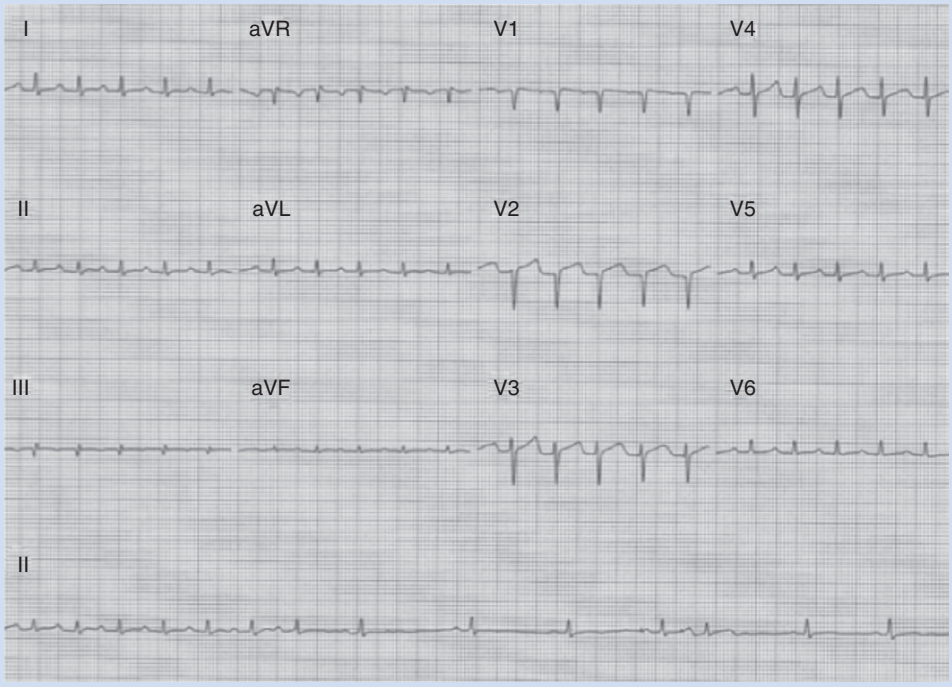
The distinguishing electrocardiographic features of PSVT reflect the underlying mechanism of the arrhythmia. The major criteria that have been used to separate these mechanisms depend on the features of onset, the position of the P wave in the R-R interval during SVT, the presence or absence of QRS alternans, cycle length variation, P-wave morphology, effects of bundle branch block (BBB), the presence of a pseudo R′ deflection in lead V1, and the presence of ventricular pre-excitation. Some of these criteria have proven to be particularly useful, but considerable overlap exists among the ECG manifestations of the different mechanisms of SVT.

Onset

Both SNRT and AVNRT are usually triggered by a premature atrial beat that differs in morphology from sinus rhythm. As shown in Figure 41-6, *A*, initiation of the tachycardia is characterized by sudden prolongation of the P-R interval because conduction from the premature beat blocks the fast pathway and conducts down the slow pathway. Re-entry occurs if the fast pathway has recovered and is capable of conducting in a retrograde direction. In contrast, a triggered or re-entrant atrial tachycardia (AT) may be initiated by an action potential duration (APD), but these arrhythmias are not heralded by marked P-R interval prolongation with the onset of tachycardia. AVRT mediated by accessory pathways may be triggered by premature atrial or ventricular beats. Electrocardiographic findings in SNRT show



A



B

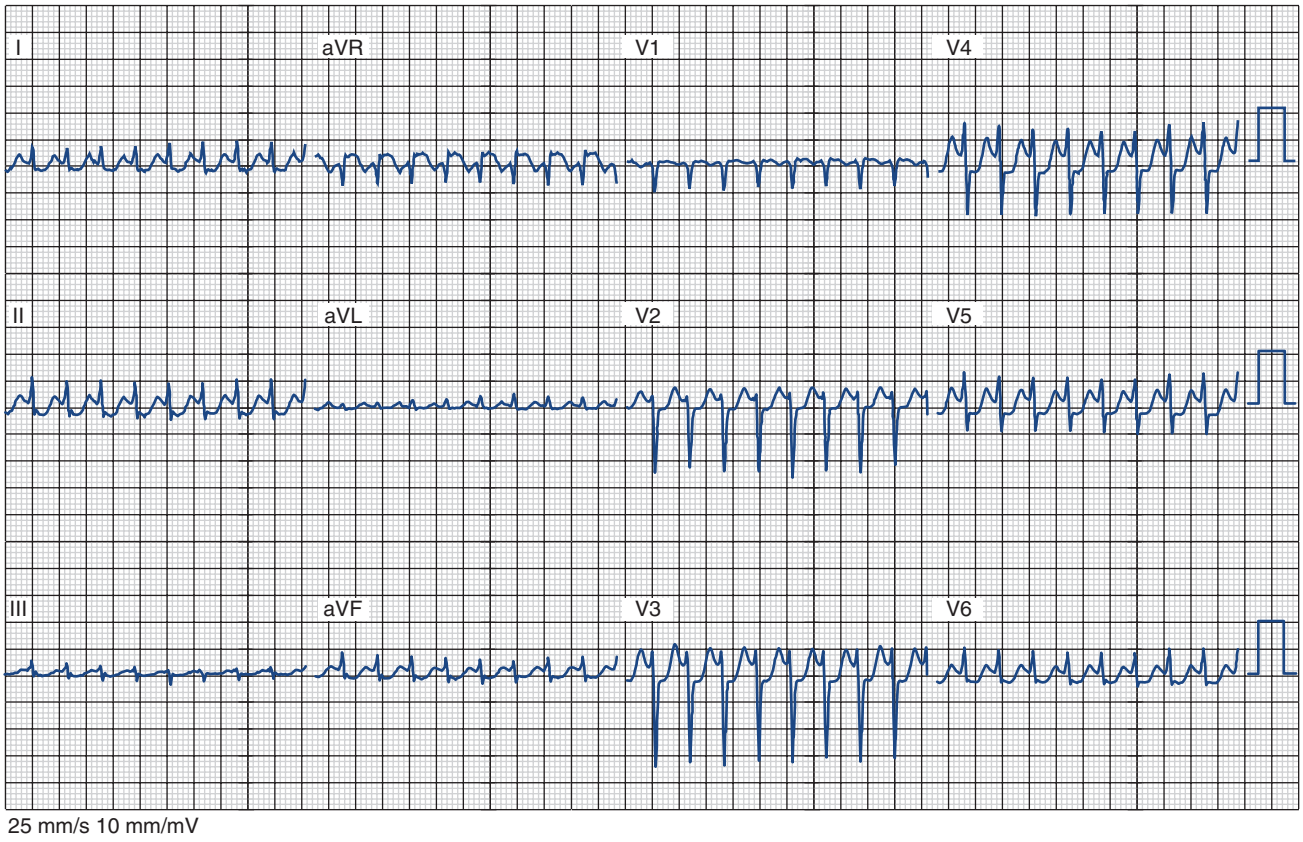
FIGURE 41-6 A, Sinus rhythm is interrupted by action potential durations (*APDs*) that have a different P-wave morphology. The second APD blocks in the fast pathway and conducts down the slow pathway to induce atrioventricular node re-entry. P waves are not evident during the tachycardia because they are buried in the QRS complex. **B,** A 12-lead electrocardiogram of sinoatrial re-entrant tachycardia with termination to sinus rhythm is shown. Note the upright P waves with similar morphology to sinus rhythm. *AVNRF*, Atrioventricular node re-entrant tachycardia.

an antegrade upright P wave during the tachycardia, morphologically similar to the P wave in sinus rhythm. Figure 41-6, *B*, shows an electrocardiogram from a patient with paroxysmal sinus tachycardia that was refractory to antiarrhythmics. Coexistence of sinoatrial re-entrant tachycardia with AVNRT has been observed. Triggering with both atrial and ventricular premature beats has been described. Ventricular ectopy can induce AVRT or AT, but it is a far less common mode of induction for these arrhythmias.

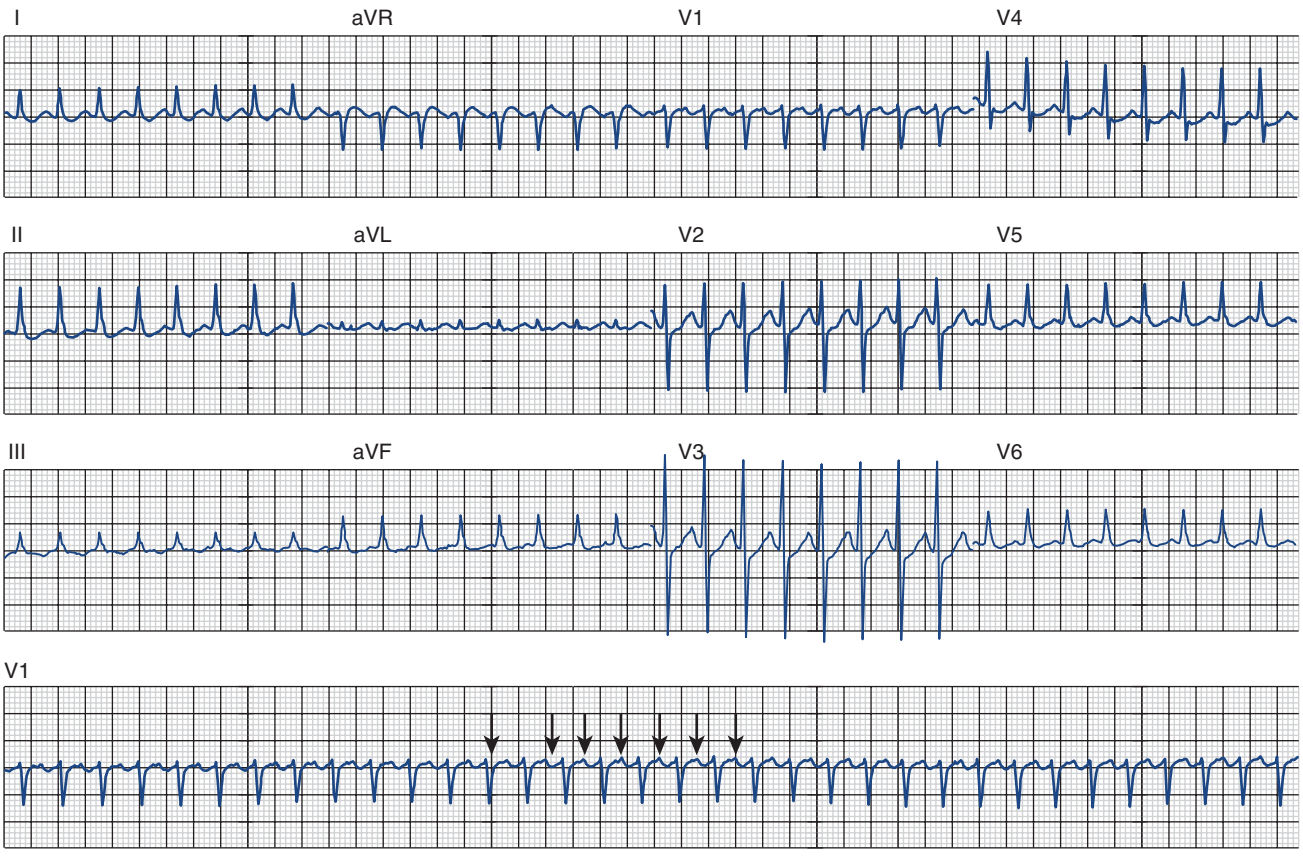
Automatic ATs are characterized by gradual acceleration and a P wave morphology that differs from sinus rhythm. Nonparoxysmal forms of sinus tachycardia, that is, IST, may show similar P-wave patterns to sinus rhythm on ECG but can demonstrate a gradual acceleration (warm-up phenomenon), which suggests enhanced automaticity. IST is characterized by an elevated HR at rest and an exaggerated HR response to physical activity or emotional stress.

Position of the P Wave

During typical AVNRT, the atria are generally activated simultaneously with the ventricles, so the P wave is buried within the QRS complex, although in some cases, it may extend into the early portion of the ST segment (Figure 41-7, *A*). In the atypical form of AVNRT, during which antegrade conduction is mediated by the fast pathway and retrograde conduction by the slow pathway, the P wave may fall into the second half of the R-R interval because of slow retrograde conduction to the atria. During orthodromic AVRT mediated by an accessory pathway, retrograde atrial activation generally begins about 70 ms after the onset of the surface QRS and extends well into the ST segment in the first half of the R-R interval (see Figure 41-7, *B*). In patients with ATs, the P wave is usually detected in the second half of the R-R interval. The exception is patients with atrial tachycardias in whom AV conduction is delayed because of the effects



A



B

FIGURE 41-7 A, Narrow-complex supraventricular tachycardia (SVT) at a rate of 240 beats/min with no retrograde or antegrade P wave visible in the R-R cycle. The tachycardia was subsequently confirmed to be type 1 atrioventricular nodal re-entrant tachycardia on electrophysiological study. **B,** Narrow-complex SVT at a rate of 206 beats/min with the retrograde P wave clearly visible in the mid-R-R cycle, especially in lead V1. The tachycardia was subsequently confirmed to be atrioventricular re-entrant tachycardia with a retrograde posteroseptal accessory pathway on electrophysiological study.

of antiarrhythmic drugs or intrinsic conduction system disease. Kalbfleisch evaluated ECGs in patients who had undergone electrophysiological study (EPS) and found that the P wave was in the first half of the R-R interval in 91% of patients with AVNRT, 87% of patients with AVRT, and 11% of patients with ATs.[50]

QRS Alternans

Green observed that ECGs of some patients with SVT exhibited QRS alternans, which, when present, was usually associated with AVRT mediated by an accessory pathway.[51] Subsequent studies by Kay and Kalbfleisch demonstrated that QRS alternans depends on the abrupt onset of SVT and is more common in rapid tachycardias. In their studies, the incidence of QRS alternans was 27% to 38% in orthodromic AVRT and 13% to 23% in AVNRT.[50,52] It was much less common in patients with ATs. The differences between the results of these studies may reflect criteria used to identify QRS alternans and the number of leads used for the recordings. For example, the alteration in QRS amplitude may only be apparent in selected leads. Recordings obtained from telemetric monitoring or using only a limited number of surface leads may not demonstrate QRS alternans quite as clearly as a 12-lead ECG.[53]

Rate and Cycle Length Alternations

Several studies have evaluated the rate of SVT without demonstrating significant differences that would be useful to discriminate the underlying mechanism.[45,50,51] Cycle length variation is relatively uncommon in the re-entrant tachycardias. One would expect re-entrant tachycardias such as AVRT and AVNRT to have relatively constant cycle lengths as they usually do, but sometimes variable conduction in one limb of the circuit may lead to variations in cycle length even during re-entry. Figure 41-8 shows unusual and striking variation in the R-R intervals recorded during orthodromic AVRT mediated by a left lateral accessory pathway in a patient who also had dual AV node physiology. The variation in R-R interval is attributable to differences in conduction through the AV node, depending on whether antegrade conduction occurred over the fast or slow pathway.

P-Wave Morphology

When a P wave can be identified during SVT, it is often difficult to determine the morphology and axis because it may be obscured by ventricular repolarization. Kalbfleisch reported that when the P wave was visible, its axis could be determined in the vertical, horizontal, and anteroposterior planes in only 32%, 11%, and 9% of patients, respectively.[50] One might expect the P-wave morphology to be more accurately analyzed during ATs because the P wave falls in the second half of the R-R interval and is less likely to be obscured by the T wave. Tang developed an algorithm to differentiate left atrial focal tachycardias from right atrial focal tachycardias on the basis of surface ECGs recorded from patients who underwent ablation of their arrhythmias.[54] In their analysis of 31 patients, no differences were observed in P waves arising from the lateral right atrium compared with the right atrial appendage. Leads aVL and V1 were most useful in distinguishing left atrial foci from right atrial foci. Right atrial foci were associated with a positive or biphasic P wave in lead aVL, whereas the P wave was negative or isoelectric in lead aVL in patients with left atrial foci. A positive P wave in lead V1 was observed in patients' left atrial foci in contrast to negative or biphasic P waves recorded from patients with right atrial foci. They also found that the P-wave morphology in the inferior leads distinguished inferior foci (negative P waves) from superior foci (positive P waves). Morton analyzed P-wave morphology from nine patients with

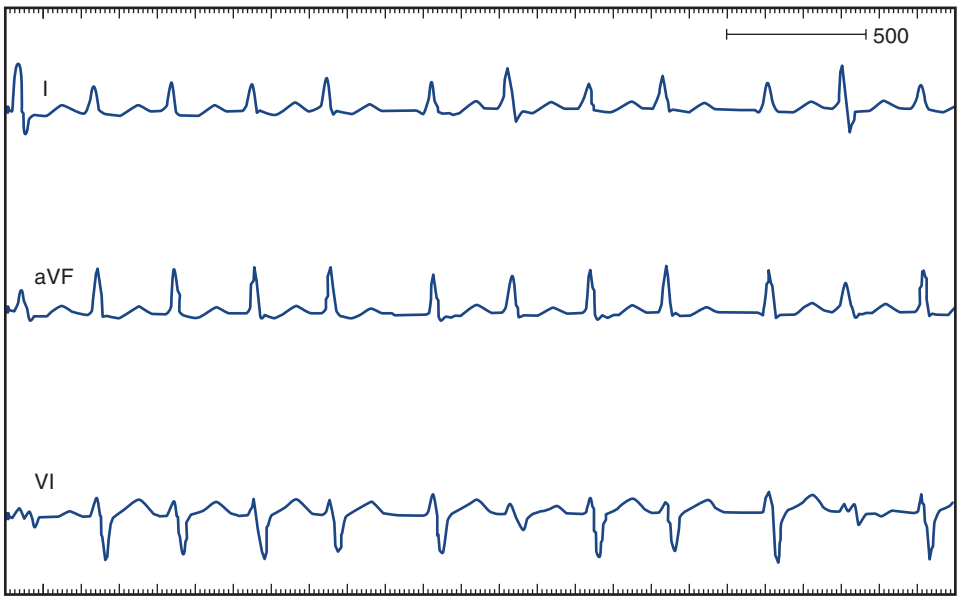


FIGURE 41-8 Surface leads I, aVF, and V1 demonstrate marked cycle length variability in a patient with a concealed left lateral accessory pathway and dual atrioventricular (AV) node physiology. The irregular R-R intervals were recorded during orthodromic AV re-entry and were attributable to intermittent conduction down the slow AV node pathway.

ATs that arose from the tricuspid annulus.[55] In their series, the P wave was upright in lead aVL, inverted in leads III and V1, and either inverted or biphasic in leads V2 to V6. Tada developed an algorithm for identifying the origin of focal right ATs on the basis of ECGs recorded from 32 patients who underwent ablation procedures.[56] They found that negative P waves in the inferior leads differentiated inferior origins from superior origins, and a negative P wave in lead aVR was characteristic of tachycardias arising along the crista terminalis. All these investigations are limited in that the number of patients studied is relatively small, and prospective analysis of P-wave morphology is often hindered by inability to accurately separate the terminal part of the T wave and P wave during the tachycardia.

Effect of Bundle Branch Block

The development of BBB during SVT may provide a clue to the diagnosis of AVRT. Coumel et al first observed that the development of BBB ipsilateral to an accessory pathway may result in cycle length prolongation (decrease in rate) because the circuit is prolonged.[57,58] Figure 41-9 was recorded during transition from SVT with left BBB to a narrow QRS from a patient with a left lateral accessory pathway. Concomitantly, the cycle length of the tachycardia decreased by 40 ms (from 300 to 260 ms), resulting in an increase in the rate from 200 to 230 beats/min. The rate of tachycardias dependent on right-sided accessory pathways may decrease with the development of right BBB, but tachycardias dependent on accessory pathways located in the septum do not change rate appreciably with BBB because the circuit is not significantly prolonged. Even when BBB develops on the same side as the accessory pathway, the rate does not invariably change because the increase in ventriculo-atrial conduction time may be associated with shortening of antegrade conduction time in the AV node so that the net effects on the tachycardia cycle length are negated.

Pseudo-R′ in Lead V1

The development of a pseudo-R′ in lead V1 is observed more frequently in AVNRT than in either AVRT or ATs. Although this is not a particularly sensitive criterion (58%), it is relatively specific for AVNRT (91%).[50] It is attributable to distortion of the terminal portion of the QRS by a retrograde P wave.

Pre-excited Tachycardias

Tachycardias associated with ventricular pre-excitation may be attributable to antidromic AVRT, AF or ATs that conduct over an accessory pathway, or tachycardias mediated by a Mahaim fiber.[59] As shown in Figure 41-10, maximal pre-excitation is present during antidromic AVRT because ventricular activation occurs exclusively through the accessory pathway. ECGs recorded during antidromic SVT show a regular, wide, monomorphic QRS complex that resembles ventricular tachycardia (VT). Retrograde P waves may be detectable during the first half of the R-R interval, but they are extremely difficult to appreciate because they are obscured by the marked repolarization abnormality associated with pre-excited complexes. When evident, P waves have a 1:1 relationship with the QRS because block of conduction in either the accessory pathway or the AV node would terminate the tachycardia. Occasionally, sudden changes in cycle length are observed during antidromic AVRT, identifying the bundle that is used during retrograde conduction.[60] During AF with ventricular pre-excitation, the ventricular rate may be rapid, the R-R intervals are irregular, and the QRS morphology varies, depending on the degree to which the ventricle is activated by the accessory pathway or the AV node. The irregular rate and QRS morphology differentiate this arrhythmia from antidromic AVRT or monomorphic VT. Patients with pre-excited R-R intervals shorter than 220 to 250 ms have accessory pathways with short refractory properties and are at increased risk for

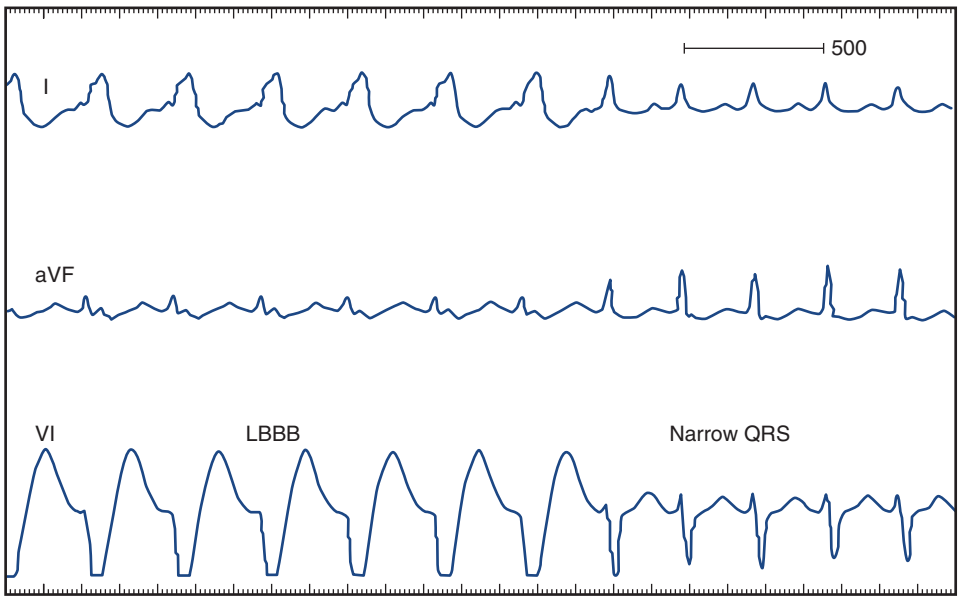


FIGURE 41-9 Surface leads I, aVF, and V1 demonstrate orthodromic atrioventricular re-entrant tachycardia during the transition from left bundle branch block (*LBBB*) to a normal QRS. The accessory pathway was located in a left lateral position. Note the increase in rate from 200 to 230 beats/min when the QRS becomes normal.

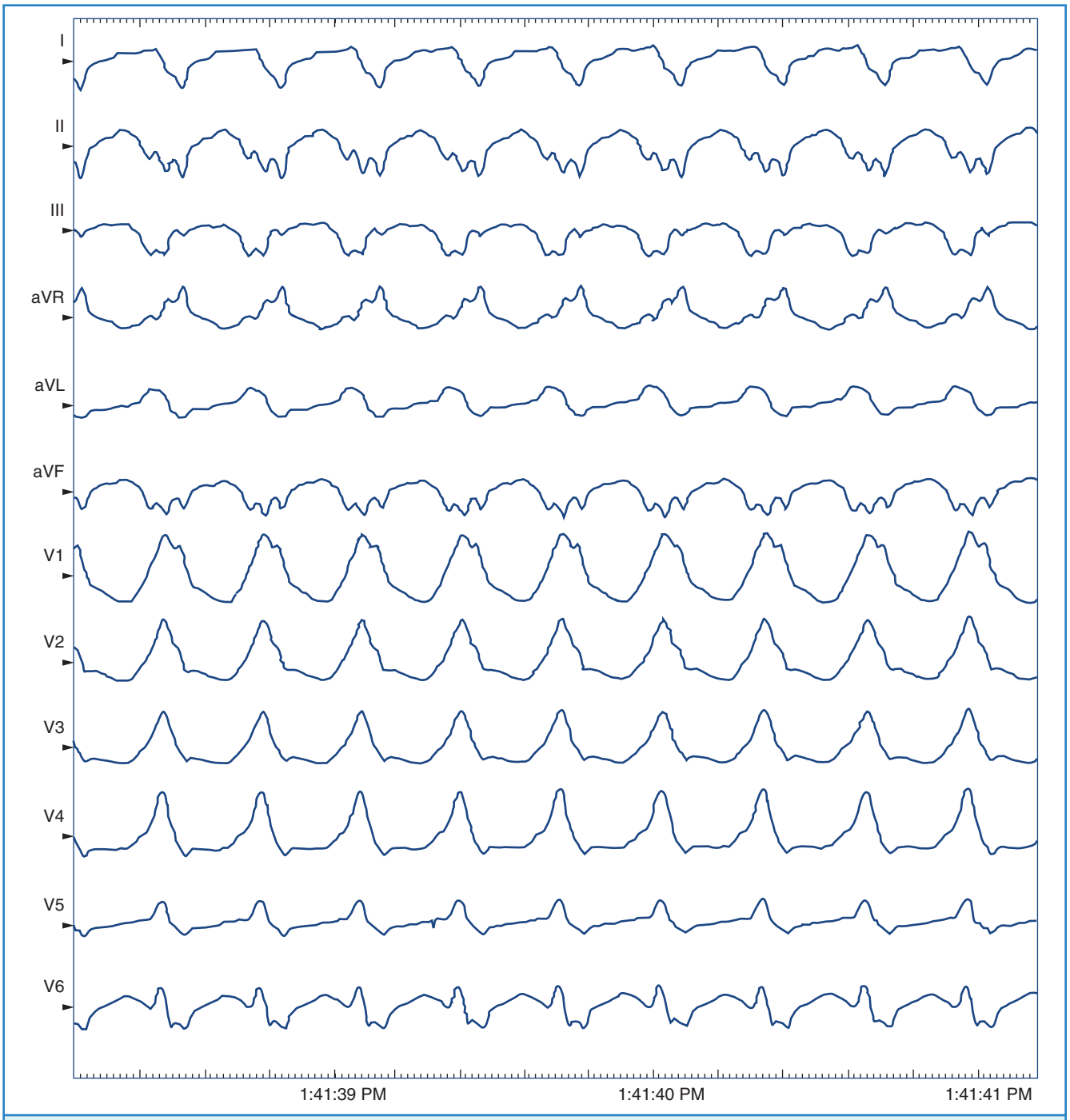


FIGURE 41-10 Twelve-lead electrocardiogram recorded during antidromic atrioventricular re-entrant tachycardia. The QRS complexes are regular and maximally pre-excited with a uniform morphology characteristic of a left lateral accessory pathway that matches antegrade pre-excited morphology in sinus rhythm or atrial pacing.

AF inducing VF because of rapid conduction over the accessory pathway.[13,61]

Tachycardias that are mediated by Mahaim fibers, as shown in Figure 41-11, exhibit a QRS morphology that resembles left BBB. The QRS axis is typically between 0 and 75 degrees; QRS duration is 0.15 seconds or less; an R wave is present in limb lead I; an rS is seen in precordial lead V1; and transition is present in the precordial leads from a predominantly negative QRS complex to a positive QRS complex in leads V4 to V6.[62]

Patterns of Ventricular Pre-excitation

The ECG pattern of ventricular pre-excitation provides useful information on the location of the accessory pathway and whether more than one pathway may be present. Several authors have studied the ECG manifestations of pre-excitation and have developed criteria for the localization of the accessory pathway.[63-69] The accuracy of these methods depends on the degree of ventricular pre-excitation at the time of the recording

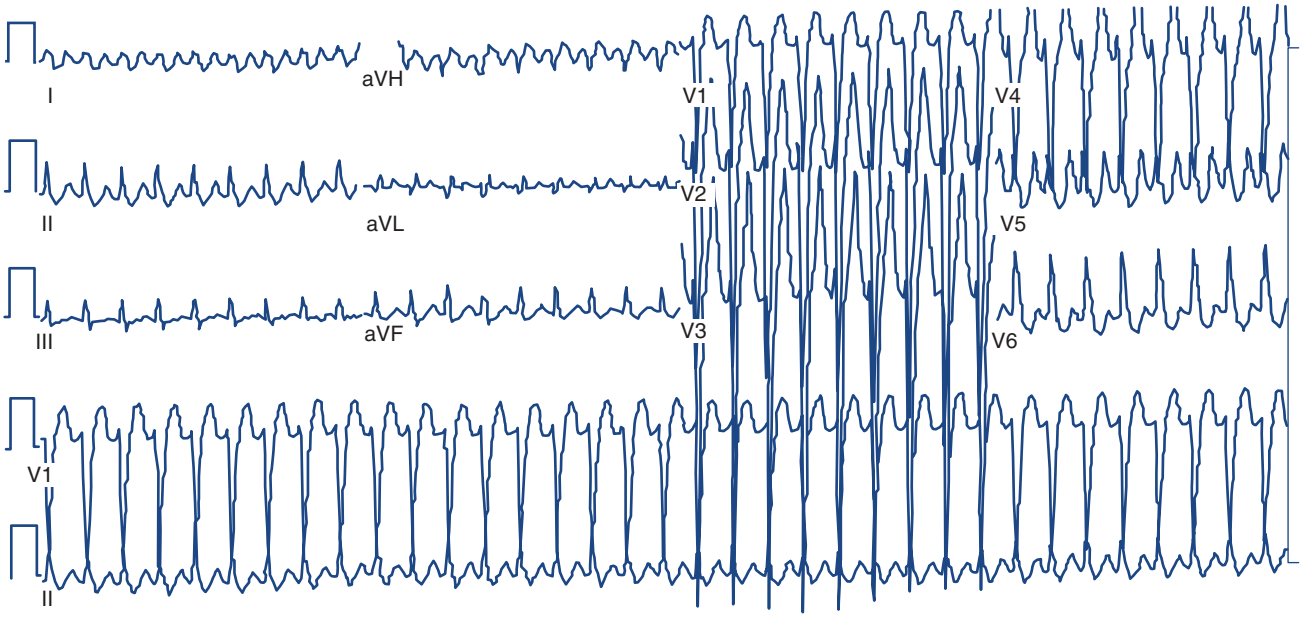


FIGURE 41-11 Characteristic 12-lead electrocardiogram recorded during macro–re-entry mediated by a Mahaim fiber. Note the QRS morphology resembling left bundle branch block with an rS configuration in lead V1. The differential diagnosis would include aberrancy, antidromic tachycardia, or ventricular tachycardia and requires electrophysiological study for confirmation.

and the presence of underlying heart disease that modifies the usual patterns of pre-excitation. These criteria have evolved over time with growing experience. The criteria are based on the concept that δ wave polarity, QRS axis, and R wave transition in the precordial leads reflect the position of the accessory pathway. When pre-excitation is pronounced, left-sided pathways have a prominent R wave in lead V1 with a positive δ wave. If the pathway is located on the posterior aspect of the mitral annulus, the polarity of the δ wave is generally negative in the inferior leads, and a QS complex is present. Pathways that are located more anterolaterally on the mitral annulus have negative δ waves and QS morphology in lead aVL, but the δ waves are positive in the inferior leads. Posterior septal pathways have negative δ waves in the inferior leads, but the R/S ratio is less than 1 in lead V1. An abrupt transition to R/S ratio greater than 1 in lead V2 occurs. Arruda found that subepicardial accessory pathways characteristically have clear negative δ waves in lead II in the first 20 ms after the onset of the δ wave.[68] Accessory pathways located on the right side exhibit an R/S ratio less than 1 in lead V1 and have delayed δ wave progression. The polarity of the δ waves in the inferior limb leads is negative if the pathway is posterior. Positive δ waves in the inferior leads suggest a more anterior position. Pathways located in the middle to anterior septum have positive δ waves in the inferior leads and may have negative δ waves in lead V1. They are distinguished by R/S ratio greater than 1 in lead III with anteroseptal pathways and R/S ratio equal to 1 with midseptal pathways.[66]

The assessment of accessory pathway locations is difficult when the pre-excitation is not pronounced. In one of the larger series, Chiang evaluated a stepwise algorithm that was based on R/S ratio in lead V2, δ-wave polarity in lead III (initial 40 ms), δ-wave polarity in lead V1 (initial 60 ms), and δ-wave polarity in lead aVF (initial 40 ms).[69] The algorithm correctly predicted the location of the accessory pathway in 93% of the patients. Arruda developed an algorithm base on 135 consecutive patients and prospectively applied it to 121 consecutive patients, with an overall sensitivity of 90% and specificity of 99%. Their criteria were based on the initial 20 ms of the δ wave in leads I, II, and aVF and R/S ratios in leads III and V1. The algorithm they used is shown in Figure 41-12. The presence of multiple accessory pathways may be recognized by variable patterns of pre-excitation with characteristics of more than one pathway or hybrid patterns that do not fit the usual algorithms. Fananapazir found that in patients with multiple pathways, more than one pattern of pre-excitation was apparent in only 32% of recordings made during sinus rhythm, but the presence of more than one pathway was recognized in 55% of recordings obtained during AF.[70]

Diagnostic Approach to the Patient with Supraventricular Tachycardia

Investigation of SVT is based on understanding the underlying mechanism of the tachycardia and clinical context in which it occurs. A systematic approach should start with the history and physical examination, which provides two types of information: (1) the presence and type of symptoms and (2) the clinical context, particularly the existence of associated heart disease. Electrocardiographic documentation of the arrhythmia is an essential prerequisite to tachycardia management.[71]

Clinical Evaluation

Careful history taking may provide valuable information. SVT may be symptomatic or asymptomatic. Palpitations caused by tachycardia are the most common symptom. Episodes of palpitations with abrupt onset and termination, followed by polyuria, suggest PSVT. This syndrome, known in the French

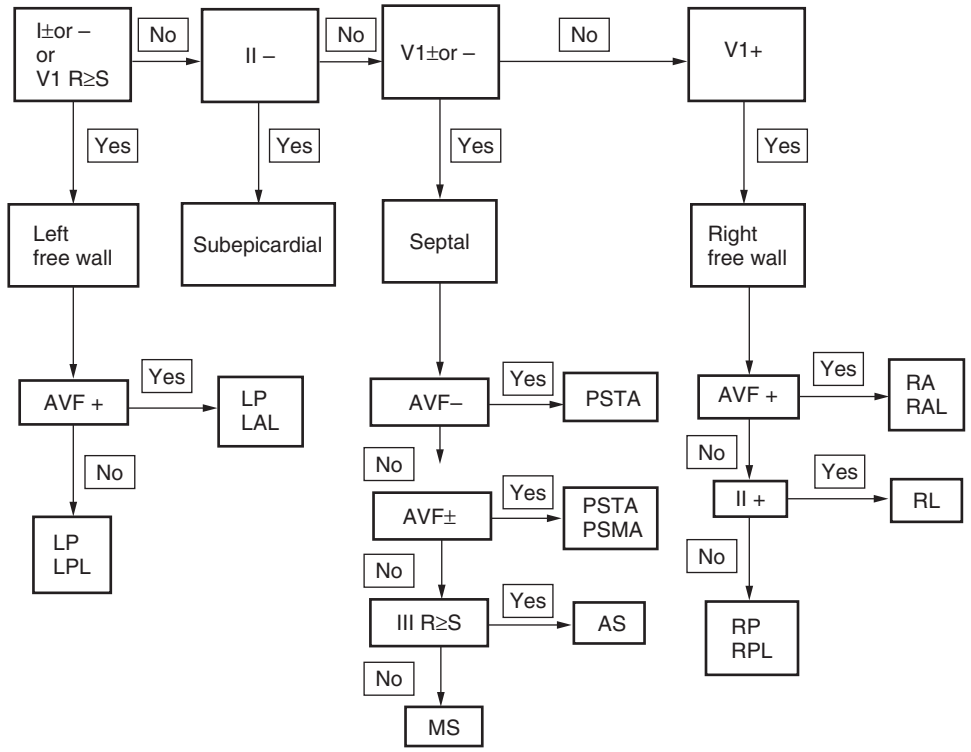


FIGURE 41-12 AS, anteroseptal; LAL, left anterolateral; LL, left lateral; LP, left posterior; LPL, left posterolateral; MSTA, midseptal tricuspid annulus; PSMA, posteroseptal mitral annulus; PSTA, posteroseptal tricuspid annulus; RA, right anterior; RAL, right anterolateral; RAPS, right anterior paraseptal; RL, right lateral; RP, right posterior; RPL, right posterolateral. *(From Arruda MS, McCleland JH, Wang X, et al: Development and validation of an ECG algorithm for identifying accessory pathway ablation site in Wolff-Parkinson-White syndrome,* J Cardiovasc Electrophysiol *9:2–12, 1998.)*

literature as "syndrome de Bouveret," was described in 1888, before the advent of electrocardiography.[2] It is characteristic of paroxysmal junctional tachycardia but may be found in other types of SVTs or VTs such as verapamil-sensitive VT. Occasionally, SVT may be the cause of syncope. A history of palpitations preceding syncope is often reported in this presentation. When syncope or presyncope occurs immediately after termination of fast palpitations, the tachycardia-bradycardia syndrome should be suspected. Other symptoms may be associated with SVT and are indicative of poor tolerance (e.g., syncope, dizzy spells, chest discomfort, dyspnea, or even pulmonary edema). SVT may be mildly symptomatic or asymptomatic and discovered incidentally on recordings performed for another reason. Sometimes, the arrhythmia is specifically suspected caused by its complications (e.g., asymptomatic paroxysmal AF in a patient with a cerebrovascular accident suspected to be of embolic origin). Physical examination is focused on any associated heart disease but, in general, paroxysmal SVT occurs in patients without organic heart disease. In contrast, heart disease is present in 70% of patients with AF.

Box 41-3 Classification of Supraventricular Tachycardias

ATRIAL ORIGIN
Atrial fibrillation
Atrial flutter
Atrial tachycardia
Enhanced automaticity: atrial focus
Re-entry: atrial or sinoatrial

AV JUNCTION
AVNRT
Common type: slow pathway anterograde/fast pathway retrograde
Uncommon type: fast pathway anterograde/slow pathway retrograde
Slow-slow: slow pathway anterograde/slow pathway retrograde
AVRT
Pre-excitation may be overt or concealed on the ECG in sinus rhythm
AV junction anterograde/accessory pathway retrograde

AV, Atrioventricular; AVNRT, *atrioventricular nodal re-entrant tachycardia;* AVRT, *atrioventricular re-entrant tachycardia.*

Differential Diagnosis of Supraventricular Tachycardia from the Electrocardiogram

Electrocardiographic documentation of the tachycardia is essential for the proper diagnosis and management of SVT (Box 41-3 and Fig. 41-13). Recording of the tachycardia episode is easily obtained when tachycardia occurs frequently or is of prolonged duration. SVT, by definition, arises above the bifurcation of the bundle of His, either in the atria or the AV junction and, therefore, is generally associated with narrow QRS complexes. SVT may sometimes present with wide QRS complexes either because the patient had a pre-existing BBB or because aberrant conduction is

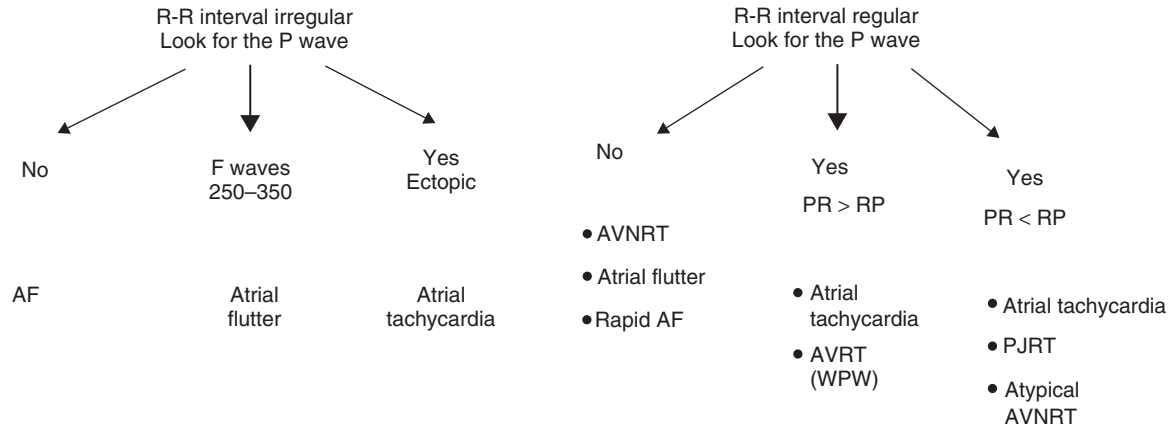


FIGURE 41-13 Diagnosis and management of supraventricular tachycardia. *AF,* Atrial fibrillation; *AVNRT,* atrioventricular node re-entrant tachycardia; *AVRT,* atrioventricular re-entrant tachycardia; *WPW,* Wolff-Parkinson-White syndrome; *PJRT,* permanent junctional reciprocating tachycardia.

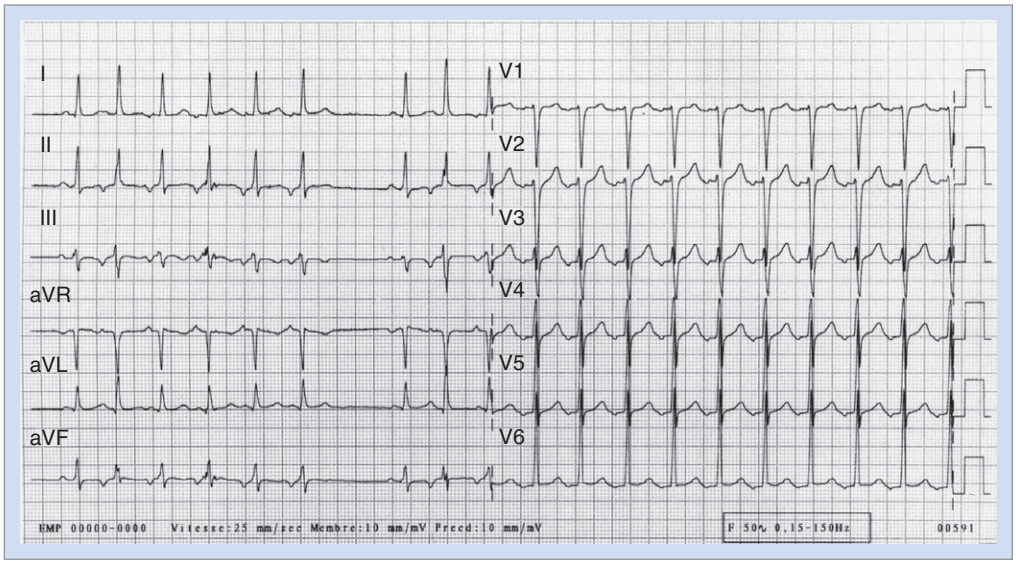


FIGURE 41-14 A 12-lead electrocardiogram of a tachycardia related to a slow conducting accessory pathway used in the retrograde direction. Note in the *left panel* that the R-R intervals are slightly irregular because the pathway is capable of decremental conduction.

present. Differentiating SVT from VT may, at times, be difficult, particularly when pre-excitation is present.

Tachycardia with Narrow QRS Complexes

Most regular SVTs use the AV node either passively as in ATs and atrial flutter or as a critical component of the circuit as in PSVT. The diagnostic approach to tachycardias with narrow QRS complexes should be undertaken in a stepwise fashion.[71-73]

The first step is to assess the regularity of the R-R interval. *If the R-R interval is irregular*, AF or atrial flutter should be considered as the most likely diagnosis (Table 41-2). However, when AF is associated with rapid ventricular response, it may seem regular. Permanent junctional reciprocating tachycardia (PJRT) is an SVT in which the R-R interval is often irregular. This tachycardia, described by Coumel et al, was found to be related to a concealed accessory connection capable of decremental conduction.[74] The tachycardia uses the AV node in the antegrade conduction and a slow conducting accessory connection in the retrograde direction (Figure 41-14). This tachycardia may be incessant, accounting for the descriptive term "permanent" in its title. It becomes sustained in clinical situations with increased catecholamine output, such as exercise or extreme emotion. It warrants therapy, as it may have a deleterious effect on cardiac function; therapy may also provide tachycardia-related symptom relief. The differential diagnoses include atypical AVNRT using the fast pathway in the antegrade direction and the slow pathway in the retrograde direction, and AT arising from the inferior atrium near the coronary sinus ostium.

When the R-R intervals have been assessed to be regular, the next step is also to look for P waves ("cherchez le P"), as

advocated by Marriott.[71] The presence, morphology, and position as to the QRS complexes are important in the diagnosis of the site of origin and for the suspected mechanism of narrow QRS complex tachycardias. When the QRS complexes are preceded by P waves, which are different in configuration from the sinus P waves and conducted with a P-R interval equal to or longer than the P-R interval of the sinus P waves, the most likely diagnosis is AT arising from an ectopic focus. The other mechanism of this type of SVT is intra-atrial re-entrant tachycardia or SART, a diagnosis that requires EPS for substantiation. If P waves have the same configuration as the sinus P waves, the differential diagnosis includes appropriate or "inappropriate" sinus nodal tachycardia. IST is a rare arrhythmia that has been recognized recently. This AT is characterized by an inappropriate and exaggerated acceleration of heart rate during physiological stresses.[75] Although its mechanism remains unconfirmed, numerous possible hypotheses as to its basis exist. These include an ectopic atrial focus located in the SA node area, a normal SA node with increased response to the sympathetic tone or failure to respond to vagal stimulation, and an intrinsic anomaly of the SA node. When P waves are submerged within the QRS complex in SVT and are therefore not identifiable, the most likely diagnosis is type 1 AVNRT (i.e., tachycardia involving the AV node and using, in the typical form, a slow pathway in the anterograde direction and a fast pathway in the retrograde direction, resulting in a P wave within or immediately after the QRS complex).[76,77] Wellens has described an electrocardiographic sign, which is suggestive of AVNRT. It consists of an incomplete BBB pattern (RSR′) in lead V1 during the tachycardia that is not present in the 12-lead ECG in sinus rhythm.[72] However, atrial flutter with 2:1 conduction should be suspected as a differential diagnosis if the ventricular rate of the SVT with narrow QRS complexes is approximately 150 beats/min. If P waves have been identified during SVT and follow the QRS complexes at a significant interval, resulting in an R-P interval equal to or greater than the P-R interval, the most likely diagnosis is orthodromic AVRT (i.e., involving the AV node in the antegrade direction and an accessory AV pathway in the retrograde direction). Other helpful electrocardiographic clues that have been reported and shed light on the mechanism of SVT include a negative P wave in leads I and V1, because of left-to-right atrial activation in AVRT using a left-sided AV connection in its retrograde limb.[77] When two recordings of the tachycardia are available, one with narrow QRS complexes and the other with left BBB with a longer cycle length, a finding first described in Paris, the diagnosis of AVRT involving a left-sided accessory connection can be made.[57,78] The presence of QRS alternation is also in favor of AVRT.

The differential diagnosis between PSVT and AF with rapid ventricular response or atrial flutter with 1:1 conduction may at times be difficult. Vagal maneuvers, particularly carotid sinus massage and adenosine injection, may be of great help in clinical diagnosis (Figure 41-15). In AVRT or AVNRT, the arrhythmia may terminate abruptly or remain unaffected. In contrast, AF or atrial flutter is rarely terminated by these techniques but can be slowed in its ventricular response, thus exposing the underlying atrial flutter or AF waves. PSVT and atrial flutter or AF may also coexist. Adenosine administration may be used as a diagnostic test to assess dual AV nodal pathway conduction, efficacy of slow pathway ablation, and detection of concealed accessory pathways.[79]

Box 41-4 shows the responses of different types of PSVT to adenosine.

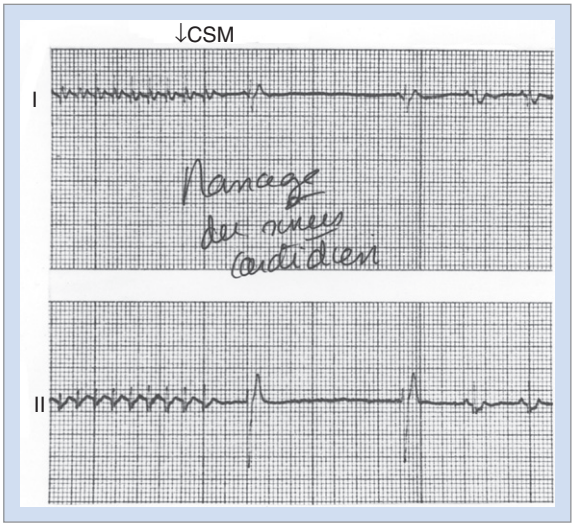


FIGURE 41-15 Termination of narrow QRS complex tachycardia with carotid sinus massage.

Box 41-4 Tachycardias with Wide QRS Complexes

1. Atrial fibrillation with conduction through an AV accessory connection (bundle of Kent)
2. Atrial flutter with 1:1 conduction through an AV accessory connection (bundle of Kent)
3. Antidromic tachycardia: bundle of Kent anterograde/AV junction retrograde
4. Tachycardia using two accessory connections: overt bundle of Kent in one ventricle anterograde; overt or concealed (on the ECG in sinus rhythm) bundle of Kent in the other ventricle retrograde
5. Tachycardia using a Mahaim fiber (AV-like structure) in the anterograde direction and the AV node in the retrograde direction
6. AV nodal re-entrant tachycardia with antegrade conduction over an accessory AV pathway ("bystander Kent")

AV, *Atrioventricular;* ECG, *electrocardiogram.*

Tachycardia with Regular Wide QRS Complex

Regular SVT may present with wide (>0.12 second) QRS complex, and differentiating SVT from VT may be difficult (Table 41-3). Another etiology of wide QRS complex tachycardia is the pre-excitation syndrome, which may be overt (WPW syndrome) or concealed (with the pathway only conducting in the retrograde direction), and this is discussed later. It bears repeating that the vast majority of regular SVTs occur in patients without organic heart disease in contrast to patients with VT. Three clues may be used in the differential diagnosis of wide QRS tachycardias.

1. The age of the patient—in the child and young adult, pre-excitation is more common than VT. In this instance, the ECG in sinus rhythm, if available, shows pre-excitation, and the ECG during the tachycardias shows an identical morphology.

2. In making this distinction in SVT diagnosis, it is necessary to locate the P wave during tachycardias. The presence of AV

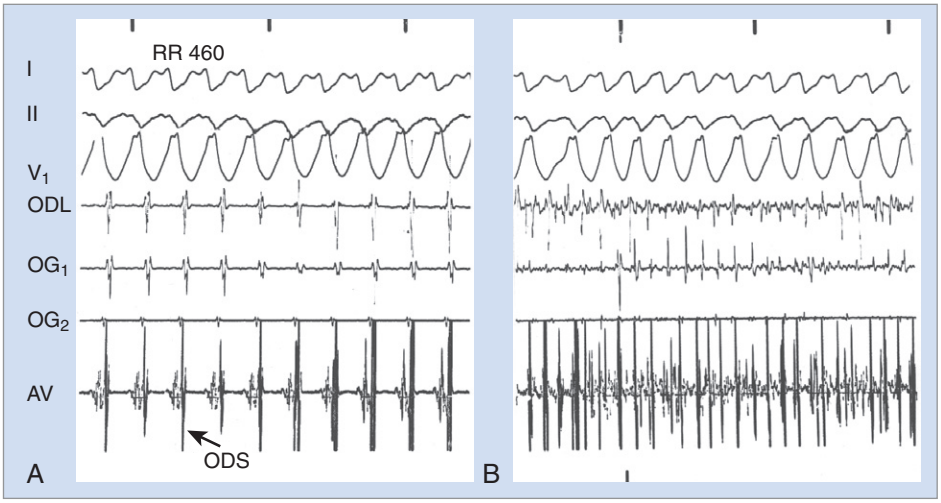


FIGURE 41-16 Tachycardias with pre-excited QRS complexes. The same leads as those in Figure 41-3 were used. **A** is consistent with an antidromic reciprocating tachycardia. **B** shows atrial fibrillation conducted over a left-sided accessory atrioventricular pathway termination of supraventricular tachycardia with vagal maneuvers.

dissociation is generally diagnostic of VT. However, it is only present in approximately 40% of VTs. Differentiating SVT from VT may require EPS with endocavitary recordings.[71,80-84]

3. Wellens et al have described a number of criteria that may be of help in differentiating SVT from VT.[84] A few that we have found particularly useful include left-axis deviation (beyond 30 degrees), QRS complexes wider than 0.14 second, and the QRS morphology in leads V1 and V6 (i.e., a monophasic R wave or a QR pattern in lead V1, or an rS or a QS pattern in lead V6), all of which favor a diagnosis of VT. Another clue that might be helpful is the presence of BBB in sinus rhythm. An identical morphology during the tachycardia is suggestive of SVT as well. When the QRS complex is narrow in sinus rhythm and wide during SVT, aberrant conduction is also a consideration. We have found it practical to consider aberrancy only when the typical pattern of right or left BBB is present during tachycardia. This still does not exclude the possible diagnosis of VT. For these reasons, it is a wise rule "to consider any tachycardia with wide QRS complexes as being VT unless proven otherwise" (Agustin Castellanos Jr, personal communication, 1997). A detailed EPS is indicated in all patients with wide QRS complex tachycardias.

Tachycardia with Pre-excited QRS Complexes

The differential diagnosis of wide QRS complex tachycardia may be extremely difficult if pre-excitation is present (Figure 41-16). Fortunately, tachycardias with pre-excited QRS complexes represent less than 5% of all wide QRS complex tachycardias. A number of mechanisms may account for a tachycardia with pre-excited QRS complexes. The most common is AF with conduction over the bundle of Kent. The R-R interval is frequently irregular, and the QRS width may change from one complex to the other. Atrial flutter with 1:1 conduction over an accessory connection is another possibility; however, this diagnosis should be suspected when the ventricular rate ranges from 250 to 300 beats/min. In a young person, a tachycardia with a left BBB and left-axis deviation should suggest the possibility of a Mahaim fiber. The other mechanisms may require endocavitary recordings and can only be ascertained by detailed EPS.

Noninvasive Investigations

As previously mentioned, electrocardiographic documentation is an essential step in the diagnostic approach to SVT. This can be achieved by several methods.

1. *Ambulatory ECG monitoring*: Ambulatory ECG recordings are only warranted when symptoms are frequent enough to allow documentation within the 24- or 48-hour recordings. Otherwise, the information provided by such monitoring is limited to the possible trigger (extrasystoles). Occasionally, monitoring of the tachycardia shows that it is similar to sinus tachycardia, making ambulatory ECG recordings extremely useful, in our experience, in the diagnosis of "inappropriate" sinus node tachycardias. Chest pain and dyspnea precipitated by the tachyarrhythmia may be the dominant or stand-alone symptoms, and monitoring may be useful in correlating these symptoms to the tachycardia.

2. *Event recorders*: If the episodes of tachycardia are infrequent or of short duration, event recorders are often useful. In recent years, the advances in technology have prompted the development of recorders with trans-telephonic transmission and will allow trans-telephonic surveillance of selected patients. Daily monitoring and symptomatic transmissions permit the clinician to assess arrhythmia-related symptoms.

3. *Telemetric monitoring*: When the tachycardia is severely symptomatic and occurs frequently enough to be recorded during a hospital stay, telemetric monitoring in the hospital offers another diagnostic option. However, as this surveillance requires hospitalization and is associated with a high cost, this technique is often impractical for any prolonged period.

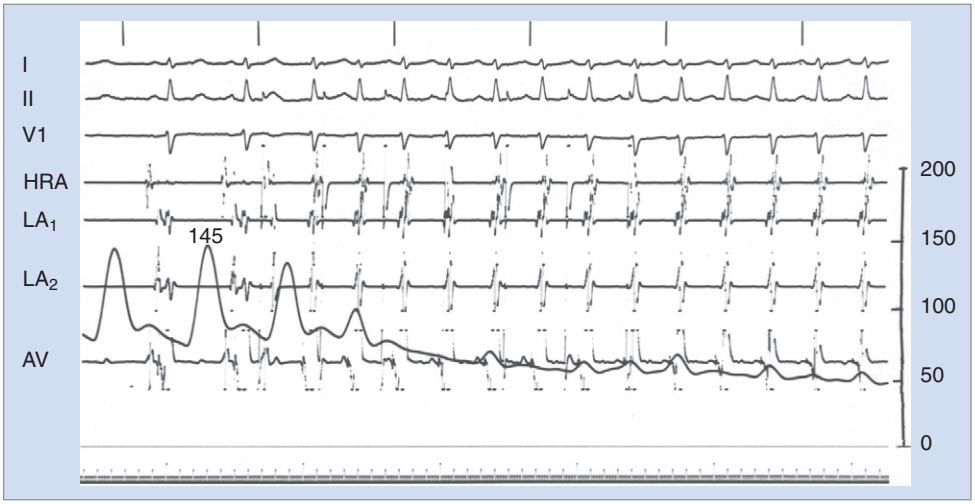


FIGURE 41-17 Recordings in a 76-year-old woman reporting tachycardia followed by syncope. *Top to bottom*, electrocardiogram leads I, II, and V1; high right atrium (*HRA*); left atrium (*LA1* and *LA2*) femoral artery pressure; and atrioventricular lead (*AV*). Note the fall of blood pressure after AV nodal re-entrant tachycardia is induced by overdrive atrial pacing.

4. *Exercise testing*: Exercise testing is particularly valuable when the tachycardia is precipitated by exercise or is otherwise believed to be catecholamine dependent. For example, AT and AF are not uncommonly induced by exercise. Although junctional tachycardias may occasionally be precipitated by exercise, this test is seldom indicated in patients with paroxysmal SVT. Exercise testing is a valuable tool in patients suspected to have IST.

5. *Implantable loop recorders and other devices*: Implantable loop recorders are subcutaneous ECG recording devices without intracardiac electrodes. They have been developed recently for symptom-ECG correlation. Loop recorders, such as the Reveal Plus system (Medtronic, Inc., Minneapolis, MN), have been used recently in patients with syncope and those with previous MI. Although such devices can document tachycardias, large-scale studies of the yield of such systems in PSVT are unavailable. Furthermore, these devices cannot reliably differentiate SVT from VT. In patients with previously implanted pacemakers or defibrillators, documentation of arrhythmia and its site of origin is generally easy to achieve.

6. *Electrophysiological study* (Figure 41-17): EPS is used for diagnostic and therapeutic purposes in patients with PSVT. SVT initiation during this procedure allows ECG documentation of the tachycardia, if it has not been previously recorded; definition of the mechanism of the tachycardia and the critical components of the circuit; evaluation of symptoms during the arrhythmia; and, if indicated, performance of radiofrequency (RF) ablation or evaluation of the efficacy of antiarrhythmic therapy. Most SVTs are caused by a re-entrant mechanism and may be induced in the laboratory using programmed electrical stimulation.[80-84] In AV junctional tachycardias, EPS permits induction of the tachycardia in more than 90% of patients with AVRT or AVNRT. In patients with AVNRT, premature atrial stimulation can demonstrate dual AV nodal conduction and induce the tachycardia to determine its mechanism.[80] The arrhythmias associated with the WPW syndrome include reciprocating or circus-movement tachycardias and atrial arrhythmias.[76,82] In some instances of AVNRT, concomitant pre-excited QRS complexes may exist because of passive conduction over an accessory pathway, which may serve as a passive bystander. Tachycardias related to Mahaim fibers have a particular electrocardiographic presentation with left BBB and left axis. The ECG in sinus rhythm shows features of WPW syndrome. EPS will often demonstrate decremental conduction over the accessory pathway.

Principles of Management

The principles of management in many forms of PSVT have undergone significant changes with better understanding of the natural history, diagnosis, and progression of these arrhythmias, as well as the development of more effective ablative and drug therapies for many of these arrhythmias. Immediate and long-term prophylactic therapy differs significantly in selection and clinical application. Immediate therapy is directed at resolution of an individual arrhythmic event. Prophylaxis is largely focused on curative approaches, although suppressive and tachycardia termination methods do exist and are occasionally applied in specific clinical scenarios. The spontaneous occurrence of a single SVT event may or may not mandate immediate therapy on the basis of symptomatology and certainly does not mandate prophylactic therapy unless recurrence is anticipated, patterns of recurrence and duration become clearer, or the event is potentially malignant or life threatening. Immediate therapy is indicated if a patient develops angina, heart failure, or syncopal symptomatology during SVT. Sustained palpitations can impair functionality and result in serious patient discomfort and require immediate termination. The immediate evaluation and diagnosis of the specific form of PSVT is critical to its future management. Figure 41-18 shows an algorithm for the treatment approach for hemodynamically stable PSVT from the 2006 ACC/AHA/ESC practice guidelines.[49]

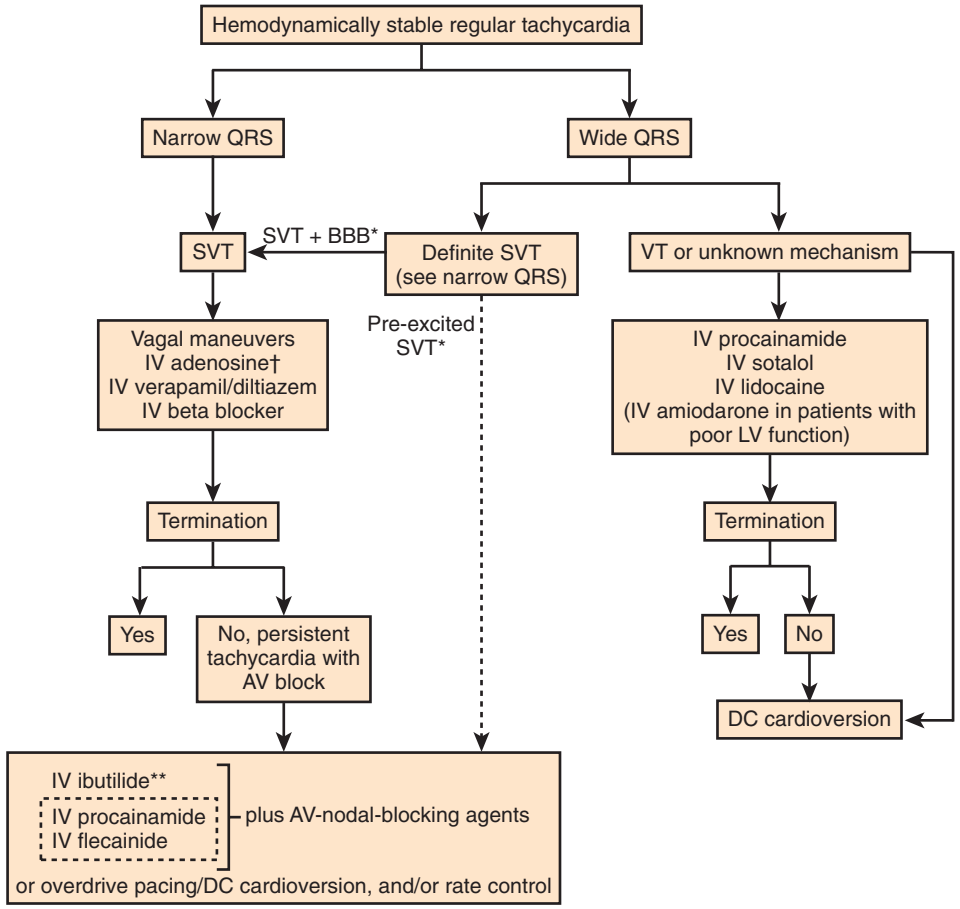


FIGURE 41-18 Acute management of patients with hemodynamically stable and regular tachycardia. *A 12-lead electrocardiogram (ECG) during sinus rhythm must be available for diagnosis. †Adenosine should be used with caution in patients with severe coronary artery disease and may produce atrial fibrillation, which may result in rapid ventricular rates in patients with pre-excitation. ‡Ibutilide is especially effective in patients with atrial flutter but should not be used in patients with ejection fraction >30% because of increased risk of polymorphic ventricular tachycardia (*VT*). *AV*, Atrioventricular; *BBB*, bundle branch block; *DC*, direct current; *IV*, intravenous; *LV*, left ventricle; *QRS*, ventricular activation on ECG; *SVT*, supraventricular tachycardia.

Certain considerations in the progression of SVT can influence prophylaxis and interventions. As mentioned earlier, a change in the pattern of SVT over time is not uncommon and should be considered in prophylaxis. In SVT observed during infancy and childhood, resolution can be observed with growth and development in some individuals. Diagnosis of these arrhythmias even in preterm infants has resulted in better characterization of the clinical outcome and therapy selection. Although in the past, observation with a conservative management approach was more prevalent in this and older populations, the advent of effective curative therapy in the form of catheter ablation has lowered the threshold for intervention in both adult and pediatric populations.

The success and safety of ablation of AVNRT, AVRT, and other focal ATs has offered promise of cure. The prevalence of these arrhythmias in young populations with the prospect of lifelong recurrent SVT has motivated physicians to quickly offer catheter ablation as definitive first-line treatment after resolution of the acute episode. Drug therapy is generally reserved for the acute management of a symptomatic episode, for short-term prophylaxis as a bridge to cure, or, rarely, in patients in whom ablation is contraindicated or not feasible. Optimal timing of ablative intervention for children and adolescents may involve delaying, if feasible, till completion of high school to permit anatomic cardiac development.

Although device therapy has had a niche role and can be effective in many of these rhythms, it is now largely relegated to an adjunctive role when implantation of a device is contemplated for other clinical indications in a patient with recurrent SVT. Device therapy is most often initiated for other indications, with activation of anti-tachycardia pacing for coexisting SVT termination. The use of device therapy in patients with failed ablation and drug therapy is an increasingly rare event.

Evidence-Based Therapy

Spontaneous termination of SVT is common and can occur quite early. Waxman et al concluded that the spontaneous termination of SVT occurred within the AV node. Further pharmacologic testing indicated that the initial hypotension during SVT onset provokes a sympathetic response to raise blood pressure, which, in turn, enhances vagal tone that can terminate the arrhythmia.[85]

Immediate therapy in this SVT usually consists of vagal or other physical maneuvers to terminate the event or the parenteral administration of a short-acting effective AV nodal–blocking agent. Commonly used vagal maneuvers include unilateral carotid sinus massage, diving reflex activation with placement of the face in cold water, or the Valsalva maneuver. These are often quite effective and can be performed by the patient or a health care professional. In a comparative clinical study, the efficacy was 19% with the initial use of the Valsalva maneuver and 11% with carotid sinus massage. However, the sequential use of both techniques improved overall success to 28%.[86]

Because of its extremely short half-life, safety, and efficacy, intravenous adenosine has become the drug of choice in the United States. A single peripheral bolus of 6 or 12 mg followed by saline bolus for rapid transit with minimal dilution is employed. In clinical trials, the efficacy of a single 6-mg intravenous bolus was 63%, rising to 91% at 12 mg.[87] Central administration is not more effective than peripheral bolus injection, but lower doses of 3 mg and 6 mg are more effective.[88] Adenosine may result in complete, but very transient, AV block or sinus arrest in individual patients; it resolves spontaneously within a few seconds, and re-initiation of SVT occurs in less than 10% of patients. In a field study, vagal maneuvers were followed by adenosine administration. A 90% conversion of PSVT occurred, consistent with dose-ranging studies, and no difference was observed in the asystolic pause seen in patients with PSVT or AF. Adenosine use may also help unmask the underlying mechanism of SVT.[89,90] It is commonly used as a test to block the AV node and elicit accessory pathway conduction during EPS and may show δ waves transiently in SVT because of AV re-entry. In other instances, it may show underlying dual AV nodal physiology in patients with AVNRT.

As adenosine is expensive, other alternative agents that are highly effective include intravenous calcium blockers such as diltiazem or verapamil, type 1 agents or β-blockers. Verapamil is typically administered as a bolus in 5-mg aliquots, and a total of 10 to 15 mg is almost invariably effective. In patients with refractory disease, use of a drug infusion may be helpful. In a direct comparison, the efficacy of intravenous verapamil was 73% in one study and did not differ significantly from adenosine, but hypotension was more common with verapamil.[91] Rarely, fast pathway block with the use of intravenous type 1 agents such as procainamide may be contemplated. Intravenous flecainide has been used in a dose of 2 mg/kg body weight and terminates AVNRT and AVRT with more than 90% efficacy.[92] Electrical re-initiation of PSVT is uncommon and is associated with a markedly slower tachycardia. Comparison of intravenous diltiazem at a dose of 0.2 mg/kg and esmolol at 0.5 mg/kg showed the superior efficacy of diltiazem.[93] New intravenous agents include dofetilide, which has been tested in WPW syndrome in patients with AF and AVRT. The overall efficacy in one study was 71%. Intravenous propafenone was also highly effective in the same patient population in another study.[94]

It is now extremely rare to use electrical anti-tachycardia therapies for acute conversion of SVT.[81] However, it is important for the treating physician to know that atrial anti-tachycardia pacing and cardioversion can be used effectively for this purpose. Bursts, programmed extrastimuli, or ramp pacing in the atrium can effectively terminate AVNRT, and this may also be achieved with rapid ventricular pacing in many patients. Thus, in the presence of pacing lead systems on a temporary or permanent basis, any of these modes may effectively terminate an episode of AVNRT without major adverse sequelae in most patients. Induction of AF may occasionally occur with atrial pacing methods, and ventricular tachyarrhythmias may be rarely initiated in a predisposed patient with rapid ventricular pacing. Direct current cardioversion is highly effective but is rarely needed even in emergent circumstances. However, in patients with syncope and very rapid PSVT, this should be considered in emergent circumstances.

Oral single-dose drug therapy to terminate a single arrhythmic event has been gaining currency, particularly in Europe. This is widely promoted in cardioversion of AF. However, this principle can be applied to a single PSVT event that is not highly symptomatic and can be tolerated by the patient. β-Blockers, calcium blockers, and even type 1 drugs can be considered, but in contrast to AF, formal efficacy and safety studies are lacking. Table 41-1 outlines current recommendations from the ACC/AHA/ESC practice guidelines that codify the sequence and options in acute management of PSVT.[49]

Prophylaxis of Recurrent Paroxysmal Supraventricular Tachycardias

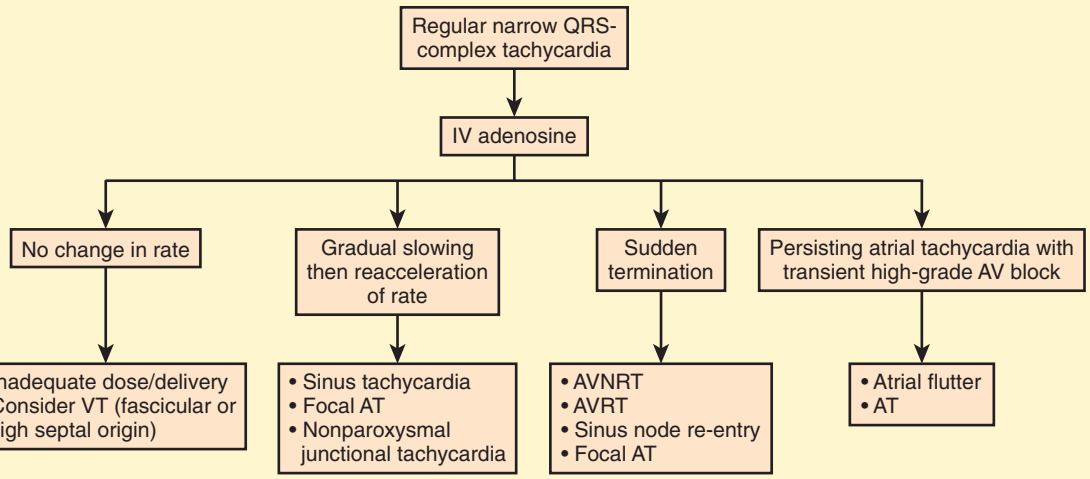
Prophylaxis of recurrent AVNRT has been attempted with drug therapy, ablation, and device therapy. Catheter ablation is the first-line therapy for prophylaxis of PSVT in virtually all populations and age groups, is curative in nature, and uses a variety of techniques.[88-90,95,96] It may be avoided in patients who have major contraindications to the procedure, such as uncontrolled infections, bleeding diatheses, unstable cardiovascular hemodynamics, and implanted prosthetic heart valves, as well as in very elderly and debilitated patients. However, successful procedures have been performed in our laboratory in patients in their tenth decade of life. In AV nodal tachycardia, the most widely used technique is ablation of the slow AV nodal pathway, whereas in AVRT, ablation of the accessory bypass tract is performed. The technical details of each technique are described in Section IX of this text. Catheter ablation can be performed using map-guided or anatomically based approaches in AV nodal re-entry but is invariably performed using map-guided methods for AVRTs, as well as in other pre-excitation syndrome substrates. In brief, slow pathway ablation is performed at or above the posterior aspect of the triangle of Koch just above the coronary sinus ostium. Fast pathway ablation is performed in the superior part of the triangle, just above the AV node–bundle of His axis. Specific ablation methods are used for free wall accessory pathways in the left or right atrium, anteroseptal, midseptal, posteroseptal, and paraseptal accessory pathways.

Finally, ablation of the nodo-ventricular and fasciculo-ventricular and atrio-His fibers has also been successfully performed with map-guided methods. The success of these techniques in suppression of recurrent SVT exceeds 90%, with complication rates of 1% or less.[95-98] Mortality is rare, with inadvertent complete AV block and myocardial perforation being the most important major complications, estimated at 1% to 2%, respectively. Successful cure of AVRT can vary, depending on the ablation site, with left free wall and posteroseptal or paraseptal pathways showing higher efficacy rates compared with right free wall or right anteroseptal pathways. Alternative ablation techniques for AV nodal tachycardia include ablation of the fast AV nodal pathway. Fast pathway ablation can be equally effective in curing AV nodal re-entry but is associated with a higher complication rate with respect to AV nodal block, approaching 5% in some series. Similarly, ablation of intermediate septal pathways in

WPW syndrome can have a similar risk of complete AV block. It is rarely necessary and generally inadvisable to perform complete AV nodal ablation in either arrhythmia. In a comparative clinical trial, catheter ablation provided superior control of symptoms and better quality of life compared with drug therapy in patients with recurrent PSVT.

Prospective clinical studies have documented a high degree of efficacy with catheter ablation in this condition. Tables 41-2 and 41-3 show the NASPE voluntary registry of 3423 procedures performed at 68 centers in the United States. The registry reports efficacy rates for AV junctional ablation, AVNRT ablation, and accessory pathway ablation by tract location at teaching and nonteaching hospitals in the United States.[98] Note that efficacy rates exceed 90% for all arrhythmias, and there is virtually no significant difference in outcome by location. In addition, comparison of data for large-volume (>100 procedures per year) and lower-volume centers did not show differences, indicating that the learning curve for the procedure was over. A slightly lower success rate was observed with right free wall or septal pathways compared with left free wall pathways. Significant complications in this series of patients undergoing AV junction ablation included a very low mortality and a small incidence of sudden cardiac death from polymorphous VT after ablation; cardiac pacing at relatively rapid rates is recommended for several weeks after AV junction ablation. For patients undergoing slow pathway ablation, the risk of second-degree AV block was 0.16%, and the risk for complete

Table 41-1 ACC/AHA/ESC Guidelines for the Management of Patients with Supraventricular Arrhythmias



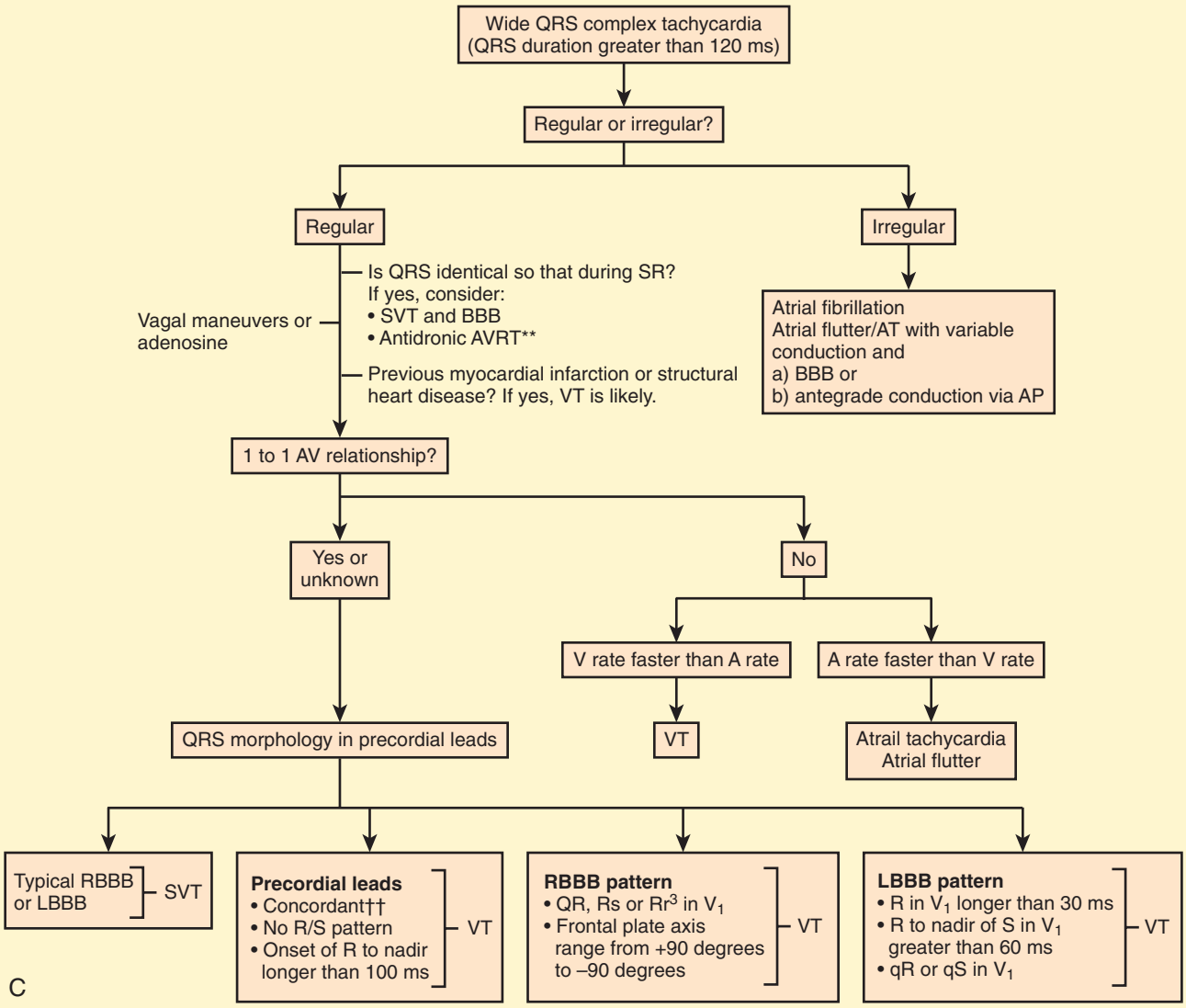
A

ECG	RECOMMENDATION*	CLASSIFICATION	LEVEL OF EVIDENCE
Narrow QRS complex tachycardia (SVT)	Vagal maneuvers	I	B
	Adenosne	I	A
	Verapamil, diltiazem	I	A
	β-Blockers	Ib	C
	Amiodarone	Ib	C
	Digoxin	Ib	C
Wide QRS complex tachycardia			
SVT + BBB	See above		
Pre-excited SVT/AF	Flecainide†	I	B
	Ibutilide†	I	B
	Procainamide†	I	B
	DC cardioversion	I	C
Wide QRS complex tachycardia of unknown origin	Procainamide†	I	B
	Sotalol†	I	B
	Amiodarone	I	B
	DC cardioversion	I	B
	Lidocaine	Ib	B
	Adenosine‡	Ib	C
	β-Blockers§	III	C
	Verapamil¶	III	B
Wide QRS complex tachycardia of unknown origin in patients with poor LV function	Amiodarone	I	B
	DC cardioversion, lidocaine	I	B

B

Continued

Table 41-1 ACC/AHA/ESC Guidelines for the Management of Patients with Supraventricular Arrhythmias—cont'd



**All listed drugs are administered intravenously.*
†Should not be taken by patients with reduced LV function.
‡Adenosine should be used with caution in patients with severe coronary artery disease because vasodilation of normal coronary vessels may produce ischemia in vulnerable territory. It should be used only with full resuscitative equipment available.
§β-Blockers may be used as first-line therapy for those with catecholamine-sensitive tachycardias, such as right ventricular outflow tachycardia.
¶Verapamil may be used as first-line therapy for those with LV fascicular VT.
***Concordant indicates that all precordial leads show either positive or negative deflections. Fusion complexes are diagnostic of VT.*
††In pre-excited tachycardias, the QRS is generally wider (i.e., more pre-excited) compared with sinus rhythm.
ACC, American College of Cardiology; AHA, American Heart Assocation; ESC, European Society of Cardiology; SVT, supraventricular tachycardia; BBB, bundle branch block; AF, atrial fibrillation; DC, direct current; LV, left ventricular.
From Blomström-Lundqvist C, Scheinman MM, Aliot EM, et al: ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias, Circulation *108: 1871–1909, 2003.*

heart block was 0.74%. Complications included a low incidence of cardiac tamponade, AV block, and rare instances of coronary occlusion and pulmonary embolism. The overall complication rate for this procedure is estimated at less than 1%.

Drug therapy has been largely relegated to temporary, intermittent, or second-line choice. Digoxin therapy, long established for this purpose, has now been supplanted by more effective β-blocker, calcium blocker, and types 1c and III drug therapy in the last two decades. In prospective clinical trials, oral flecainide therapy was associated with an actuarial 79% to 82% freedom from symptomatic PSVT events compared with only 15% on placebo at 60 days ($P < .001$).[99] The median time to the first symptomatic PSVT event was greater in the flecainide group, and the interval between attacks was increased by flecainide. Similarly, propafenone reduced recurrent SVT in prospective studies by 80%.[100,101] Oral verapamil was shown to be effective in the prophylaxis of SVT in comparison with placebo, with reduced need for pharmacologic cardioversion and lower event rates.[102]

Table 41-2 Percentage of Successful Ablations and Complications for Teaching vs. Nonteaching Hospitals

PROCEDURE	TEACHING HOSPITAL	SUCCESS (%)	NONTEACHING HOSPITAL	SUCCESS (%)
AV junction	171/176	95.8	458/470	93.2
AVNRT	456/476	97.2	705/732	97.4
AP (total)	255/275	92.7	372/399	93.2
Left free wall	160/172	93.6	232/247	93.9
Right free wall	26/27	96.3	54/56	96.4
Septal	75/83	90.4	90/103	87.4

AV, atrioventricular; AVNRT, *atrioventricular nodal re-entrant tachycardia;* AP, *accesory pathway.*

Table 41-3 Percentage of Successful Ablations and Complications in Medical Centers, by Patient Number (1998)

	With >100 Cases (% Success)	With <100 Cases (% Success)
AV junction	354/366 (96.7)	275/280 (98.2)
AVNRT	603/627 (96.2)	558/581 (95.8)
AP (total)	315/339 (92.9)	312/335 (93.1)
Left free wall	201/216 (93.1)	191/202 (94.6)
Right free wall	37/39 (94.9)	43/44 (97.7)
Septal	144/160 (90.0)	85/98 (86.7)

AV, atrioventricular; AVNRT, *atrioventricular nodal re-entrant tachycardia; AP, accessory pathway.*

In a comparison with flecainide therapy, it was equally effective and well tolerated. In one study, both drugs showed a marked reduction in the frequency of attacks of PSVT, with a small advantage for flecainide.[103] Thirty percent of patients on flecainide had resolution of symptomatic attacks versus 13% of the patients on verapamil ($P = .026$). Eleven percent of patients discontinued flecainide, and 19% discontinued verapamil for inefficacy at 1 year. Both drugs were well tolerated; 19% of the flecainide group discontinued therapy because of adverse effects, compared with 24% discontinuing verapamil for this reason. Randomized controlled trials of propafenone with placebo show a sixfold increase in time to first PSVT recurrence at a dose of 600 mg/day.[101] Although the higher dose of 900 mg was even more effective, if tolerated, a significant increase in adverse effects occurred. Comparative studies have shown propafenone and flecainide to have similar efficacy and safety.[101] Newer agents include dofetilide, azimilide, and sotalol.[104-106] Data on dofetilide are limited, but at a dose of 500 µg/day, dofetilide is equally effective as propafenone at a relatively low dose of 450 mg/day. The probability of freedom from recurrent PSVT was 50% and 54%, respectively, with a 6% probability on placebo. Thus these efficacy rates remain well below levels seen with catheter ablation, which explains why this approach has been relegated to being a second-line therapy. In addition, the improvement of quality of life with catheter ablation is superior to that with medical therapy. The improvement in quality of life was seen in patients with moderate or severe symptoms caused by PSVT. The safety profile of type 1c agents in older adults is also of concern because of the risk of proarrhythmia.

Tables 41-4 and 41-5 outline current recommendations for the long-term management of AVNRT and SVT, respectively, associated with pre-excitation syndromes. The guidelines focus on the level of evidence and support for each therapeutic option. For a more detailed discussion of the guidelines, the reader is referred to the original policy statement.[49]

Sinoatrial Tachycardias

SART and IST are usually managed with pharmacologic and if refractory nonpharmacologic approaches. SART can be treated with calcium channel or β-adrenergic blockers as the first-line therapy.[49,107] These are sometimes are poorly tolerated because of adverse effects. Prophylaxis of SART is now feasible with either drug therapy or ablation therapy. Although few large clinical series have been reported, successful clinical experience with verapamil, diltiazem, and noncardioselective β-blockers has been reported.[49,108] Ivabradine is a new drug that selectively blocks the funny current (*if*). It has been used in both paroxysmal and nonparoxysmal forms of IST with early success.[109] Ivabradine reduced average and maximal heart rate on Holter monitoring, with an increased tolerance of physical stress. More recently, mapping of the right atrium has been performed to locate the tachycardia origin and perform catheter ablation.[110,111] RF ablation of the mapped site has been effective in prevention of recurrences, but proximity to the sinus node can result in potential damage and risk of sinus node dysfunction.[111,112] Table 41-6 outlines the recommendations from the ACC/AHA/ESC practice guidelines for these arrhythmias.[49]

Table 41-4 Current Recommendations for Long-Term Management of AVNRT

CLINICAL PRESENTATION	RECOMMENDATION	CLASS	LEVEL OF EVIDENCE	REFERENCES
Poorly tolerated AVNRT with hemodynamic intolerance	Catheter ablation	I	B	58
	Verapamil, diltiazem, β-blockers, sotalol, amiodarone	IIa	C	58
	Flecainide,* propafenone*	IIa	C	
Recurrent symptomatic AVNRT	Catheter ablation	I	B	58
	Verapamil	I	B	59
	Diltiazem, β-blockers	I	C	60
	Digoxin†	IIb	C	
Recurrent AVNRT unresponsive to β-blockers or calcium channel blocker and patient not desiring RF ablation	Flecainide,* propafenone,* sotalol	IIa	B	53, 61-65
	Amiodarone	IIb	C	66
AVNRT with infrequent or single episode in patients who want complete control of arrhythmia	Catheter ablation	I	B	
Documented PSVT with only dual AV nodal pathways or single echo beats demonstrated during electrophysiological study and no other identified cause of arrhythmia	Verapamil, diltiazem, β-blockers, flecainide,* propafenone	I	C	
	Catheter ablation‡	I	B	
Infrequent, well-tolerated AVNRT	No therapy	I	C	58
	Vagal maneuvers	I	B	
	Pill in the pocket	I	B	
	Verapamil, diltiazem, β-blockers	I	B	
	Catheter ablation	I	B	67

**Relatively contraindicated for patients with coronary artery disease, LV dysfunction, or other significant heart disease.*
†Digoxin is often ineffective because its pharmacologic effects can be overridden by enhanced sympathetic tone.
‡Decision depends on symptoms.
AVNRT, Atrioventricular nodal re-entrant tachycardia; RF, radiofrequency; PSVT, paroxysmal supraventricular tachycardia; AV, atrioventricular.
From Blomström-Lundqvist C, Scheinman MM, Aliot EM, et al: ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias, Circulation *108:1871–1909, 2003.*

Surgical Ablation of Atrioventricular Nodal Re-entrant Tachycardia

Surgical ablation of PSVT has been well developed, and established and progressively refined techniques have been used since the 1980s. The surgical basis for SVT ablation involves resection or modification of the substrate for the arrhythmia; many of these principles that have been pioneered and applied have now come into vogue in catheter ablation procedures. Experimental studies have refined surgical techniques since the original description of SVT control by ligature of the bundle of His.[102] Since that time, complete AV block has been avoided, and modification of selective pathways with preservation of normal AV conduction has been pursued. In animal studies, McGuire et al disconnected the anterior part of the AV node, which resulted in mild impairment of AV nodal conduction and destruction of ventriculo-atrial conduction in 50% of the animals.[37] This helped define the contribution of each of these connections to AV conduction patterns in this animal model. It also suggested that the fast pathway is the preferred route of conduction through the AV node, but other inputs can assume these responsibilities with limited loss of efficacy. This became the basis for one surgical approach to cure AVNRT by fast pathway interruption. More recently, slow pathway interruption by surgical or catheter ablation methods has become the procedure of choice, with lower risk of impaired AV conduction and a high degree of efficacy.[88,89] However, in case of failure, ablation alternatives such as elimination of the fast pathway or left-sided connections should be considered.

Accessory pathway ablation using the endocardial or epicardial approach, with linear incision at the mapped pathway location, was widely used in the 1980s until it was supplanted by catheter ablation.[113,114] Near-perfect efficacy has been described in the largest series, with mortality rates of less than 1% in patients without cardiac disease or other surgical procedures.[115] The details of the mapping and surgical technique are beyond the purview of this chapter and are described elsewhere in this text or in referenced literature. Suffice it to state that the epicardial approach to accessory pathway eliminated the need for cardiopulmonary bypass, and cryoablation of the AV groove resulted in a safe and highly effective procedure. Other energy sources such as laser have also been applied clinically.[116] The usefulness of this technique lies in the ability to perform curative ablation procedures in patients with PSVT undergoing cardiac surgery for other indications and in patients with failed catheter ablation attempts, particularly if multiple accessory pathways are present. The role of this approach in SA node re-entry or nonparoxysmal sinus tachycardia or other ATs is less well established. Although surgical success in select patients has been reported, this is not as effective an approach in these substrates.[117]

Table 41-5 Current Recommendations for Long-Term Management of SVT Associated with Pre-excitation Syndromes

ARRHYTHMIA	RECOMMENDATION	CLASSIFICATION	LEVEL OF EVIDENCE	REFERENCE(S)
WPW syndrome (pre-excitation and symptomatic arrhythmias), well tolerated	Catheter ablation	I	B	55, 123-125
	Flecainide, propafenone	IIa	C	64, 124, 126-137
	Sotalol, amiodarone, β-blockers	IIa	C	138-142
	Verapamil, diltiazem, digoxin	III	C	143
WPW syndrome (with AF and rapid-conduction or poorly tolerated AVRT)	Catheter ablation	I	B	55, 57, 113, 123, 144, 145, 146-148
AVRT, poorly tolerated (no pre-excitation)	Catheter ablation	I	B	55, 57, 113, 123, 144, 145, 146-148
	Flecainide, propafenone	IIa	C	64, 124, 126-137
	Sotalol, amiodarone	IIa	C	138-142
	β-Blockers	IIb	C	143
	Verapamil, diltiazem, digoxin	III	C	143
Single or infrequent AVRT episode(s) (no pre-excitation)	None	I	C	
	Vagal maneuvers	I	B	
	Pill in the pocket: verapamil, diltiazem, β-blockers	I	B	54, 149
	Catheter ablation	IIa	B	55, 57, 113, 123, 144, 145, 146-148
	Sotalol, amiodarone	IIb	B	138-142
	Flecainide, propafenone	IIb	C	64, 124, 126-137, 143
	Digoxin	III	C	
Pre-excitation, asymptomatic	None	I	C	
	Catheter ablation	IIa	B	55, 57, 113, 124, 144, 145, 146-148

SVT, *Supraventricular tachycardia;* WPW, *Wolff-Parkinson-White;* AF, *atrial fibrillation;* AVRT, *atrioventricular re-entrant tachycardia.*
From Blomström-Lundqvist C, Scheinman MM, Aliot EM, et al: ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias, Circulation *108:1871–1909, 2003.*

Table 41-6 Recommendations from the ACC/AHA Practice Guidelines

TREATMENT	RECOMMENDATION	CLASSIFICATION	LEVEL OF EVIDENCE	REFERENCE(S)
Medical	β-Blockers	I	C	
	Verapamil, diltiazem	IIa	C	
Interventional	Catheter ablation—sinus node modification/elimination	IIb	C	44-51

From Blomström-Lundqvist C, Scheinman MM, Aliot EM, et al: ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias, Circulation *108:1871–1909, 2003.*

Device Therapy

The use of anti-tachycardia devices for PSVT termination and prevention only has historical significance except in a few specific situations with newer devices. It is mentioned here for completion, as well as for limited use in future devices. Early studies established the efficacy of anti-tachycardia pacemakers in recurrent PSVT.[118-121] Atrial burst and ramp pacing have been shown to be highly effective in termination of PSVT and common atrial flutter with implanted pacemaker devices.[122] Prevention of PSVT in different substrates has also been shown. Permanent dual-chamber pacing with a short A-V interval can prevent re-entrant PSVT caused by collision of the atrial and ventricular wavefronts in the critical elements of the PSVT circuit. This pacing mode has been employed effectively for this purpose. Long-term management of PSVT is feasible with automatic and patient activated anti-tachycardia pacing.[119-121] Current devices have these pacing modes available in their repertoire. The use of these modes may be considered in patients with implanted pacemakers or pacemaker defibrillators for other arrhythmia indications, who have coexisting PSVT of modest frequency. Incessant or highly frequent PSVT should be considered for ablative therapy.

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CHAPTER 42

Atrial Fibrillation

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Epidemiology

Incidence and Prevalence

Atrial fibrillation (AF) is the most common sustained arrhythmia, with the incidence of 3.1 cases in men and 1.9 cases in women per 1000 person-years in the population younger than 64 years, rising to 19.2 per 1000 person-years in those 65 to 74 years, and as high as 31.4 to 38 in octogenarians.[1] A rising proportion of the older population, markedly improved survival from previously fatal cardiovascular conditions, and a recently observed trend toward a continuous increase in the incidence of AF among younger age groups will result in a considerable increase in the number of patients with AF over the next 4 decades. The Framingham Study in the United States and the Rotterdam Study in Europe have estimated lifetime risk for development of AF to be 1 in 4 for men and women aged 40 years and older.[2,3] Projected data from national databases have predicted that the number of patients with AF in the United States is expected to reach 5.6 to 15.9 million by 2050, particularly if the incidence of AF continues to rise (Figure 42-1).[4-6] A similar increase in the proportion of population with AF is likely to be seen in Western Europe.[3,7] However, even these projections may represent conservative estimates because of silent and short transient episodes of AF, which are likely to be diagnosed more frequently because of increased awareness of the arrhythmia, improved diagnostic tools, and a wider use of implantable rhythm-control or rhythm-monitoring devices.[8]

Age, Gender, and Ethnicity

A series of epidemiologic studies have identified age to be one of the major determinants of risk of developing AF, with odds of 1.1 to 5.9 depending on the initial age and morbidity of a cohort studied and the duration of follow-up.[9-12] In the Framingham Heart Study, the risk of AF was increased approximately twofold per decade of age in both men and women.[11] Increased rates of AF related to age are attributed to inherent changes in the atria occurring with aging (e.g., fatty metamorphosis, myocyte degeneration, fibrosis), accumulation of risk factors, and progression of the underlying disease.

Men are affected almost twice as often and are diagnosed with AF at a younger age compared with women, but recent analyses have suggested that women with AF have more comorbidities, higher mortality rate, and higher risk of stroke and treatment-related complications (e.g., proarrhythmia or bleeding) compared with their male counterparts.[11-15]

The prevalence of AF is higher in white populations.[16-19] In the Atherosclerosis Risk in Communities (ARIC) Study, age-adjusted incidence rates of AF were highest in white men and lowest in black women (7.45 and 3.67 per 1000 person-years, respectively).[17] In the health survey of 664,754 U.S. veterans, white men were significantly more likely to have AF compared with all other races except Pacific Islanders (odds ratio [OR] compared with blacks, 1.84; vs. Hispanics, 1.77; vs. Asians, 1.41; vs. Native Americans, 1.15; $P < .001$).[18] The prevalence and distribution of associated risk factors also depended on ethnicity. Thus white men were more likely to have valvular heart disease, coronary artery disease (CAD), and congestive heart failure (CHF); blacks had the highest prevalence of hypertension; and Hispanics had the highest prevalence of diabetes. Racial differences remained after adjustment for age, body mass index, and underlying pathology. In a meta-analysis of seven randomized clinical trials in patients with acute coronary syndrome (ACS), the prospectively collected information on the development of AF indicated that the rates of AF were lower in Asian patients than in white patients (4.7% vs. 7.6%; OR, 0.65; 95% confidence interval [CI], 0.50 to 0.84; $P = .001$).[19] This contradicts the finding of a greater prevalence of unfavorable risk factors for AF in nonwhite populations.[20] Nonwhite races have also been reported to be at higher risk of intracranial hemorrhage as a complication of anticoagulation therapy (hazard ratio [HR], with whites as referent, 4.06 for Asians, 2.06 for Hispanics, and 2.04 for blacks).[21] Thus the link between ethnicity and risk of AF as well as the therapy for AF remains to be further investigated.

Associated Disease and Risk Factors

AF is commonly associated with underlying cardiovascular or endocrine pathology (Figure 42-2). The primary pathologies underlying or promoting the occurrence of AF vary more than for any other cardiac arrhythmia, ranging from autonomic imbalance through organic heart disease to metabolic disorders (Table 42-1). Hypertension, heart failure, and ischemic and valvular heart disease, particularly mitral stenosis, are the most common associations and risk factors for the development and progression of AF. Valvular heart disease of rheumatic etiology, one of the main causes of AF, with an odds of 2 to 3 and greater in early studies, no longer holds its leading role but is still important in the developing countries or in the very old.[9-11]

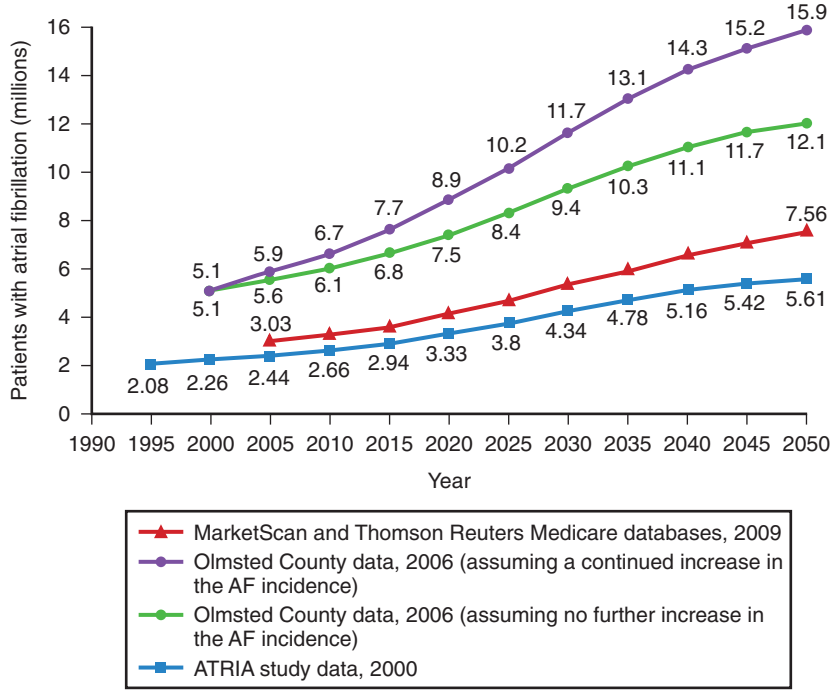


FIGURE 42-1 Estimates of the number of individuals with atrial fibrillation in the United States by 2050. *(Data from Go AS, Hylek EM, Phillips KA, et al: Prevalence of diagnosed atrial fibrillation in adults: National implications for rhythm management and stroke prevention. The Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study,* JAMA *285:2370–2375, 2001; Miyasaka Y, Barnes ME, Gersh BJ, 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 *114:119–125, 2006; and Naccarelli GV, Varker H, Lin J, Schulman KL: Increasing prevalence of atrial fibrillation and flutter in the United States,* Am J Cardiol *104:1534–1539, 2009.)*

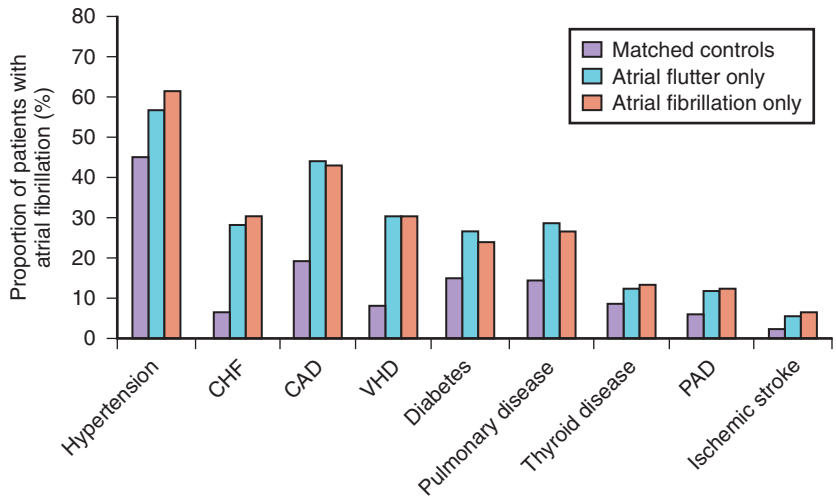


FIGURE 42-2 Prevalence of common comorbidities in patients with atrial fibrillation (n = 222,605), atrial flutter (n = 5376), and age- and gender-matched control subjects without the arrhythmia (n = 242,534). The difference between patients with atrial fibrillation or flutter and matched controls was statistically significant ($P < .001$) for all comorbidities. *CHF*, Congestive heart failure; *CAD*, Coronary artery disease; *VHD*, ventricular heart disease; *PAD*, pulmonary artery disease. *(From Naccarelli GV, Varker H, Lin J, Schulman KL: Increasing prevalence of atrial fibrillation and flutter in the United States,* Am J Cardiol *104:1534–1539, 2009.)*

Heart Failure

An increasing number of surviving patients with left ventricular impairment has led to CHF emerging as one of the leading risk factors for AF associated with a threefold to almost sixfold increase in the risk of AF.[10,12,13] The prevalence of AF associated with CHF varies from 4% to 50%, depending on New York Heart Association (NYHA) class (Figure 42-3).[22] The occurrence of CHF in middle age confers an 8% risk of developing AF over a 10-year period if the patient's age at time of CHF diagnosis was 55 to 64 years, which rises to more than 30% if CHF was diagnosed at age 45 to 54 years.[13]

CHF may precipitate AF by increasing volume and pressure load, which leads to atrial dilation and stretch and altered atrial electrophysiology, including shortening of the atrial effective refractory period, a major determinant of the arrhythmia. Hypertrophy of atrial myocytes and patchy fibrosis result in numerous areas of conduction delay or block favoring micro–re-entry. Calcium overloading and activation of stretch-mediated ion channels increase the likelihood of afterdepolarizations and triggered activity in the atria.

Diastolic left ventricular dysfunction with subsequent increases in filling pressures, which is common in older adults, mediates atrial remodeling and is associated with a 5.26-fold increased risk of AF.[23] The incidence of AF in patients with CHF and preserved left ventricular systolic function is 20% to 30%.[24]

Table 42-1 Risk Factors and Associations of Atrial Fibrillation

CARDIAC	NONCARDIAC	INTERVENTIONS
STRUCTURAL HEART DISEASE	**PATHOLOGIC**	**CARDIAC**
Valvular heart disease, particularly mitral	Diabetes mellitus	Coronary artery bypass grafting
Hypertension or increased pulse pressure	Thyrotoxicosis or subclinical hyperthyroidism	Valvular repair or replacement
Congestive heart failure and diastolic dysfunction	Chronic obstructive pulmonary disease	Surgical correction for congenital heart disease
Myocardial infarction	Lung cancer	**NONCARDIAC**
Ischemic heart disease	Chronic renal disease	Thoracic surgery, particularly pulmonary
Hypertrophic cardiomyopathy	Obesity (BMI)	Surgical procedures requiring general anesthesia
Dilated cardiomyopathy	Metabolic syndrome	**SUBSTANCE USE AND ABUSE**
Atrial septal defect	Sleep apnea	Alcohol excess
Myocarditis or pericarditis	Pheochromocytoma	Caffeine (trigger)
ARRHYTHMIAS	Electrolyte disturbances	Smoking
Sick sinus syndrome	**PHYSIOLOGICAL**	Thyroxine
Atrial tachycardia and atrial flutter	Male gender	Cytotoxic agents
WPW syndrome (accessory pathway)	Aging	Recreational drugs (cannabis, MDMA)
Long P-R interval	Tall stature	Anabolic steroids
GENETIC	Endurance training	
Familial lone AF	**BIOMARKERS**	
Short QT syndrome	Atrial natriuretic peptide, brain natriuretic peptide	
Brugada syndrome	Cross-reactive protein, tumor necrosis factor-α, interleukin-6	
Long QT syndrome (rare)		

AF, *Atrial fibrillation;* BMI, *body mass index;* MDMA, *3,4-methylenedioxymethamphetamine ("ecstasy");* WPW, *Wolff-Parkinson-White.*

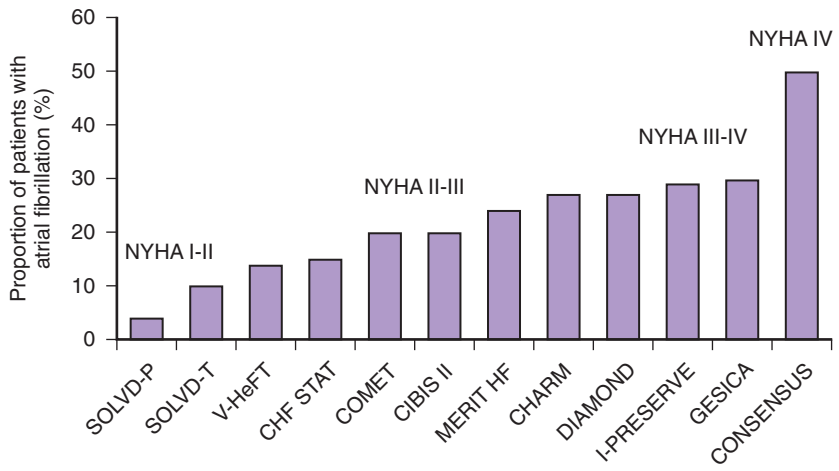


FIGURE 42-3 Prevalence of atrial fibrillation in selected heart failure studies. *NYHA*, New York Heart Association. *Study acronyms:* Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity; Congestive Heart Failure: Survival Trial of Antiarrhythmic Therapy; Cardiac Insufficiency Bisoprolol Study; Carvedilol or Metoprolol European Trial; Cooperative North Scandinavian Enalapril Survival Study; Danish Investigations of Arrhythmia and Mortality on Dofetilide; Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina; Metoprolol CR/XL Randomised Intervention Trial in Heart Failure; *I-PRESERVE*, Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction; *SOLVD-P*, Studies of Left Ventricular Dysfunction–Prevention; *SOLVD-T*, Studies of Left Ventricular Dysfunction–Treatment; Vasodilator-Heart Failure Trial.

Hypertension

Hypertension is the most prevalent condition associated with AF, with a rate of approximately 70% (see Figure 42-2). It is a firmly established risk factor for the development of AF, as shown by many epidemiologic surveys, and increases the risk of AF by a factor of 1.5 to 2.[10-13] The risk has been shown to rise proportionally to the level of blood pressure, although iatrogenic hypotension has been linked to AF, suggesting a J-shaped relationship between blood pressure and AF.[12,25,26]

Myocardial Infarction

AF is a common complication of ACS, occurring de novo in 6% to 15% of patients with myocardial infarction (MI); the incidence is higher (10% to 20%) if patients with a history of atrial tachyarrhythmias are included.[27] Patients with ST-segment elevation MI (STEMI) are more likely to develop AF compared with patients with other types of ACS (8% vs. 6.4%), and the presence of early left ventricular systolic dysfunction and CHF has been consistently shown to increase the likelihood of AF by a factor of 1.58 to 3.28.[27,28]

Previous MI was associated with an increased risk of subsequent AF by a factor of 1.4 to 3.62, but this association is less well established for CAD without MI because these two entities have not been adequately distinguished in epidemiologic studies.[9,10,12] It is reasonable to consider CAD, particularly with evidence of reversible ischemia, a risk factor because it may promote formation of the substrate for AF (e.g., due to atrial ischemia).

Diabetes

Diabetes mellitus has been identified as a risk factor for AF. In the Framingham Heart Study, diabetes mellitus was associated with a 1.4-fold increased risk of AF in men and 1.6-fold increase in women.[10] Its relevance as a risk factor has been confirmed in recent population-based surveys and meta-analyses of randomized controlled studies. A report from the Veterans Health Administration Hospitals database with 845,748 participants has shown that type 2 diabetes increases the risk of AF by a factor of 2.13.[29] A systematic review of 11 studies involving 108,703 cases of AF in more than 1.6 million individuals has revealed that patients with diabetes have a 40% greater risk of AF compared with their nondiabetic counterparts.[30]

The cause-and-effect association between diabetes and AF has not been fully elucidated as, for example, no substantial evidence that type 1 diabetes increases risk of AF exists. Patients with type 2 diabetes mellitus often have other comorbidities and risk factors that may predispose to AF, such as older age, hypertension, CHF, CAD, obesity, and sleep apnea, and the effect of confounding is significant. Although hyperglycemia may directly affect the electrophysiological properties of the atria, causing intra-atrial conduction delay and promoting structural remodeling by activation of the AGE-RAGE (advanced glycation end product–receptor for AGE) system and upregulation of circulating tissue growth factors, insulin resistance associated with type 2 diabetes may also be an important contributor.[31,32]

Cardiomyopathies

AF occurs in association with *hypertrophic cardiomyopathy* in 18% to 28% of patients, with an annual incidence of 2%.[33,34] The prevalence of AF is higher in patients older than 50 years with evidence of left ventricular systolic dysfunction, and its occurrence is associated with limiting symptoms and increased morbidity from CHF (a threefold increase) and stroke (an 8- to10-fold increase) and an almost quadrupled mortality rate. A genetic predisposition to AF is seen in some forms of hypertrophic cardiomyopathy: an *Arg663His* mutation in the β-cardiac myosin heavy chain gene has been identified in patients with a specific phenotype of familial hypertrophic cardiomyopathy presenting with moderate septal left ventricular hypertrophy, predominantly localized in the proximal segment of the interventricular septum, and a 47% prevalence of AF.[35]

Dilated cardiomyopathy (DCM) can promote AF via the same mechanisms as CHF of ischemic etiology; that is, atrial overload, stretch, and fibrosis. Some types of mutations in the *lamin A/C* gene linked to DCM have also been shown to be associated with increased risk of progressive conduction system disease, atrial myopathy, and AF.[36]

Pre-excitation Syndrome

AF is found in 30% of patients with *Wolff-Parkinson-White (WPW) syndrome* and is associated with increased risk of sudden cardiac death (SCD).[37] Unlike the atrioventricular (AV) node, accessory pathways usually exhibit rapid, nondecremental conduction, and if the effective refractory period of an accessory pathway is short (<250 ms), this may result in a rapid ventricular response during AF, with subsequent degeneration to ventricular fibrillation (VF). In some patients with an accessory pathway or a dual AV node, AV re-entrant tachycardia (AVRT) and AV node re-entrant tachycardia (AVNRT) can trigger AF.

Thyrotoxicosis

Thyrotoxicosis has a classic, but relatively minor, association with AF, whereas latent hyperthyroidism, which has been shown to be associated with an almost threefold increase in the age-adjusted incidence of AF in the Framingham Heart Study, is likely to have a greater impact in the general population.[38] In the prospective population-based Rotterdam Study in older individuals, free thyroxine levels within the normal range showed a graded association with risk of AF (HR for highest vs. lowest quartile, 1.62).[39] Convincing evidence that hypothyroidism may increase risk of AF does not exist.[6]

Smoking

Smoking as a risk factor has been debated, but recent analyses from the Atherosclerosis Risk in Communities (ARIC) and the Rotterdam studies have provided evidence linking smoking to the risk of AF in the general population, with a hazard ratio of 1.51 to 2.05 in current smokers and 1.32 to 1.49 in former smokers.[40,41] In the highest tertile of accumulated smoking amount (>675 cigarette-years), the incidence of AF was 2.1 times greater than in those who never smoked.

Alcohol

High alcohol intake has been consistently associated with risk of AF, but the effects of light or moderate consumption are less clear, and some have suggested a neutral or even protective effect. A recent systematic review has reported a monotonic dose-response causal relationship between alcohol and onset of AF.[42] Compared

with nondrinkers, individuals consuming 24, 60, and 120 g of alcohol daily had relative risk of 1.08, 1.44, and 2.09, respectively (men), and 1.07, 1.42, and 2.02, respectively (women). Recent meta-analysis of 14 studies has shown that for each 10-mg increase per day in alcohol intake, the risk of AF increased by 1.08 (95% CI, 1.05 to 1.10; $P < .001$).[43]

Caffeine

In addition to a series of case reports, recent analyses from the Framingham Heart Study, the Danish Diet, Cancer, and Health Study, and the Women's Health Study found no association between caffeine intake and the incidence of AF.[44-46] In a canine model with enhanced AF inducibility caused by the stimulation of the ganglionated plexi, the presence of caffeine reduced the propensity for AF.[47] It is possible that excessive caffeine consumption may trigger AF in individuals with a predominantly adrenergically mediated mechanism of the arrhythmia, but this association could not be detected in the epidemiologic studies.

Postoperative Atrial Fibrillation

AF may occur in about 30% of patients after isolated coronary artery bypass grafting (CABG), 40% of patients after valve surgery, and 50% of patients after combined coronary artery and valvular surgery.[48] Most cases of AF occur during the first 3 to 4 days, and more than 90% have a paroxysmal form. Postoperative AF is associated with increased morbidity and mortality rates, largely because of stroke and circulatory failure and longer hospital stay. Atrial flutter (AFL) and atrial tachycardias (ATs), including multifocal AT, are also common.

Risk factors include conventional clinical variables such as age, hypertension, left ventricular dysfunction, chronic obstructive pulmonary disease (COPD), renal impairment, and specific surgical aspects such as inadequate cardioprotection and hypothermia, right coronary artery grafting, and a longer bypass time.[49] The incidence of postoperative atrial tachyarrhythmias is lower with minimally invasive techniques.

Other Risk Factors

Pneumonia is a one of the reversible causes of AF, whereas COPD, which is observed in 10% to 15% of patients with AF, increases the propensity to AF, such as by inflammatory mechanisms; therefore it has been identified as a risk factor for AF, although its exact impact is unknown.[50] The presence of COPD can contribute to progression of AF to a more sustained form.[51]

Chronic renal dysfunction has recently been linked to increased risk of AF. In the ARIC study, reduced glomerular filtration rate (GFR), particularly in association with macroalbuminuria, increased risk of developing AF over 1 decade by 13-fold.[52] In a population-based cohort of African-American and white American adults 45 years or older enrolled in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, individuals with chronic renal failure stage 1 to 2, 3, and 4 to 5 had the age-, race-, and gender-adjusted odds ratios for AF of 2.67, 1.68, and 3.52, respectively.[53]

Congenital heart disease (particularly, atrial septal defect [ASD]) and pre-excitation syndrome caused by accessory pathways are also associated with AF. AT, "incisional" AFL, and AF may occur after surgical repair of congenital heart disease.

Emerging Risk Factors

New risk factors such as obesity (relative risk [RR], 1.2 to 2.3), metabolic syndrome, a prolonged P-R interval on an electrocardiogram (ECG) (RR, 1.2 to 2.7), P-wave duration (1.15 per standard deviation increase), sleep apnea (RR, 2.2 to 3), psychological stress and negative emotions, endurance athletic training (RR, 5.3), visceral adipose tissue (pericardial fat) detected by computer tomography (CT) (RR, 1.11 to 1.18), and tall stature (RR, 1.7 for height >180 cm) have all been reported in association with AF.[54] A series of biomarkers of inflammation and oxidative stress (cross-reactive protein, interleukin [IL]-6, intercellular adhesion molecule (ICAM)-1, tumor necrosis factor [TNF]-α), hemodynamic stress (atrial natriuretic and brain natriuretic peptides [ANP and BNP]), and cardiac damage (troponin) have emerged as predictors of incident AF.[54]

Genetic Factors

Among many risk factors for AF, genetic predisposition to AF or specific genetically predetermined forms of the arrhythmia have also been identified. Among the participants in the Framingham Heart Study, a parental history of AF increased the risk of AF in the offspring by a factor of 1.4 after adjustment for AF risk factors and AF-related genetic variants (Figure 42-4).[55] Genetic variation may play even a greater role in the pathogenesis of lone AF (see

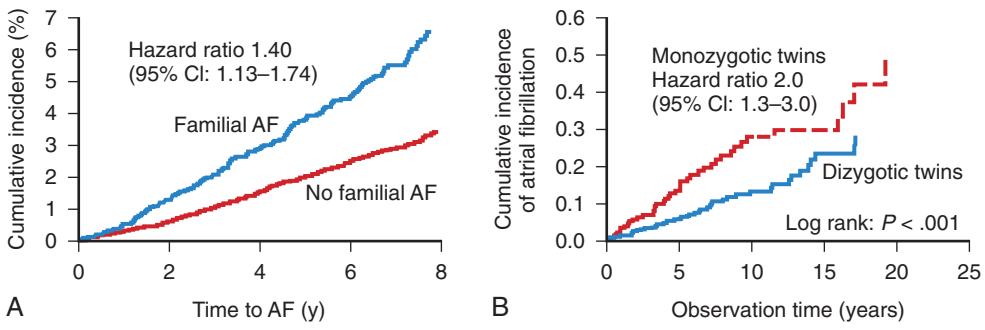


FIGURE 42-4 A, Incidence of atrial fibrillatin (*AF*) by the presence or absence of antecedent AF in a first-degree relative in the Framingham Heart Study. **B,** Incidence of AF ain monozygotic and dizygotic twins in the Danish Twin Study. *CI*, Confidence interval. *(From Lubitz SA, Yin X, Fontes JD, et al: Association between familial atrial fibrillation and risk of new-onset atrial fibrillation,* JAMA *304:2263–2269; and Christophersen IE, Ravn LS, Budtz-Joergensen E, et al: Familial aggregation of atrial fibrillation: a study in Danish twins,* Circ Arrhythm Electrophysiol *2:378–383, 2009.)*

below). AF in association with known genetic conditions such as Brugada syndrome and short QT interval syndrome is highly prevalent. The genetic substrate for AF ranges from a large kindred with monogenic forms of AF with rare genetic mutations and high penetrance to common genetic polymorphisms in a variety of different genes in general populations.

Monogenic mutations associated with AF have been described in the number of genes encoding several potassium channels (e.g., *KCNQ1* and *KCNE2*, which encode α- and β-subunits, respectively, of the I_{Ks} channel; *KCNA5* and *KCNJ2,* encoding Kv1.5 and Kir 2.1 channels underlying the I_{Kur} and I_{K1} currents, respectively), and α- and β-subunits of the sodium channels (*SCN5A* and *SCN1/2B*) as well as a number of non–ion channel mutations in the nucleoporin gene (*NUP155*), connexin-40 gene (*GJA5*), and ANP gene.[56] However, monogenic forms of AF are rare and, at the population level, AF heritability is likely to be determined by aggregate effects of multiple common genetic variants interacting with environmental factors.

Population-based genome-wide association studies (GWASs) have identified a variety of single-nucleotide polymorphisms near the *PITX2* (paired-like homeodomain 2) gene on chromosome 4q25 that almost double the susceptibility to AF in general populations of European and Asian descents.[57,58] Other common variants include *ZFHX3* (zinc finger homeobox 3) on chromosome 16q22, and *KCNN3* (a calcium-activated, small conductance potassium current, which is also involved in atrial repolarization) on chromosome 1p21.

However, the mechanism by which these genetic variations lead to AF remains unknown. The *PITX2* gene encodes a transcription factor expressed in the heart and lungs and is critical for antenatal determination of right-left asymmetry, with one of its isoforms, *PITX2C*, being involved in the specification of the left atrium and pulmonary vein myocardium and suppression of a default program for sinoatrial node formation in the left atrium. Mutations in *PITX2C* may be associated with greater chances of ectopic foci occurring in the pulmonary veins triggering AF.

Lone Atrial Fibrillation

Idiopathic or lone AF constitutes approximately half the cases of paroxysmal AF and 20% of persistent AF, particularly in relatively young patients. However, when studied in detail, some may have evidence of inflammation and atrial myocarditis, mild diastolic ventricular dysfunction, subclinical thyroid disease, autoimmune disorders, or sinus node dysfunction. In other words, lone AF may be an indication that a structural defect has not yet manifested to a level that can be detected.

Lone AF poses a higher risk of heritability. Relatives of patients with lone AF are at a substantially increased risk of developing AF compared with the general population, suggesting a Mendelian genetic contribution to the etiology of this common trait. Analysis of the Danish Twin Study has revealed an increased risk of AF among monozygotic twins compared with dizygotic twins (22% vs. 12%), with the heritability of AF estimated at 62% (compared with 80% heritability of height and 35% heritability of the QT interval).[58,59]

GWASs have linked an SNP in *KCNN3* to a greater risk of lone AF with an odds ratio of 1.52.[60] The angiotensin-converting enzyme (ACE) insertion/deletion (I/D) polymorphism was associated with electrical remodeling in patients with lone AF.[61]

Vagally Mediated and Adrenergically Mediated Atrial Fibrillation

The balance between sympathetic and vagal influences plays an important role both in the initiation and prediction of AF. Two types of autonomic-induced AF exist. Adrenergically mediated episodes of AF are typically triggered by exercise and emotional stress (Figure 42-5), commonly associated with polyuria, and occur mainly during the day. Vagally mediated AF is characterized by male predominance, younger age, minimal tendency to progress to permanent AF, and onset at rest or at night. Episodes of vagal AF are typically preceded by progressive bradycardia. β-Blockers are treatment of choice in AF with a predominant adrenergic component but may worsen symptoms in patients with vagally mediated AF.

However, patients who can be classified in terms of sympathetic or adrenergic forms of AF typically represent the extreme of either sympathetic or parasympathetic influence, and the overall prevalence of typical vagally or adrenergically mediated AF is relatively low. In 1517 patients with paroxysmal AF included in the Euro Heart Survey, vagally mediated AF was found in 6% and adrenergically mediated AF was found in 15%.[62]

Classification

AF is classically divided into three types on the basis of its presentation, duration, and response to therapy (if applicable): paroxysmal, persistent, and permanent. *Paroxysmal* AF is a self-terminating arrhythmia; although the duration of paroxysms may vary greatly (with the upper limit arbitrarily set at 7 days), the majority will terminate within 48 hours. The 48-hour time point is clinically important because after this, the likelihood of spontaneous conversion is low, and anticoagulation must be considered. If AF lasts longer than 7 days or requires pharmacologic or electrical cardioversion, it is referred to as *persistent* AF. If AF does not convert spontaneously and is refractory to cardioversion or other rhythm control interventions and if the physician or the patient chooses not to pursue the rhythm control strategy and allow the AF to remain, the term *permanent* ("accepted") AF is applied.

The 2010 European Society of Cardiology (ESC) guidelines introduced a *longstanding persistent* category for AF, which typically lasts for 1 year or more before a rhythm control intervention is attempted (Figure 42-6).[63] This allows for a permanent form to be redesignated as longstanding persistent AF, that is, amenable to restoration and maintenance of sinus rhythm, mainly because of the increased success of ablation therapies.

First-onset AF is the first clinical presentation of the arrhythmia; first-onset AF can be paroxysmal or persistent or be classified as permanent if accepted by the patient and physician. First-detected AF may be a single nonrecurrent event secondary to a reversible or transient cause, or it may evolve into recurrent paroxysmal or persistent AF. The onset of AF may be asymptomatic, and the first detected episode should not be regarded as necessarily the true onset. In the mixed forms, AF episodes may or may not terminate spontaneously, and the disease often progresses from paroxysmal to persistent AF and eventually to permanent (or accepted) AF.

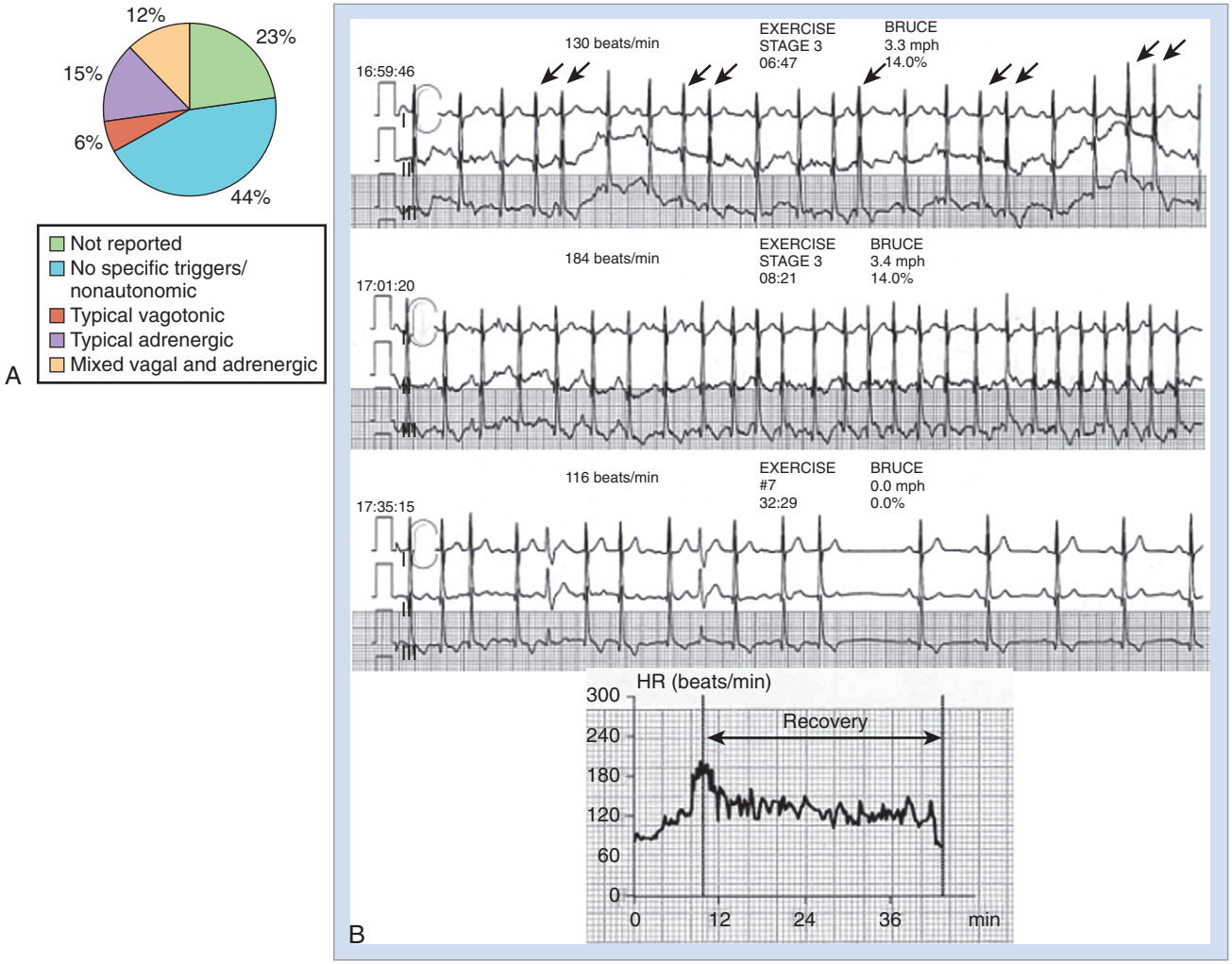


FIGURE 42-5 A, Prevalence of different types of autonomic trigger patterns in 1517 patients with paroxysmal atrial fibrillation in the European Survey on Atrial Fibrillation. **B,** An electrocardiogram and a heart rate histogram demonstrating onset of exercise-induced atrial fibrillation preceded by frequent atrial premature beats (*arrows*) and runs of atrial tachycardia in a 45-year-old man without any structural heart disease. The exercise test was terminated once atrial fibrillation occurred. Note spontaneous termination and recurrence of brief episodes of atrial fibrillation in the recovery phase. Stable sinus rhythm was restored after 32 minutes. *HR*, Heart rate. *(From De Vos CB, Nieuwlaat R, Crijns HJ, et al: Autonomic trigger patterns and anti-arrhythmic treatment of paroxysmal atrial fibrillation: Data from the Euro Heart Survey,* Eur Heart J *29:632–639, 2008.)*

Progression of Atrial Fibrillation

AF is a progressive disease because of the continuous remodeling of the atria caused by the AF itself, changes associated with aging, progression of underlying heart disease, and genetic and environmental factors. Progression from first-diagnosed or recurrent paroxysmal AF to persistent or permanent AF occurs, on average, at the rate of 5% to 15% per year, depending on a number of factors such as age at presentation and the presence of underlying heart disease (Table 42-2).[64,65]

Factors, independently associated with the progression of AF in the European Survey on AF, formed a HATCH score to predict progression of AF (***h***ypertension, ***a***ge >75 years, ***t***ransient ischemic attack [TIA] or stroke, ***C***OPD, ***h***istory of stroke or heart failure). CHF and stroke were assigned 2 points each and the remaining factors 1 point each. Almost half the patients with a high HATCH score of 6 to 7 had AF progression after 1 year compared with only 6% of those with a HATCH score of 1. Rates of progression are higher in patients who presented with first-onset persistent AF, with 35% to 40% developing permanent arrhythmia by the end of the first year since diagnosis.[66] Pursuing the aggressive rhythm control strategy with antiarrhythmic drugs, pulmonary vein ablation or both and, when necessary, cardioversion can alter the natural course and prevent or delay progression of AF.

Progression of AF is linked to structural atrial remodeling, accumulation of electrically silent fibrotic tissue, and transformation of AF from a primary electrical disorder requiring specific triggers such as atrial premature beats (APBs), pulmonary vein tachycardia, and neurohumoral stimuli (trigger-dependent AF) into a substrate-dependent variety (Figure 42-7). Patients with lone AF have been reported to have the lowest progression rates of approximately 1% to 2% per year.[67] Atrial remodeling occurs in both lone AF and AF associated with cardiovascular disease, but it is thought to be more pronounced in the latter. However, recent

studies employing delayed enhancement magnetic resonance imaging (MRI) techniques have demonstrated the presence of extensive fibrosis primarily accumulated in the left atrial posterior wall in patients with lone AF compared with healthy individuals without AF.[68] Patients with lone AF were found to have a similar amount of fibrosis of the left atrium as those with associated cardiovascular and metabolic disease.

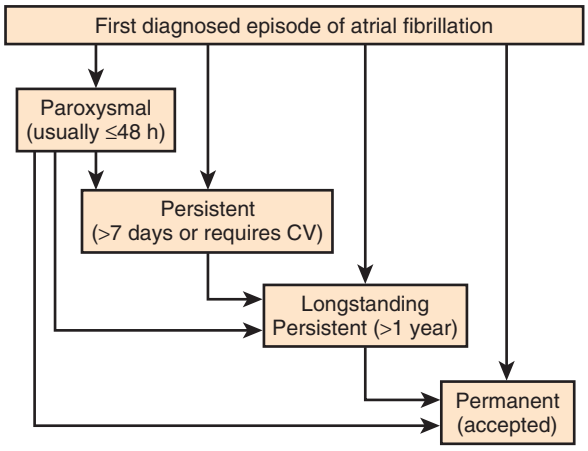


FIGURE 42-6 Classification of atrial fibrillation (AF) based on the time course of the arrhythmia, and possible transition between three forms of the arrhythmia, proposed by the European Society of Cardiology in 2010. AF tends to progress from paroxysmal (self-terminating, usually <48 hours) to persistent [non–self-terminating or requiring cardioversion), longstanding persistent (lasting longer than 1 year), and eventually to permanent (accepted) AF. First-onset AF may be the first of recurrent attacks or already be deemed permanent. *CV*, Cardioversion.

Consequences of Atrial Fibrillation

The clinical significance of AF lies predominantly in high risk of ischemic stroke and heart failure and increased subsequent death. The occurrence of AF is commonly associated with worsening of pre-existing cardiovascular disease. New-onset AF in CHF has been linked to clinical deterioration and poor prognosis.[22] Patients with concomitant AF and hypertension had a two- to threefold greater risk of developing stroke and CHF or dying.[69] AF is associated with increased in-hospital and long-term mortality rates in patients with MI.[27,70] AF leads to more hospital admissions than any other arrhythmia and presently costs approximately 1% of the health care budget in the Western countries.

Stroke

The presence of AF has been estimated to increase the risk of stroke by about fivefold.[71] Whereas the effects of hypertension, CAD, and CHF on the risk of stroke become progressively weaker with advancing age, the impact of AF remains significant. In the Framingham Study, the annual risk of stroke attributable to AF among patients aged 50 to 59 years is 1.5% and increases to 23.5% in those older than 80 years.[71] Approximately 15% of neurologically asymptomatic patients enrolled in the Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation (SPINAF) study had evidence of one or more previously undiagnosed cerebral infarcts on CT images of the brain.[72] The risk is considerably higher in patients with previous stroke or TIA.

Strokes associated with AF are usually more severe and confer a high risk of subsequent morbidity, mortality, and poor functional outcome independent of the underlying heart disease. Risk of recurrent stroke is high, particularly within the first year, because of hemostatic abnormalities following the index event. The report from the Framingham Study has revealed that stroke associated with AF was nearly twice as likely to be fatal, and

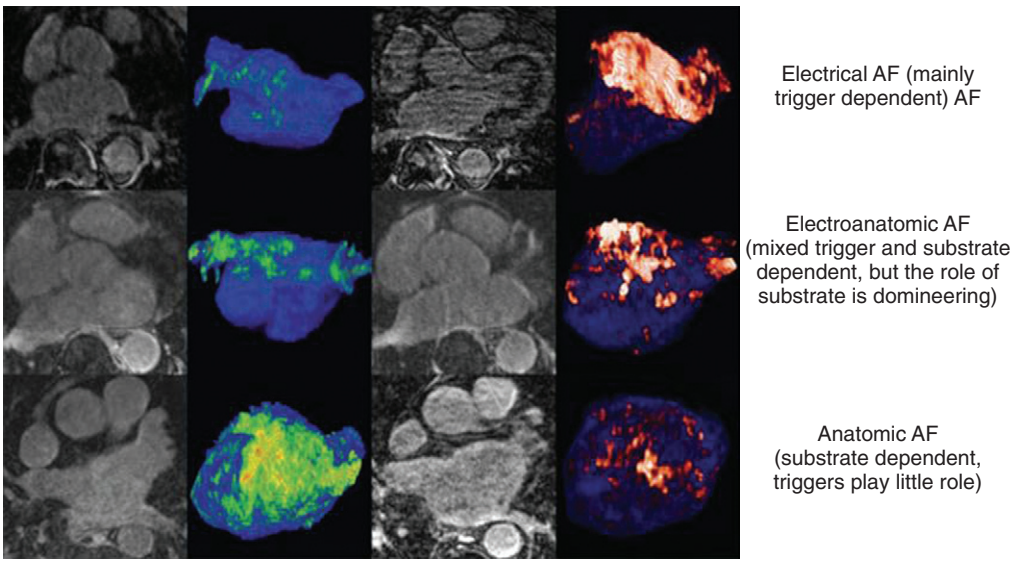


FIGURE 42-7 Stages of progression of atrial fibrillation assessed by delayed-enhancement magnetic resonance imaging. *(From Mahnkopf C, Badger TJ, Burgon NS, et al: Evaluation of the left atrial substrate in patients with lone atrial fibrillation using delayed-enhanced MRI: Implications for disease progression and response to catheter ablation,* Heart Rhythm *7:1475–1481, 2010.)*

Table 42-2 Rates of Progression of Paroxysmal Atrial Fibrillation to Persistent or Permanent Atrial Fibrillation

STUDY	NO. PATIENTS	AGE (YEARS)	TYPE OF AF	FOLLOW-UP (YEARS)	PROGRESSION OF AF	PREDICTORS OF PROGRESSION (RISK)
European Heart Survey (2010)	1219	64 ± 13	Paroxysmal; lone AF: 17%	1	15%; permanent: 8%; in subgroup with lone AF: 7% (persistent or permanent)	Age >75 years (1.57), heart failure (2.22), hypertension (1.52), stroke/TIA (2.02), COPD (1.51)
RECORD-AF (2011)	2137	65.1 ± 12	Recent-onset paroxysmal AF	1	15%; permanent, 9%	Heart failure (2.2), hypertension (1.5), rate control (3.2) In subgroup with rhythm control as the initial strategy: heart failure (1.9), hypertension (1.8), heart rate (1.01)
Sakamoto (Tokyo) (1995)	137	No progression: 62.4 ± 11 With progression: 70.1 ± 8.2	First-detected paroxysmal AF	1	Sustained AF ≥6 months: 22%	Age ≥65 years, heart failure, CTR ≥50%, diabetes, LA ≥38 mm, LVEF ≤0.76, f waves in V_1 ≥2 mm
Abe (Osaka) (1997)	122	61 ± 12	Paroxysmal; lone AF: 21%	2.16	Sustained AF ≥6 months: 11.5%	Left atrial size, abnormal P-wave signal-averaged ECG‡
Fauchier (Tours) (2010)	2167	71 ± 14	Paroxysmal	2.6	14.1%	Age >75 years, heart failure, hypertension, COPD, number of electrical cardioversions, dilated cardiomyopathy, prosthetic valve
UK GPRD (2005)	418	Men: 67 ± 11, women: 7 3 ± 10	First-detected paroxysmal AF; no comorbidity: 32%	2.7	11% at 1 year, 17% at 2.7 years	Valvular heart disease (2.7), moderate to high alcohol intake (3.0)
Al-Khatib (Durham) (2010)	231	60 ± 13	Paroxysmal; lone AF: 41.6%	4	8% at 1 year, 18% at 4 years	Age (1.82 per decade), AF at presentation (3.56)
Pappone (Milan) (2008)	106	57.5 ± 11.5	First-detected paroxysmal; lone AF: 51%	5	Recurrent paroxysmal: 52.8% Persistent: 53.3%* Permanent: 35.5%* In subgroup with lone AF: 3.7% persistent, 1.8% permanent	Age (1.19), heart failure (11.2), diabetes (17.3), drug therapy vs. ablation
Rostagno (Florence) (1995)	106	63 ± 11	First-detected paroxysmal, lone AF	6	Recurrent paroxysmal: 55.6%, sustained: 4.7%	—
Takahashi (Tokyo) (1980)	94	60	First-detected paroxysmal AF; lone AF: 24.5%	>6	Sustained AF ≥6 months: 20.2%-25.3%	Rheumatic valvular disease; frequency of paroxysms
CARAF (2005)	757	64 (median)	First-detected paroxysmal AF	8	8.6% at 1 year 24.7% at 5 years Any recurrent AF: 63.2% at 5 years	Age (1.4 per decade), cardiomyopathy (2.41), aortic stenosis (3.04), mitral regurgitation (1.69), LA enlargement (3.05-4.17)
Danish Study (1986)	426	66 (median)	Paroxysmal AF	9 (median)	33.1%	Underlying heart disease, thromboembolism
Parkinson (UK) (1930)	200	50	Paroxysmal; lone AF: 9%	~10	28%; in subgroup with no or minor heart disease: 10%	Rheumatic valvular disease; frequency of paroxysms
Kato (Tokyo) (2004)	171	58.3 ± 11.8	First-detected, paroxysmal AF	14	57% at 10 years, 77% at 15 years	Age (1.27 per decade), myocardial infarction (2.33), valvular heart disease (2.29), LA enlargement (1.39)
Olmsted County (MN) (1987)	88	44	Lone AF	14.8	Recurrent paroxysmal AF: 58%; sustained AF: 12%	—
Olmsted County (MN) (2007)	71	44.2 ± 11.7	Lone AF: 48%; Paroxysmal AF: 52% persistent	25.2	31% (30-year probability: 29%)†	Age (1.7 per decade), QRS abnormalities (3.2)§

Odds ratio or hazard ratios given in parentheses.
**In patients taking antiarrhythmic drugs (n = 45).*
†In the majority of patients within 15 years.
‡Filtered P-wave duration ≥145 ms and the root-mean-square voltage of the last 30 ms of the filtered P wave <3 μV.
§QRS ≥110 ms, QRS notching, small R in the precordial lead.
AF, *Atrial fibrillation;* CARAF, *Canadian Registry of Atrial Fibrillation;* COPD, *chronic obstructive pulmonary disease;* CTR, *cardiothoracic ratio;* ECG, *electrocardiogram;* GPRD, *General Practice Research Database;* LVEF, *left ventricular ejection fraction;* TIA, *transient ischemic attack.*

functional deficits were more likely to be severe among survivors.[73] Nearly three quarters of stroke victims with AF were severely dependent in activities of daily living (ADLs) compared with about one third of their counterparts with sinus rhythm.

Dementia

Dementia as a consequence of AF has been only recently recognized. Evidence from the large ongoing prospective Intermountain Heart Collaborative Study database, AF was independently associated with all dementia types, and the risk was the highest in the younger group (<70 years), with an HR of 2.2 for vascular dementia, 3.34 for senile dementia, and 2.3 for Alzheimer disease after adjustment for age and comorbidities.[74] According to data from the Olmsted County, Minnesota, in patients with a mean age of 71 years, the rate of dementia associated with AF was 2.7% at 1 year and 10.5% at 5 years.[75] The diagnosis of dementia in the presence of AF was associated with a marked increased risk of subsequent mortality by factor of 3.49 in men and 3 in women.

In patients with hypertension and underlying microvascular dysfunction and patients with impaired left ventricular systolic function and CHF, the occurrence of AF may predispose to further impairment of cerebral perfusion and earlier manifestation of dementia. Multiple silent cerebral infarctions, subclinical strokes, and TIAs, as well as microbleeds resulting from the combination of suboptimal blood pressure control and anticoagulation, can be found in a significant proportion of patients with AF and may underlie the early cognitive decline. Other mechanisms operating in AF such as inflammation and endothelial dysfunction are possible contributors.

Tachycardia-Induced Cardiomyopathy

AF may compromise left ventricular systolic function and worsen CHF because of fast, uncontrolled ventricular rates, irregularity of ventricular response, and loss of atrial systolic input. Loss of AV synchrony is associated with impaired diastolic filling, reduced stroke volume, and elevated diastolic atrial pressure, resulting in an approximately 20% reduction in cardiac output.[22] An irregular ventricular response further decreases cardiac output and increases right atrial pressure and pulmonary capillary wedge pressure independent of rate. Increased adrenergic stimulation to maintain adequate cardiac output in the setting of heart failure will facilitate AV conduction and favor the progression of cardiomyopathy. AF has been reported to confer a threefold risk of worsening CHF.[76] In patients with CHF secondary to diastolic dysfunction, the occurrence of AF may be particularly hazardous.

Less commonly, AF with fast, uncontrolled ventricular rates may cause symptomatic left ventricular dysfunction in patients with no or minimal structural heart disease. Such ventricular dysfunction associated with significant heart dilatation and symptoms of heart failure is termed *tachycardia-induced cardiomyopathy*. It is usually applied to persistent forms of the arrhythmia, and it is generally accepted that sustained ventricular rates of above 120 beats/min may pose a risk but may also occur in individuals with frequent paroxysms, in whom rate control is difficult. Tachycardia-induced cardiomyopathy may reverse completely after sinus rhythm is restored or adequate ventricular rate control is achieved either by pharmacologic or nonpharmacologic means (Figures 42-8 and 42-9).

Hospitalizations

According to some surveys, the number of AF-related hospitalizations almost tripled in 2000 compared with the previous 2 decades and continues to grow, probably because of an increasing proportion of the population surviving to very old age with greatly improved health care. Patients with AF can be admitted for treatment of AF (e.g., cardioversion, initiation of antiarrhythmic drug therapy, or ablation) and cardiovascular adverse events (e.g., proarrhythmia, progression of heart failure, stroke, or MI) or noncardiac causes. Analysis from the Atrial Fibrillation Follow up Investigation of Rhythm Management (AFFIRM) trial has linked cardiovascular hospitalization with increased risk of subsequent death.[77] The association between cardiovascular hospitalization

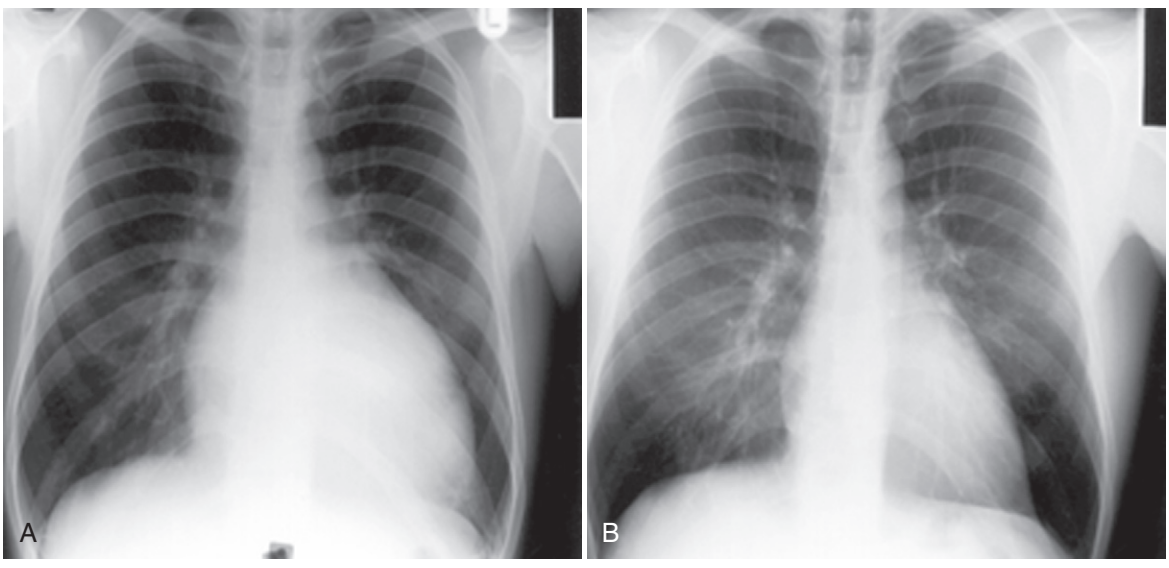
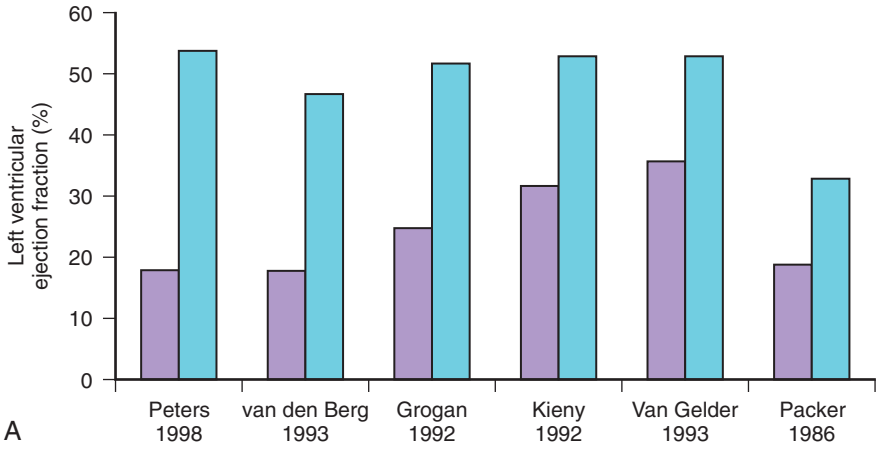
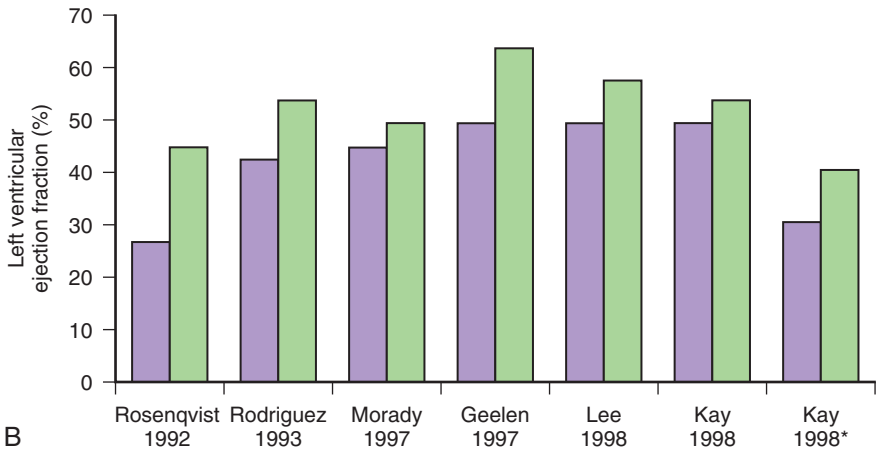


FIGURE 42-8 Reversal of cardiac enlargement on chest radiographs 3 months after restoration of sinus rhythm.





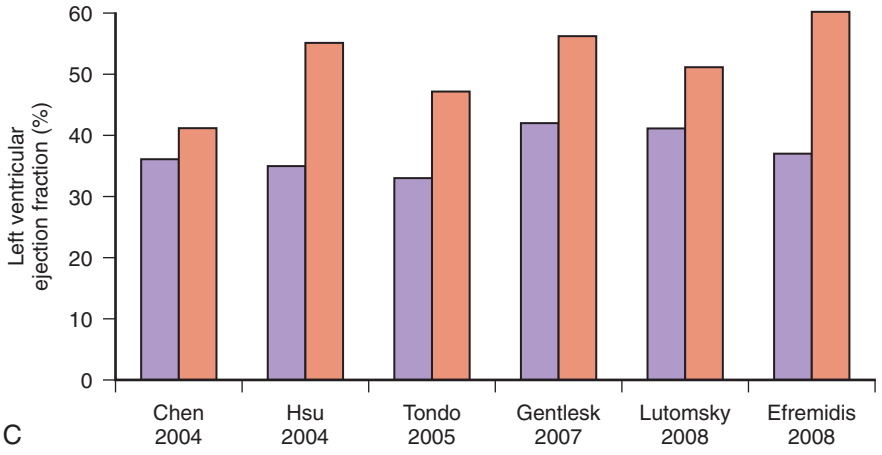


FIGURE 42-9 Improvement of left ventricular function after rate control and pharmacologic or electrical cardioversion (**A**), atrioventricular nodal ablation or modification (**B**), and pulmonary vein isolation/left atrial ablation in the setting of heart failure (**C**). *Asterisks* note patients with significantly decreased left ventricular function at baseline.

and adverse outcome has also been reported in the Stockholm Cohort Study of Atrial Fibrillation, which showed that individuals who spent more than 2% of their follow-up period in the hospital with a cardiovascular diagnosis had a significantly higher mortality rate than those who had spent less time in the hospital (36 vs. 8.2 deaths per 100 patient-years).[78] Time in-hospital greater than 2% increased the risk of subsequent death by a factor of 2.5, and rehospitalization for cardiovascular reason within 3 months increased the risk of death by a factor of 1.4 in the early cohort and 2.43 in the later cohort, for which a better account of therapy was available.

Quality of Life

Patients with AF generally have impaired quality of life compared with healthy control subjects—matched samples from the general population or patients with stable CAD—and is similar on most scales to health impairment seen in patients

with MI or CHF and more significant structural heart disease.[79] The degree of reported reductions in quality of life is determined by the form of AF and the presence of other diseases that may affect the individual perception of health. Thus patients with multiple comorbidities are more likely to report poorer quality of life compared with patients with established AF and those with less significant underlying heart disease. Paroxysmal AF is usually symptomatic and is associated with impaired quality of life. Patients with this variety report better quality of life and had significantly higher scores in physical functioning, vitality, mental health, and emotional health when they perceive themselves to be in sinus rhythm.[80] Women are more likely to report poor quality of life compared with men, despite comparable severity of underlying pathology. Even patients with asymptomatic AF report a significantly poorer perception of general health and decreased global life satisfaction compared with their healthy counterparts, despite similar scores on all other scales.[81]

Both antiarrhythmic drug therapy and ablation-based therapies have been shown to render a significant proportion of AF asymptomatic, which may result in improvement in quality of life. Of interest, when quality of life was compared in patients with AF who were randomly assigned to AV node ablation or AV node modification, ablation was shown to result in a greater improvement in quality of life and reduction of symptoms compared with modification, probably because of better control of the rate and regularity of ventricular response after abolishing fibrillatory conduction to the ventricles.[82] Recently, several AF-specific quality of life questionnaires have been proposed, but all require validation.[83,84]

Silent Atrial Fibrillation

AF is typically associated with a variety of symptoms: palpitations, dyspnea, chest discomfort, fatigue, dizziness, and syncope (Figure 42-10).[85] The paroxysmal forms are more likely to be symptomatic and frequently present with specific symptoms, whereas the permanent forms are usually associated with less-specific symptoms. However, a substantial proportion of patients may not experience any symptoms or these symptoms may be subtle and may not be reported.

The prevalence of sustained silent AF found incidentally during routine physical examinations, preoperative assessments, occupation assessments, or population surveys is believed to be 25% to 30%, but modern implantable rhythm control devices such as pacemakers and implantable cardioverter defibrillators (ICDs) have revealed that up to 50% to 60% may have unsuspected episodes of the arrhythmia, with almost half of these lasting more than 48 hours.[8,86] Patients with unrecognized AF do not receive appropriate preventive therapy and are at greater risk of stroke or, in the case of persistent rapid ventricular rates, tachycardia-induced cardiomyopathy. For example, AF may be found incidentally in about 20% to 25% of admissions for stroke.

Studies that used regular ECG monitoring have demonstrated that up to 90% of recurrences may go unreported by patients but can only be detected by daily transtelephonic ECG transmission (Figure 42-11).[87] The clinical significance of very short paroxysms of AF, which are difficult to detect by conventional methods of rhythm monitoring but can be logged by implantable device diagnostics, has recently been demonstrated in the The Relationship Between Daily Atrial Tachyarrhythmia Burden from Implantable Device Diagnostics and Stroke Risk (TRENDS) study in patients

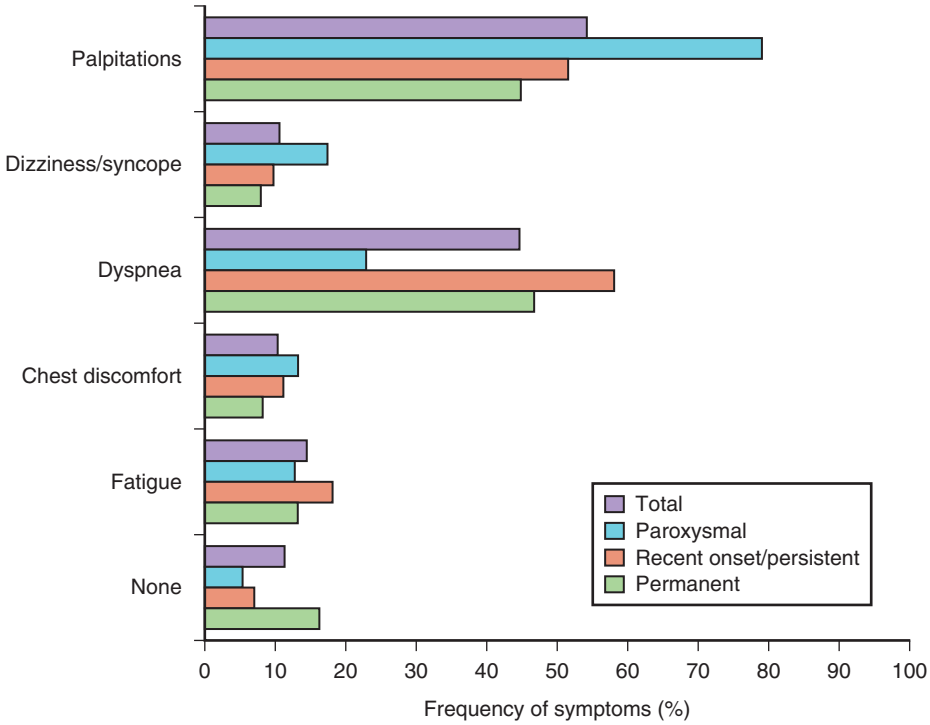


FIGURE 42-10 Distribution of symptoms in different forms of atrial fibrillation. *(Modified from Lévy S, Maarek M, Coumel P, et al, on behalf of the College of French Cardiologists: Characterization of different subsets of atrial fibrillation in general practice in France: The ALFA Study,* Circulation *99:3028–3035, 1999.)*

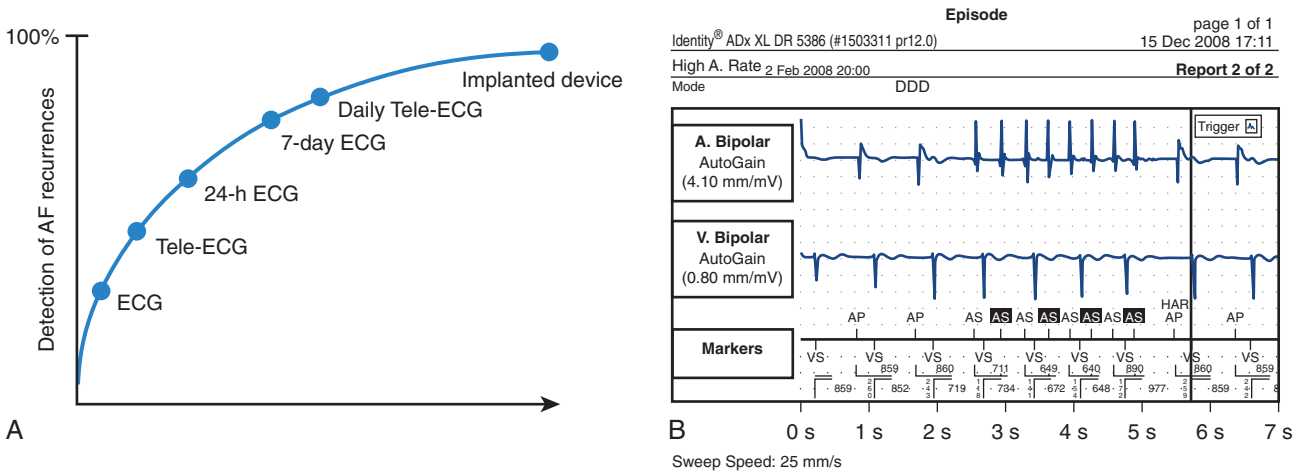


FIGURE 42-11 A, Diagnostic yield of different methods for monitoring of atrial fibrillation. **B,** An example of a fast atrial rate episode logged in pacemaker diagnostics in a patient without a history of atrial tachyarrhythmias. *ECG*, Electrocardiogram. *(From Arya A, Piorkowski C, Sommer P, et al: Clinical implications of various follow up strategies after catheter ablation of atrial fibrillation,* Pacing Clin Electrophysiol *30:458–462, 2007.)*

Table 42-3 Atrial Fibrillation and Death in Epidemiologic Studies

STUDY	NO. PATIENTS	AGE (YEARS)	FOLLOW-UP (YEARS)	MORTALITY RISK
Framingham Study (1998)	5202; 612 (11.9%) with AF	55-94	40	ACM: 1.5 (1.2-1.8) for men, 1.9 (1.5-2.2) for women No heart disease: ACM: 2.4 (1.8-3.3) for men, 2.2 (1.6-3.1) for women
Manitoba Study (1995)	3983 male aircrew recruits, 299 (7.5%) with AF	18-62	154,131 person-years	ACM: 1.31 CVM: 1.41
Marshfield Epidemiologic Study Area (2002)	58,820; 577 with AF	71	4775 person-years	ACM: 2.4 (1.9-3.1) Lone AF, ACM: 2.1 (0.96-4.5)
Paris Prospective Study (1999)	7746 male civil servants with lone AF	43-52	27	ACM: 1.95 (1.13-3.37) CVM: 4.31 (2.14-8.68)
UK cohort (2002)	6035 general practice patients, 1035 with AF	40-89	AF: 1898; control: 9261 person-years	ACM: 2.5 (2.1-3.0)
Olmsted County Study (MN) (2007)	4618	73	5.3	ACM: 2.08 (2.01-2.16) Excluding first 4 months after diagnosis: 1.66 (1.59-1.73)

ACM, All-cause mortality; AF, *atrial fibrillation;* CVM, *cardiovascular mortality.*

treated with a pacemaker for sinus node dysfunction.[88,89] AF burden of 5.5 hours or greater on any of 30 prior days doubled the risk of a thromboembolic event.

Furthermore, an exact definition of "asymptomatic" AF does not exist. A patient may claim to have no symptoms but report feeling much better after cardioversion. Studies have also shown that quality of life is reduced even when a patient is classified as asymptomatic.[81] Level of acceptable symptoms may also vary according to age and comorbidities.

Mortality

Association of AF with death has been demonstrated in epidemiologic studies. Data from the Framingham Study suggest that the risk of death conferred by AF is nearly doubled even in the absence of identifiable structural heart disease.[90] The risk of death associated with AF is significantly higher in women than in men (OR, 1.9 vs. 1.5). Data from other epidemiologic studies are convincing (Table 42-3). AF is an independent predictor of death in patients with a range of cardiovascular pathologies: CHF, hypertension, MI with left ventricular dysfunction, and ACS. AF increases cause-specific mortality: SCD, death from heart failure, and fatal strokes. A mechanistic basis for the link between AF and each of the components of total mortality does exist (Figure 42-12). Although the exact mechanism by which AF can increase the risk of SCD in the general AF population (apart from rare cases of SCD in WPW syndrome) has not been well established, proarrhythmia from antiarrhythmic drugs and ischemia-induced VT and VF, particularly in patients with severe underlying disease, are plausible explanations.

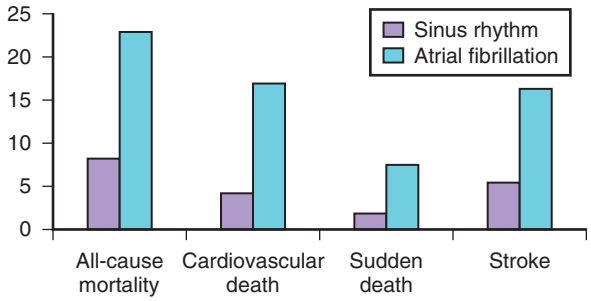


FIGURE 42-12 Cause-specific morbidity and mortality in patients with atrial fibrillation and hypertension with left ventricular hypertrophy in the Losartan Intervention for End Point Reduction in Hypertension study. *(From Wachtell K, Hornestam B, Lehto M, et al: Cardiovascular morbidity and mortality in hypertensive patients with a history of atrial fibrillation: The Losartan Intervention for End Point Reduction in Hypertension (LIFE) study,* J Am Coll Cardiol *45:705–711, 2005.)*

Current data do not offer a definitive answer whether AF truly is an independent risk factor for death or whether it is a marker indicating a sicker patient. However, even lone AF has been reported to entail 4.2-fold increase in all-cause mortality and an almost twofold increase in cardiovascular mortality, including SCD, in the Paris Prospective Study.[91]

Costs

The high lifetime risk for AF and increased longevity underscore the important public health burden imposed by AF across the world. The majority of AF expenditure constitutes hospital charges for frequent and often prolonged admissions for AF and particularly its costly complications such as stroke and heart failure. In addition, the cost of caring for patients with other cardiovascular pathologies is significantly higher in the presence of AF. The cost of caring for patients with AF also continues to be significantly higher during the 2 to 3 years after initial hospitalization. The arrhythmia costs of the health care budget in the United Kingdom and has almost doubled (0.9% to 2.4%) over the past 5 years.[92] Direct cost estimates ranged from $2000 to $14,200 per patient-year in the United States and from €450 to €3000 in Europe.[92] Inpatient care accounts for 50% to 70% of the annual direct costs.

Based on data from the retrospective analysis of three federally funded databases in the United States in 2001, total annual costs for treatment of AF were estimated at $6.65 billion, including $2.93 billion (44%) for hospitalizations for AF, $1.95 billion (29%) for the incremental inpatient cost of AF as a comorbid diagnosis, $1.53 billion (23%) for outpatient treatment of AF, and $235 million (4%) for prescription drugs.[93]

Relationship Between Atrial Fibrillation and Atrial Flutter

Epidemiology

Data on the prevalence and incidence of AFL in the general population are limited. The report from the Marshfield Epidemiologic Study Area (MESA), based on a selected sample of 58,820 residents served by the Marshfield Clinic in Wisconsin, suggests that the incidence of AFL is 0.88 per 1000 person-years, but this figure includes 58% of individuals in whom both AFL and AF have been diagnosed.[94] As a sole arrhythmia, the incidence of AFL is relatively low and clearly stands at less than 1%.

Like that of AF, the incidence of AFL increases markedly with age, from 5 per 100,000 of individuals younger than 50 years to 587 per 100,000 in those older than 80 years. Similar to AF, which is more common in men, AFL is observed 2.5 times more frequently in men than in women (6.06 vs. 2.65 per 100,000 persons aged 70 to 79 years and 9.16 vs. 4.12 per 100,000 persons older than 80 years).

Associated Disease and Prognosis

AFL is commonly associated with organic heart disease (see Figure 42-2). In the MESA population, nearly all cases of AFL were linked to comorbid conditions such as CHF, hypertension, and COPD or occurred in association with a specific precipitating event (i.e., major surgery, pneumonia, or acute MI).[94] Only 1.7% of cases had no structural cardiac disease or precipitating causes (lone AFL).

AFL and AF share similar risk factors and have the same risk of CHF and thromboembolism in the presence of risk factors for stroke. Similar to AF, AFL is associated with an increase in mortality rate by a factor of 1.7 as a sole arrhythmia and a factor of 2.5 if it coexists with AF (Figure 42-13).[95]

Interrelationship

Typical AFL is a classic macro–re-entrant arrhythmia that develops from a functional conduction block at the cavotricuspid isthmus.[96] This mechanism of initiation and maintenance is markedly different from AF, and typical AFL can be cured relatively easily by ablation. Furthermore, AFL and AF respond differently to antiarrhythmic drugs. In this respect, patients with AFL should be distinguished from patients with AF.

However, the close clinical interrelationship between AF and AFL should not be disregarded. In many instances, AFL is preceded by a transitional rhythm in the form of AF of variable duration, which facilitates the occurrence of a functional block between the venae cavae necessary for the maintenance of the AFL macro–re-entrant circuit. Conversely, clinical and experimental studies in postoperative AF and in the canine sterile pericarditis model have demonstrated that a very fast AFL may lead to AF.[96]

The close interrelationship between AF and AFL is reflected in the high prevalence of patients in whom both arrhythmias coexist and the significant proportion of patients (30% to 70%) who develop AF after successful ablation of the cavotricuspid isthmus for AFL, even if AF has never been documented before ablation. In a recent meta-analysis of long-term outcomes of ablation for typical AFL (158 studies, 10,719 patients), the overall incidence of AF was 33.6% during an average follow-up of 15 months; AF occurred in 23.1% of patients with no history of AF and in 52.7% of patients with a history of AF before ablation.[97] Such a high proportion of patients developing AF within a relatively short time after ablation suggests that AFL may be an early marker of atrial remodeling that forms a substrate for AF. In contrast, antiarrhythmic drugs with sodium channel–blocking properties, such as class IC agents and amiodarone, which slow conduction in the atria, can convert AF into AFL, probably by facilitating the

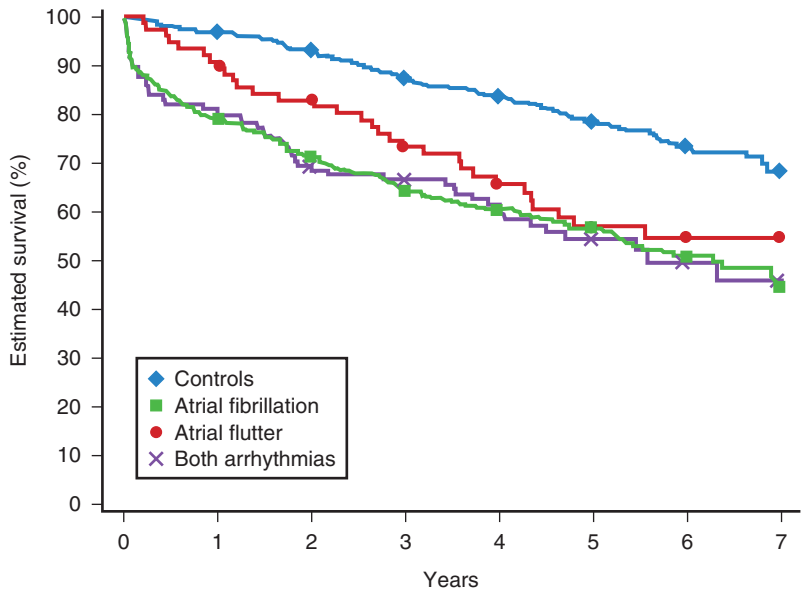


FIGURE 42-13 Kaplan-Meier curves of survival in patients with atrial tachyarrhythmias. *(From Vidaillet H, Granada JF, Chyou PH, et al: A population-based study on mortality among patients with atrial fibrillation or flutter,* Am J Med *113:365–370, 2002.)*

formation of functional block in the right atrium. Ablation of the cavotricuspid isthmus has been effectively used in such patients to prevent the recurrence of AF.

Anatomy and Pathology

Structurally, the atria are complex structures because of the gaps in their walls for the openings of the connecting veins and for the valvular openings. The conduction of the cardiac impulse from the sinus node to the AV node travels through preferential pathways formed by the remaining myocardium. In discussing the atria, the anatomy of the right and left atria and their venous connections, the sinus and AV nodes, the nodal approaches, and the pathologic changes that may be involved in atrial arrhythmias are all considered. Gross dissections of the atrial walls help reveal the complex arrangement of the myocardial strands that make up the atrial walls.[98] Even though the myocardial strands do not precisely replicate the syncytia of myocytes that are visible only on microscopy, they provide a useful guide to the general orientation of the myocytes, allowing inferences to be made on the direction of conduction.[99-101] On histology, pathologic changes in the atrial myocardium occur from middle age onward. Myocyte loss occurs to varying extents followed by replacement with fat and fibrous tissue.[102] In the normal aging process, some myocytes may be atrophied, some are hypertrophied, and others are in various stages of degeneration. The conduction tissues are also affected by aging-related changes.[103] Furthermore, the atrial chambers become enlarged even in normal individuals with sinus rhythm older than 50 years.[104] Myocyte hypertrophy, myolysis, apoptosis, and irreversible fibrosis are more pronounced in patients with atrial arrhythmias.

Right Atrium

The dominant feature of this chamber is the large, triangular shaped appendage, which is located anterolaterally (Figures 42-14 and 42-15). Usually, a fat-filled groove, corresponding internally to the terminal crest (*crista terminalis*), can be seen along the lateral wall. The sinus node is located subepicardially in this groove, close to the superior cavoatrial junction (see Figure 42-15). In most individuals, the node is located anterolaterally in a tadpole shape with the head nearest the junction and the tail penetrating into the musculature of the terminal crest.[105] In approximately 10%, the node is horseshoe shaped and located mediolaterally in the terminal groove.[106] Right atrial musculature often extends superiorly over the wall of the superior vena cava (SVC), unlike inferiorly where atrial muscle fades out or terminates close to the entrance of the inferior vena cava (IVC). Prongs of sinus node tissues often interdigitate with the musculature of the terminal crest and may even extend into the muscular sleeves that surround the SVC (see Figure 42-15).[105,107] The tail portion often fragments into clusters of specialized cells toward the middle or even lower portions of the terminal crest. The prongs and the clusters may have some role in focal atrial tachycardia (AT).

The terminal crest demarcates the junction between the rough-walled atrial appendage and the smooth-walled venous (intercaval) appendage on the endocardial surface. Most commonly it is ridgelike and composed of myocardial strands that are aligned longitudinally.[108] An extensive array of pectinate muscles arise nearly perpendicularly from the terminal crest to spread throughout the entire wall of the appendage, reaching to the lateral and inferior walls of the atrium (see Figure 42-14) to the atrial vestibule that separates the appendage from the tricuspid annulus. The pectinate muscles branch into fine and interconnecting muscle bundles. In between the bundles, the wall of the appendage is very thin, almost parchment-like in some cases. Potentially, this arrangement may play a role in initiating intra-atrial re-entry.

The atrial vestibule is the smooth muscular rim that surrounds the tricuspid orifice (see Figure 42-14, *B*) and the short extensions of its musculature inserting into the atrial surface of the leaflets. Importantly, the inferior to inferolateral segment of the right atrial vestibule, as viewed in left anterior oblique projection, is the anterior part of the cavotricuspid isthmus, the isthmus that is targeted as the zone of slow conduction in common AFL.[109,110]

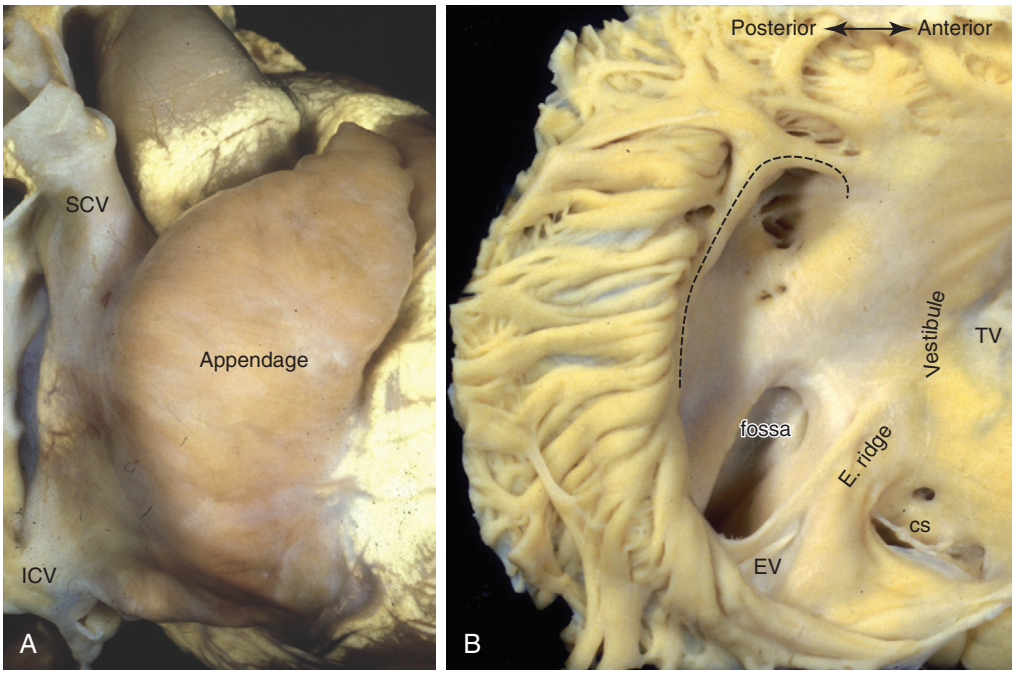


FIGURE 42-14 A, This heart viewed from the right side shows the triangular-shaped appendage of the right atrium. **B,** An incision parallel to the atrioventricular junction has been made in the right atrial appendage and its parietal wall reflected posteriorly so that the atrial septum is seen en face as if in right anterior oblique (*RAO*) projection. The parietal wall displays the thin atrial wall between the pectinate muscles that arise from the terminal crest (*broken line*). The oval fossa is surrounded by a muscular rim. The eustachian valve (*EV*) guards the orifice of the inferior vena cava. *cs*, Coronary sinus orifice; *IVC*, inferior vena cava; *SVC*, superior vena cava; *TV*, tricuspid valve.

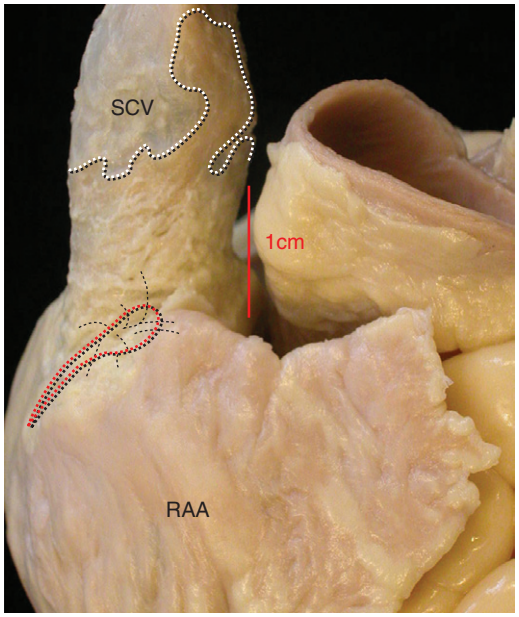


FIGURE 42-15 This heart viewed from the front shows the myocardial sleeve extending over the outer surface of the superior vena cava (*SVC*). The distal margin of the sleeve is irregular (*white dots*). The *red dotted line* marks the location of the sinus node and the *short dotted lines* represent prongs of nodal tissues. *RA*, Right atrial appendage.

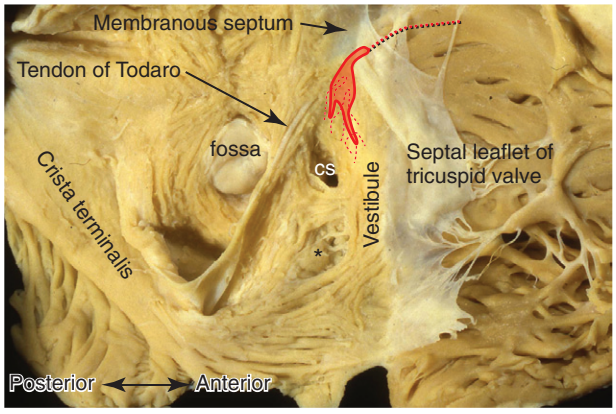


FIGURE 42-16 The endocardium of the right atrium has been removed to display the arrangement of the myocardial strands in the atrial wall. The triangle of Koch is revealed. The orange shape denotes the compact atrioventricular node and its inferior extensions while the *bold broken line* represents the continuation of the atrioventricular conduction axis. The zone of transitional cells (*short orange lines*) feeds into the compact node from inferiorly, posteriorly, and superiorly. The *asterisk* denotes the sub-eustachian sinus. cs, Coronary sinus orifice.

The posterior part of the isthmus contains the terminal ramifications from the terminal crest as it approaches the orifice of the IVC (Figure 42-16).[109] While the anterior part of the isthmus is always muscular, being the atrial vestibule, the middle and posterior parts are highly variable in topography and wall thickness.[111,112] The posterior part adjoining the eustachian valve tends to be composed of fibrous tissues, but the middle part contains variable extents and thicknesses of criss-crossing muscle bundles separated by thin membranous tissue (Figure 42-17). A pouchlike recess, the sub-eustachian sinus, is common and is

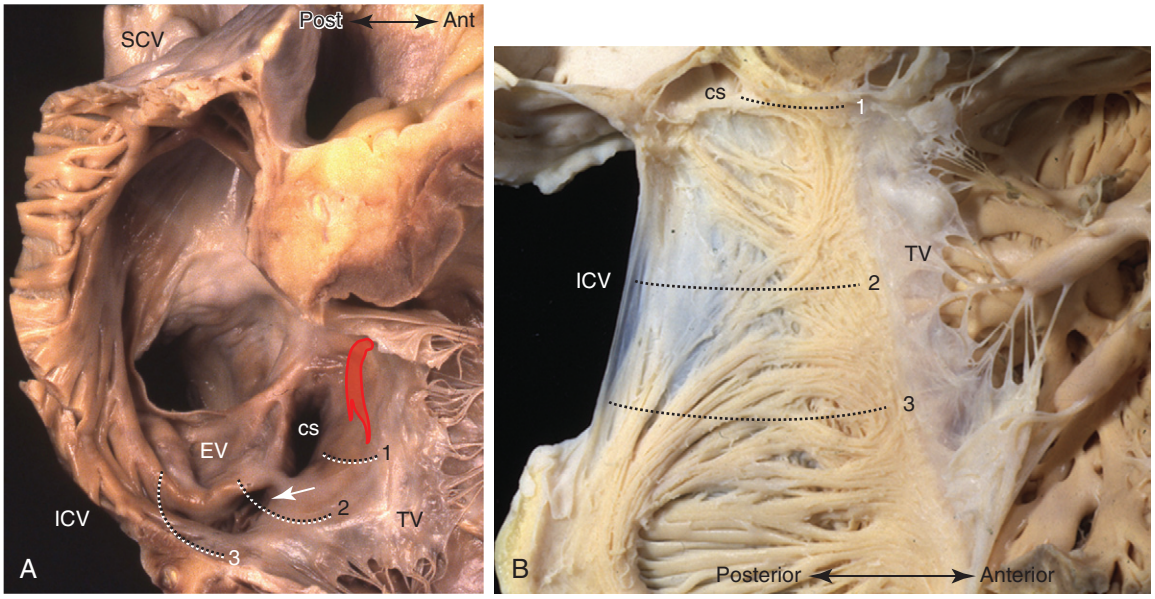


FIGURE 42-17 A, This dissection of the right atrium displays the three isthmuses in the cavotricuspid area. The portion of the isthmus between the coronary sinus (*cs*) and the tricuspid valve (*TV*) is the paraseptal isthmus (*1*). It is the shortest of the three but is nearest to the compact atrioventricular node. The inferior isthmus (*2*) often includes the pouchlike sub-eustachian sinus (*white arrow*). The inferolateral isthmus (*3*) is the longest and passes through some of the distal pectinate muscles arising from the terminal crest. **B,** The endocardium has been removed to show the morphologic components of the three isthmuses (*1, 2, 3*). In this heart, the posterior half of the inferior isthmus (*2*) is mainly a thin fibrous wall, practically devoid of myocardium. *EV*, Eustachian valve; *ICV*, inferior vena cava; *SCV*, superior vena cava.

5 mm or more deep in 20% of patients.[113] The eustachian valve, which guards the entrance of the IVC, is variably developed. Usually, it is a triangular flap of fibrous or fibromuscular tissue that inserts medially to the eustachian ridge, or the sinus septum, which is the border between the fossa ovalis and the coronary sinus. The free border of the eustachian valve continues as a tendon of Todaro, which runs in the musculature of the sinus septum.[114] It is the posterior border of the triangle (of Koch) that delineates the location of the AV node (see Figure 42-16).[115,116] The anterior border is marked by the hinge line of the septal leaflet of the tricuspid valve. Superiorly, the central fibrous body is the landmark for the penetrating bundle of His. Thus the inferior border of the triangle is the orifice of the coronary sinus, together with the vestibule immediately anterior to it. This vestibular portion, also known as the *septal isthmus* or, more accurately, the *paraseptal isthmus* (see Figure 42-17), is the area often targeted for ablation of the slow pathway in AVNRT. Although the body of the compact node is located toward the apex of Koch's triangle, it sends two prongs inferiorly toward the mitral and tricuspid orifices. The rightward extensions have been implicated in this arrhythmia.[117] This area also contains the zone of transitional cells that provides the inferior and posterior inputs to the compact node. The so-called *fast pathway* in AVNRT corresponds to the area of musculature close to the apex of the triangle of Koch. The superior zone of transitional cells and myocardial strands from the anterior limbic band of the fossa ovalis sweep into this area overlying the body of the compact node.

Left Atrium

Although the left atrium has similar component parts as the right atrium, its fingerlike appendage is distinctive. It can have a variable number of lobes, bends, or branches, but characteristically, the appendage is a cul-de-sac with a narrow opening to the rest of the chamber (Figure 42-18).[118] In contrast to the right atrium, no terminal crest or sinus node is present in the left atrium. The so-called *ridge* (crest) on the endocardial surface between the left atrial appendage (LAA) and the left superior pulmonary vein is an infolding of the atrial wall (Figure 42-19) that contains the remnant of the vein of Marshall and neural elements on the epicardial side. Nearly all the pectinate muscles in the left atrium are confined within the appendage. They form a complicated network lining the endocardial surface. The major part of the atrium, including the septal component, is smooth walled. The smoothest parts are the walls forming the atrial body, the superior and posterior walls that make up the large pulmonary venous component, and the vestibule that is the atrial outlet. Like the right vestibule, the left atrial vestibule also extends a very short distance over the atrial surface of the mitral leaflets. Although appearing fairly uniform, the atrial walls are composed of three or more overlapping "layers" of differently aligned myocardial strands.[98,119,120] The "layers" are not insulated by fibrous tissue sheaths, but abrupt changes in orientations may account for the unusual patterns of conduction.[121] Marked regional variations in thickness are also present.[122,123] A small area of the anterior wall just behind the aorta is usually thin, whereas the superior wall, or dome, is thicker but tends to thin out near the left pulmonary veins.

The transition between the atrium and the vein is smooth. The musculature of the atrial wall extends to varying lengths onto the outside of the venous walls, with the longest sleeves along the upper veins (Figure 42-20).[119,124,125] The right lower veins tend to have the shortest extensions or none at all. The sleeves closest to the venous insertions are thicker and more complete around the vein. Nerve bundles and ganglionated plexi are abundant at the venoatrial junctions and the adjoining walls.[126,127] The margins of

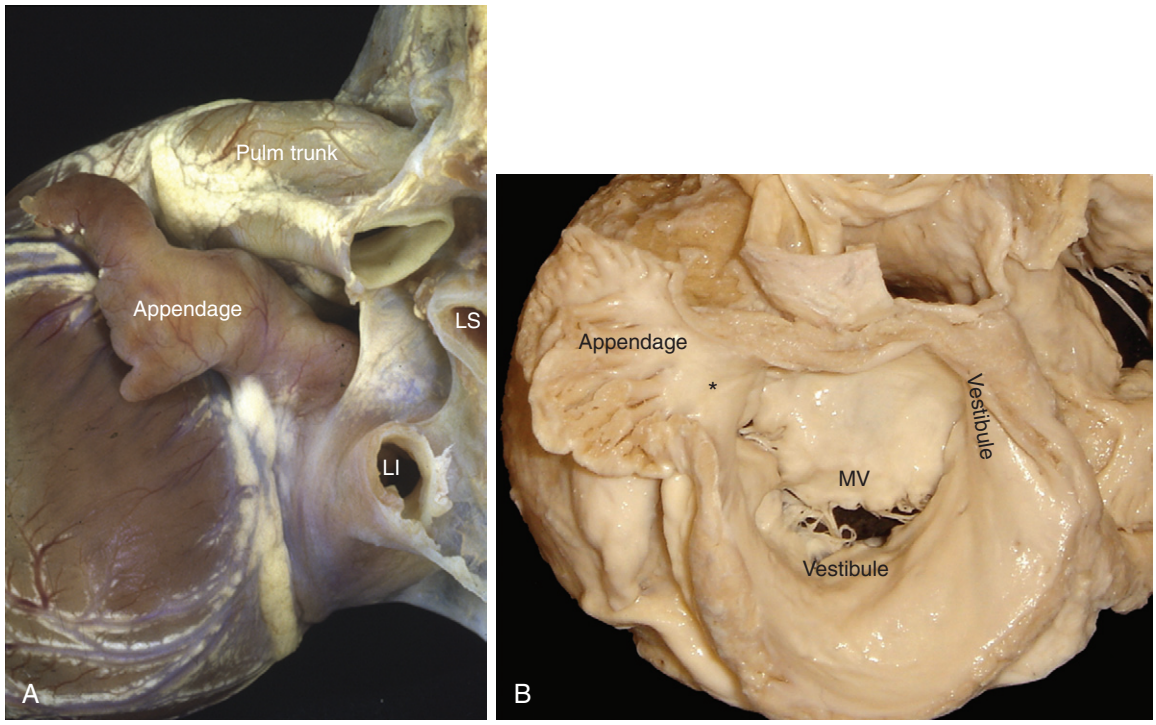


FIGURE 42-18 A, This heart viewed from the left displays a characteristic fingerlike left atrial appendage. **B,** Pectinate muscles line the endocardial surface of the appendage. The appendage communicates with the body of the atrium through a narrow orifice (*asterisk*). *LI,* Left inferior; *LS*, left superior pulmonary vein.

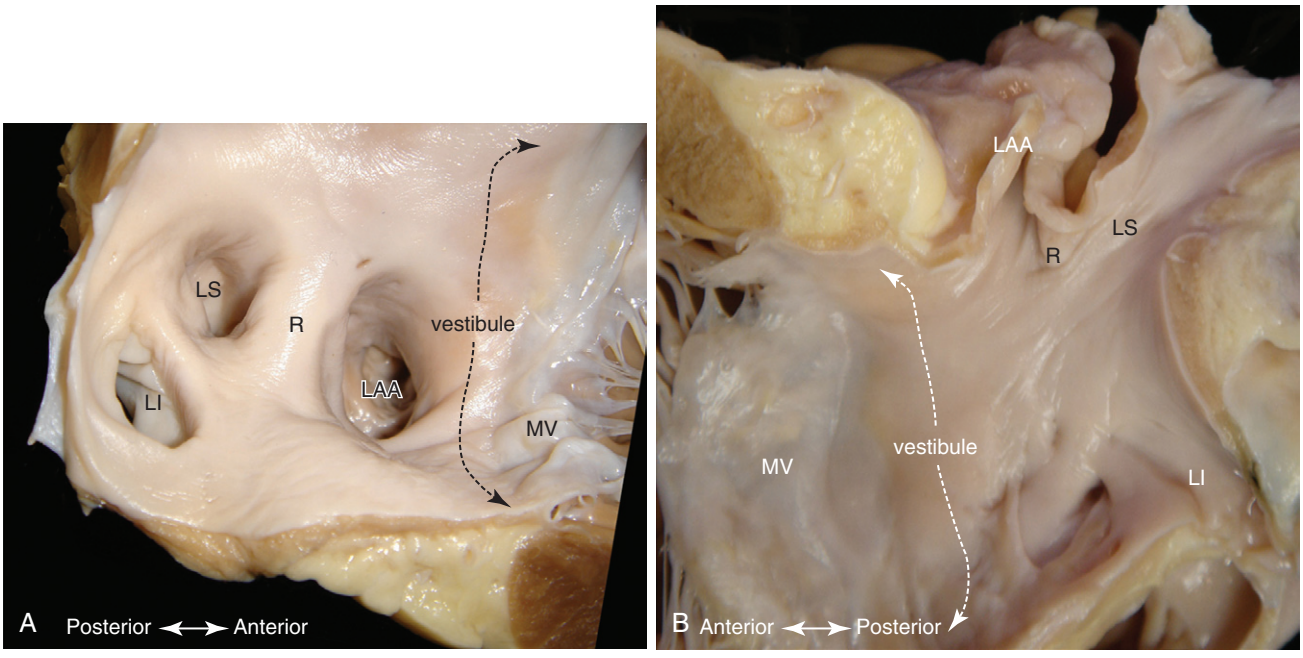


FIGURE 42-19 A, The so-called ridge (*R*) lies between the orifice of the left superior (*LS*) pulmonary vein and the left atrial appendage (*LAA*). **B,** The ridge, when transected, reveals it is an infolding of the atrial wall. *MV,* Mitral valve.

the sleeves become thinner and irregular toward the lung hila. Pathologic studies have been inconclusive regarding the role of these myocardial sleeves in triggering AT and AF because they are found in asymptomatic adults as well as in patients with atrial arrhythmias. Like the myocardium of the atrial body, the sleeves also undergo aging changes. Islands of viable myocytes among fibrotic areas are often found (see Figure 42-20).[125] Myocyte hypertrophy, fibrosis, and sleeve discontinuity are more frequently seen in tissues from patients with AF.[128] Other studies have shown mainly circularly orientated myocardial fibers with interdigitating

longitudinally and obliquely orientated fibers in the sleeves.[101,124] These may set the scene for micro–re-entry.[129]

Although nodelike cells have been described in murine models, they have never been found human tissues until in the study by Perez-Lugones and colleagues, but controversy remains.[124,125,130-132] Recently, interstitial cells of Cajal, previously identified as capable of providing pacemaker activity in the gut, were described for the first time in human atrial myocardium. They were found in higher density in the myocardial sleeves of pulmonary veins from patients with AF.[133-135]

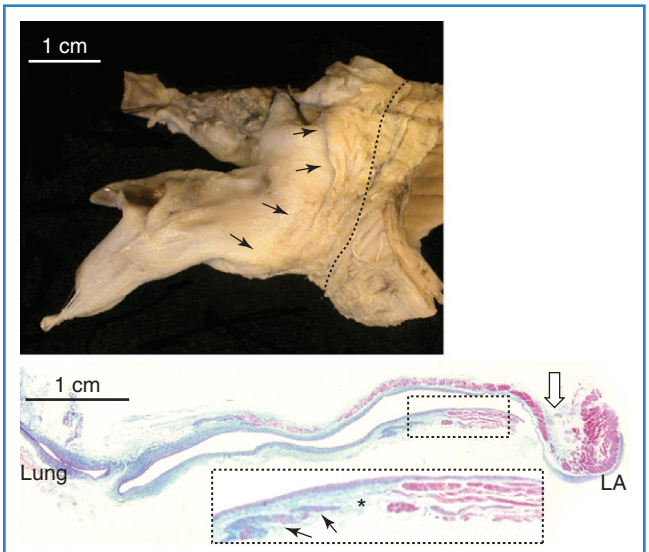


FIGURE 42-20 A, This right superior pulmonary vein has muscular extensions over its outer surface. *Arrows* indicate the irregular distal margins and the *broken line* marks the area of the venoatrial junction. **B,** This histologic section shows myocardium stained in red and fibrous tissue stained in green. Nerves branches are present at the venoatrial junction (*open arrow*). The muscular sleeve fades out toward the lung hilum. The enlargement (*inset*) shows an area of interruption in the sleeve (*asterisk*) and islands of myocytes amongst fibrous tissue (*arrows*).

Atrial Septum and Inter-atrial Connections

Viewed from the right atrium, the endocardial aspect of the true septum is confined to the valve of the fossa ovalis and the raised muscular rim (limbus) that is immediately around it (see Figure 42-14, *B*). The rim is an infolding of the right atrial wall harboring on its epicardial surface the fatty tissues of the inter-atrial groove. Although belonging to the right atrium, the leftward part of the muscular fold apposing the valve of the fossa continues into the musculature of the left atrial wall. The left atrial aspect of the septum is the valve itself. In most adult hearts, the fossa valve is thin, ranging from 0.4 mm to 3.4 mm. It usually is composed of two myocardial layers separated by fibrous tissue and sandwiched by fatty tissue beneath the endocardial surfaces.[136,137] This arrangement may explain asynchronous and discordant activation of the right and left septal surfaces, as observed by Lemery and colleagues, and may participate in the left septal flutter circuit, as reported by Marrouche and colleagues.[138,139]

Muscular continuity between the atria peripheral to the septum is frequently found as bridges in the subepicardium.[101,102,136] In the majority of hearts, the most prominent inter-atrial bridge is Bachmann's bundle (Fig. 42-21, *A*). This is a broad muscular band that runs in the subepicardium connecting the anterior right atrial wall of the superior cavoatrial junction with the anterior wall of the left atrium. The myocardial strands in Bachmann's bundle, as in the terminal crest, are well aligned. The posterior and inferior bridges joining the left atrium to the intercaval area on the right provide the potential for posterior breakthrough of sinus impulse (see Figure 42-21, *B*).[139] In one third of hearts, the

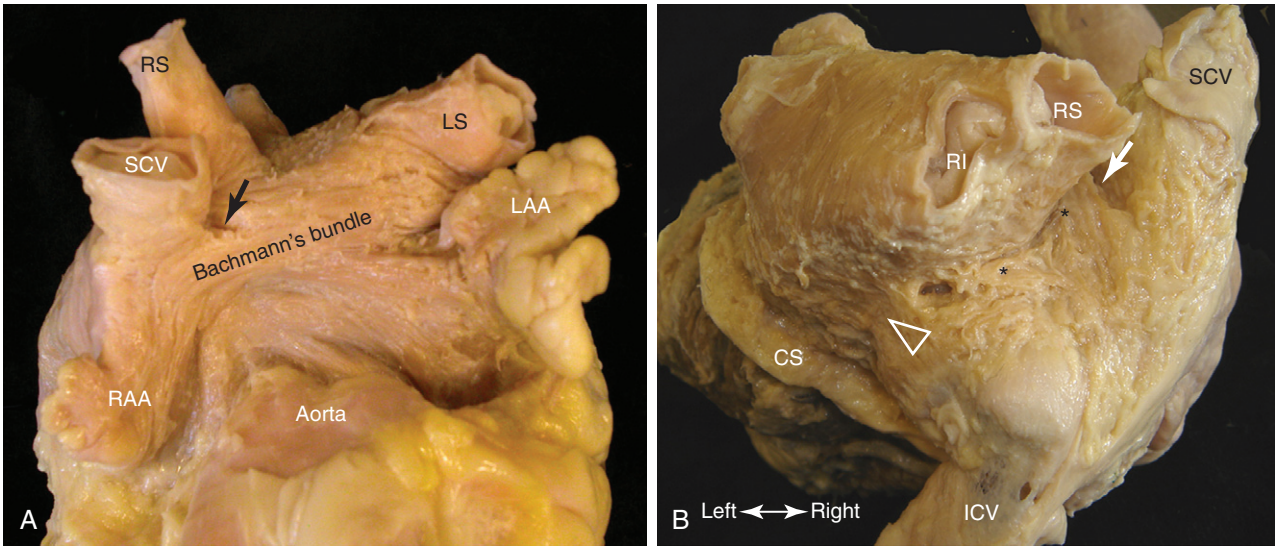


FIGURE 42-21 A, The aorta has been pulled forward and the tips of the right and left atrial appendages (*RAA*, *LAA*) have been deflected to show the anterior aspect of the atria. Bachmann's bundle crosses the interatrial groove (*arrow*) and has mainly parallel alignment with the myocardial strands. **B,** This heart viewed from the right and inferior aspect has been dissected to reveal a broad band of muscle (*open triangle*) crossing the interatrial groove (*arrow*), and smaller interatrial bridges (*asterisks*). cs, Coronary sinus; *IVC*, inferior vena cava; *LS*, left superior; *RI*, right inferior; *RS*, right superior pulmonary vein; *SVC*, superior vena cava.

inferior inter-atrial connection is thicker or as thick as Bachmann's bundle.[136] Multiple smaller inter-atrial bridges are frequently present, giving the potential for macro–re-entry. Some connect the muscular sleeves of the right pulmonary veins to the right atrium, and some connect the SVC to the left atrium.[101,120] Inferiorly, further muscular bridges from the left atrial wall often overlie and run into the wall of the coronary sinus.[120] Fine bridges connecting the remnant of the vein of Marshall to the left atrium have also been demonstrated.[140]

Pathologic Substrates

In assessing pathologic changes in the myocardium for atrial arrhythmia, consideration must be given to changes associated with normal aging. Further compounding the issue are well-recognized conditions in older adults, such as senile amyloidosis, sick sinus syndrome, CAD, hypertensive heart disease, CHF, which can affect the myocardium as well as conduction tissues. Increased connective tissue, fibro-fatty changes, myocyte degeneration in the myocardium, and fibro-fatty degeneration or fibrosis of the conduction tissues are common. In patients with arrhythmias, some investigators reported increased interstitial fibrosis, myocyte myolysis, and inflammatory infiltrates in AF.[141-144] In addition, recent microinfarcts are more often found in prominent muscle bundles such as the terminal crest and Bachmann's bundle of AF patients, which suggests that atrial MI may be more common than previously thought.[145]

Patients with congenital heart disease are prone to developing arrhythmias as part of the natural history of longstanding hemodynamic alterations. Factors implicated include chronic volume overload, pulmonary hypertension, and ventricular dysfunction. Atrial arrhythmias, AFL, and AF are common in patients who had previous surgical intervention in the atria for congenital heart defects (e.g., ASD), Mustard or Senning procedures for atrial re-direction, or the Fontan procedure. Atrial re-direction procedures for complete transposition of the great arteries require long incision lines and numerous suture lines that result in narrow channels of the myocardium being bounded by incisional scars, or a scar and a natural obstacle, setting the scene for re-entry. The older variants of the Fontan procedure did not exclude the right atrium from high systemic venous pressure. Consequently, the atrium becomes enlarged and hypertrophied. The surgical incisions and subsequent scarring contribute to arrhythmogenesis. Furthermore, in both atrial re-direction and Fontan procedures, suture lines close to the sinus node area risk compromising the sinus node or its blood supply.

Postoperative AF, AFL, or both are common complications following cardiac surgery for acquired heart disease or after thoracotomy. As yet, the pathologic substrates are unclear, but age-related structural changes in the atria, such as dilatation, fibrosis, and loss of conduction tissues, are among the contenders.

Clinical Electrocardiography

The differentiation of AF from AFL has practical implications when physicians interpret ECGs because it may influence decisions regarding the use of antiarrhythmic drugs, the magnitude of energy used for cardioversion, and referral for ablation procedures.

Table 42-4 Predominant Flutter Wave Morphology in Typical Clockwise and Counterclockwise Right Atrial Flutter

ECG LEAD	CLOCKWISE FLUTTER	COUNTERCLOCKWISE FLUTTER
II, III, aVF	Positive or negative	Negative
I	Positive	Biphasic or isoelectric
aVL	Biphasic or isoelectric	Positive
V1	Negative or biphasic	Positive
V6	Positive	Negative

Atrial Flutter

AFL is more organized than AF, features a saw-toothed pattern of regular activation that is particularly apparent in leads II, III, and aVF, and does not have an isoelectric baseline between deflections. The rate is typically 240 to 300 beats/min. Major types of AFL include typical (isthmus dependent, clockwise, and counterclockwise AFL) and atypical (isthmus independent) AFL. In the presence of anatomically predetermined slow conduction in the crista terminalis, atrial stimuli wavefront creates unidirectional block in the isthmus and maintains the AFL re-entry circuit. In typical AFL (Figure 42-22) that rotates *counterclockwise* in the right atrium, the flutter waves are inverted in leads II, III, aVF, and V6 and upright in lead V1. Biphasic or negative deflections in V1 are less common. Leads I and aVL usually have low amplitude deflections.[146,147] When the activation sequence is reversed (*clockwise* rotation), the flutter waves may be upright in leads II, III, and aVF and inverted in lead V1. Wide negative deflections in lead V1 and a positive flutter wave in V6 are characteristic of clockwise rotation in the right atrium.[146,147] The flutter waves are positive in V6. The surface lead characteristics that differentiate clockwise and counterclockwise AFL are summarized in Table 42-4.

Counterclockwise Atrial Flutter

The silent isoelectric zone of the ECG that precedes the negative deflections in the inferior leads corresponds to activation of the low right atrium and isthmus between the tricuspid annulus and the IVC and precedes activation of the left atrium, which begins from the lower septum.[146-152] The left atrial activation sequence is the predominant determinant of the flutter wave morphology (Figure 42-23, *A*).

In typical counterclockwise right AFL, the left atrium is activated from both the inferior septum and the superior septum.[148] The posterior wall is activated preferentially from the inferior septum, and the anterior wall is activated from the superior septum. Activation of the lateral wall of the left atrium reflects variable inputs from both regions. Studies showed that left atrial activation coincided with the negative component in leads I, II, III, aVF, and V6 and the first flat or slowly rising component in V1. Activation of the lateral wall of the right atrium coincided with the positive deflections in leads I, V1, and V6 and the upstroke component in the inferior leads. The plateau duration in lead III correlated with the time required for conduction through the isthmus between the tricuspid annulus and the IVC.

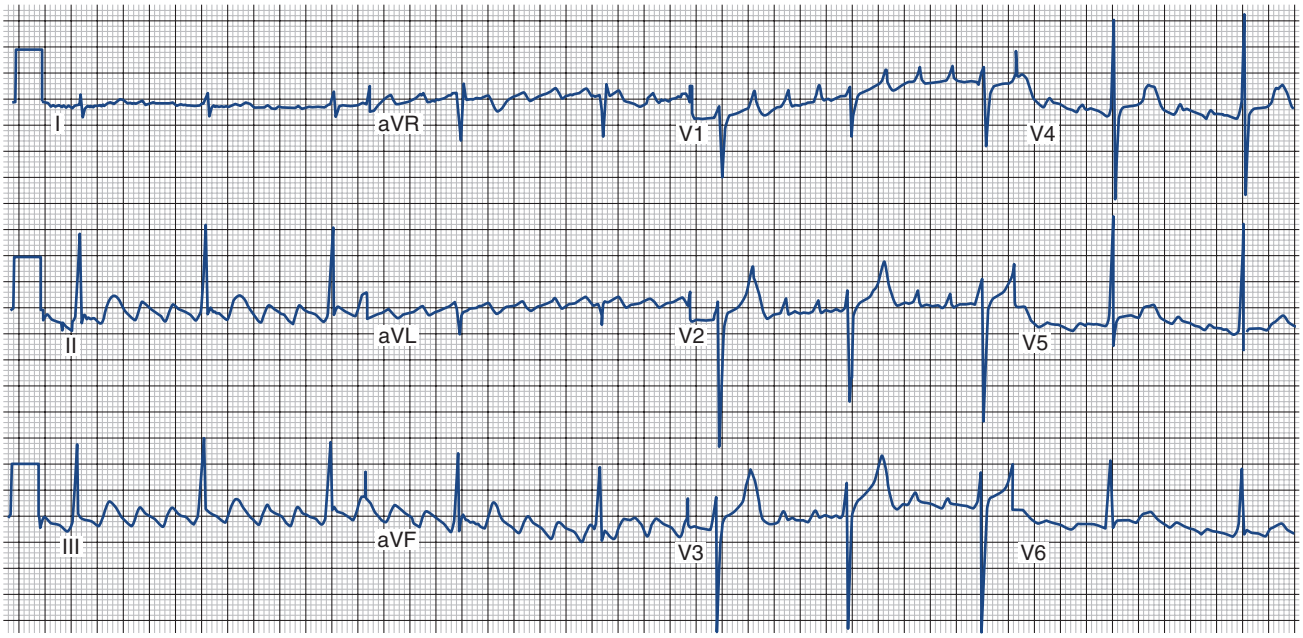


FIGURE 42-22 Twelve-lead electrocardiogram from a young athlete showing typical counterclockwise atrial flutter ay 300 beats/min with 3:1 atrioventricular block. Note the presence of left ventricular hypertrophy.

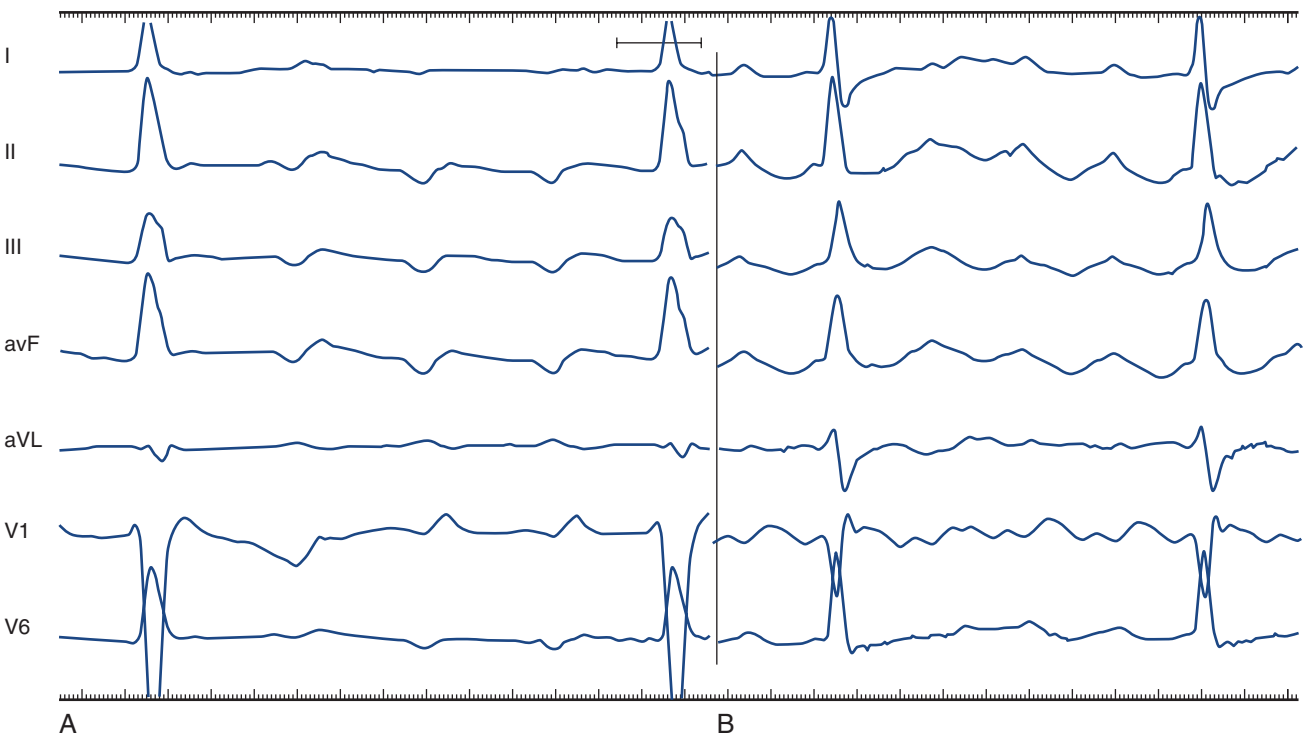


FIGURE 42-23 A, Typical counterclockwise atrial flutter. The F waves are negative in leads II, III, aVF, and V6 and positive in V1, corresponding to the wavefront traveling down the lateral wall of the right atrium, through the eustachian ridge, and up the interatrial septum. **B,** Reverse (clockwise) atrial flutter. Note the reverse polarity of the F waves: positive in leads I, II, III, avF, and V6 and biphasic in V1.

In studies using body surface mapping with simultaneous endocardial mapping, the flutter wave cycle length could be divided into three time segments.[151] Caudocranial activation of the right atrial septum occurred in conjunction with proximal-to-distal activation along the coronary sinus and corresponded to the initial segment of the flutter wave. Craniocaudal activation of the right atrial free wall occurred during the intermediate portion of the flutter wave, and activation of the lateral sub-eustachian isthmus occurred during the terminal flutter wave.

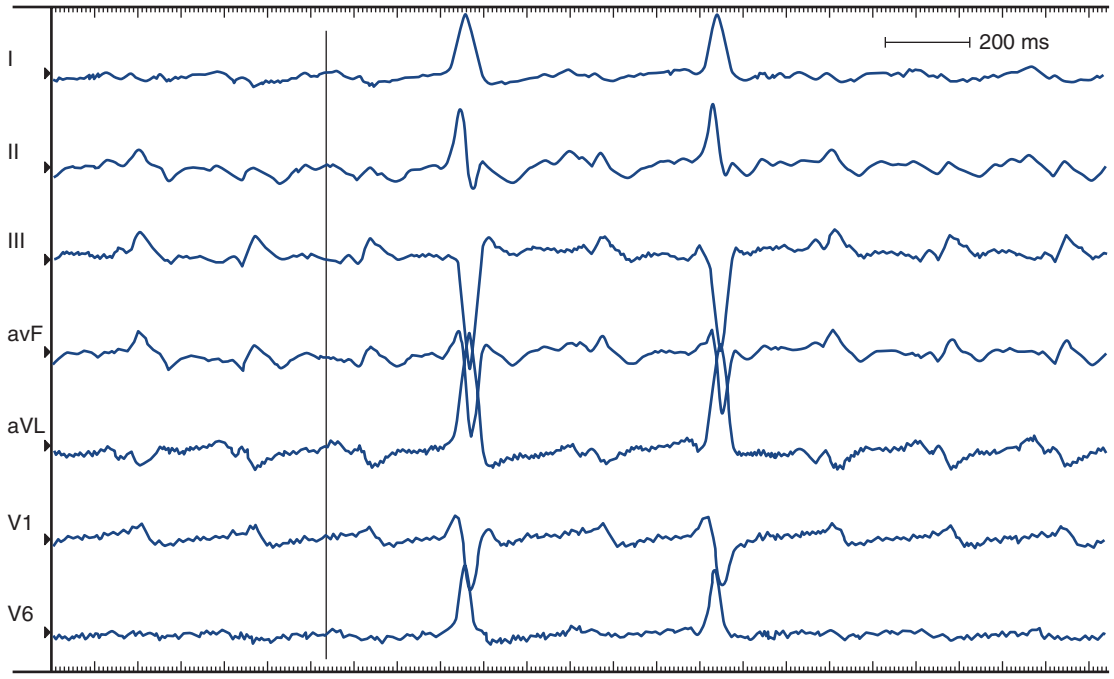


FIGURE 42-24 Atrial flutter after a Fontan operation. Neither typical nor reverse typical pattern of atrial activation can be seen. It is "incisional" atrial flutter in which the wavefront circulates around the scar.

Clockwise Atrial Flutter

The silent or isoelectric zone of clockwise AFL is shorter compared with counterclockwise AFL.[146,147,151] In studies, a saw-tooth pattern with a negative deflection in the inferior leads observed in clockwise AFL was interpreted as being very similar to the pattern observed in counterclockwise AFL.[146] A shorter plateau phase was accompanied by widening of the negative component of the flutter wave. A negative flutter wave in V1 was a constant finding, and flutter waves were predominantly positive in V6 (see Figure 42-23, *B*). Caudal to cranial activation of the lateral wall of the right atrium corresponded to the end of the plateau and the descending part of the negative portion of the flutter wave. The ascending portion of the flutter wave corresponded to the descending activation of the septum and occurred synchronously with proximal-to-distal activation in the coronary sinus.

Activation of the lateral right atrium from caudal to cranial corresponded to an inverted component on the inferior leads of variable amplitude just before the development of upright notched flutter waves.[147] In some patients, this period was an electrically silent isoelectric segment. However, in this study, all the patients with clockwise AFL had prominent upright flutter waves in the inferior leads. The upstroke began when the wavefront of activation reached the superior part of the crista terminalis in the vicinity of Bachmann's bundle. This also corresponded with the onset of the major deflections in the precordial leads. The bulk of the flutter wave was presumably determined by the left atrium.

During clockwise AFL, a dominant breakthrough to the left atrium in the high anteroseptal area and a second breakthrough in the low posterior septal area were observed.[148,149] Left atrial activation was coincident with positive components on the surface of ECG leads I, II, II, aVF, and V6 and the first negative component in V1. Activation of the lateral wall of the right atrium coincided with the negative components in lead I, inferior leads, and V6. The body surface maps attributed the initial segment of the flutter wave to craniocaudal excitation of the right atrial septum.[151] The intermediate segment corresponded to excitation of the isthmus and proximal-to-distal activation along the coronary sinus. The terminal segment corresponded to caudocranial excitation of the right free wall.

Difficulties with Electrocardiogram Interpretation

The interpretation of AFL morphologies depends on a sufficient degree of AV block to separate the flutter wave from ventricular activation and repolarization. Atypical forms of AFL with diverse flutter wave morphologies that do not have a standard nomenclature complicate ECG assessments. Sometimes, the flutter wave morphology is low in amplitude or may be obscured by ventricular repolarization when the ventricular response is rapid. ECGs of atypical right atrial macro–re-entrant circuits can be difficult to interpret.[152,153] Complex forms of left atrial macro–re-entry, which may resemble typical right AFL, tend to have predominantly positive flutter waves in V1.[154] Several types of atypical AFL were demonstrated, including AFL in the low right atrial free wall, AFL involving the high right atrium (SVC–atrial septum area), and AFL involving two or four pulmonary vein orifices, mitral annulus isthmus, and the fossa ovalis area.

Figure 42-24 was recorded from a patient who had undergone a Fontan operation to treat transposition of the great vessels. The patient developed AFL, which involved rotation around a scar on the lateral aspect of the right atrium.

The differentiation of focal AT from AFL may also be confusing. When AFL is treated with antiarrhythmic drugs, the rate may decrease appreciably and overlap with the rate of focal AT that

ranges from 130 to 240 beats/min (rarely 300 beats/min). The isoelectric segment is generally longer, but it may be difficult to distinguish from AFL if the rate is rapid.

Atrial Fibrillation

AF consists of rapid oscillations or fibrillatory waves that vary in size, shape, and timing (Figure 42-25). The ventricular response to AF depends on the electrophysiological properties of the AV node, the effects of drugs, and the balance between sympathetic and parasympathetic tones. The R-R intervals are irregular unless the patient has AV block or a paced rhythm. Paroxysmal AF appears to be highly dependent on initiation by atrial ectopy: 93% of spontaneous episodes of paroxysmal AF were triggered by atrial premature depolarizations, and 6.4% were preceded by typical AFL as documented by 12-lead Holter recordings.[152] The morphology of the initiating P waves was used to estimate the origin of triggering events: 77.5% arose from the left atrium, 2% were of right atrial origin, and 13.5% were nonspecific. Generally, an increase was observed in the frequency of atrial ectopy in the 30 seconds that preceded the onset of AF. The beats that initiated AF had shorter coupling intervals than those that failed to initiate AF.[155] More than half the episodes were also preceded by cycle length variation with short-long sequences. Although there appeared to be qualitative differences in the homogeneity of right atrial activation in paroxysmal AF compared with chronic AF, no consistent ECG criteria have been developed to distinguish the standard 12-lead ECG morphology of chronic and paroxysmal AF.[156]

Basic Electrophysiology

The basic mechanisms underlying cardiac arrhythmias are discussed in detail in Chapters 3 and 4 and are not repeated here. This section deals in detail with the present state of knowledge about the basic electrophysiology of AF.

Historical Aspects

In the late 1800s, AF was shown to be the mechanism underlying "delirium cordis," in which the heart was noted to beat without any apparent regularity. With the subsequent development of electrocardiography and of methods to study cardiac electrophysiology, three basic theories about the mechanism of AF emerged.[157] These mechanisms are illustrated in Figure 42-26.

Mines and Garrey observed the occurrence of regular re-entry and fibrillation in cardiac tissue preparations and considered AF to be caused by continuous irregular re-entrant activity occurring in a dyssynchronous fashion in various atrial regions ("multiple circuit re-entry"; see Figure 42-26, *A*). Garrey first put forward the idea that fibrillation requires a critical mass of tissue to

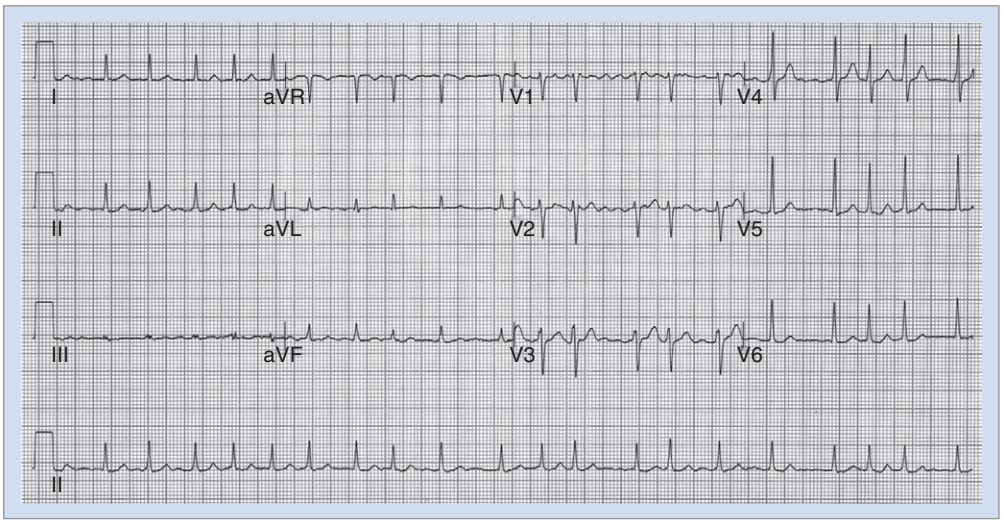


FIGURE 42-25 Twelve-lead electrocardiogram of atrial fibrillation. Note the presence of fibrillatory f waves, better seen in lead V1, that substitute normal P-wave activity, and an irregular ventricular response.

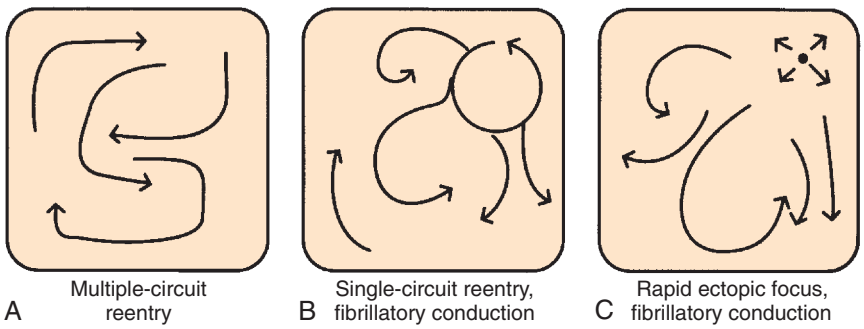


FIGURE 42-26 Theories of atrial fibrillation mechanisms in the early twentieth century.

support a sufficient number of irregular re-entrant wavefronts to maintain the arrhythmia.

Lewis believed that AF is caused by a single rapid macro–re-entry circuit (see Figure 42-26, *B*), with wavefronts emanating from the primary "driver" circuit breaking against regions of varying and greater refractoriness, producing "fibrillatory conduction" and the irregular global activity characterizing the arrhythmia.[158] Others held that AF is caused by very rapid activity, with either a single source giving rise to fibrillatory conduction (see Figure 42-26, *C*) or multiple ectopic foci producing fibrillation by virtue of dyssynchronous activity and colliding wavefronts. In the subsequent years, various lines of evidence pointed to the relevance of multiple circuit re-entry to clinical AF, and from then until relatively recently, multiple circuit re-entry (see Figure 42-26, *A*) was widely assumed to be the dominant mechanism underlying clinical AF.

Moe refined the concept of multiple circuit re-entry by suggesting that activity during AF need not involve complete re-entry circuits beginning and ending at the same location but, rather, simultaneous wavelets that either extinguish (not contributing to arrhythmia maintenance) or succeed in continuously encountering excitable tissue and maintaining the arrhythmia.[159] Moe viewed the maintenance of AF as a probabilistic function of tissue properties and size, with a minimum temporal density of re-entrant wavelets needed to sustain the arrhythmia.

Allessie subsequently added a quantitative element to Moe's reasoning by emphasizing the importance of the wavelength (Figure 42-27). The wavelength (see Figure 42-27, *A* and *B*) is the distance traveled by a cardiac impulse during the refractory period (refractory period ± conduction speed) and indicates the shortest path length that can maintain re-entry. In circuits shorter than the wavelength, the head of the impulse will impinge on a still-refractory tail after one cycle, and the impulse will die out. According to Allessie's "leading circle" concept of functional re-entry, functional re-entry circuits naturally form around a perimeter equal to the wavelength.[160] Allessie postulated that shorter wavelengths favor AF maintenance by increasing the number of simultaneous functional re-entrant circuits that the atria can accommodate (see Figure 42-27, *C*). A corollary of this notion is that multiple circuit re-entry AF can be terminated or prevented by increasing the refractory period and consequently the wavelength, thereby reducing the number of circuits possible and making AF maintenance less likely (see Figure 42-27, *D*).[161] By contrast, factors that reduce the wavelength (such as short refractory periods and slow conduction) should favor AF.[162] Atrial dilatation should also favor re-entry by increasing atrial size and thereby increasing the number of circuits that the atria can accommodate (see Figure 42-27, *E*).[163] Heterogeneity in refractory properties should favor AF by promoting the fractionation of impulses into multiple re-entrant wavefronts.

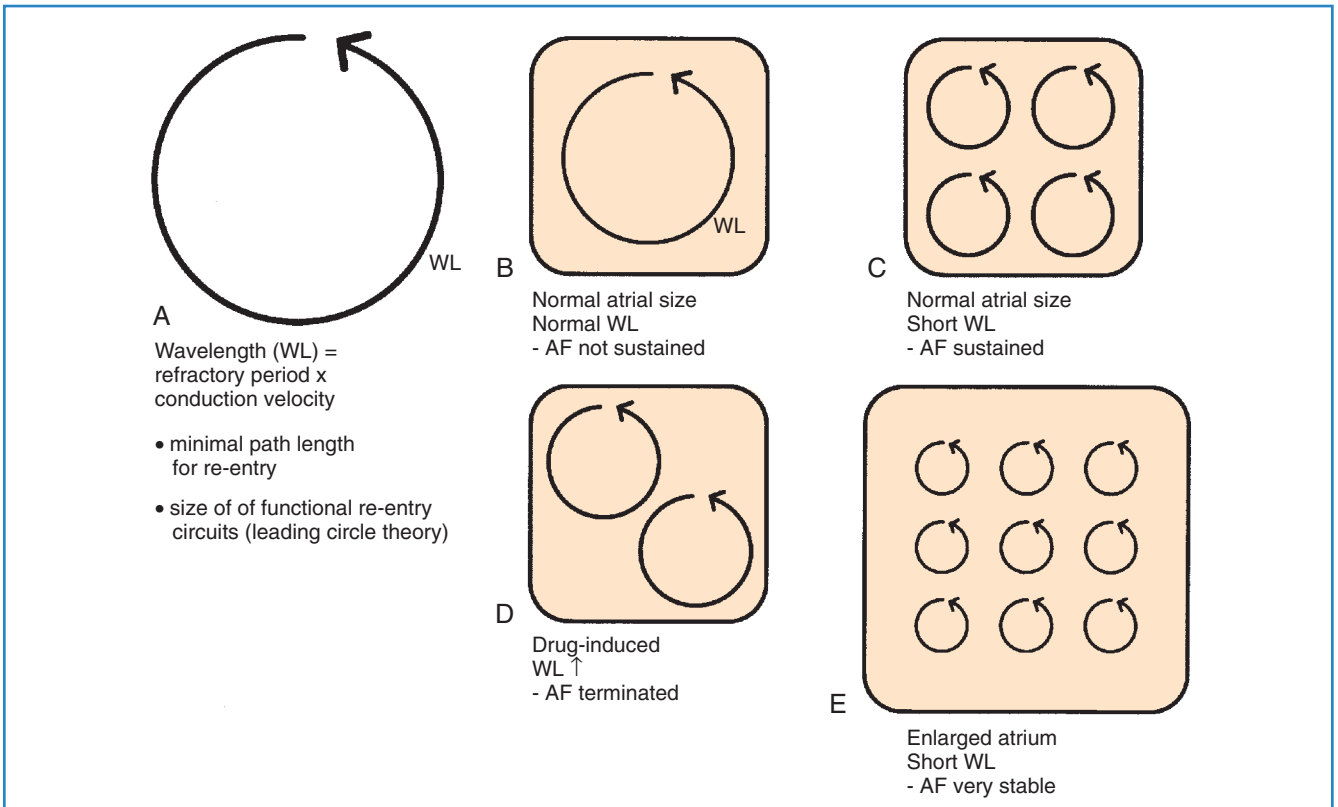


FIGURE 42-27 A, The role of the wavelength (*WL*) in determining minimum circuit size for re-entry and the size of functional re-entry circuits according to the leading circle concept. **B,** In atria of normal size with normal wavelength values, the atria cannot support multiple circuit re-entry; even if atrial fibrillation is induced, it usually stops spontaneously. **C,** If the wavelength is reduced (e.g., by vagal stimulation or electrical remodeling), enough circuits can be accommodated to maintain atrial fibrillation (*AF*) even in normal atria. **D,** Drugs that increase refractory period increase wavelength and circuit size, thereby making AF harder to sustain, promoting cardioversion and sinus rhythm maintenance. **E,** If the atria are enlarged and have short wavelengths, AF tends to be very stable and sinus rhythm very hard to produce and maintain.

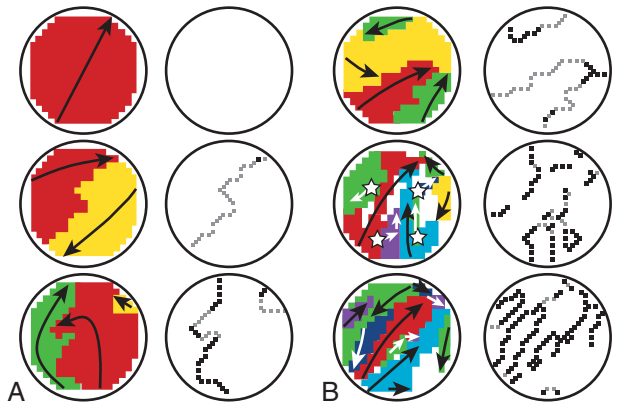


FIGURE 42-28 Intraoperative epicardial wave maps of the right atrium of three patients with acute AF (**A**) and 3 patients with persistent AF (**B**).The boundaries between the waves are plotted next to the wave maps. *Gray pixels* indicate interwave time differences of ≤12 ms (collision). *Black pixels* indicate time differences >12 ms (block). *(FromAllessie MA, de Groot NM, Houben RP, et al: Electropathologic substrate of long-standing persistent atrial fibrillation in patients with structural heart disease: Longitudinal dissociation,* Circ Arrhythm Electrophysiol *3:606–615, 2010.)*

In recent years, more sophisticated models of functional re-entry have been developed, such as the "spiral wave" model. A spiral wave involves continuous activity in a spiral pattern, somewhat like a hurricane. It differs from a leading circle in that the center of the spiral wave re-entry is excitable but not activated (like the eye of a hurricane), and the perpetuation of activity is determined by the angle of curvature of radiating activity. The consequences of the spiral wave activity concept for the initiation and maintenance of AF are poorly understood at the moment; therefore the leading circle remains the point of reference for understanding multiple circuit re-entry.

Recently, a significant increase in longitudinal dissociation, consisting of lines of block running parallel to the atrial muscle has been found during intraoperative epicardial mapping in patients with persistent AF as opposed to patients with acutely included AF (Figure 42-28).[164] The amount of dissociation was sixfold greater in longstanding persistent AF, suggesting that it may play a role in the self-perpetuation of the arrhythmia.

Electrical Remodeling

A key concept in understanding AF is that of electrical remodeling.[165] It has become obvious over the past few years that atrial electrical properties are altered by sustained AF such that the atria become more susceptible to the initiation and maintenance of the arrhythmia.[166] The primary factor driving AF-induced remodeling appears to be AT, and similar changes can be produced by other atrial tachyarrhythmias such as AFL and AT. Electrical remodeling occurs in a time-related fashion following the onset of AF and likely involves a series of adaptations stimulated by increased cellular calcium (Ca^{2+}) loading from the increased rate of activation, with Ca^{2+} entering the cell with each activation.[167] The electrophysiological changes caused by tachycardia-induced atrial electrical remodeling are summarized in Figure 42-29.

Short-term changes involve functional alterations, primarily Ca^{2+} current (I_{Ca}) inactivation, that reduce the action potential duration (APD), the refractory period, and the wavelength and thereby promote AF. Longer-term changes include alterations in the production of ion channel proteins, among which a key alteration appears to be downregulation in the L-type Ca^{2+} current ($I_{Ca.L}$) that maintains the plateau of the action potential and triggers cardiac contraction.[168] $I_{Ca.L}$ downregulation reduces APD and attenuates APD adaptation to rate, which is largely caused by tachycardia-dependent $I_{Ca.L}$ reduction (that normally reduces APD at fast rates). In addition, sodium (Na^+) current also appears to be reduced, decreasing conduction velocity, and the intercellular coupling channel protein, connexin 40, is reduced in a heterogeneous fashion. The resulting heterogeneous reductions in atrial wavelength make AF more likely to sustain itself and increase the vulnerability of the atria to AF re-induction should the arrhythmia be terminated.

The concept of atrial electrical remodeling caused by AF is very important because it explains why paroxysmal AF tends to become chronic, why longer-lasting AF is more difficult to treat, and why AF recurrence is particularly likely the first few days after electrical cardioversion. However, for remodeling to occur, AF needs to be sustained for significant periods. Therefore other mechanisms must be involved in triggering and maintaining AF before remodeling can occur.

Structural Remodeling

Autopsy studies of atrial tissues from patients with AF often show extensive atrial fibrotic changes, particularly in association with conditions such as mitral valve disease, CHF, and senescence. Recent clinical studies suggest that patients with AF have activation of the atrial renin-angiotensin system and related mitogen-activated protein kinases with profibrotic actions. In an animal model of CHF, sustained AF can be induced fairly readily, with an underlying substrate that involves local conduction abnormalities related to intense atrial interstitial fibrosis. AF in this model sometimes has the appearance of macro–re-entry with fibrillatory conduction, consistent with the mechanism illustrated in Figure 42-26, *B*.[169] In addition to causing abnormalities in conduction, structural remodeling is often associated with atrial dilatation, favoring AF, as illustrated in Figure 42-27, *E*. Cellular electrical properties are also altered in CHF but not in the same way as with atrial tachycardia-induced electrical remodeling.[169] APD is not shortened, so the wavelength is not reduced; however, the activity of the Na^+-Ca^{2+} exchange current (NCX) is increased. The NCX exchanges Ca^{2+} accumulated in the cell during the action potential for extracellular Na^+, with one intracellular Ca^{2+} ion exchanged for three extracellular Na^+ ions. Thus, the NCX carries one net positive charge into the cell with each cycle. When NCX activity is enhanced, delayed afterdepolarizations (DADs) and triggered ectopic activity can result. CHF therefore favors AF both by creating a structural substrate for atrial re-entry and by producing a functional basis for atrial ectopic activity that can trigger re-entry.

Significance of Ectopic Activity

Many patients with AF have enhanced atrial ectopic activity originating in the pulmonary vein region. These ectopic foci can promote AF both by triggering atrial re-entry in the presence of a susceptible substrate and by causing rapid atrial tachycardias that cause electrical remodeling, which then creates the re-entrant substrate for AF. Less commonly, ectopic activity in patients with AF can originate in other atrial sites such as the venae cavae and the ligament of Marshall, an anatomic remnant structure close to

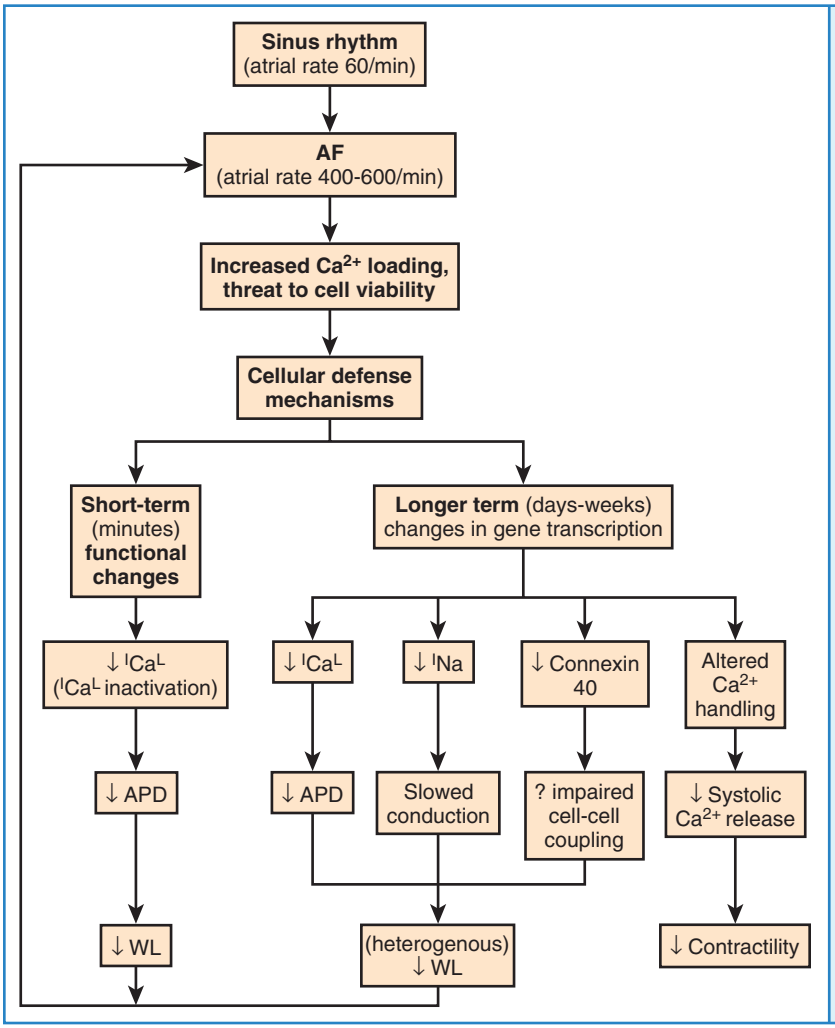


FIGURE 42-29 Mechanisms involved in atrial electrical remodeling induced by atrial fibrillation (*AF*). Similar mechanisms operate for any form of atrial tachycardia. Atrial tachycardia increases intracellular calcium (*Ca*) loading, which initiates a series of physiologic changes, some of which (e.g., decreased ^{I}Ca) reduce cellular Ca^{2+} entry and prevent potentially lethal Ca^{2+} overload. Protection against Ca^{2+} overload comes at the expense of decreased wavelength (*WL*), which promotes AF. *$^{I}CA^{L}$*, L-type calcium current; *Na*, sodium; *^{I}APD*, action potential duration.

the great cardiac vein. Irrespective of the site of origin of atrial ectopy, effective ablation of the ectopic site can prevent AF recurrence, indicating its importance in the pathophysiology of the arrhythmia.

Determinants of the Ventricular Response

In addition to the physiological factors controlling the occurrence and maintenance of atrial arrhythmia in AF, a very important determinant of the clinical manifestations is the ventricular response rate. The two largely independent determinants of the ventricular response are (1) the rate and regularity of atrial activity, particularly at the entry to the AV node; and (2) the refractory properties of the AV node itself. The pattern of atrial input is an important determinant of the ventricular response, but decreases in atrial rate do not always cause a reduced ventricular response. The central, compact portion of the AV node is composed of tissue with a slow, $I_{Ca,L}$-dependent upstroke ("slow-channel tissue"). Conduction through slow-channel tissue is not all or none: Impulses entering the AV node during its relatively refractory period can penetrate partway and then die out, leaving the AV node partially refractory for the next impulse. Thus, not only does the impulse fail to conduct, but it makes it more difficult for the next impulse reaching the AV node to conduct as well. This "concealed conduction" means that a very rapid, irregular input into the AV node can be associated with a lower ventricular response rate than a slower, more regular atrial activation pattern. Drugs that slow the atrial rate during AF, such as class IC antiarrhythmic agents, can, therefore, sometimes produce a paradoxical and potentially dangerous increase in the ventricular response rate.

The second important determinant of the ventricular response is the functional state of the AV connection. Normally, it is the refractory properties of the slow-channel tissue in the AV node that determine the ventricular response. Drugs that interfere with conduction through slow channel tissues, such as $I_{Ca.L}$-antagonists (diltiazem or verapamil), β-adrenoceptor antagonists (which oppose the conduction-enhancing effect of background β-adrenergic tone), and digitalis (which acts by vagal enhancement), increase the filtering function of the AV node and slow the ventricular response rate. Unlike slow-channel tissue, with a refractory period determined largely by the time required for recovery of $I_{Ca.L}$ following depolarization, the refractory period of "fast-channel" tissues (with I_{Na}-dependent upstrokes) is determined by APD. APD (and consequently the refractory period) of fast-channel tissues decreases markedly at faster rates. Thus, when the atria are connected to the ventricles by an accessory bypass tract of fast-channel tissues (as in WPW syndrome), the

bombardment of the bypass tract at very rapid rates during AF may result in very short refractory periods and dangerously rapid ventricular response rates caused by conduction across the accessory pathway during AF.

Synthesis of Physiological Determinants in Atrial Fibrillation

Figure 42-30 presents a synthesis of the physiological determinants of AF described earlier. Ectopic activity plays an important role by triggering re-entry and AF in the presence of a vulnerable substrate such as that created by structural remodeling. In addition, continuous atrial ectopic activity can generate ATs that cause atrial electrical remodeling, which produces a substrate for AF. Thus ectopic activity can result in both the substrate for AF (atrial remodeling) and the trigger that acts on the substrate to cause the arrhythmia. Other atrial tachyarrhythmias (including AFL, AVRT, and AVNRT) can also cause tachycardia-dependent remodeling and produce a substrate for AF, accounting (at least in part) for the occurrence of AF in association with these arrhythmias in some patients. If AF is induced by any mechanism, electrical remodeling will ensue, causing heterogeneous wavelength decreases that promote multiple circuit re-entry. Thus, electrical remodeling tends to make multiple circuit re-entry the final common pathway of AF, irrespective of the initial mechanism of the arrhythmia. As discussed earlier, even though AF may begin as macro–re-entry with fibrillatory conduction (as in some cases of experimental heart failure–related AF) or as a rapidly discharging focus with fibrillatory conduction, by the time patients get medical attention, they may already have multiple circuit AF because of remodeling.

Recent discoveries regarding AF mechanisms cast an interesting light on the theories of AF in the early twentieth century, as illustrated in Figure 42-26. Recent work suggests that all the original ideas regarding AF mechanisms are probably accurate for some subsets of patients. Furthermore, the subsequent dominance of the multiple circuit re-entry concept is also well founded, since electrical remodeling acts to make multiple circuit re-entry the final common pathway of AF in many cases. The dynamic nature of AF mechanisms needs to be considered to understand the mechanisms of the arrhythmia and to optimize therapy in any given patient.

Investigations

A detailed algorithm for evaluation of patients with newly diagnosed AF has been proposed by the Canadian Cardiovascular Society (CCS) and incorporates medical, family and social histories; physical examination; risk assessment; and essential investigations (Box 42-1).[170]

History

Etiology and Pattern

The initial evaluation of a patient with AF must first consider the presence and nature of the underlying pathology, which may act as a major clinical cause of the arrhythmia, as a precipitant, or as both. In a significant proportion of patients, several such factors can be simultaneously involved. Although AF is more likely to occur in conjunction with cardiovascular disease or cardiovascular intervention, it is not uncommon for it to be provoked or aggravated by various extracardiac factors (e.g., alcohol and substance abuse and intensive aerobic training). Identification and treatment of underlying pathologies such as acute illnesses or correctable metabolic disorders, in particular thyrotoxicosis, are essential because the precipitating agent can be eliminated and the arrhythmia may terminate spontaneously and may not recur.

Next, the duration and pattern of AF (e.g., first detected, paroxysmal, persistent, or unknown duration), the symptomatic status, and clinical impact should be assessed, and the risk of potential complications and progression should be estimated. This assessment is important for the subsequent selection of appropriate investigations from the extensive range of possible tests. The assessment allows the determination of the principal management strategies, including the restoration and maintenance of sinus rhythm (the rhythm control strategy), control of the ventricular rates, and lifelong anticoagulation (Table 42-5).

Clinical factors obtained from the history and physical evaluation largely determine (1) whether the patient should be

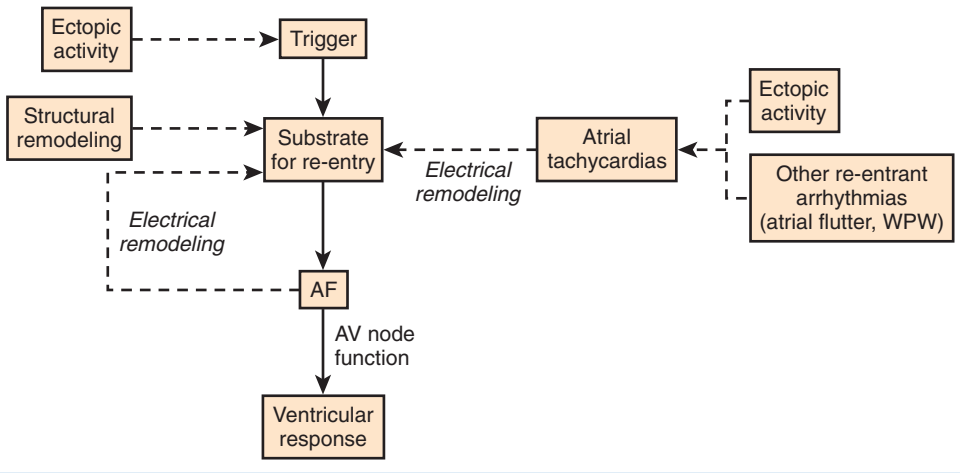


FIGURE 42-30 Synthesis of physiological determinants of atrial fibrillation (*AF*) and its consequences in terms of the ventricular response. *WPW*, Wolff-Parkinson-White syndrome; *AV*, atrioventricular.

Table 42-5 Aims of and Tests for the Evaluation of a Patient with Atrial Tachyarrhythmias

AIM/TEST	CARDIOVERT ACUTELY?	CAN NONPHARMACOLOGIC MANAGEMENT BE FIRST LINE?	SELECT RHYTHM VS. RATE CONTROL	ESTIMATE RISK FOR PROARRHYTHMIA	RULE OUT UNDERLYING DISEASE	ASSESS ARRHYTHMIA PATTERN	EVALUATE CLINICAL IMPACT	ESTIMATE RISK FOR STROKE AND NEED FOR AC	PREDICT EFFECTIVENESS OF TREATMENT
History	+++	+++	+++	++	+	++	++	+++	++
Physical examination	+++	+	+++	+++	+	++	+	+	+
Blood tests	+++	—	++	+	—	—	+	?	—
Electrocardiogram	+++	++	+	+++	++	+	++	—	+
Holter recording	++	+++	+	+	++	++	++	—	+
Event recorder	?	+++	+	—	++	—	+	—	+
Echocardiogram	+++	—	++	+++	—	++	+	+++	++
Radiographs	+++	—	++	++	—	++	—	—	+
Exercise	++	++	++	—	—	+	+	—	+
TEE	+	—	+	+++	—	+	—	+++	+
EPS	++	+++	++	—	+++	++	++	—	++
QoL questionnaire	?	+	+++	—	—	+	—	—	+

+++, Very important, almost always should be involved in decision; ++ often should be used, sometimes to answer a specific question; + may be useful for confirmation of existent knowledge or as a source of additional information; ?, not established if the hypothesis of hypercoagulative state is confirmed and reliable markers are established; AC, *anticoagulation;* EPS, *electrophysiological study;* QoL, *quality of life;* TEE, *transesophageal echocardiography.*

Box 42-1 Baseline Evaluation in Patients with Atrial Fibrillation Proposed by the Canadian Cardiovascular Society

History and physicial examination
- Establish pattern (new onset, paroxysmal, persistent, permanent)
- Establish severity (including impact on quality of life)

Identify etiology
- Identify reversible causes (hyperthyroidism, ventricular pacing, supraventricular tachycardia, exercise)
- Identify risk factors whose treatment could reduce recurrent AF or improve overall prognosis (hypertension, sleep apnea, left ventricular dysfunction)

Take social history to identify potential triggers (alcohol, intensive aerobic training)

Elicit family history to identify potentially heritable causes of AF (particularly lone AF)

Determine thromboembolic risk

Determine bleeding risk to guide appropriate antiplatelet or antithrombotic therapy

Review prior pharmacologic therapy for AF, both for efficacy and adverse events

Measure blood pressure and heart rate

Determine patient height and weight

Comprehensive precordial cardiac examination and assessment of jugular venous pressure and carotid and peripheral pulses to detect evidence of structural heart disease

12-Lead electrocardiogram

Document presence of AF by electrocardiography

Assess for structural heart disease (myocardial infarction, ventricular hypertrophy, atrial enlargement, congenital heart disease) or electrical heart disease (ventricular pre-excitation, Brugada syndrome)

Identify risk factors for complications of therapy for AF (conduction disturbance, sinus node dysfunction, repolarization); document baseline P-R, Q-T, or QRS intervals

Echocardiogram
- Document ventricular size, wall thickness, and function
- Evaluate left atrial size (if possible, left atrial volume)
- Exclude significant valvular or congenital heart disease (particularly atrial septal defects)
- Estimate ventricular filling pressures and pulmonary arterial pressure

Complete blood count; coagulation profile; and renal, thyroid and liver function

Fasting lipid profile, fasting glucose

AF, *Atrial fibrillation.*
From Healey JS, Parkash R, Pollak T, et al, for the CCS Atrial Fibrillation Guidelines Committee: Canadian Cardiovascular Society atrial fibrillation guidelines 2010: Etiology and initial investigations, Can J Cardiol *27(1):31–37, 2011.*

cardioverted immediately (usually with direct current shock) or delayed permitting performance of transesophageal echocardiography (TEE) to exclude left atrial thrombosis, particularly when the arrhythmia lasted more than 24 to 48 hours, and an attempt of pharmacologic cardioversion; (2) the nature and extent of further investigations, and (3) the evaluation of optimal treatment strategies.

Symptoms

The ESC and CCS guidelines introduced score systems to quantify the severity of AF-related symptoms and their impact on quality of life: the European Heart Rhythm Association (EHRA) and the Severity of Atrial Fibrillation (SAF) (Table 42-6) scales.[63,170] Both scales are based on a subjective perception of symptoms by the patient and include four and five grades, respectively, ranging from the asymptomatic status to severe symptoms disrupting every day activity and significantly affecting quality of life.

Table 42-6 Assessment of Symptoms Related to Atrial Fibrillation and Impact on Quality of Life by EHRA score and CCS SAF Scale

EHRA CLASS	SYMPTOMS
EHRA I	No symptoms
EHRA II	Mild symptoms; normal daily activity not affected
EHRA III	Severe symptoms; normal daily activity affected
EHRA IV	Disabling symptoms; normal daily activity discontinued
SAF SCORE	**IMPACT ON QUALITY OF LIFE**
Class 0	No symptoms
Class 1	Minimal effect on quality of life
Class 2	Minor effect on quality of life
Class 3	Moderate effect on quality of life
Class 4	Severe effect on quality of life

CCS SAF, *Canadian Cardiovascular Society; Severity of Atrial Fibrillation;* EHRA, *European Heart Rhythm Association.*
From Camm AJ, Kirchhof P, Lip GY, 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 *12:1360–1420, 2010; Healey JS, Parkash R, Pollak T, et al, for the CCS Atrial Fibrillation Guidelines Committee: Canadian Cardiovascular Society atrial fibrillation guidelines 2010: Etiology and initial investigations,* Can J Cardiol *27(1):31–37, 2011.*

Many cases of AF are discovered incidentally and are thought to be truly asymptomatic. However, symptoms are often not perceived as physicians tend to focus on palpitations as the most important feature of the arrhythmia, but patients are often more aware of exertional dyspnea, poor exercise tolerance and fatigue, especially if the ventricular rate is slow (see Figure 42-10).[85] The true impact of the disease may be missed, and patients with longstanding, unrecognized, and untreated arrhythmia may be exposed to high risk of thromboembolic complications or tachycardia-induced left ventricular dysfunction with stroke and heart failure being the first clinical manifestations. Many patients may have both silent and symptomatic bouts of the arrhythmia, and considerable discrepancy exists between reported symptoms and documented rhythms. For example, patients may complain of episodic palpitations when rapid or highly irregular ventricular rates are present but may not be aware of their arrhythmia during slow ventricular rates (Figure 42-31). Therapeutic intervention may render AF asymptomatic or modify the patient's perception of the arrhythmia.

Electrocardiography

12-Lead Electrocardiogram

The diagnosis of any arrhythmias requires electrocardiographic documentation, the probability of which can be increased by using a standard ECG, rhythm strips obtained during the arrhythmia, ambulatory Holter recording, trans-telephonic or telemetric monitoring, and loop event recorders, including implantable devices.

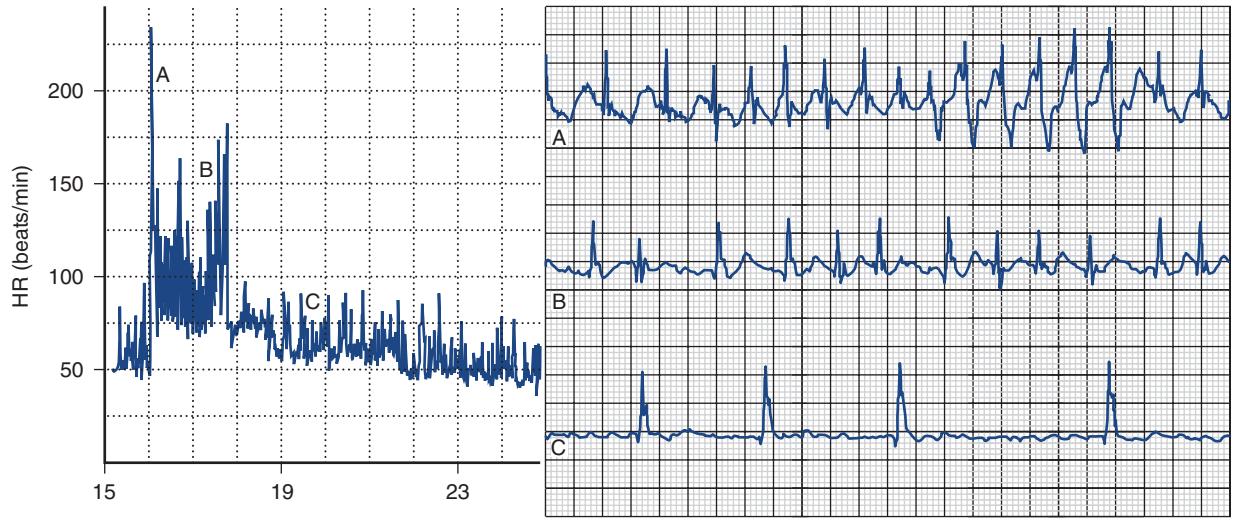


FIGURE 42-31 Holter monitor tachogram and electrocardiogram strips from a patient with atrial fibrillation. **A,** Symptomatic episode of the arrhythmia with a rapid ventricular rate response (>200 beats/min). **B,** Symptomatic episode of the arrhythmia with a slower but irregular ventricular rhythm. **C,** Asymptomatic episode with a slow ventricular rate response. In such "intermittently symptomatic atrial fibrillation," the presence of frequent asymptomatic periods can be mistakenly assumed for sinus rhythm. *HR*, Heart rate.

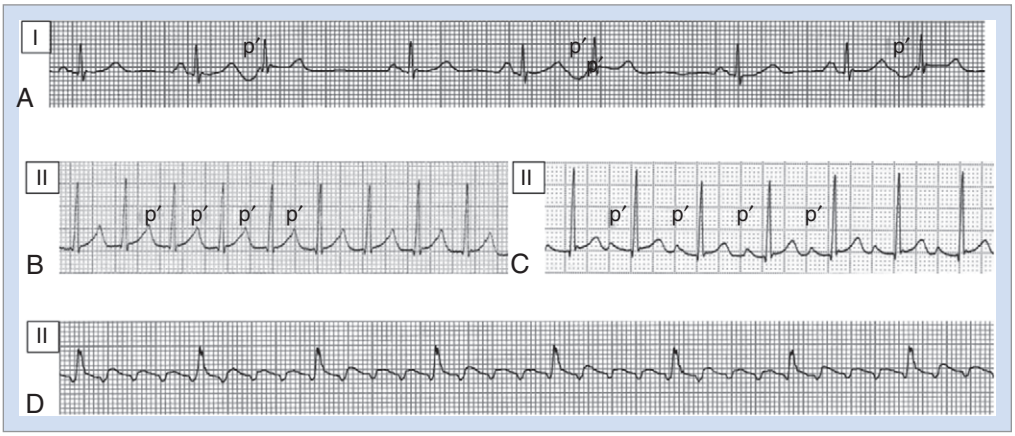


FIGURE 42-32 **A,** Frequent premature beats can mimic an irregularly irregular rhythm typical for atrial fibrillation. **B,** Atrial tachycardia with ventricular rates of 140 beats/min before treatment. **C,** Atrial tachycardia is still present after the initiation of sotalol but ventricular rates are significantly slower (100 beats/min). **D,** Atrial flutter with constant atrioventricular conduction mimicking a normal, regular pulse.

A proper evaluation of the 12-lead ECG is vital for several reasons. Firstly, the diagnosis must be confirmed (see Figure 42-25), and the type of the arrhythmia should be differentiated, as confusion may arise from other causes of irregular pulse, for example, frequent atrial or ventricular premature beats or intermittent heart block (Figure 42-32). Conversely, a regular, relatively slow pulse can be found in patients with AFL or AT if the ventricular rate is pharmacologically slowed down (see Figure 42-32). AF may coexist with complete heart block where atrial fibrillatory activity is visible as the baseline but where the ventricular rhythm is slow and regular. Second, the presence of pre-excitation syndrome on baseline ECG determines further investigation and management. Third, evidence of left atrial enlargement during sinus rhythm, previous MI, ST-segment and T-wave changes, left ventricular hypertrophy, and axis deviation can be useful in the identification of coexistent disease and assessment of risk of recurrence. Finally, monitoring of the P-R and Q-T intervals and the QRS complex width is essential for the prevention of proarrhythmias during antiarrhythmic drug therapy.

Holter Monitoring

Ambulatory 24-hour Holter monitoring usually is useful for the diagnosis of frequent paroxysms of the arrhythmia and for the assessment of the effects of rate-slowing agents if rate control was selected as a principal management strategy (Figure 42-33). In some cases, it may provide information pertinent to the principal management of the arrhythmia, as documentation of frequent

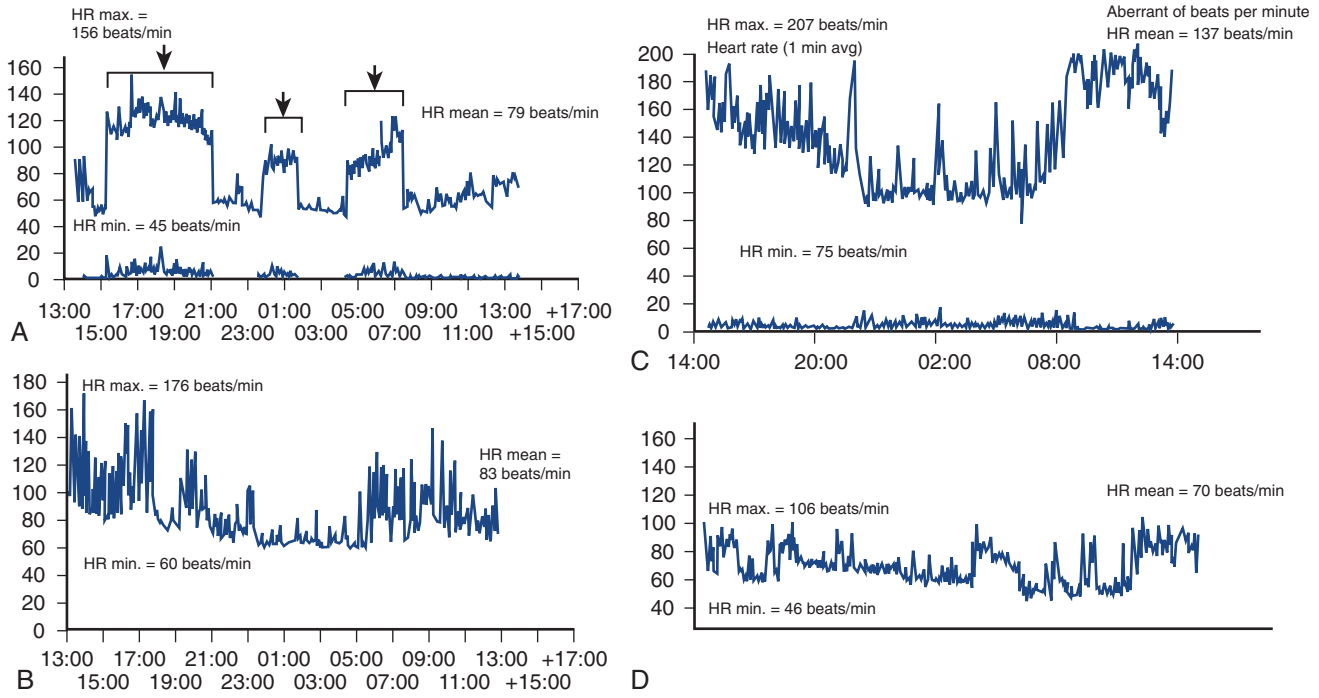


FIGURE 42-33 **A,** A Holter monitor heart rate (*HR*) histogram plotted against time showing at least three paroxysms of atrial fibrillation with fast ventricular rates within 24 hours (*arrows*). **B,** A Holter histogram of extremely frequent, multiple short-lived episodes of atrial fibrillation ("incessant" paroxysmal atrial fibrillation). **C,** A Holter monitor histogram in a patient with permanent atrial fibrillation before treatment. **D,** The same patient as **C** during rate control therapy.

atrial premature beats or fast atrial tachycardia preceding AF may be crucial for the selection of nonpharmacologic treatment alternatives (Figure 42-34). Digital ambulatory recorders, which enable standard 12-lead configurations similar to that of the digital diagnostic-quality 12-lead ECG machines, may increase diagnostic accuracy.

Loop Recorders

When paroxysms of the arrhythmia are infrequent or when asymptomatic episodes are suspected, a loop event recorder with transtelephonic or telemetric facilities can offer long-term, continuous ECG monitoring and event-specific recording. ECG loop recorders have a retrospective (loop) memory, which continuously records and deletes the patient's ECG. They can be both implantable and external devices and have a patient activation function that allows the patient to activate ECG storage as a result of symptoms and an auto-activation feature that allows the automatic capture of arrhythmic events. The probability of capturing the arrhythmic event varies from 65% to 88% (Figure 42-35).[171] Implantable loop recorders are superior to Holter monitoring systems in the diagnosis of very infrequent arrhythmic attacks, determination of onset patterns, identification of asymptomatic arrhythmias, assessment of treatment efficacy, and detection of proarrhythmias.[172]

One of such devices, Reveal XT (Medtronic Inc., Minneapolis, MN) has been tested in patients who underwent pulmonary vein ablation and has been shown to identify AF recurrences with a 92% positive predictive accuracy.[173] These devices can be useful in identifying AF as a cause of cryptogenic strokes when no specific risk factors are present.

Exercise Stress Test

Exercise stress test can be used for exclusion of adrenergically mediated or exercise-induced AF and for the assessment of the effectiveness of rate control therapy in patients with permanent AF (Figure 42-36). It is also generally performed in individuals with suspected CAD, especially, if type IC antiarrhythmic drug therapy is planned.

Blood Tests

Essential blood tests include a full blood count and hemoglobin, serum electrolytes, including serum potassium and magnesium levels, and the assessment of thyroid function. A lipid profile is often warranted in patients with risk factors for CAD. Of interest, several reports identified the association between low levels of high-density lipoprotein (HDL) cholesterol and risk of AF.[174]

Thyrotoxicosis accounts for 1% to 2% of new cases of AF but abnormal thyroid function tests can be found in 4% to 12.5% of AF patients.[39] Recognition of a hyperthyroid state is important because cardioversion and long-term maintenance of sinus rhythm are unlikely as long as the underlying condition persists. Thyroid hormones have a direct positive chronotropic effect and may enhance cardiac sensitivity to catecholamines by increasing β-adrenergic receptor density. In some patients, no obvious symptoms of hyperthyroidism are present or only subtle signs of an overactive thyroid are present (apathetic hyperthyroidism), and the arrhythmia can be the only clinical marker of the disease.

Anemia may contribute to dyspnea or may precipitate atrial tachyarrhythmias. The white cell count may suggest the presence

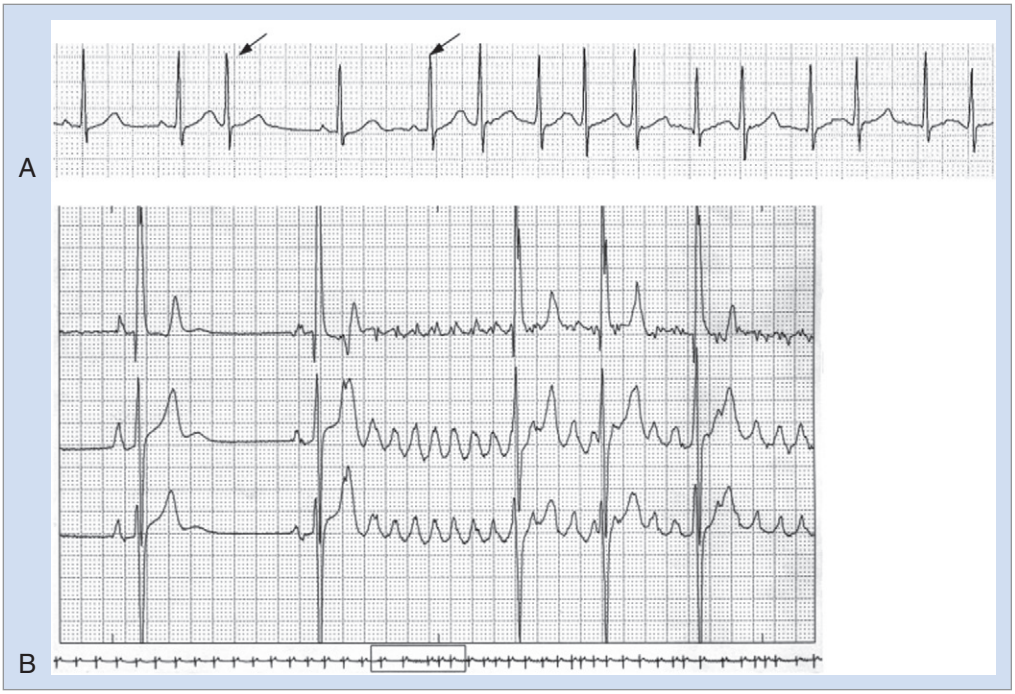


FIGURE 42-34 A, A Holter monitor strip showing initiation of atrial fibrillation by atrial premature beats (*arrows*) **B,** A Holter electrocardiogram recording of onset of the arrhythmia in a patient with paroxysmal atrial fibrillation. Note the presence of focal atrial tachycardia with a cycle length of 190 to 200 ms, which initiates atrial fibrillation. Because this arrhythmia is likely to originate from the region of the pulmonary veins and may be amenable to radiofrequency catheter ablation, the next step in investigation should be electrophysiological study.

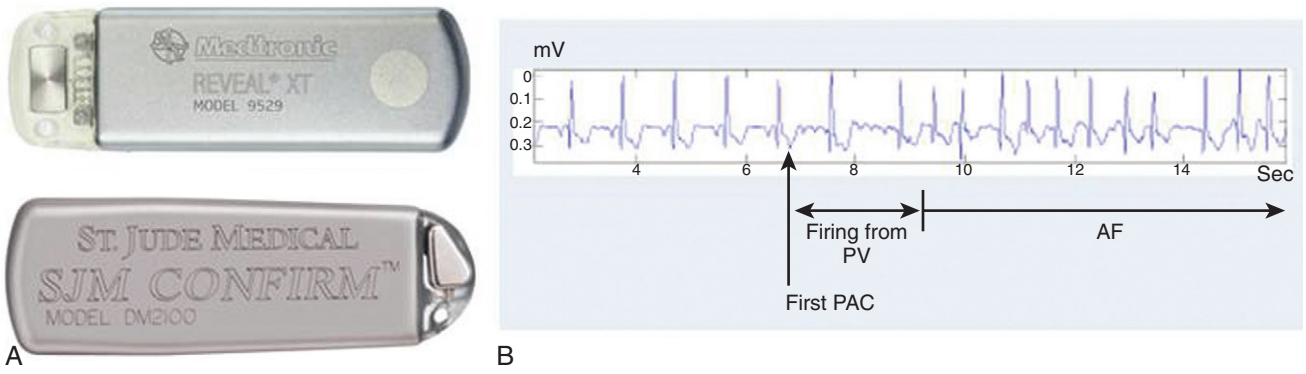


FIGURE 42-35 A, Currently available implantable loop recorders. **B,** A rhythm strip from the Reveal XT device (Medtronic Inc.) demonstrating onset of atrial fibrillation. Note an atrial premature beat followed by the run of fast atrial tachycardia, possibly from the pulmonary vein, preceding atrial fibrillation. *(Courtesy A. Vincent, Medtronic Inc., Minneapolis, MN).*

of inflammatory mechanisms precipitating the arrhythmia. Measures of the acute phase response, such as the erythrocyte sedimentation rate (ESR) and C-reactive protein, may give further guidance where inflammatory or malignant processes are suspected. Increased levels of C-reactive protein have been associated with the development of AF in the general population and with recurrent AF after cardioversion and may be a marker of the inflammatory mechanism underlying the arrhythmia but currently are only measured for research purposes.[174]

Serum liver enzyme levels, in particular that of γ-glutamyltransferase, may be helpful when alcohol is suspected as a cause of AF. Thyroid and liver function monitoring is mandatory during therapy with amiodarone, and creatinine clearance is essential while adjusting the dose of dofetilide.

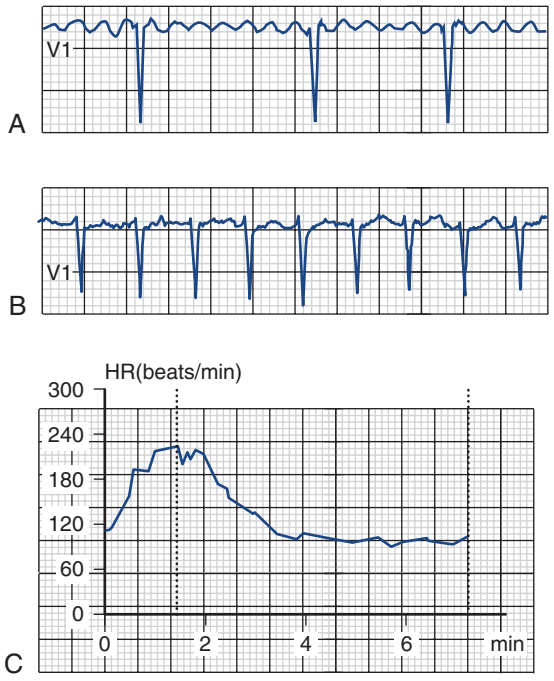


FIGURE 42-36 Inadequate ventricular rate control during exercise in a patient with permanent atrial fibrillation treated with digoxin only. **A,** Baseline electrocardiogram. **B,** An electrocadiogram after 1.5 minutes of exercise stress test. **C,** A tachogram showing a rapid increase in ventricular rates immediately after the beginning of exercise.

Imaging

Echocardiography

TTE is essential if active management is contemplated. Valve heart lesions, severe enough to cause AF, are usually evident on clinical examination but may not be discovered. Echocardiographic measurement of left ventricular hypertrophy and left ventricular dysfunction is important for the guidance of prophylactic antiarrhythmic drug therapy in patients with hypertension and CHF. The left atrial volume at the time of mitral valve opening is now routinely measured (Figure 42-37, *A*). Three-dimensional echocardiography allows assessing left atrial volumes at different phases of the cardiac cycle. TTE can be effectively used to assess left atrial mechanical function, but its sensitivity in diagnosis of an LAA thrombus is low.

Transesophageal echocardiography (TEE) is capable of providing high-quality images of cardiac structure and function and is the most sensitive and specific technique to detect the presence of thrombi in the left atrium and the LAA, which have been found in 5% to 15% of patients with AF prior to cardioversion (see Figure 42-37, *B*).[175] TEE has proved to be useful in the stratification patients with AF and AFL with regard to risk of ischemic stroke and has been suggested for the guidance of elective cardioversion.[176]

Left Atrial Imaging

New techniques such as three-dimensional echocardiography, color tissue Doppler imaging, speckle tracking, and delayed enhancement cardiac MRI are increasingly being used to determine left atrial function and structure.[177] Cardiac CT and MRI are routinely used to ascertain the anatomy of the left atrium and pulmonary veins prior to ablation and as part of image integration with real-time electroanatomic mapping during ablation (see Chapter 17). Left atrial volume and the amount of fibrosis (Utah score) have been linked to the progression of AF (see Figure 42-7) and the risk of stroke and can be used to guide the ablation strategy.[68,178] These imaging techniques can potentially be used for the assessment of reversal of atrial remodeling and efficacy of therapy.

Brain Imaging

In patients with a suspected history of TIAs, CT or MRI imaging can reveal previous silent cerebral infarcts and influence the decision in favor of life-long anticoagulation (see Figure 42-37, *C* and *D*). Recently, the presence of microbleeds on Baring imaging has been linked to increased risk of subsequent ischemic and hemorrhagic strokes.[179] Microbleeds are particularly significant in patients with AF on oral anticoagulation. Of note, a lower risk of hemorrhagic stroke on therapy with new anticoagulants such as dabigatran compared with warfarin can probably be explained by the fact that the latter penetrates the hemato-encephalic barrier and may have a local effect.

Electrophysiological Study

Electrophysiological study (EPS) is indicated for the identification of the specific arrhythmia mechanism, for example, in patients with suspected AVRT or AVNRT, which may trigger AF. EPS can also identify sinus node dysfunction and define the mechanism of wide QRS complex tachycardia. The mechanisms of AF, mapping, and effectiveness of therapy can be judged and are dealt with in more detail in Chapters 28, 91, and 93.

Principles of Practice

The fundamental principles of therapy of AF include (Figure 42-38): (1) risk stratification and prevention of thromboembolic complications and stroke; (2) ventricular rate control, if expedient restoration and maintenance of sinus rhythm is impossible or not contemplated (e.g., accepted AF); (3) electrical or pharmacologic restoration and maintenance of sinus rhythm; (4) selection of an appropriate long-term rhythm control strategy and identification of AF amenable to ablation; (5) identification and correction of risk factors and elimination of precipitating agents; and (6) treatment of the underlying pathology. Therapies currently available for management of AF are summarized in Table 42-7.

Anticoagulation

Pathogenesis of Stroke in Atrial Fibrillation

Absence of organized mechanical contraction of fibrillating atria with a consequent increase in atrial pressure, atrial stretch, and dilation caused by multiple pathophysiological mechanisms compensating for reduced cardiac output, generate conditions for blood stasis and thrombus formation (Figure 42-39).[180] Atrial

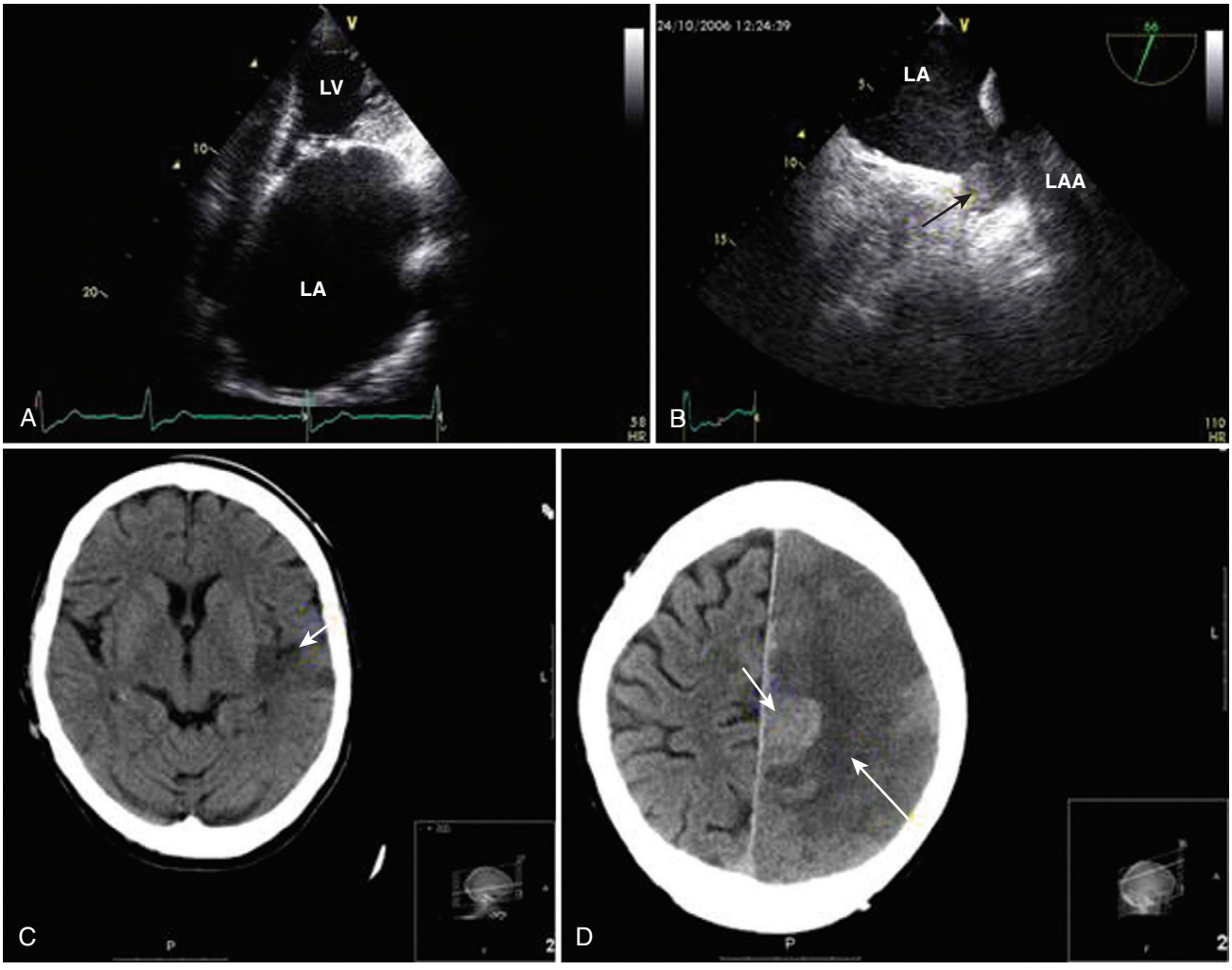


FIGURE 42-37 **A,** A gigantic left atrium in a patient with atrial fibrillation and mitral stenosis. **B,** Left atrial appendage thrombus (*arrow*) detected by transesophageal echocardiography in a patient with atrial fibrillation (AF). Note the presence of spontaneous echo contrast in the left atrium. **C,** A computed tomographic image of cerebral infarct (*arrow*) in a patient with AF but without neurologic symptoms (silent infarct). **D,** A computed tomographic image of acute ischemic stroke (*arrow*) with subsequent hemorrhagic transformation (*thick arrow*) in a patient with AF. *LA*, Left atrium; *LAA*, left atrial appendage; *LV*, left ventricle.

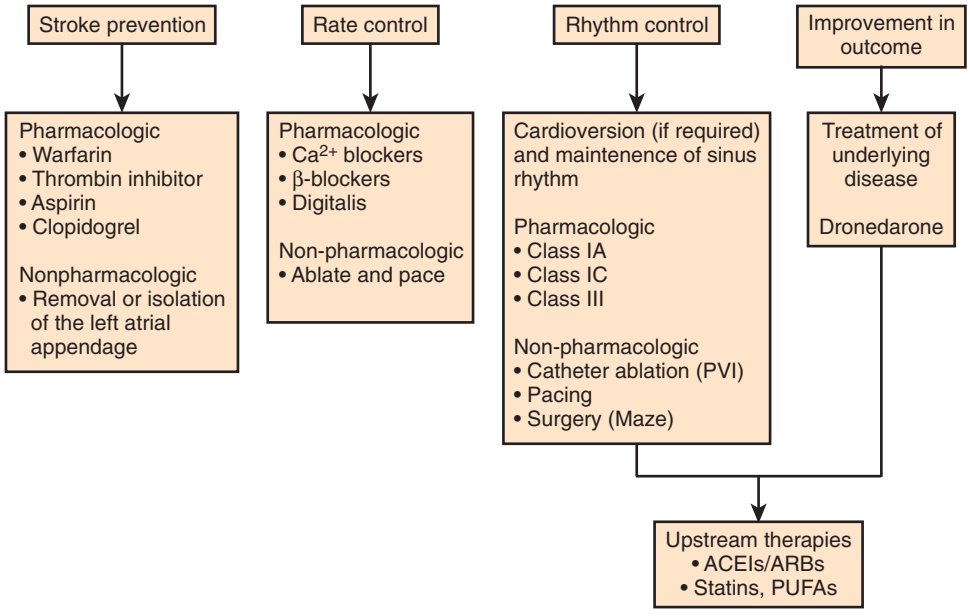


FIGURE 42-38 Principles of management of atrial fibrillation. *ACEI*, Angiotensin-converting enzyme inhibitor; *ARBs*, angiotensin receptor blockers, *PUFAs*, polyunsaturated fatty acids; *PVI*, pulmonary vein isolation.

Table 42-7 Management Strategies in Atrial Tachyarrhythmias

STRATEGY	ADVANTAGES	DISADVANTAGES	INDICATIONS
Pharmacologic rhythm control	Symptom relief	Low probability of remaining in sinus rhythm in the long term (approximately 50%-60% at 1-2 years)	Recurrent paroxysmal AF
	Normal intracardiac and systemic hemodynamics	Often need for repeat cardioversion	Recurrent persistent AF after cardioversion, espectially if highly symptomatic
	Prevention or delay of electrophysiological and structural remodeling, atrial enlargement	No reduction in mortality rate or thromboembolic events	Recurrent paroxysmal or persistent AFL if ablation therapy is impossible or ineffective
	Availability, low cost	Risk of noncardiac adverse effcts	Recurrent paroxysmal or incessant AT if ablation therapy is impossible or ineffective
	Relatively wide antiarrhythmic drug choice	Need for anticoagulation in high-risk patients if increased likelihood of recurrence or asymptomatic recurrence of the arrhythmia	
	No intervention, often may be started on an outpatient basis		
	Leaves other, nonpharmacologic options if treatment fails		
Pharmacologic rate control	Reduction in symptoms	Impaired intracardiac and systemic hemodynamics	Permanent AF
	Availability, low cost	Insufficient rate control with one drug, need for polypharmacy	"Accepted" AF if mildly symptomatic or asymptomatic and in those >65 years
	Easy to start and control	Risk of proarrhythmia and bradycardia (e.g., digoxin)	Persistent AF in patients with NHYA heart failure class >II
	Comparable results with rhythm control in terms of mortality rate and thromboembolic events	Risk of noncardiac adverse events	"Accepted" AFL if ablation therapy is impossible or ineffective
	Leaves other, nonpharmacologic options if therapy fails	Need for lifelong anticoagulation	
		No long-term prevention of atrial remodeling	
"Ablate and place"	Significant symptom improvement	Renders patients dependent on pacemakers	Highly symptomatic, drug-refractory AF
	Some improvement in cardiac performance (exercise tolerance, ejection fraction)	Risk of thromboembolic complications; need for anticoagulation therapy	Inadequate pharmacologic rate control
	Improvements in quality of life	Pharmacologic rhythm control may be needed	Contraindications for pharmacologic therapy
	Mortality rate does not differ from that of pharmacologic rate control	No long-term prevention of atrial remodeling; progression to a permanent form	
		Right ventricular pacing may be deleterious in the long term (systolic dysfunction)	
AV node modification	Comparable with the "ablate and pace" strategy	High percentage of complete AV block, resulting in pacemaker implantation	Highly symptomatic, drug-refractory AF
		Risk for thromboembolic complications; need for anticoagulation therapy	
		Irregularity of ventricular rate may be accompanied by symptoms	
		Often need for additional pharmacologic rate control	
		Fast AV conduction may restore in the long term	
Isthmus ablation	"Cures" typical AFL with a 95% success rate	AF is not completely abolished	Typical AFL
	May redule the incidence of AF triggered by AFL	Incidence of AF postablation varies from 10% to 74%	AFL as a result of AAD for AF
		If AF was converted to AFL by AADs, these should be continued after ablation of AFL	Incisional re-entrant AFL, if a vulnerable isthmus is identified

Continued

Table 42-7 Management Strategies in Atrial Tachyarrhythmias—cont'd

STRATEGY	ADVANTAGES	DISADVANTAGES	INDICATIONS
Ablation for focal or macro–re-entrant AT	"Cures" AT with a 75%-86% success rate	Difficulty with identification of an arrhythmogenic focus or the re-entry circuit	Focal AT
	May reduce the incident of AF triggered by AT	Rate of recurrence is 8%, but follow-up is limited	Macro–re-entrant AT after atrial septal defect closure, Fontan and Mustard procedures
		Rate of significant complications, including cardiac perforation and AV block, is 1%-2%	
Pulmonary vein isolation	Renders AV entirely curable if successful; best success rate is 66%; up 20 85% with circumferential pulmonary vein isolation	Difficulty with identification of all arrhythmogenic foci	AF triggering by rapid AT from local foci (usually in the pulmonary vein)
		High rate of recurrence; need for repeat procedure	
		Risk of pulmonary vein stenosis or thrombosis (up to 42% less with new techniques, 1%-2%)	
		Risk of thromboembolism (0.5%)	
		Limited to paroxysmal AF	
		Need to continue AADs in 23% of cases	
Intraoperative or surgery-based Maze procedure	Renders AF entirely curable if successful; long-term success rate is 80% (32%-93%) and up to 99% with AADs	Need for expanded linear ablation not limited to one atrium	Highly symptomatic, drug-refractory AF
		High degree of tissue trauma	Patients undergoing cardiac surgert (coronary bypass, valve repair or replacement)
		Incomplete lesions may be arrhythmogenic	
		Increased procedure time	
Left atrium isolation	"Cures" AF; success rate is 71%, with transection extended to the right atrium, 85%	Probably same as Maze procedure	Same as Maze procedure
Atrial defibrillator	Converting AF or AFL with a synchronized low-energy atrial shock	Considerable discomfort	Infrequent, asymptomatic, drug-refractory AF or AFL not amenable to ablation (probably with minimal structural heart disease)
	Can be performed on an outpatient basis	Poor compliance	
	Shock can be administered promptly or delayed	High incidence of early recurrence	
	Prevention or delay of electrophysiological and structural atrial remodeling, atrial enlargement, and progression to a permanent form	Need for repeat shock	
		Limited data in patients with structural heart disease	
Atrial or dual-chamber pacing	Provide physiological pacing with normal intracardiac hemodynamics	No reduction in all-cause mortality rate with DDD(R) vs. VV(R) pacing modes	Conventional bradycardia indications and recurrent pacemaker arrhythmias, predominantly AF
	May prevent or reduce progression to a permanent form in the long term (>2 years), especially in patients with no history of arrhythmias and patients with sick sinus syndrome but no AV block	Efficacy of antitachycardia packing has not yet been proven	
	Painless antitachycardia pacing to terminate organized atrial rhythms	No reduction in arrhythmia burden has been reported	

Table 42-7 Management Strategies in Atrial Tachyarrhythmias—cont'd

STRATEGY	ADVANTAGES	DISADVANTAGES	INDICATIONS
	A variety of preventive atrial pacing algorithms to modify the substrate and suppress triggers of AF	Some therapies (e.g., high-frequency burst) are available on an inpatient basis only	
	Potential for pacing from specficsites (Bachmann's bundle, triangle of Koch) or multi-site pacing as an add-on therapy to drugs or ablation	Risk of thromboembolic complications remains; need for lifelong anticoagulation therapy Often need for adjunctive AAD therapy Right ventricular pacing may be deleterious in the long term Technical difficulty with placing additional electrodes	
Dual-chamber ICD	Painless antitachycardia pacing to terminate organized atrial rhythms	Efficacy of antitachycardia pacing and preventive pacing has not yet been proven	Patients with both ventricular and atrial arrhythmias, structural heart disease, impaired left ventricular function, with high risk of proarrhythmia on AADs
	A variety of preventive atrial pacing algorithms to modify the substrate and suppress triggers of AF	Some therapies (e.g., high-frequency burst) are available on an inpatient basis only	
	Converting arrhythmia with a synchronized low-energy atrial shock administered promptly or delayd	Risk of thromboembolic complications remains; need for lifelong anticoagulation therapy	
	May prevent degeneration of AF into ventricular fibrillation	Risk of electrical proarrhythmia remains unclear Disadvantages of atrial shock are similar to those with stand-alone defibrillator, but there is a possibility of overdrive packing to prevent frequent shocks Expensive, not widely available Technically difficult with placing specific electrodes (e.g., coronary sinus) Potential risk of inappropriate shock due to sensing problems (e.g., far-field oversensing)	

AADs, *Antiarrhythmic drugs;* AF, *atrial fibrillation;* AFL, *atrial flutter;* AT, *atrial tachycardia;* AV, *atrioventricular; ICD, implantable cardioverter-defibrillator;* NYHA, *New York Heart Association.*

stretch results in the increased production of ANP and decreased secretion of vasopressin, which may cause hemoconcentration within the fibrillating atria. A hypercoagulable state and increased platelet activation have been found in association with AF, adding to the risk of thrombus formation. Endothelial injury and systemic inflammation are also contributory factors. The left atrium andthe LAA, particularly because of its anatomic features (distensibility and trabeculations), are the main source of cardioembolic emboli in AF.[181] With TEE, left atrial thrombi can be found in about 14% of patients with AF or AFL, even if they were effectively anticoagulated, and spontaneous echocardiographic contrast can be seen in 52% of patients.[176-178,181] The LAA is the source of thrombi in 80% to 90% of patients.[182]

Risk Stratification

Stroke

A number of models have been devised to predict the risk of stroke and the likelihood of benefit from therapy with either warfarin or aspirin. Patients with valvular AF (mitral valve stenosis or prosthetic valves) are considered high risk, independently of other risk factors, and anticoagulation is mandatory in this patients.[183] Major risk factors for stroke in nonvalvular AF were identified on the basis of the pooled analysis of 1593 untreated patients from five primary-prevention trials of warfarin (known as Atrial Fibrillation Investigators' risk stratification model) and the results from 2012 participants from the aspirin arms of the Stroke Prevention in Atrial Fibrillation I to III (SPAF) studies.[184-186] Both reports have shown that hypertension, prior stroke or TIA, diabetes, and advanced age are all associated with increased risk of stroke. The SPAF investigators also introduced left ventricular dysfunction and female gender as risk factors. According to these schemes, patients with no major risk factors have a 0.9% to 1% probability of stroke, those with 1 (or 2) risk factors are at moderate risk, which is estimated at 2.6% to 5.7%, and individuals with more than 2 risk factors have a risk of stroke of 7.1% to 8.1%. All subsequent risk stratification schemes used a combination of these factors.

The most widely accepted $CHADS_2$ scheme is an amalgamation of individual risk factors: **c**ongestive heart failure, **h**ypertension, **a**ge >75 years, **d**iabetes mellitus, each of which is assigned one point, and prior **s**troke or TIA, which is given 2 points (hence,

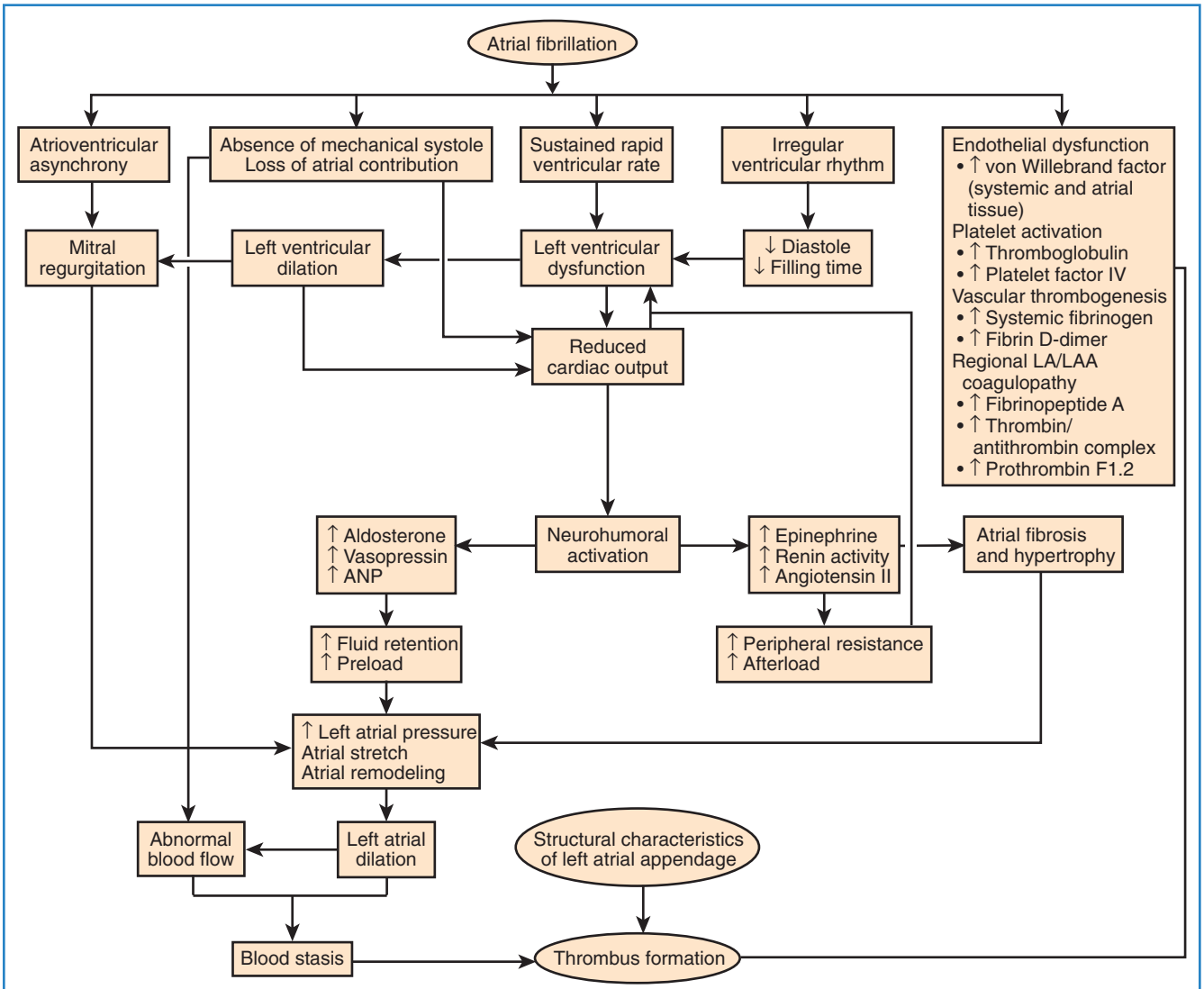


FIGURE 42-39 Pathogenesis of thrombus formation in atrial fibrillation. *AF*, Atrial fibrillation; *ANP*, atrial natriuretic peptide; *LA*, left atrium; *LAA*, left atrial appendage.

the subscript "2").[185-187] The $CHADS_2$ score system was designed to simplify the determination of stroke risk in general practice. Using this system, the stroke rate per 100 patient-years without anti-thrombotic therapy is expected to increase by a factor of 1.5 for each 1-point increase from 1.9 for a score of 0, to 18.2 for the highest score of 6 (Table 42-8).

Although it provides a valuable first step in identifying patients for whom anticoagulation is mandatory, the $CHADS_2$ scheme allows a rather crude estimate of stroke risk as it does not take into consideration less validated risk factors such as gender, age between 65 and 75 years, the presence of obstructive artery disease (coronary, carotid, peripheral), chronic kidney dysfunction and proteinuria, and thyrotoxicosis. Furthermore, it underappreciates the importance of advanced age (>75 years), which is probably a more powerful risk factor than previously thought. Some of these factors have been incorporated in the CHA_2DS_2VASc system adopted by the ESC guidelines (Table 42-9).[187]

The advantage of the CHA_2DS_2VASc system is that is appears to perform best identifying patients at truly low risk of stroke and those who would benefit from anticoagulation but who would be deemed as low risk by other risk stratification systems (Figure 42-40).

Although TEE is not routinely used for this purpose, it can offer further refining of risk stratification based on specific findings such as an enlarged LAA with reduced inflow and outflow velocities and thrombi and complex aortic plaque (thick >4 mm, mobile, pedunculated).[188] Assessment of indexes of hypercoagulability and endothelial dysfunction or damage (e.g., von Willebrand factor, P-selectin, fibrin, D-dimer, thrombomodulin) for prediction of stroke in AF remains a research tool.

Bleeding

The efficacy of anti-thrombotic therapy for the prevention of ischemic stroke should be balanced against the risk of major hemorrhagic complications, particularly cerebral hemorrhage, which is usually fatal or significantly disabling. The risk of hemorrhagic events is related to the intensity of anticoagulation, patient

Table 42-8 $CHADS_2$ Stroke Risk Stratification in Nonvalvular Atrial Fibrillation

HISTORY	$CHADS_2$ RISK SCORE
Prior stroke or TIA	2
Age >75 years	1
Hypertension	1
Diabetes mellitus	1
Heart failure	1

$CHADS_2$ SCORE	ADJUSTED STROKE RATE (%/YEAR) (95% CI)
0	1.9 (1.2-3.0)
1	2.8 (2.0-3.8)
2	4.0 (3.1-5.1)
3	5.9 (4.6-7.3)
4	8.5 (6.3-11.1)
5	12.5 (8,2-17.5)
6	18.2 (10.5-27.4)

$CHADS_2$, Cardiac failure, hypertension, age, diabetes, stroke [doubled] risk stratification system; TIA, *transient ischemic attack;* CI, *confidence interval.*
From Gage BF, Waterman AD, Shannon W, et al: Validation of clinical classification schemes for predicting stroke: Results from the National Registry of Atrial Fibrillation, JAMA *285:2864–2870, 2001; and Van Walraven WC, Hart RG, Wells GA, et al: A clinical prediction rule to identify patients with atrial fibrillation and a low stroke risk while taking aspirin,* Arch Intern Med *163:936–943, 2003.*

age, and fluctuations of previously therapeutic international normalized ratio (INR) values caused by drug or food interactions.[189] Overall, randomized trials comparing outcomes of therapy with full-dose warfarin versus placebo did not show unacceptably higher rates of major hemorrhagic complications, including intracranial bleeding, most of which occurred in patients older than 75 years.

An assessment of bleeding risk is part of patient assessment prior to initiating anticoagulation.[190] Several risk stratification schemes for bleeding in AF populations have been proposed:

Table 42-9 CHA_2DS_2VASc Stroke Risk Stratification in Nonvalvular Atrial Fibrillation

HISTORY	CHA_2DS_2VASC RISK SCORE
Congestive heart failure or left ventricular dysfunction	1
Hypertension	1
Age ≥75 years	2
Diabetes mellitus	1
Stroke, TIA, or thromboembolic vascular disease (CAD, CArD, PAD)	2
Age 65-74 years	1
Gender (female)	1

CHA_2DS_2VASc, Cardiac failure, hypertension, age (doubled), diabetes, stroke (doubled); vascular disease: myocardial infarction, aortic plaque, peripheral arterial disease; CAD, *coronary artery disease;* TIA, *transient ischemic attack;* CArD, *complex aortic plaque disease;* PAD, *pulmonary artery disease.*

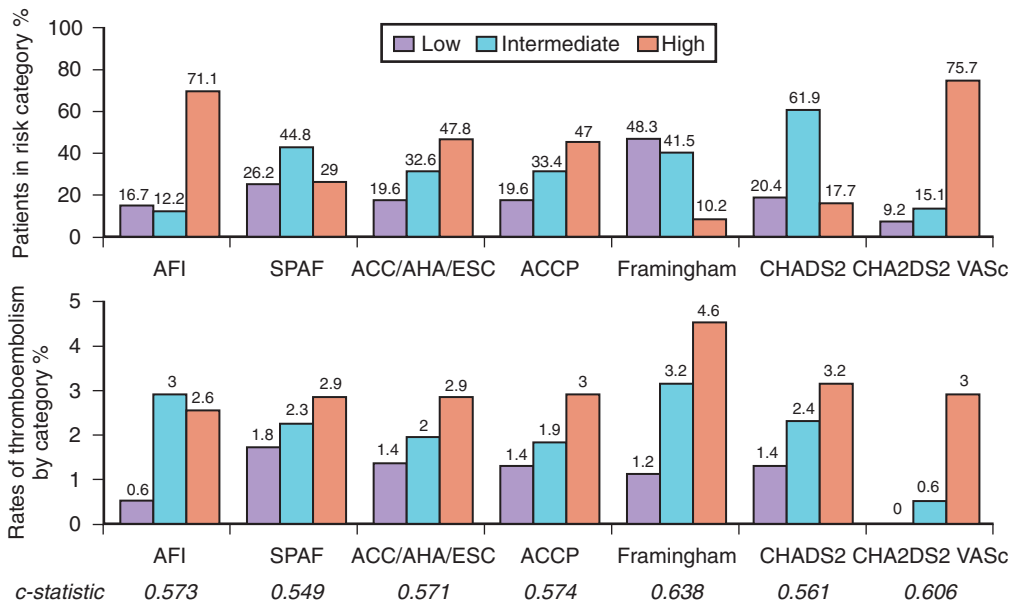


FIGURE 42-40 Performance of the CHA_2DS_2VASc risk stratification scheme compared with other currently used risk stratification systems. Note that CHA_2DS_2VASc scheme better identifies patients with truly low risk of thromboembolic events. *(From Lip GY, Nieuwlaat R, Pisters R, et al: Refining clinical 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 *137:263–272, 2010.)*

Table 42-10 Risk Stratification for Bleeding

HEMORR$_2$HAGES*	SCORE	HAS-BLED†	SCORE
Hepatic or renal disease	1	**H**ypertension	1
Ethanol abuse	1	**A**bnormal renal or liver function	1 or 2
Malignancy	1	**S**troke	1
Older age (≥75)	1	**B**leeding	1
Reduced platelet count	1	**L**abile INR	1
Re-bleeding	2	**E**lderly (age >65 years)	1
Hypertension (uncontrolled)	1	**D**rugs or alcohol	1 or 2
Anemia	1		
Genetic factors	1		
Excessive fall risk	1		
Stroke	1		

**Validated in 3791 Medicare patients with atrial fibrillation (mean age, 80.2 years; 57% women) and event rates: 5.2 bleeds per patient-year (67.3% gastrointestinal, 15.4% intracranial, 17.3% other); hazard ratios 0.91 vs. 0.85 for patients on acetylsalicylic acid or no therapy.*
†Validated in 3978 patients with nonvalvular atrial fibrillation with known thromboembolic status at 1 year in the Euro Heart Survey; c-statistic = 0.72 (similar to HEMORR$_2$HAGES).
INR, *International normalized ratio.*
From Gage BF, Yan Y, Milligan PE, et al: Clinical classification schemes for predicting hemorrhage: Results from the National Registry of Atrial Fibrillation (NRAF), Am Heart J *151:713–719, 2006; and Pisters R, Lane DA, Nieuwlaat R, et al: 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 *138:1093–1100, 2010.*

HEMORR$_2$HAGES and HAS-BLED (Table 42-10).[191,192] The limitation of these schemes is that they share many risk factors that have also been linked to stroke.

Therapy

Aspirin and Clopidogrel

Aspirin acts by irreversibly acetylating platelet cyclooxygenase-1, thereby blocking arachidonic acid metabolism and the formation of thromboxane A_2, which potentiates platelet aggregation and the release of granule contents. It is less effective when stasis and enhanced coagulation, rather than platelet activation in response to endothelial injury, are the principal mechanisms of thrombosis as occurs in the fibrillating atria or in the venous system. Consequently, therapy with aspirin reduced the risk of stroke by about 20%, with the variable magnitude of the effect, depending on the study design and dose range.[193] In direct comparisons with warfarin in older adults enrolled in the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study, aspirin was associated with a 48% higher risk of stroke compared with adjusted-dose warfarin, whereas no differences in bleeding complications were seen.[194] Aspirin alone is not recommended for the prevention of stroke, and alternative therapies (e.g., LAA occlusion devices) should be used for stroke prevention in patients who cannot take warfarin.

Clopidogrel selectively and irreversibly blocks platelet P2Y12 adenosine diphosphate (ADP) receptors and prevents ADP-induced platelet activation. A combination of aspirin with clopidogrel has been tested in the W ("W" stands for "warfarin") arm of the Atrial fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE) in 6706 high-risk patients with AF.[195] The study was stopped prematurely because of the clear superiority of warfarin. A 44% increase in a composite primary endpoint of stroke, systemic embolism, MI, and vascular death and a 72% increase in any stroke associated with antiplatelet therapy were seen, whereas the likelihood of ischemic stroke was more than doubled.

However, combination therapy outperformed aspirin alone in the twin ACTIVE A study, which showed a modest, but statistically significant, 11% reduction the primary endpoint and a 28% reduction in the rate of stroke.[196] Therefore, the combination therapy may be used in patients with contraindications to warfarin, although a risk of clopidogrel (as well as aspirin) resistance exists.[197]

Warfarin

Warfarin, a vitamin K antagonist, reduces the synthesis of biologically inactive forms of thrombin and clotting factors VII, IX and X, which requires vitamin K. Anticoagulation with adjusted-dose warfarin (target INR, 2.5; range, 2 to 3) is recommended in all patients at risk but without a contraindication. This strategy is also pertinent for patients with moderate risk on the basis of an individualized approach that balances the risks and benefits of oral anticoagulation or aspirin, but preference should be given to warfarin. Warfarin has consistently reduced the risk of ischemic stroke or systemic embolism by about two thirds compared with no treatment and by 30% to 40% compared with aspirin in high-risk patients with AF (Figure 42-41).[193] The number needed to treat (NNT) to prevent one stroke has been estimated to be 100 patient-years for those at low risk (≤2% per year) compared with 25 patient-years for those at high risk (≥6% per year).

International Normalized Ratio Monitoring

Despite it proven efficacy, warfarin is substantially underused (Table 42-11). Warfarin has a narrow therapeutic window, and its management is complicated by multiple drug interactions and variations in dietary intake of vitamin K, prompting regular, and sometimes intense, monitoring of coagulation parameters and dose adjustment, and stringent control of diet, alcohol, and co-medications. Warfarin has a relatively slow onset of action (2 to 7 days), and early thrombogenic risk increases because of the depletion of natural anticoagulation proteins C and S. Intracranial bleeding is the most serious complication with warfarin, as it is associated with high mortality or disability rates.

Genetic determination of the response to warfarin also exists. Patients with variant alleles (CYP2C9*2 and CYP2C9*3) of the liver cytochrome P-450 2C9 (CYP2C9) isoenzyme, which is involved in warfarin metabolism, are slow metabolizers of warfarin and can be exposed to higher concentrations of the drug and the associated risk of over-anticoagulation. Conversely, individuals with polymorphisms in the gene encoding for the vitamin K epoxide reductase complex 1 (VKORC1), which is the target protein for warfarin, exhibit increased resistance or a greater sensitivity to warfarin.[198] Although it is possible to screen patients for

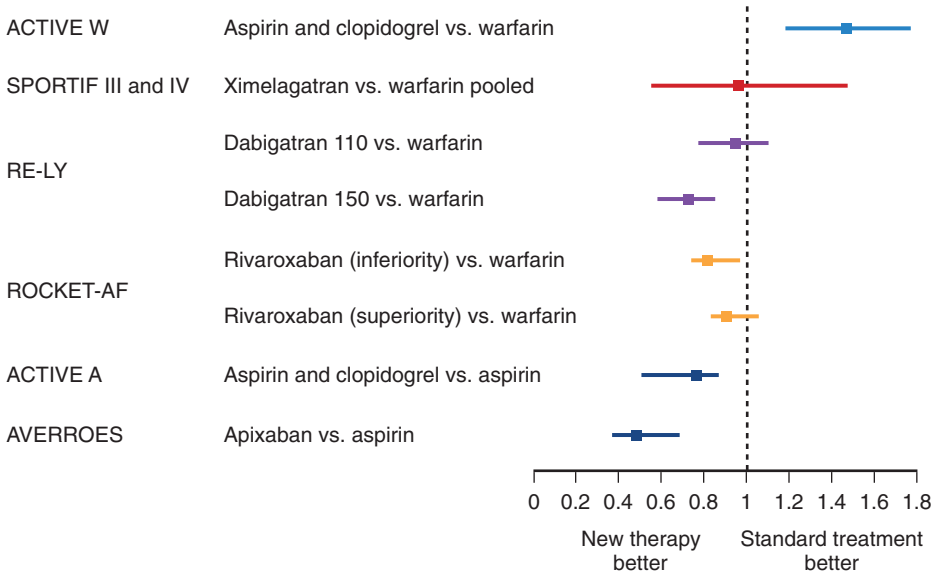


FIGURE 42-41 Performance of new antithrombotic therapies versus standard treatment for the prevention of stroke and systemic embolism associated with atrial fibrillation.

Table 42-11 Use of Warfarin for Prevention of Atrial Fibrillation–Related Stroke in Epidemiologic Studies

STUDY	NO. PATIENTS	YEAR	$CHADS_2$ SCORE	WARFARIN GIVEN
ATRIA (1999)	11,082	1996–1997	75% ≥65 years 50% HTN, 28.5% CHF 28% CAD, 17% diabetes	35.4% ≥85 years 59.3% with ≥1 risk factor 62.1% of "ideal" candidates
SCAF (2006)	2796	2002	62% with indications for anticoagulation	54%
Euro AF (2006)	5333	2003–2004	82%-90% high risk	~85% $CHADS_2$ 6 ~60%-65% $CHADS_2$ 3-5 ~58% $CHADS_2$ 1 ~40%-50% $CHADS_2$ 0
Glazer (2007)	572	2001–2002	73% high risk	59%
EXAMINE AF (2006)	1596	2004–2005	84% high risk	64% 70% treated by cardiologists 58% treated by general physicians 55% treated by internists
US MarketScan database (2010)	171,393	2003–2007	61.6% $CHADS_2$ 1-2 18.4% $CHADS_2$ 3-6	42.1%$CHADS_2$ 3-6 43.5% $CHADS_2$ 1-2 40.1% $CHADS_2$ 0 Warfarin uninterrupted: 29.6% $CHADS_2$ 3-6 33.3% $CHADS_2$ 1-2 34.1% $CHADS_2$ 0

$CHADS_2$, Cardiac failure, hypertension, age, diabetes, stroke [doubled] risk stratification system; CAD, coronary artery disease; CHF, congestive heart failure; HTN, hypertension. See text for expansion of study names.

their potential response to warfarin by using genetic testing, it is limited by associated costs and availability.

Strict INR control is essential to ascertain the highest efficacy and safety of anticoagulation with warfarin, but it is difficult to achieve for the reasons mentioned above. The intensity of anticoagulation with an INR in the range between 2 and 3 is considered to achieve maximum efficacy in the prevention of stroke and an acceptable level of risk of bleeding (Figure 42-43).[199] A population-average model estimated that INR should be maintained within the therapeutic range for at least 60% of the time on therapy to ensure any benefit from anticoagulation; below this threshold, little benefit of anticoagulation exists.[200] Compared with the

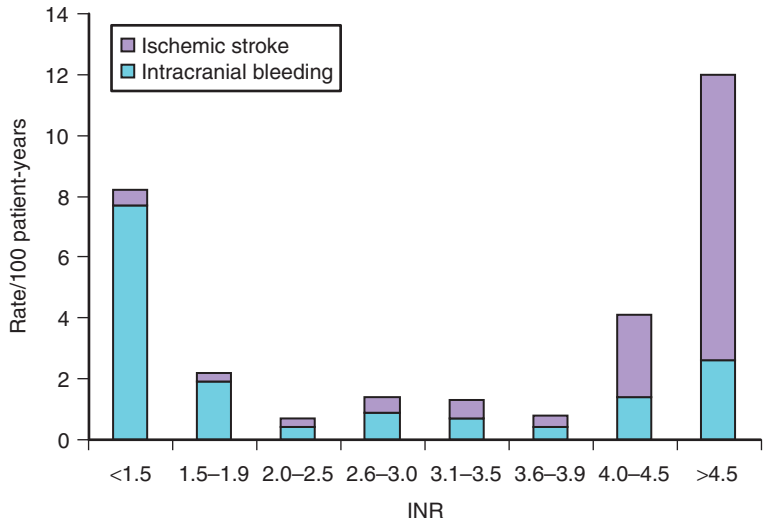


FIGURE 42-42 Effects of intensity of anticoagulation on incidence rates of ischemic stroke and intracranial hemorrhage in a cohort of 13,355 patients with atrial fibrillation. *INR*, International normalized ratio. *(Modified from Hylek EM, Go AS, Chang Y, et al: Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation,* N Engl J Med *349:1019–1026, 2003.)*

Table 42-12 New Anticoagulants for Prevention of Stroke in Atrial Fibrillation

DRUG	ACTION	PHASE III TRIAL	COMPARATOR	DESIGN	NO. PATIENTS
Dabigatran	Direct thrombin inhibitor	RE-LY	Warfarin	Noninferiority, PROBE	18,500
Apixaban	Factor Xa inhibitor	AVERROES ARISTOLE	Aspirin Warfarin	Superiority, double-blind Noninferiority, double-blind, double-dummy	5600 18,000
Rivaroxaban	Factor Xa inhibitor	ROCKET AF	Warfarin	Noninferiority, double-blind, double-dummy	14,269
Edoxaban	Factor Xa inhibitor	ENGAGE	Warfarin	Noninferiority, double-blind, double-dummy	16,500
Tecarfarin	Vitamin K antagonist	EmbraceAC	Warfarin	Superiority	612

See text for expansion of study names.

recommended INR values, INR less than 2 confers a 3.6-fold increased risk of stroke in patients younger than 75 years and a twofold increased risk in those older than 75 years, whereas INR above 4 is associated with an exponential increase in bleeding risk. Self-monitoring of INR has a limited applicability.[43]

Anticoagulation in Atrial Flutter

AFL is now considered to be associated with the risk of stroke as in AF, in the presence of risk factors. This is further supported by the fact that AF often coexists with AFL. TEE studies have shown that LAA flow velocity is lower in patients with AFL compared with sinus rhythm but higher than during AF. In the Flutter Atriale Società Italiana di Ecografia Cardiovascolare (FLASIEC) study, 2.4% of patients with AFL had left atrial thrombi.[201] The same criteria for anticoagulation should therefore be applied in patients with isolated AFL as recommended for AF.

New Anticoagulants

Two main avenues of research into new anticoagulants emerged: (1) oral direct thrombin inhibitors (dabigatran) and (2) factor Xa inhibitors (e.g., rivaroxaban, apixaban, edoxaban) (Table 42-12). A brief summary is provided below, and the reader is referred to Chapter 82 for a detailed treatment of the subject.

Dabigatran

Dabigatran is a competitive oral direct thrombin (factor IIa) inhibitor that inhibits thrombin-dependent conversion of fibrinogen to fibrin and thrombin-induced platelet aggregation. It binds to fibrin-bound, clot-bound, and free thrombin. Dabigatran etexilate is a prodrug, is converted by esterase-catalyzed hydrolysis to its active form, dabigatran. This conversion is independent of the cytochrome P-450 system, making drug-drug and drug-diet interactions less likely. Dabigatran has a rapid onset of action (approximately 2 hours), and the steady state is usually reached after 3 days of therapy. It has a predictable pharmacokinetics and pharmacodynamics and does not require monitoring. Dabigatran is available in two doses (150 mg twice daily and 75 mg twice daily in the United States; 150 mg twice daily and 110 mg twice daily in Europe). As the drug is eliminated mainly via the renal pathway, patients with chronic kidney disease can be exposed to 1.5 to 6 times higher concentrations of the drug and should therefore receive a lower dose.

No specific antidote exists in case bleeding occurs, but this is offset by rapid elimination of the drug and the possibility of its removal by dialysis. If necessary, the anticoagulation effect can be assessed using the activated partial thromboplastin time (aPTT), which is prolonged by dabigatran; thrombin time; and ecarin clotting time. The limitation of the aPTT test is it low sensitivity because the drug concentration and aPTT are not linearly related.

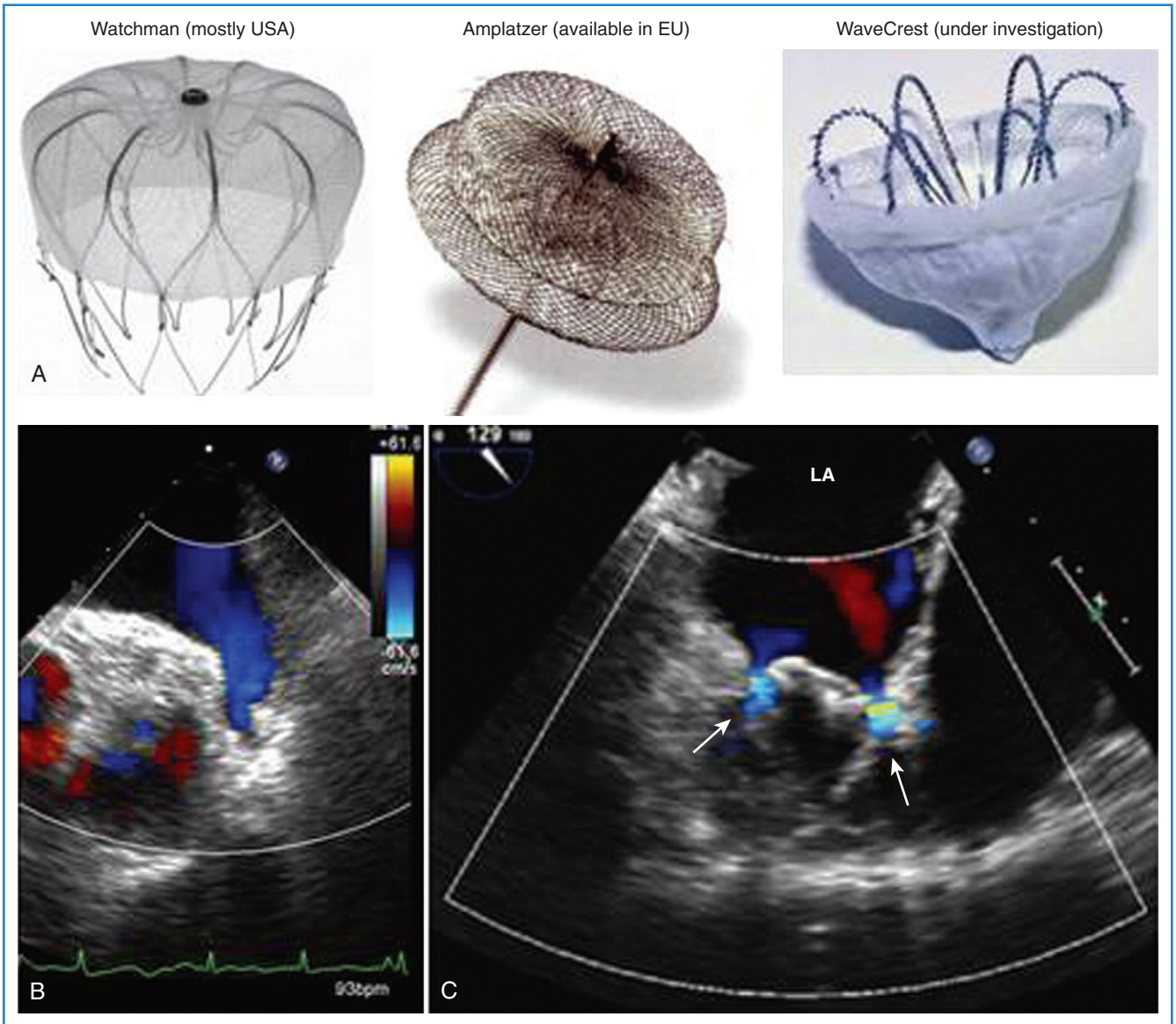


FIGURE 42-43 A, Left atrial appendage (LAA)–occluding devices currently available or under investigation. **B,** Transesophageal echocardiogram showing a patent LAA before implantation of the Watchman (Atritech) LAA occluder system. **C,** No blood flow in the LAA after implantation.

The efficacy and safety of two doses of dabigatran (110 mg twice daily or 150 mg twice daily) compared with open-label warfarin has been demonstrated in the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial with more than 18,000 patients with AF and cardiovascular and thromboembolic risk (average age, 72 years; mean CHADS score, 2.1; and history of MI [17%], stroke [20%], and CHF [32%]).[202]

Both doses of dabigatran performed better compared with warfarin despite tight INR control (64% of the time within the therapeutic range) (see Figure 42-41). Dabigatran 110 mg twice daily had similar efficacy for the primary endpoint of stroke or systemic embolism (event rates per year, 1.54% vs. 1.71% on warfarin; $P < .001$ for noninferiority) with fewer major bleeds and fewer hospitalizations, and dabigatran 150 mg twice daily had better efficacy (event rates per year, 1.11% vs. 1.71% on warfarin; $P < .001$ for superiority), lower mortality rate, and similar major bleeding rates. Compared with warfarin, the risk of major bleeds was 20% lower for dabigatran 110 mg twice daily (3.57% vs. 2.87% per year) but similar for 150 mg twice daily (3.57% vs. 3.32% per year). Importantly, intracranial bleeds were significantly less with both doses of dabigatran than with warfarin. However, high-dose dabigatran was associated with significantly more gastrointestinal bleeds compared with warfarin.

Consequently, the American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Practice Guidelines recommended dabigatran as a useful alternative to warfarin for the prevention of stroke in AF.[203] No evidence of its performance in patients with prosthetic heart valves or hemodynamically significant valve disease exists, and the drug should not be used in these patients as well as in individuals with severe renal

failure (creatinine clearance <15 mL/min), or advanced liver disease.

The 150 mg twice daily dose should be used for a patient at low risk of bleeding (e.g., HAS-BLED score of 0 to 2) because of its greater efficacy in the prevention of stroke but lower rates of intracranial hemorrhage and similar rates of major bleeding events compared with warfarin. If a patient has a measurable risk of bleeding (e.g., HAS-BLED score of ≥3) or renal impairment, low-dose dabigatran may be considered, although no evidence exists for the efficacy of a 75 mg twice daily dose.

Factor Xa Inhibitors

Three oral factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban) have been studied in large phase III trials, and two other drugs (betrixaban and darexaban) have completed advanced phase II studies. Their anticoagulation effect is realized via the inhibition of a factor Xa, which is, unlike parenteral drugs (fondaparinux and indaparinux), independent of antithrombin III, and the subsequent reduction in the generation of thrombin without affecting the activity of thrombin itself. The majority of oral factor Xa inhibitors affect both free-bound and clot-bound factor Xa as well as prothrombinase activity.

Rivaroxaban is primarily eliminated by renal excretion (approximately 60% to 65%); therefore patients with renal impairment are at 1.5- to twofold increased risk of overexposure to the drug. Drug-drug interactions are minimal because only a small proportion of rivaroxaban is metabolized via the CYP3A4/3A5 pathway. Like other oral factor Xa inhibitors, rivaroxaban prolongs aPTT and the prothrombin time in a linear fashion. The advantage of rivaroxaban over dabigatran is a once-daily formulation (20 mg).

Rivaroxaban proved to be at least as effective as warfarin in preventing AF-related strokes in 14,264 patients enrolled in a double-blind, double-dummy (unlike the RE-LY study)trial, the Rivaroxaban Once Daily, Oral, Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) trial.[204] The primary outcome of stroke or systemic embolism occurred in 1.7% in the rivaroxaban group and 2.2% in the warfarin group (*P* for noninferiority <.001). In the prespecified on-treatment analysis, rivaroxaban was associated with a 21% reduction in the primary endpoint events compared with warfarin (1.7% vs. 2.15%; *P* = .015) (see Figure 42-41). Similar to dabigatran, rivaroxaban causes fewer intracranial bleeding compared with warfarin (0.5% vs. 0.67%).

Apixaban at 5 mg twice daily significantly outperformed aspirin in the Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) trial of 5599 patients, who, for a variety of reasons, were not candidates for warfarin.[205] Apixaban reduced the risk of stroke or systemic embolism by 55% compared with aspirin (1.6% vs. 3.7%) without an increase in the risk of major bleeding (1.4% vs. 1.2%; *P* = .57; Figure 42-41).

Apixaban 5 mg twice daily (or 2.5 mg twice daily for patients at risk of bleeding, e.g., very old, with renal impairment) and *edoxaban* 30 and 60 mg once daily are being compared with warfarin in two large double-blind, double-dummy studies: Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) in more than 18,000 patients with AF and Effective Anticoagulation with Factor xA Next Generation in Atrial Fibrillation (ENGAGE-AF) in 16,500 patients with a $CHADS_2$ score of 2 or more.

In the future, although the choice between new anticoagulants will be influenced by specific drug characteristics (e.g., dyspepsia and gastrointestinal bleeding associated with dabigatran), it will likely be driven by physicians' experience and preference.

Left Atrial Appendage Occluder Devices

A meta-analysis of 23 studies in approximately 5000 subjects with rheumatic or nonrheumatic AF in settings of cardiac surgery, autopsy, or TEE, which revealed that LAA thrombi were found in 57% cases of rheumatic AF and 91% of nonrheumatic AF, has set the stage to investigate the benefit of LAA occlusion.[206] LAA excision is often performed adjunct to open-heart surgery in patients with AF. LAA ligation or ectomy via thoracoscopy or a limited sternotomy is not widely used, but new tools are under development. Transcatheter devices are discussed in detail in Chapter 98. Early studies showed the feasibility and safety of a percutaneous LAA transcatheter occluder (*PLAATO*, ev3 Inc., Plymouth, MN).[207] Successful occlusion of LAA was achieved in 90% of patients, with acceptable perioperative morbidity and mortality rates. The incidence of stroke was 2.3% per year compared with the 6.6% per year expected rates of stroke with no warfarin administration warfarin according to the $CHADS_2$. Several other devices (see Fig. 42-43) are currently under investigation (see Chapter 98).

The performance of the Watchman device (Atritech, Plymouth, MN) against dose-adjusted warfarin has been tested in the Protection in Patients with Atrial Fibrillation (PROTECT-AF) study of 800 patients with a $CHADS_2$ score of 1 or less.[208] After implantation, warfarin was continued for 45 days to allow endothelialization of the device. Warfarin was discontinued and replaced with aspirin and clopidogrel for 6 months if TEE at 45 days showed either no or minimal flow into the LAA and no thrombus and no clinical events occurred. At 45 days, 85% of patients in the device group were able to discontinue warfarin. The primary composite endpoint of all strokes, systemic thromboembolism, and cardiovascular or unexplained death and systemic thromboembolism occurred at a rate of 3 per 100 patient-years in the device group and 4.4 per 100 patient-years in the warfarin group. However, the primary safety endpoints, which included peri-procedural events (stroke and long-term bleeding or device embolization) were more common in the device group (7.4 vs. 4.4 per 100 patient-years), with pericardial tamponade occurring in 5.5%. This has been explained by a steep learning curve; in the subsequent Continued Access Protocol (CAP) registry, the incidence of pericardial effusion decreased to 1.1%.[209] The performance of the device will be further tested in several randomized controlled studies and registries (Table 42-13).

Rhythm Control Versus Rate Control Strategies

Two prime treatment strategies are rhythm control and rate control. Intuitively, rhythm control is a more attractive treatment strategy, as it offers physiological rate control, normal atrial activation and contraction, the correct sequence of AV activation, and normal hemodynamic and AV valve function and theoretically eliminates factors that encourage thrombosis within the atria and embolization of blood clots to potentially critical part of the circulation. Advantages of the rate control approach include

Table 42-13 Clinical Experience and Ongoing Studies with Watchman* Left Atrial Appendage Occluder System

STUDY	NUMBER OF PATIENTS	SITES	COMPARATOR	RESULTS
Pilot	66	8	No	318 patient-years of follow-up 30 patients with ≥5 years of follow-up
PROTECT-AF	800 (453 with device)	59	Warfarin	1500 patient-years of follow-up Mean follow-up: 27 months per patient Demonstrated noninferiority to warfarin
CAP (Registry)	567	26	No	Significantly improved safety results
ASAP	100	4	No	Patients with contraindications to warfarin
EVOLVE	43	3	No	Evaluation of next-generation Watchman
PREVAIL	400	50	Warfarin	Same endpoints as in PROTECT-AF Revised inclusion/exclusion criteria: $CHADS_2$ score ≥2 Enrolment started November 2010

See text for expansion of study names.
**Atritech, Plymouth, MN.*

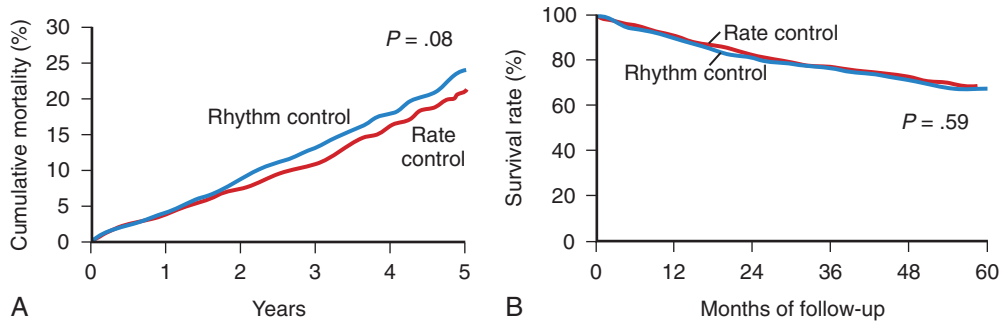


FIGURE 42-44 Kaplan-Meier curves for cumulative all-cause mortality in the rhythm control group and the rate control group in the Atrial Fibrillation Follow up Investigation of Rhythm Management (AFFIRM) (**A**) and Atrial Fibrillation Congestive Heart Failure (AF-CHF) (**B**) trials. *(From Wyse DG, Waldo AL, DiMarco JP, et al: A comparison of rate control and rhythm control in patients with atrial fibrillation,* N Engl J Med *347:1825–1833, 2002; Roy D, Talajic M, Nattel S, et al, for the Atrial Fibrillation and Congestive Heart Failure Investigators: Rhythm control versus rate control for atrial fibrillation and heart failure,* N Engl J Med *358:2667–2677, 2008.)*

avoiding the potential toxicity of antiarrhythmic drugs and the risks and discomfort associated with electrical cardioversion or invasive ablation for recurrences of AF.

However, sinus rhythm with normal AV conduction may not be an alternative to the arrhythmia, since sinus node disease may be the underlying problem, and chronotropic incompetence may well be present. Atrial conduction and mechanical function may be seriously impaired, and atrial contraction may not contribute much to cardiac output. Furthermore, it is not unusual for patients to be relieved of their symptoms when the arrhythmia is established and becomes permanent. Often, the only symptoms that remain are a minor limitation of exercise tolerance and a subtle reduction in the quality of life. Therefore a genuine equipoise exists as to whether it is best to accept the arrhythmia while controlling the ventricular rate and preventing thromboembolic complications with anticoagulant therapy or to restore and maintain sinus rhythm.

The difficulties in rhythm control management, principally the high AF recurrence rate, and the concern for serious adverse effects associated with antiarrhythmic drug therapy finally led to rate control versus rhythm control studies. The major studies were the AFFIRM trial, the Rate Control Versus Electrical Cardioversion (RACE) trial and, most recently, the Atrial Fibrillation Congestive Heart Failure (AF-CHF) trial (Table 42-14).[210-212] A series of pilot studies, including the Pharmacological Intervention in Atrial Fibrillation (PIAF), Strategies of Treatment of Atrial Fibrillation (STAF), and How to Treat Chronic Atrial Fibrillation (HOT CAFÉ), among others, were also performed.[213-215] These studies all directly and prospectively compared the effect of rhythm control treatment strategies versus rate control strategies on patient outcomes. In general, a trend toward improved survival and less serious cardiovascular adverse events has been seen in association with rate control rather than with rhythm control.

The AFFIRM study of 4060 AF patients aged 65 years or older with at least one risk factor for stroke was the only one designed to assess the mortality benefit of different strategies in AF.[210] The mean follow-up was 3.5 years, with a maximum of 6 years. No difference was seen in the primary endpoint of all-cause mortality as well as quality of life and functional status between rate control and rhythm control (Figure 42-44, *B*). It was, however, clear that these trials had not included younger, active, or highly symptomatic patients, and the concept of an initial rate control strategy

Table 42-14 Clinical Outcomes in Rhythm-Control vs. Rate-Control Studies

				RHYTHM CONTROL VS. RATE CONTROL					
STUDY	**NO. PATIENTS**	**FOLLOW-UP (YEARS)**	**PRIMARY ENDPOINT**	**DIFFERENCE IN PRIMARY ENDPOINT**	**ALL-CAUSE MORTALITY**	**THROMBOEMBOLIC EVENT**	**CHF**	**HOSPITALIZATION**	**QUALITY OF LIFE**
PIAF	252	1	Symptom improvement	Symptoms improved in 70 vs. 76 patients ($P = .317$)	Not assessed	Not assessed	Not assessed	69% vs. 24% ($P = .001$)[a]	No difference
STAF	200	1.6	ACM, CV event, CPR, TE	5.54%/year vs. 6.09%/year ($P = .99$)	2.5%/year vs. 4.9%/year	3.1%/year vs. 0.6%/year	Better with rate control	54% vs. 26% ($P < .001$)	No difference
HOT CAFÉ	205	1.7	ACM, TE, bleeding	No difference (OR, 1.98; 95% CI, 0.28-22.3; $P > .71$)	3 (2.9%) vs. 1 (1%)	3 (2.9%) vs. 1 (1%)	No difference	74% vs. 12% ($P < .001$)	Not reported
RACE	522	2.3	CV death, hospitalization for CHF, TE, bleeding, pacemaker, adverse event on AAD	22.6% vs. 17.2% (HR, 0.73; 90% CI, 0.53-1.01; $P = .11$)	6.8% vs. 7%	7.9% vs. 5.5% rhythm control vs. rate control	4.5% vs. 3.5%	More in rhythm control	No difference
AFFIRM	4060	3.5	ACM	23.8% vs. 21.3% (HR, 1.15; 95% CI, 0.99-1.34; $P = .08$)	As above	Stroke: 7.1% vs. 5.5% ($P = .79$)	2.7% vs. 2.1% ($P = .58$)	80% vs. 73% ($P < .001$)*	No difference
AF-CHF	1376	3.1	CV mortality	27% vs. 25% (HR, 1.06; 95% CI, 0.86-1.3; $P = .59$)	32% vs. 33% ($P = .68$)	3% vs. 4% ($P = .32$)	28% vs. 31% ($P = .17$)	46% vs. 39% ($P = .0063$)	Not yet available
CRRAFT	144	1	Clinical improvement	Significant improvement with rhythm control	0 vs. 5 ($P = .023$)		Functional class improved in 60% vs. 17.5% ($P = .0014$)	8.9% vs. 15% ($P = .51$)	Improved in 86.7% vs. 50% ($P = .033$)
J-RHYTHM	823	1.6	ACM, TE, bleeding, hospitalization for CHF, adverse event	15.3% vs. 22% ($P = .0128$)	4 (1%) vs. 3 (0.7%)		0.5% vs. 1.5%	Not reported	Better with rhythm control

*Including hospitalization for cardioversion.

AAD, *Antiarrhythmic drug;* ACM, *all-cause mortality;* AF, *atrial fibrillation;* AF-CHF, *Atrial Fibrillation and Congestive Heart Failure;* AFFIRM, *Atrial Fibrillation Follow-up Investigation of Rhythm Management;* CHF, *congestive heart failure;* CI, *confidence interval;* CPR, *cardiopulmonary resuscitation;* CRRAFT, *Control of Rate Versus Rhythm in Rheumatic Study in Rheumatic Atrial Fibrillation Trial;* CV, *cardiovascular;* HOT CAFÉ, *How to Treat Chronic Atrial Fibrillation;* HR, *hazard ratio;* OR, *odds ratio;* PIAF, *Pharmacological Intervention in Atrial Fibrillation;* QoL, *quality of life;* RACE, *Rate Control versus Electrical Cardioversion;* RR, *relative risk;* STAF, *Strategies of Treatment of Atrial Fibrillation;* TE, *thromboembolic event.*

From Savelieva I, Waldo A, Camm AJ: Atrial fibrillation: Rhythm and rate control therapies. In Yusuf S, Cairns JA, Camm AJ, et al, editors: Evidence-based cardiology, *New York, 2009, Wiley-Blackwell, pp 531–567.*

should not have been automatically applied to their management.

Post hoc analysis of the AFFIRM trial, after correction for any mismatch of baseline characteristics, demonstrated that being in sinus rhythm was an advantage but that use of the then-available antiarrhythmic drugs was associated with increased risk of death.[216]

In the AF-CHF trial, rate- and rhythm-control strategies were compared specifically in 1376 patients with an ejection fraction (EF) of 35% or less and NYHA class II to IV heart failure.[212] Amiodarone was the drug of choice for AF suppression and sinus rhythm maintenance, but sotalol and dofetilide were used in selected cases. The study showed no benefit of rhythm control in addition to optimal medical therapy with regard to the primary endpoint (cardiovascular mortality) (see Figure 42-44, *B*) as well as prespecified secondary endpoints, including total death, worsening heart failure, stroke, and hospitalization.

The closely similar primary endpoint results for the rhythm-control and rate-control strategies were probably caused by a general failure to achieve a clear difference with respect to rhythm and rate status in the two arms of the trials. Ideally, the rhythm-control arm should have comprised patients who were in sinus rhythm, and the rate control arm should have consisted mostly of patients in AF. This was not usually the case; for example, in the AFFIRM trial, only 60% of the rhythm-control arm were maintained in sinus rhythm, whereas 40% of the rate-control arm had reverted spontaneously to sinus rhythm.

The results of rate-control versus rhythm-control studies highlighted the limitations of the current therapies to achieve and maintain sinus rhythm. Long-term maintenance of sinus rhythm has proven difficult to achieve in patients with persistent AF, and the method is time consuming and expensive because of the costs of antiarrhythmic drugs and the increased need for hospitalization. Thus the trend toward rate control on the grounds of safety may be reversed if safer and more effective rhythm control therapies become available.

Restoration of Sinus Rhythm

Electrical Cardioversion

The overall success rate is 90% to 95% with electrical cardioversion for AF that occurred less than 48 hours earlier and decreases to 72% to 78% if the arrhythmia is present for 1 year (Figure 42-45).[217] Longer duration of the arrhythmia, greater weight, and higher transthoracic impedance are associated with lower shock success. Left atrial size does not predict the outcome of cardioversion (which is successful in 83% of patients with a significantly enlarged left atrium), and neither does advanced age. Studies in older patients have demonstrated that the efficacy rate and the incidence of complications of electrical cardioversion are not significantly higher than in younger individuals, suggesting that a patient should not be refused electrical restoration of sinus rhythm merely on the grounds of age.[218] Age and advanced atrial remodeling are probably more important determinants of the subsequent long-term maintenance of sinus rhythm.

AFL can be converted with a direct current shock as low as 25 to 50 J but because a 100-J shock is almost always successful, it should be considered for the initial shock strength. In AF that has lasted less than 30 days, sinus rhythm can be restored by a shock of 100 J, but it is recommended that cardioversion should be started with the initial shock energy level of 200 J or greater. In those with AF of longer duration, in heavier individuals, or in those with COPD and pulmonary emphysema, an initial setting of 300 to 360 J is appropriate (Figure 42-46). Success may occur on the third or subsequent attempt at an intensity that initially

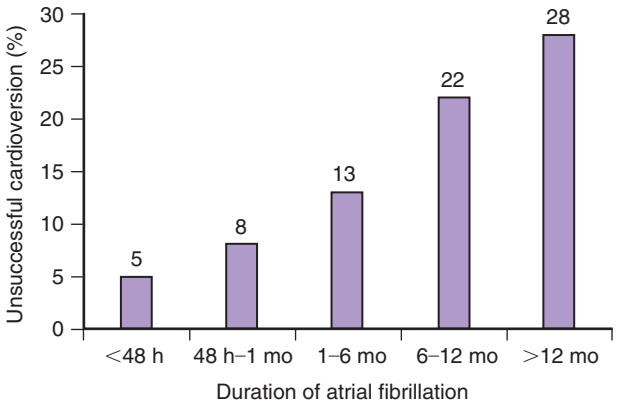


FIGURE 42-45 Prevalence of unsuccessful electrical cardioversion as a function of duration of the arrhythmia. (Modified from Elhendy A, Gentile F, Khanderia BK, et al: Predictors of unsuccessful electrical cardioversion in atrial fibrillation, *Am J Cardiol* 89;83–86, 2002.)

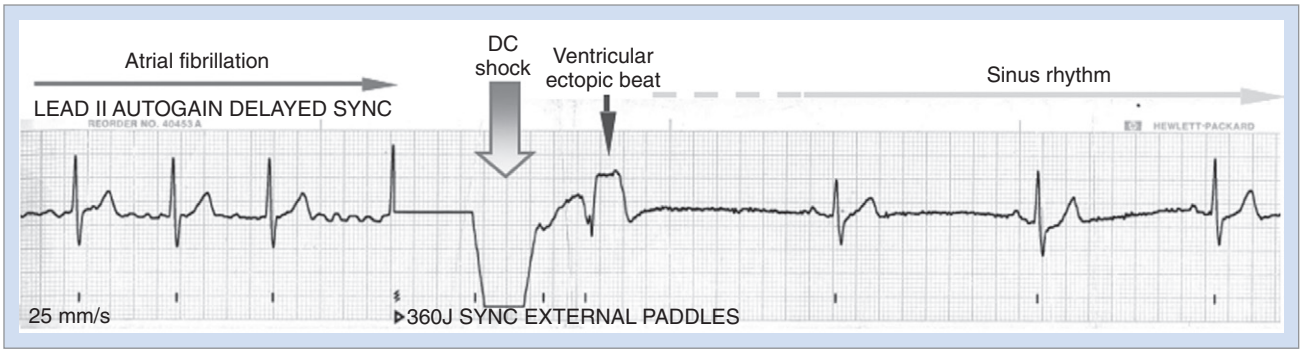


FIGURE 42-46 Electrical cardioversion of atrial fibrillation. *DC*, Direct current.

proves ineffective. The higher energy levels required for electrical cardioversion of AF compared with that for AFL and other supraventricular tachyarrhythmias can probably be attributed to larger amount of tissue being in a partially refractory state, during which the defibrillation threshold is four times higher than in the resting state.

For successful cardioversion, the current vector must transverse a critical atrial mass, and the anteroposterior electrode position appears to provide the optimal current vector direction. The energy requirement tends to be lower and the success rate greater (87% vs. 76%) with the anteroposterior (sternum and left scapula) alignment compared with the anterolateral (ventricular apex and right infraclavicular area) alignment of the electrode paddles.[219] However, depending on the individual patient, the anterolateral electrode position may be more effective.

The use of biphasic waveform of direct current (DC) appears to achieve a higher rate of conversion to sinus rhythm at a lower energy level compared with the monophasic waveform.[220] In contrast to the monophasic waveform, the biphasic waveform is relatively insensitive to changes in transthoracic impedance because of impedance compensation, which ensures a constant current in the first phase. The result is a decrease in defibrillation threshold by approximately one third. In the randomized, double-blind BiCard study, the success rate was consistently higher for truncated exponential biphasic shock than for monophasic shock at the shared energy level of 100 J (60% vs. 22%) and 200 J (90% vs. 53%).[220] The biphasic waveform is also associated with a lower frequency of dermal injury.

Early Recurrence after Cardioversion

Early recurrence of AF has been reported in 10% to 30% patients, usually within 1 minute of successful cardioversion, resulting in the reduction of the primary success rate of cardioversion.[221,222] The majority (91%) of episodes being initiated by an atrial premature beat with a short coupling interval and 9% occurring after a preceding bradycardia (Figure 42-47).[222] Early recurrence of AF often requires repeat shock, usually at higher energy level and in combination with antiarrhythmic drugs. Anecdotal evidence suggests that overdrive atrial pacing after cardioversion may prevent early recurrence of AF by eliminating triggers of the arrhythmia such as short-long sequences produced by frequent atrial premature beats and bradycardia.[222]

A variety of antiarrhythmic drugs, including propafenone, flecainide, sotalol, ibutilide, and amiodarone, have recently been shown to prevent early recurrence and to facilitate either external or internal electrical conversion of atrial tachyarrhythmias.[223-226] The synergistic effect with antiarrhythmic drugs may be attributed to the prolongation of the atrial effective refractory period (ERP), conversion of AF to a more organized atrial rhythm, and suppression of APBs immediately after restoration of sinus rhythm. However, pretreatment with antiarrhythmic drugs may also favor ventricular proarrhythmias and bradycardia in the presence of sinus node dysfunction. Data on the use of verapamil and diltiazem for facilitating electrical cardioversion have been inconclusive.

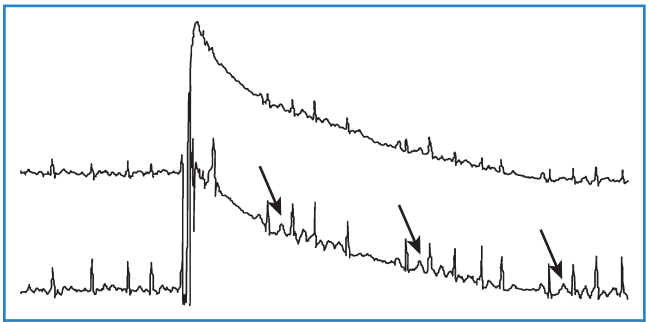


FIGURE 42-47 Early recurrence of atrial fibrillation within seconds after successful electrical cardioversion. Note the presence of atrial premature beats (*arrow*) that initiates atrial fibrillation.

Complications of Electrical Cardioversion

Complications associated with electrical cardioversion are mainly related to thromboembolic events, which have been reported to occur at a rate of 1% to 7% in the absence of anticoagulation therapy, and various, usually transient, tachyarrhythmias and bradyarrhythmias such as ventricular and supraventricular premature beats, runs of SVT, bradycardia, and short periods of sinus arrest.[227,228] VT or VF may be precipitated by electrolyte imbalance (hypokalemia, hypomagnesemia) or digitalis intoxication.

Transient ST-segment elevation and increased cardiac enzymes plasma levels (primarily, creatine kinase), which may occur following electrical cardioversion, are not considered to be associated with clinically significant myocardial damage. In patients with underlying organic heart disease and significantly impaired left ventricular function, a small risk of the development of acute heart failure and pulmonary edema exists because of a sudden reduction in cardiac output from postcardioversion-related bradycardia and the absence of mechanical contribution of the stunned atria.

Although external cardioversion is feasible in patients with implanted pacemakers and ICDs, electricity conducted along an implanted lead may cause local myocardial injury, resulting in an increase of pacing threshold or exit block and loss of capture and necessitating reprogramming of the device to increase generator output. The risk is lower with an anteroposterior position of defibrillator electrodes and in pacemakers with bipolar lead systems. However, the device should be interrogated immediately before and after cardioversion to verify appropriate function.

Anticoagulation During Cardioversion

Early evidence suggests a significantly lower incidence of thromboembolic complications associated with electrical cardioversion for atrial tachyarrhythmias in patients receiving oral anticoagulation compared with those without anticoagulation therapy (0.8% vs. 5.3%).[227] The beneficial effects of anticoagulation are probably associated with thrombus organization and adherence to the atrial wall or to complete thrombus resolution after a month of therapy. Therefore, for patients undergoing elective cardioversion, oral anticoagulation with warfarin (target INR, 2.5; range, 2 to 3) is recommended for at least 4 weeks before the procedure and should be continued for at least 4 weeks after cardioversion or indefinitely in the presence of risk factors for stroke. In patients presenting with their first AF episode of less than 48 hours duration, cardioversion may be performed without delay, provided that it is covered with low-molecular-weight heparin. Postcardioversion anticoagulation should be considered if thromboembolic risk factors are present.

Cardioversion Guided by Transesophageal Echocardiography

TEE has emerged as the most sensitive and specific imaging technique for the detection of left atrial thrombi, also permitting assessment of the LAA flow. The TEE-guided strategy with short-term anticoagulation is a safe and effective alternative in patients for whom early cardioversion is deemed clinically beneficial. It is ideal for inpatients with recent-onset AF and AFL or individuals at high risk of bleeding complications during prolonged anticoagulation therapy. The rate of embolic events did not differ between patients assigned to TEE-guided cardioversion and those assigned to the conventional strategy of anticoagulation for 3 weeks prior to cardioversion, but the incidence of major and minor hemorrhagic complications was significantly lower in the TEE-guided group compared with the conventional therapy group (2.9% vs. 5.5%).[176]

Pharmacologic Cardioversion

Pharmacologic cardioversion is considered to be most effective if initiated within 7 days after the onset of the arrhythmia, in which case restoration of sinus rhythm can be achieved in nearly 70% of patients, but the success rate decreases significantly if AF persists beyond this limit. The likelihood of spontaneous conversion varies greatly but is mainly determined by the duration of the arrhythmia, the number of previous recurrences, and the severity of underlying heart disease. Spontaneous conversion to sinus rhythm may occur in up 66% of patients within 24 hours after onset of the arrhythmia (Figure 42-48) and in only 17% of those with the arrhythmia of longer duration (OR, 1.8).[229]

Pharmacologic cardioversion can be achieved with oral or intravenous medication. Antiarrhythmic drugs with proven efficacy for cardioversion of atrial tachyarrhythmias are listed in Table 42-15. An intravenous agent is usually chosen when used as an alternative to electrical cardioversion in hemodynamically stable patients in the hospital setting. The choice of the drug is determined by the presence of underlying heart disease (Figure 42-49).

Flecainide and Propafenone

Class IC agents, flecainide and propafenone, are reserved for the treatment of patients without any form of ischemic heart disease or CHF. Intravenous propafenone and flecainide are extremely effective in cardioversion of recent-onset AF (usually 1 to 72 hours), with conversion rates as high as 80% to 90% within an hour after the start of infusion.[230,231] Class IC agents may cause 1:1 AV conduction with a rapid ventricular response because of the slowing of the atrial rate, so concomitant administration of AV node–blocking agents (β-blockers, verapamil, or diltiazem) is mandatory. Other cardiovascular effects include reversible QRS widening and, rarely, left ventricular decompensation from the negative inotropic effect.

Class IC drugs usually are ineffective for conversion of AFL. They slow conduction within the re-entrant circuit and prolong the flutter cycle length but rarely interrupt the circuit, and a greater risk of 1:1 AV conduction is present. The efficacy rates are reported to be as low as 13% to 40% with intravenous flecainide and propafenone. Anecdotal evidence suggests that class IC agents can terminate AT.[232]

Pill-in-the-Pocket Approach

The advantage of propafenone and flecainide is that they can be administered orally for the cardioversion of AF; the conversion rates are comparable with those achieved with intravenous formulations, although the effect is expectedly delayed. In a meta-analysis of 1843 patients from 27 studies, intravenous or oral propafenone demonstrated a placebo-subtracted efficacy of 31.5% at 4 hours and 32.9% at 8 hours.[233] After oral administration of a single loading dose of propafenone (usually 450 to 600 mg) or flecainide (usually 200 to 300 mg), sinus rhythm was restored in 51% to 59% at 3 hours and 72% to 78% at 8 hours, respectively, compared with respective conversion rates of 18% and 39% on placebo.[234] Across the studies, the success rates ranged from 56% to 83% for propafenone and from 57% to 68% for flecainide.[235]

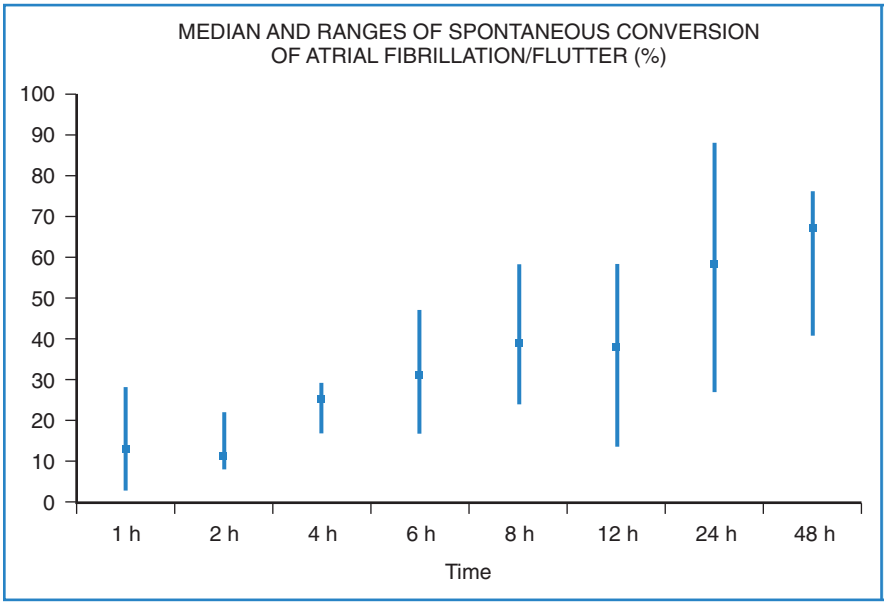


FIGURE 42-48 Incidence of spontaneous conversion to sinus rhythm of recent onset (<7 days) atrial fibrillation or atrial flutter in prospective, randomized, placebo-controlled studies. *(Modified from Slavik RS, Tisdale JE, Borzak S: Pharmacologic conversion of atrial fibrillation: A systemic review of available evidence,* Prog Cardiovasc Dis *44:121–152, 2001.)*

Table 42-15 Antiarrhythmic Drugs for Pharmacologic Conversion of Atrial Tachyarrhythmias

DRUG	ROUTE OF ADMINISTRATION	DOSE	CLASS RECOMMENDATION FOR ARRHYTHMIA ≤7 DAYS	CLASS RECOMMENDATION FOR ARRHYTHMIA >7 DAYS	POTENTIAL ADVERSE EFFECTS
Dofetilide	Oral	125-500 mg twice daily*	I	I	QT prolongation; torsades de pointes; contraindicated if creatinine clearance <20 mL/min
Ibutilide	IV	1 mg over 10 min; repeat 1 mg if necessary	I	IIA	QT prolongation; torsades de pointes; hypotension
Flecainide	Oral or IV	Loading dose 200-300 mg or 1.5-3.0 mg/kg over 10-20 min	I	IIB	Rapidly conducted atrial flutter; possible deterioration of ventricular function in the presence of organic heart disease
Propafenone	Oral or IV	Loading dose 450-600 mg or 1.5-2.0 mg/kg over 10-20 min	I	IIB	
Amiodarone	Oral or IV	Inpatient: 1200-1800 mg daily in divided doses until 10 g total; then 200-400 mg daily Outpatient: 600-800 mg daily until 10 g total; then 200-400 mg daily 5-7 mg/kg over 30-60 min intravenously; then 1200-1800 mg daily oral until 10 g total; then 200-400 mg daily	IIA	IIA	Hypotension; bradycardia; QT prolongation; torsades de pointes (rare); gastrointestinal upset; constipation; phlebitis
Quinidine	Oral	750-1500 mg in divided doses over 6-12 hours + rate-slowing drug (verapamil or β-blocker)	IIB	IIB	QT prolongation; torsades de pointes; QRS widening; rapid atrial flutter; hypotension; gastrointestinal upset
Procainamide†	IV	1000 mg over 30 min (33 mg/min) followed by 2 mg/min infusion	IIB	IIB	QRS widening; torsades de pointes; rapid atrial flutter
Sotalol†	Oral	80 mg initial dose; then160-320 mg in divided doses	III	III	QT prolongation; torsades de pointes; bradycardia

**Dose depends on creatinine clearance: >60 mL/min, 500 mg; 40-60 mL/min, 250 mg; 20-40 mL/min, 125 mg twice daily.*
†Less effective or incompletely studied agents; dose regimens vary in different studies.

In a proof-of-concept study in a selected cohort of 210 patients who had been successfully treated in hospital with either oral flecainide or propafenone for paroxysmal AF, a single oral dose taken within 5 minutes of noticing palpitations was associated with termination of the arrhythmia and an almost 10-fold reduction in the monthly number of visits to emergency departments.[236] It is mandatory that the efficacy and safety of this strategy is first tested in the hospital.[237]

Ibutilide

Class III ibutilide has proved to be effective for conversion of AF and particularly AFL in randomized, placebo-controlled studies and direct comparisons with procainamide and sotalol (Table 42-16).[238-240] The conversion rate for AFL is twice as much higher than for AF (63% vs. 31%), with ibutilide administered intravenously as a 10-minute infusion of 1 to 2 mg.[238] In direct comparison studies, ibutilide was more effective than procainamide (76% vs. 14%) and sotalol (70% vs. 19%) for conversion of AFL.[239,240] The success rates for conversion of AF were lower: 51% compared with 21% on procainamide and 44% compared with 11% on sotalol. The rate of successful conversion decreases if the arrhythmia persists for more than 7 days: from 71% to 57% for AFL and from 46% to only 18% for AF. Higher doses of ibutilide administered as two successive infusions of 1 mg are usually required for termination of AF.[238]

Like many of the class III antiarrhythmic drugs, ibutilide may cause significant Q-T interval prolongation and ventricular proarrhythmias. The incidence of sustained polymorphic VT requiring electrical cardioversion has been reported to be 0.5% to 1.7%; for nonsustained VT, the incidence is 2.6% to 6.7%.[238,240] Data are not

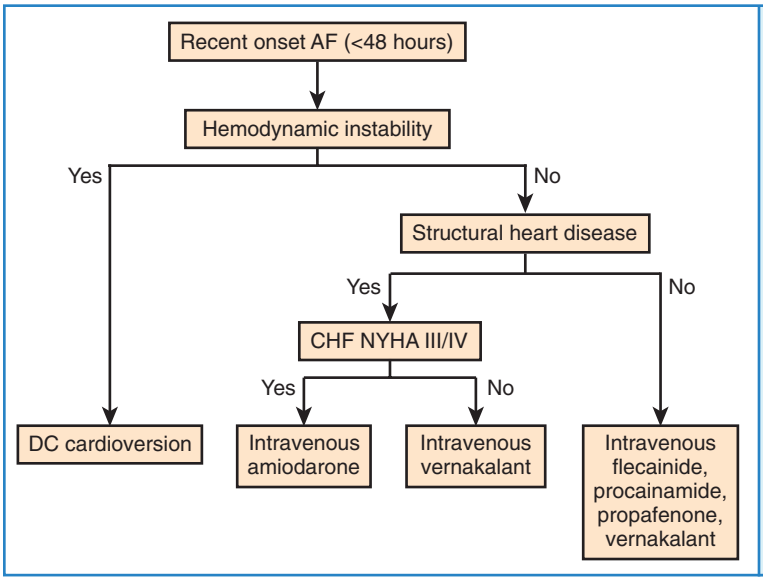


FIGURE 42-49 Selection of electrical or pharmacological cardioversion and antiarrhythmic drugs for pharmacologic cardioversion of acute atrial fibrillation (*AF*). *CHF*, Congestive heart failure; *DC*, direct current; *NYHA*, New York Heart Association.

sufficient to support the use of ibutilide in patients with significant structural heart disease.

Sotalol

The efficacy of sotalol for the cardioversion for AF and AFL is not superior to that of digoxin and placebo; therefore, it is not recommended for termination of atrial tachyarrhythmias, but it is effective for rate control. The conversion rate was 11% to 13% with sotalol versus 14% on placebo in the double-blind phase and 30% in the open-label phase.[241] Bradycardia and hypotension are the most common adverse effects with an incidence of 6.5% and 3.7%, respectively.[240] The failure of sotalol to terminate atrial tachyarrhythmias relates to its ability to prolong the atrial ERP at lower atrial rates but not during rapid AF or AFL (reverse use-dependency).

Dofetilide

On the basis of the results of three large prospective studies—Danish Investigations of Arrhythmia and Mortality on Dofetilide (DIAMOND), Symptomatic Atrial Fibrillation Investigative Research on Dofetilide (SAFIRE-D), and European and Australian Multicenter Evaluative Research on Atrial Fibrillation Dofetilide (EMERALD)—the oral formulation of dofetilide has attained a class I indication for the cardioversion of both recent-onset AF and persistent AF, and patients with significant structural heart disease (see Table 42-16) are included.[242-244] In the DIAMOND-AF substudy of 506 patients with AF or AFL at baseline, 75% of whom had symptomatic heart failure and an EF less than 35%, treatment with dofetilide at the maximum dose of 500 μg twice daily was associated with a greater rate of conversion to sinus rhythm (44% vs. 14%) and a greater probability of remaining in sinus rhythm at 1 year (79% vs. 42%). [242]

The incidence of torsades de pointes varies between 0.6% and 3.3%, with more than three quarters of episodes occurring during the first 3 to 4 days of drug initiation. Dofetilide appears to be safe in patients with MI and CHF; the dosage, however, should be adjusted according to renal function.

Amiodarone

Amiodarone can be used for the cardioversion of AF of any duration. A meta-analysis of 13 randomized controlled studies with 1174 patients has shown that intravenous amiodarone is more effective in converting AF and AFL compared with placebo, with a 44% superiority and almost equal effectiveness as class IC antiarrhythmic drugs; however, the effect is delayed by 24 hours.[245] At 8 hours, the probability of restoration of sinus rhythm is 65% higher with flecainide or propafenone than with amiodarone.

Intravenous amiodarone has a modest effect on atrial refractoriness and, therefore, is moderately effective in terminating the arrhythmia in the emergency setting, but unlike class IC agents, amiodarone does not have any negative inotropic effect, controls the ventricular rate, and is associated with a low incidence of torsades de pointes. All this makes it safe to be used in patients with advanced structural heart disease. Amiodarone prolongs the Q-T interval but, unlike pure class III agents, exhibits a low arrhythmogenic potential (less than 1%). The most common effects of intravenous amiodarone are hypotension and relative bradycardia. Data supporting the use of amiodarone as first-line treatment of AFL and AT are inconsistent, but theoretically, it is preferred for patients with poor ventricular function.

Procainamide

The class IA drug procainamide has been shown to facilitate conversion of AF of less than 48 hours, but its efficacy is limited in AF of longer duration. The conversion rates with procainamide administered intravenously at a dose 1000 to 1200 mg over 30 minutes ranged from 21% to 70%.[246] Procainamide can only be used when myocardial ischemia, MI, left ventricular hypertrophy, or left ventricular systolic dysfunction are not evident. Although no specific evidence exists, the drug is usually avoided in diastolic CHF.

Vernakalant

Vernakalant is a new arrhythmic drug agent with an affinity for ion channels specifically involved in repolarization processes in atrial tissue, in particular, the ultra-rapid potassium repolarization

Table 42-16 Studies of Class III Antiarrhythmic Drugs for Conversion and/or Maintenance of Sinus Rhythm in Patients with Atrial Fibrillation

STUDY	DRUG	NO. PATIENTS	FOLLOW-UP	CONVERSION RATE	RECURRENCE RATE	TORSADES DE POINTES
Ibutilide Repeat Dose Study[39]	Ibutilide 1.5 mg or 2 mg IV	266; 50% with AFL	24 h	47% converted on ibutilide vs. 2% on placebo; converted 63% AFL vs 31% AF	NA	8.3% on ibutilide; 1.7% required electrical cardioversion
Randomized study of Ibutilide vs. Procainamide[40]	Ibutilide 1-2 mg IV vs. procainamide 1.2 g IV	127; 33% with AFL	24 h	58.3% converted on ibutilide vs. 18.3% on procainamide; AFL 76% vs. 14%, AF 51% vs. 21%	NA	0.8% on ibutilide
Ibutilide/Sotalol Comparator Study (ISCS)[34]	Ibutilide 1 mg or 2 mg IV vs. d,l-sotalol 1.5 mg/kg IV	319; 18.5% with AFL	72 h	AFL: 56%-70% converted on ibutilide vs. 19% on sotalol AF: 20%-44% converted on ibutilide vs. 11% on sotalol	NA	0.9% on ibutilide 2 mg; 0.5% required electrical cardioversion; none on sotalol
d,l-Sotalol Atrial Fibrillation/Flutter Study Group[110]	d, l-sotalol 160, 240, 320 mg	253; 20% with AFL	1 year	NA	Time to first AF recurrence: 106, 229, 175 days on sotalol 160, 240, 320 mg vs. 27 days on placebo	None
SOCESP[112]	Sotalol 160-320 mg vs. quinidine 600-800 mg	121	6 mo	After cardioversion	26% on sotalol vs. 32% on quinidine; time to first AF recurrence 69 vs. 10 days AF ≤72 hours: 7% relapsed on sotalol vs. 36% on quinidine AF >72 hours: 67% relapsed on sotalol vs. 32% on quinidine	5% on sotalol vs. 2% on quinidine
Bellandi[111]	Sotalol 240 mg Propafenone 450-900 mg	300	1 year	After cardioversion	27% relapsed on sotalol vs. 37% on propafenone and 65% on placebo	4% on sotalol; 2% required cardioversion
PAFAC[93]	Sotalol 320 mg Quinidine + verapamil 320/160 mg	848	1 year	After cardioversion	67% relapsed on sotalol vs. 65% on quinidine and 83% on placebo	2.3% on sotalol; ventricular tachycardia 0.5% on sotalol vs. 1.1% on quinidine
SOPAT[94]	Sotalol 320 mg Quinidine + verapamil 480/240 mg, 320/160 mg	1012	1 year	After cardioversion	~50% relapsed on sotalol or quinidine vs. 38% on placebo; time to first AF recurrence: 146 days on sotalol vs. 149 (low dose) and 150 (high dose) on quinidine	None; ventricular tachycardia 0.4% on quinidine high dose
CTAF[114]	Amiodarone 200 mg vs. sotalol 160-320 mg or propafenone 450-600 mg	403	1.3 year	After cardioversion	35% on amiodarone vs. 63% on sotalol or propafenone	1 (1%) on propafenone
CHF-STAT[55]	Amiodarone 800 mg for 2 weeks; 400 mg for 50 weeks; maintenance dose 300 mg	667; 103 with AF at baseline	4.5 years	31.3% on amiodarone vs. 7.7% on placebo	New-onset AF: 4% on amiodarone vs. 8% on placebo	Not stated
SAFE-T[36]	Amiodarone 300 mg for the first year, 200 mg thereafter; sotalol 320 mg	665	4.5 years	27.1% converted on amiodarone, 24.2% on sotalol vs. 0.8% on placebo	Time to first AF recurrence: 487 days on amiodarone, 74 days on sotalol vs. 6 days on placebo	1 (0.4%) on sotalol

Continued

Table 42-16 Studies of Class III Antiarrhythmic Drugs for Conversion and/or Maintenance of Sinus Rhythm in Patients with Atrial Fibrillation—cont'd

STUDY	DRUG	NO. PATIENTS	FOLLOW-UP	CONVERSION RATE	RECURRENCE RATE	TORSADES DE POINTES
DDAFFS[44]	Dofetilide 8 μg/kg IV	96, 18% with AFL	24 h	30.3% converted on dofetilide vs. 3.3% on placebo	NA	3% on dofetilide
DIAMOND-AF[48]	Dofetilide 500 μg	506	1.5 years	44% on dofetilide vs. 14% on placebo	21% on dofetilide vs. 54% on placebo	3.3% on dofetilide
SAFIRE-D[46]	Dofetilide 250, 500, 1000 μg	225	1 year	6.1%, 9.8%, 19.9% on dofetilide vs. 1.2% on placebo	60%. 63%, 42% on dofetilide vs. 75% on placebo	0.8% on dofetilide; 1 (0.4%) proarrhythmic death
EMERALD[47]	Dofetilide 250, 500, 1000 μg	671	Phase 1: 72 h; phase 2: 2 years	6%, 11%, 29% on dofetilide vs. 5% on sotalol at 72 h	60%, 48%, 34% on dofetilide vs. 79% on placebo at 1 year	3 (0.45%) torsades de pointes; 1 (0.15%) sudden cardiac death

AF, *Atrial fibrillation;* AFL, *atrial flutter;* CHF-STAT, *Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy;* CTAF, *Canadian Trial of Atrial Fibrillation;* DDAFS, *Danish Dofetilide in Atrial Fibrillation and Flutter Study;* DIAMOND-AF, *Danish Investigations of Arrhythmia and Mortality on Dofetilide;* EMERALD, *European and Australian Multicenter Evaluative Research on Dofetilide;* NA, *not available;* PAFAC, *Prevention of Atrial Fibrillation After Cardioversion;* SAFE-T, *Sotalol Amiodarone Atrial Fibrillation Efficacy Trial;* SAFIRE-D, *Symptomatic Atrial Fibrillation Investigative Research on Dofetilide;* SOCESP, *Cardiology Society of São Paulo Investigators;* SOPAT, *Suppression of Paroxysmal Atrial Tachyarrhythmias.*

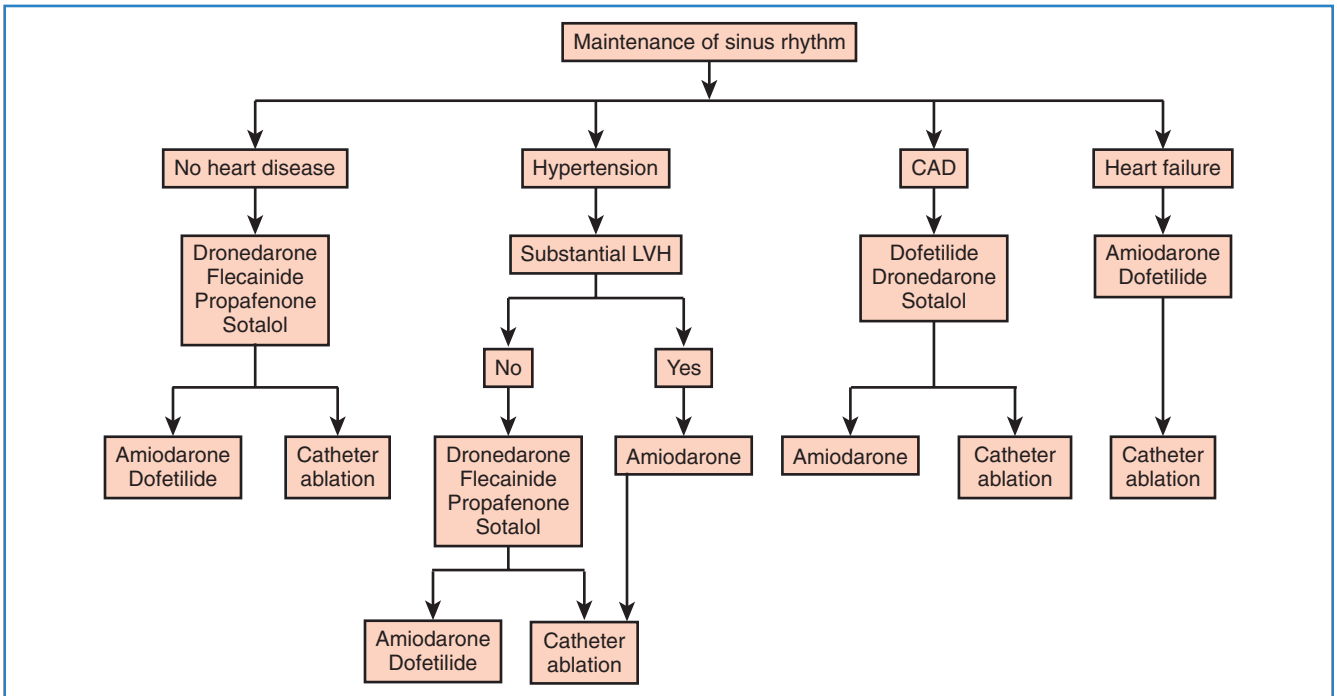


FIGURE 42-50 Recommendations for maintenance of sinus rhythm in atrial fibrillation ACCF/AHA/HRS Focused Update. *CAD*, Coronary artery disease; *LVH*, left ventricular hypertrophy. *(From Wann LS, Curtis AB, January CT, et al: 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (updating the 2006 guideline): A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines,* Circulation *4[123]:104–123, 2011.)*

current I_{Kur}. Although the I_{Kur} current is the main target of vernakalant, its mechanism of action involves blockade of several ion channels such as I_{to}, and I_{Na}, but little impact occurs on the major currents responsible for ventricular repolarization, such as I_{Kr} and I_{Ks} currents.

The efficacy of vernakalant was investigated in one dose-finding and three medium-sized randomized clinical studies and a phase IV open-label study (Table 42-17).[247] In the randomized, double-blind, placebo-controlled Atrial arrhythmia Conversion Trials (ACT), vernakalant was shown to be significantly more effective than placebo in converting AF of less than 7 days (51.7% and 51.2% compared with 4% and 3.6%, respectively).[248,249] Vernakalant was administered as a 10-minute infusion of 3 mg/kg, and if AF persisted after 15 minutes, a second infusion of 2 mg/kg was given. The median time to conversion was 8 to 11 minutes and the majority of patients (75% to 82%) converted after the first dose (Figure 42-50). The highest efficacy was observed in AF of up to 72 hours (70% to 80%). The results were reproduced in the

Table 42-17 Summary of Clinical Studies of Vernakalant in Atrial Fibrillation

STUDY	NO. PATIENTS	PATIENT CHARACTERISTICS	DOSE OF VERNAKALANT	PLACEBO CONTROLLED	PRIMARY ENDPOINT	OUTCOME VS. PLACEBO/ CONTROL
CRAFT	56	AF 3-72 h	IV 0.5 mg/kg + 1 mg/kg *or* IV 2 mg/kg + 3 mg/kg	Yes	Conversion to SR during infusion or within 30 minutes after the last infusion	Converted to SR: 61% vs. 5%, $P < .001$; patients in SR at 30 min 56% vs. 5%, $P = .016$; only higher dose was effective
ACT I	336	AF 3 h to 45 days (3 h to 7 days, n = 220; 8-45 days, n = 116)	IV 3 mg/kg + 2 mg/kg	Yes	Conversion to SR within 90 minutes of drug initiation in AF 3 h to 7 days	Converted to SR: 51.7% vs. 4%, $P < .001$
ACT II	150	AF 3-72 h between 24 h and 7 days after cardiac surgery	IV. 3 mg/kg + 2 mg/kg	Yes	Conversion to SR within 90 min of drug initiation in AF 3 h to 7 days	Converted to SR: 47% vs. 14%, $P < .001$
ACT III	262	AF 3 h to 45 days (3 h to 7 days, n = 170; 8-45 days, n = 69)	IV 3 mg/kg + 2 mg/kg	Yes	Conversion to SR within 90 min of drug initiation in AF 3 h to 7 days	Converted to SR: 51.2% vs. 3.6%, $P < .001$
ACT IV	167	AF 3 h to 45 days (3 h to 7 days, n = 170; 8-45 days, n = 69)	IV 3 mg/kg + 2 mg/kg	No	Conversion to SR within 90 min of drug initiation in AF 3 h to 7 days	Converted to SR: 50.9%
Prevention trial	159	Persistent AF after pharmacologic (vernakalant) or electrical cardioversion	Oral 300 or 600 mg bid	Yes	SR at 1 mo	Maintained SR at 1 mo: 61% (each group) vs. 43% on placebo
Prevention trial, preliminary results	446	Persistent AF after pharmacologic (vernakalant) or electrical cardioversion	Oral 150, 300, or 500 mg bid	Yes	SR at 3 mo	Maintained SR at 3 mo on 500 mg bid: 51% vs. 37% on placebo, $P < .05$; lower doses reduced AF rates, but not significant vs. placebo

ACT, *Atria Arrhythmia Conversion Trial;* AF, *atrial fibrillation;* CRAFT, *Controlled Randomized Atrial Fibrillation Trial;* IV, *intravenous;* SR, *sinus rhythm.*
Data from references 249 to 252.

open-label ACT IV study, in which vernakalant restored sinus rhythm in 50.9% within 14 minutes after the start of treatment. Vernakalant was significantly less effective in converting AF of more than 7 days and did not convert AFL. In direct comparisons, vernakalant was significantly superior to intravenous amiodarone in restoring sinus rhythm within 90 minutes after infusion (51.7% vs. 5.2%; $P < .0001$).[250]

The drug was well tolerated, with no significant QT prolongation or drug-related torsades de pointes. However, in the ACT I study, the QTc values after infusion were greater in the vernakalant group than in the placebo group, and 24% of patients in the vernakalant group had QTc greater than 500 ms as opposed to 15% in the placebo group, but no torsades de pointes was reported during the first 24 hours after infusion.[248] The most common adverse effects of vernakalant were dysgeusia, sneezing, and nausea (>5%). The drug is not indicated in patients with hypotension, severe aortic stenosis, and advanced CHF.

Prevention of Recurrence

Prophylactic drug therapy to prevent recurrence of the arrhythmia is recommended for patients with symptomatic paroxysmal AF with frequent paroxysms and for those with recurrent persistent AF when the likelihood of maintenance of sinus rhythm is uncertain. After cardioversion, approximately 25% to 50% of patients will experience recurrence of persistent AF within the first 1 to 2 months (early recurrence). Thereafter, the recurrence rate is about 10% per year (late recurrence). The goals of prophylactic antiarrhythmic drug therapy include prevention of the recurrence of AF or modification of paroxysms of the arrhythmia rendering them less symptomatic, less frequent, and less sustained or rendering them self-terminating, which may result in the reduction of AF burden and may be associated with a decrease in the risk of progression of AF and its complications such as left ventricular dysfunction. Underlying structural heart disease is essential for the selection of an antiarrhythmic drug if the strategy of restoration and maintenance of sinus rhythm is a therapeutic option (Figure 42-51).[197]

Usually, antiarrhythmic drug therapy is not necessary, except in the case of a rate-slowing agent, if the cause of the arrhythmia, for example, acute illness or thyrotoxicosis, is transient or can be completely eliminated medically.

β-Blockers

β-Blockers are modestly effective in preventing AFL and AF and are mainly used for rate control. Exceptions are adrenergically mediated AF, AF caused by thyrotoxicosis, and AF associated with

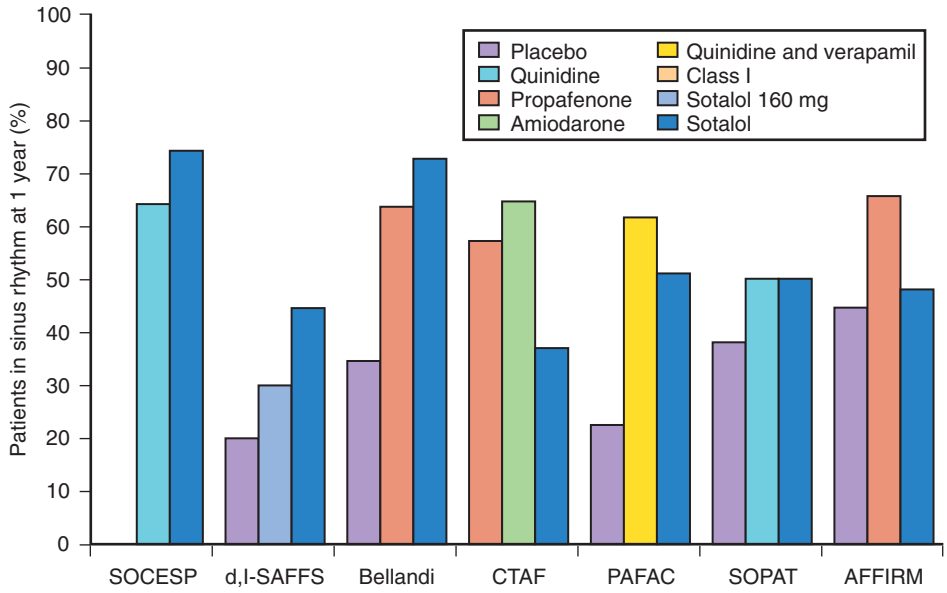


FIGURE 42-51 Efficacy of sotalol in comparison with other antiarrhythmic drugs for maintenance of sinus rhythm in patients with atrial fibrillation. *AFFIRM*, Atrial Fibrillation Follow up Investigation of Rhythm Management; *CTAF*, Canadian Trial of Atrial Fibrillation; *d,l-SAFFS*, d,l-Sotalol Atrial Fibrillation/Flutter Study; *PAFAC*, Prevention of Atrial Fibrillation After Cardioversion; *SOCESP*, Cardiology Society of São Paulo Investigators; *SOPAT*, Suppression of Paroxysmal Atrial Tachyarrhythmias.

heart surgery, in which case β-blockers may be the first-line therapy. Anecdotal evidence suggests that β-blockers may be more effective than placebo and equally effective as sotalol in preventing AF after electrical cardioversion.[251,252]

β-Blockers may prevent the development of AF associated with CHF. A meta-analysis of 7 studies in 11,952 patients showed that therapy with β-blockers, as background therapy with ACE inhibitors and diuretics, was associated with a statistically significant reduction in the incidence of new-onset AF from 39 to 28 per 1000 patient-years (a 27% reduction in relative risk).[253]

Propafenone and Flecainide

A number of randomized, controlled studies addressed the long-term efficacy of class IC antiarrhythmic drugs in AF. Propafenone and flecainide are recommended as first-line therapy for AF in patients without significant structural heart disease such as CHF, hypertension with left ventricular hypertrophy, previous MI, or CAD with documented myocardial ischemia. Both propafenone and flecainide reduced the recurrence rate by two thirds, with no one drug showing an advantage over the other.[254] In a meta-analysis of propafenone, the incidence of recurrent AF was 55.4% (51.3% to 59.7%) at 6 months and 56.8% (52.3% to 61.3%) at 1 year.[233] All-cause mortality associated with propafenone was 0.3%.

The efficacy of a sustained-release (SR) propafenone formulation, which allows twice-daily dosing, has been studied in the North American Recurrence of Atrial Fibrillation Trial (RAFT) and its European equivalent, ERAFT.[255,256] Both studies have shown that propafenone SR is superior to placebo in prolonging the time to first symptomatic recurrence of paroxysmal AF in patients with minor structural heart disease. In the RAFT study, which included 523 patients with onset of AF within 1 to 1.5 years prior to enrolment, time to AF recurrence was prolonged from 41 days on placebo to 112, 291, and more than 300 days on propafenone SR 225, 325, and 425 mg twice daily, respectively.[255] Sixty-five percent of patients treated with the highest dose of 425 mg twice daily were free of symptomatic AF at the end of follow-up compared with only 20% in the placebo group, although the adverse effect rate was higher than with low-dose regimens. The ERAFT study randomized 293 patients with paroxysmal AF of longer duration (approximately 5 years) and more frequent paroxysms to propafenone SR 325 mg or 425 mg twice daily or placebo.[256] The time to the first recurrence of the arrhythmia was shorter than in the RAFT study but still was prolonged from 5 days on placebo to 19 and 24 days on lower dose and high-dose propafenone. The effects of propafenone were consistent in all subgroups, including patients with structural heart disease and long-term arrhythmia. However, patients with significant underlying heart pathology were minimally represented in both studies.

Sotalol

The class III antiarrhythmic drug properties and the benefits of the rate-slowing action of sotalol prompted several randomized, placebo-controlled and comparator studies, many of which reported a higher efficacy of sotalol compared with that of placebo, quinidine, and propafenone (see Table 42-17 and Figure 42-41).[257-260] Sotalol has proved to be an effective and safe prophylactic antiarrhythmic drug for AF in the absence of CHF, MI, or hypertension with significant left ventricular hypertrophy. Because of its β-blocking effect, sotalol offers the additional benefit of ventricular rate slowing during recurrences.

In the d,l-Sotalol Atrial Fibrillation/Flutter dose efficacy study of 253 patients (20% with AFL), sotalol significantly prolonged the time to first symptomatic recurrence of the arrhythmia documented by transtelephonic monitoring from 27 days on placebo to a maximum of 229 days in the active treatment group.[257] The dose of 120 mg twice daily was reported to be both safe and

effective in maintaining sinus rhythm compared with lower and higher dose regimens (160 mg/day and 320 mg/day, respectively). Hypotension and bradycardia are the most common cardiovascular adverse effects of sotalol, with an incidence of 6% to 10%. Proarrhythmias associated with Q-T interval prolongation were observed in 1% to 4% of patients, usually within 72 hours of the first dose.

However, subsequent studies reported the limited efficacy of sotalol compared with amiodarone, dofetilide, and the combination of quinidine and verapamil.[87,261-263] In the Canadian Trial of Atrial Fibrillation (CTAF), sotalol was significantly inferior to amiodarone in the long-term maintenance of sinus rhythm (37% vs. 65%).[261] The Prevention of Atrial Fibrillation After Cardioversion (PAFAC) study demonstrated a 50% recurrence rate with sotalol during 1 year of daily transtelephonic ECG monitoring compared with 38% on the combination of quinidine and verapamil.[87] In the Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T) study, sotalol 160 mg twice daily was superior to placebo but less effective than amiodarone in preventing AF recurrence after pharmacologic or electrical cardioversion (the median time to recurrence was 6 days on placebo, 74 days of sotalol, and 487 days on amiodarone).[262] 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 similar to that of class I antiarrhythmic drugs and inferior to that of amiodarone in the AFFIRM substudy (48%, 45%, and 66%, respectively).[263]

Dofetilide

Unlike class IC agents and sotalol, dofetilide is safe to use in patients with previous MI, CHF, or both. In the DIAMOND-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 µg twice daily compared with placebo (79% vs. 42%).[242] Dofetilide had no effect on mortality rate in patients in whom AF persisted during the study, but restoration and maintenance of sinus rhythm was associated with a 56% reduction in death.

In the dose-ranging Symptomatic Atrial Fibrillation Investigative Research on Dofetilide (SAFIRE-D) study of 325 patients with persistent AF or AFL for 2 to 26 weeks, dofetilide exhibited a dose-related effect: 40%, 37%, and 58% patients receiving 250, 500, and 1000 µg of dofetilide, respectively, were in sinus rhythm after 1 year compared with 25% in the placebo group.[243] The median time to relapse was 31, 179, and more than 365 days, respectively, for the three dofetilide dose groups and 27 days for placebo. Dofetilide was almost twice as effective for the long-term prevention of AFL than of AF (73% vs. 40%).

The major safety concern about dofetilide is its torsadogenic potential, which is dose related. The incidence of torsades de pointes varied between 0.6% and 3.3%, with more than three quarters of episodes occurring during the first 3 to 4 days of drug initiation; it is therefore mandatory to initiate dofetilide in the hospital. Dofetilide is excreted predominantly via the kidneys, and its dose should be adjusted for creatinine clearance; the drug should not be prescribed in patients with significantly impaired renal function (creatinine clearance >20), hypokalemia, hypomagnesemia, or a Q-T interval of longer than 500 ms. If the Q-T interval is prolonged to greater than 500 ms or more than 15% versus baseline, the dose should be reduced.

Amiodarone

The potential of amiodarone to maintain sinus rhythm in patients with AF, particularly in association with significant structural heart disease, has been repeatedly shown in observational and prospective, randomized, controlled studies. Therapy with amiodarone reduced the incidence of sustained recurrence of AF by 57% compared with sotalol and propafenone (Figure 42-52).[261] Data from the Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy (CHF-STAT) substudy showed that patients who received amiodarone had fewer recurrence of AF and were twice as less likely to develop new AF compared with placebo.[264] The safety of amiodarone was indirectly demonstrated in the AF-CHF study.[212]

Given its neutral effect on all-cause mortality, amiodarone should be considered a drug of choice for management of atrial

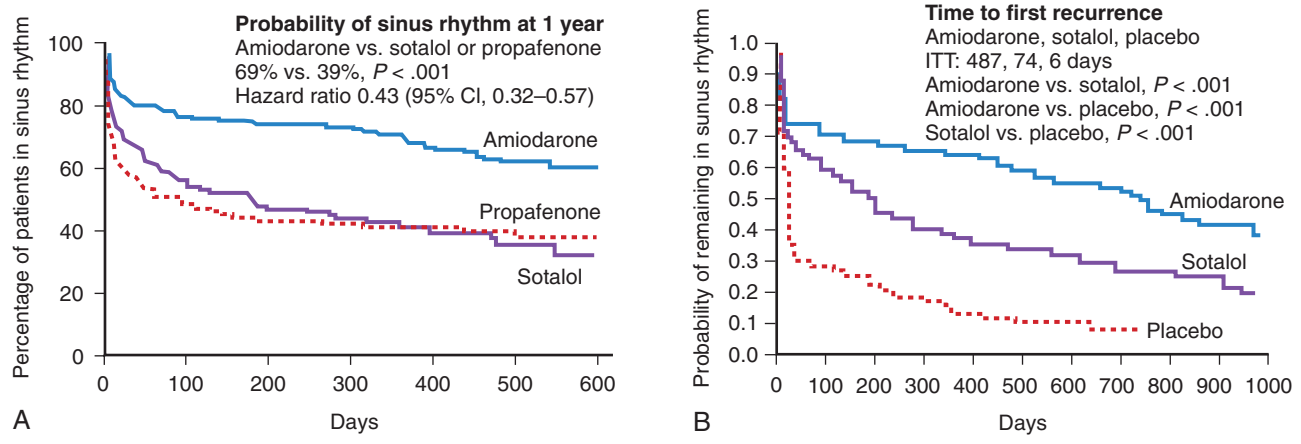


FIGURE 42-52 Probability of remaining free from recurrent atrial fibrillation with amiodarone and sotalol in the Canadian Trial of Atrial Fibrillation (CTAF) (**A**) and in the Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T) (**B**). *ITT*, Intention to treat. *(From Roy D, Talajic M, Dorian P, et al, for the Canadian Trial of Atrial Fibrillation Investigators: Amiodarone to prevent recurrence of atrial fibrillation,* N Engl J Med *342:913–920, 2000; and Singh BN, Singh SN, Reda DJ, et al, Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T) Investigators: Amiodarone versus sotalol for atrial fibrillation,* N Engl J Med *352:1861–1872, 2005.)*

Table 42-18 Summary of Clinical Studies of Dronedarone in Atrial Fibrillation

STUDY	NO. PATIENTS	PATIENT CHARACTERISTICS	DOSE OF DRONEDARONE	PLACEBO CONTROLLED	PRIMARY ENDPOINT	FOLLOW-UP (mo)	OUTCOME
DAFNE	199	After cardioversion	400 mg bid 600 mg bid 800 mg bid	Yes	Time to first AF recurrence	6	Dronedarone 400 mg bid significantly prolonged median time to first AF recurrence vs. placebo: 60 vs. 5.3 days, $P = .026$); relative risk reduction 55% (95% CI, 28%-72%; $P = .001$)
EURIDIS	615	After cardioversion	400 mg bid	Yes	Time to first AF recurrence	12	Median time to first AF recurrence was 41 days on dronedarone vs. 96 days on placebo ($P = .01$)
ADONIS	630	After cardioversion	400 mg bid	Yes	Time to first AF recurrence	12	Median time to first AF recurrence was 59 days on dronedarone vs. 158 days on placebo ($P = .002$)
EURIDIS and ADONIS pooled	1237	After cardioversion	400 mg bid	Yes (n = 409)	All-cause mortality and hospitalizations	12	Dronedarone reduced the primary endpoint vs. placebo by 27% (95% CI, 7%-43%; $P = .01$)
ERATO	630	Permanent AF with ventricular rates >80 beats/min on rate-control therapy	400 mg bid	Yes	Mean 24-hour ventricular rate at 2 weeks	1	Ventricular rates were 12 beats/min lower on dronedarone vs. placebo
ANDROMEDA	617	Congestive heart failure; EF <35%	400 mg bid	Yes	All-cause mortality	6	Stopped early because of increased mortality rate in the dronedarone arm (8% vs. 3.8% on placebo; hazard ratio, 2.3)
ATHENA	4628	Paroxysmal or persistent AF with risk factors	400 mg bid	Yes	All-cause mortality and hospitalizations for cardiac causes	21 ± 5	Dronedarone reduced the primary endpoint vs. placebo by 24% ($P <$ .001)

ACE, *Angiotensin converting enzyme;* ADONIS, *American-Australian-African trial with Dronedarone in Atrial Fibrillation or Flutter for the Maintenance of Sinus Rhythm;* AF, *atrial fibrillation;* ANDROMEDA, *Antiarrhythmic trial with Dronedarone in Moderate to Severe Heart Failure Evaluating Morbidity Decrease;* 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;* CI, *confidence interval;* DAFNE, *Dronedarone Atrial Fibrillation study after Electrical Cardioversion;* EF, *ejection fraction;* ERATO, *Efficacy and Safety of Dronedarone for the Control of Ventricular Rate; EURIDIS, European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm.*
From Savelieva I, Camm J: Anti-arrhythmic drug therapy for atrial fibrillation: current anti-arrhythmic drugs, investigational agents, and innovative approaches, Europace *10:647–665, 2008.*

tachyarrhythmias in patients with CHF, hypertrophic cardiomyopathy, and hypertension in the presence of significant left ventricular hypertrophy. In addition to its antiarrhythmic effects, the beneficial effects of amiodarone include its ability to control fast ventricular rates, which may be particularly deleterious in patients with advanced heart disease; however, its long-term use as a rate-slowing agent is not recommended because of multi-organ toxicity.

Dronedarone

Dronedarone exhibits multiple electrophysiological effects, because of which it is similar to amiodarone, but it is devoid of iodine substituents and is believed to have a better side effect profile. The antiarrhythmic potential of dronedarone and the effects on mortality and morbidity have been studied in two high-quality, medium-sized efficacy and safety trials, and a recently completed large-scale survival trial (Table 42-18).[265,266] The European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm (EURIDIS) and its American-Australian-African equivalent ADONIS have shown that dronedarone 400 mg twice daily (n = 828) was superior to placebo (n = 409) in the prevention of recurrent paroxysmal and persistent AF and was also effective in controlling ventricular rates.[265] In the European trial, the median time to the recurrence of arrhythmia (the primary endpoint) was 41 days in the placebo group and 96 days in the dronedarone group ($P = .01$). In the American-Australian-African

counterpart, the corresponding time was 59 and 158 days, respectively ($P = .002$).

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).[265] Subsequently, the 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 (ATHENA) trial with 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.[266] 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.

However, two studies have identified patient subgroups in whom dronedarone may cause harm. First, the Antiarrhythmic Trial with Dronedarone in Moderate to Severe Heart Failure Evaluating Morbidity Decrease (ANDROMEDA) in patients with severe CHF was stopped prematurely after 627 patients out of the 1000 planned were enrolled because an interim safety analysis revealed an increase in deaths in the dronedarone arm compared with the placebo arm (8% vs. 13.8%; HR, 2.13; 95% CI, 1.07 to 4.25; $P = .027$).[267] The adverse outcome of ANDROMEDA appears largely explained by an increase in creatinine in dronedarone-treated patients being misinterpreted as progressive renal failure (caused by its effect on renal tubular excretion), prompting inappropriate discontinuation of otherwise life-saving treatment with ACE inhibitors or angiotensin receptor–blocking drugs. Consequently, the excess mortality rate related to dronedarone was secondary to CHF. The risk of death was the greatest in patients with severely depressed ventricular function, and more hospitalizations for heart failure occurred in the dronedarone arm.

Second, the Permanent Atrial Fibrillation Outcome Study (PALLAS) in patients with permanent AF and risk factors was also stopped prematurely because of an increase in adverse events in the dronedarone arm.

Therefore dronedarone is currently recommended for reducing the need for hospitalization for cardiovascular events in 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 CHF.[197]

Investigational Antiarrhythmic Agents

A raft of other amiodarone analogues is currently at various stages of development (Figure 42-53).[237] Celivarone (SSR149744C) has been studied in a phase II dose-ranging study, Maintenance of Sinus Rhythm in Patients with Recent Atrial Fibrillation or Flutter (MAIA), with 673 patients who were randomized to one of four doses (50, 100, 200, or 300 mg once daily) or to placebo. As with dronedarone, the higher doses of celivarone tended to be less effective than the lower doses. The lowest incidence of the recurrence at 90 days was 52.1% in the celivarone 50 mg compared with 67.1% in the placebo group.

An oral formulation of *vernakalant* has been investigated in medium-sized phase II studies.[268] In a double-blind, placebo-controlled study (n = 446), patients treated with vernakalant 600 mg twice daily were more likely to maintain sinus rhythm at 3 months after pharmacologic or electrical cardioversion compared with placebo (51% vs. 37%). Torsades de pointes or drug-related deaths were not reported in this study.

Evidence suggests that an antianginal drug, ranolazine, an inhibitor of the delayed sodium current, may also produce an antiarrhythmic effect. Ranolazine increases atrial post-repolarization refractoriness and delays conduction velocity, which may reduce the likelihood of AF. Small uncontrolled or poorly controlled studies suggest that ranolazine may be effective therapy for AF.[269] Phase III studies of ranolazine in AF are presently planned.

Where to Initiate Antiarrhythmic Drug Therapy

The issue of the proper site for the initiation of antiarrhythmic drug therapy for atrial tachyarrhythmias revolves around considerations of risk and practicality.[270] Antiarrhythmic drugs that prolong repolarization confer an increased risk of proarrhythmia, particularly in the presence of baseline Q-T interval prolongation. The rate of torsades de pointes with class III agents is 0.9% to 3.3%. Ibutilide and dofetilide exhibit reverse use dependence, that is, a greater potential to increase the ERP at slower heart rates, resulting in proarrhythmic QT prolongation during bradycardia. Amiodarone may be an exception from these observations; although it prolongs the Q-T interval and drug-induced torsades de pointes has been reported, the risk of proarrhythmia appears to be negligible. In contrast to most class III antiarrhythmic drugs, which preferentially prolong the M cell APD of the mid-myocardial layer and exaggerate trans-mural heterogeneity of repolarization, amiodarone prolongs the APD of all ventricular cell subtypes. However, it does so the least in M cells, thereby reducing the trans-mural dispersion of repolarization. Class IC agents are known to convert AF into AFL and slow atrial activity to 200 beats/min leading to 1:1 AV conduction.

Assessment of the efficacy and prompt recognition of adverse effects such as bradycardia, conduction abnormalities, Q-T interval prolongation, proarrhythmias, and idiosyncrasy favor in-hospital initiation. Patients at expectedly high risk of developing adverse effects or those in whom sinus node function is unknown should be hospitalized for the initiation of antiarrhythmic drug therapy. For some antiarrhythmic agents (e.g., dofetilide), a formal mandate for in-hospital initiation exists. However, in the absence of proarrhythmic concerns and formal labeling, convenience and cost-effectiveness favor out-of-hospital initiation (e.g., oral propafenone and flecainide in patients with lone tachyarrhythmias). The same approach is valid for amiodarone, given its long elimination half life and low probability of developing torsades de pointes.

Table 42-19 summarizes current recommendations on in-hospital or out-of-hospital initiation of antiarrhythmic drug treatment. As a general rule, antiarrhythmic drugs should be started at a lower dose with upward titration, reassessing the ECG as each dose change is made or concomitant drug therapies are introduced. Transtelephonic monitoring is used to provide surveillance of heart rate, P-R and Q-T interval durations, QRS width, and assessment of the efficacy of treatment. Of note, even with in-hospital initiation, antiarrhythmic agents impose a risk of proarrhythmia developing later in the course of therapy, which may be facilitated by progression of underlying heart disease, electrolyte abnormalities, drug interactions, and changes in absorption, metabolism, or clearance.

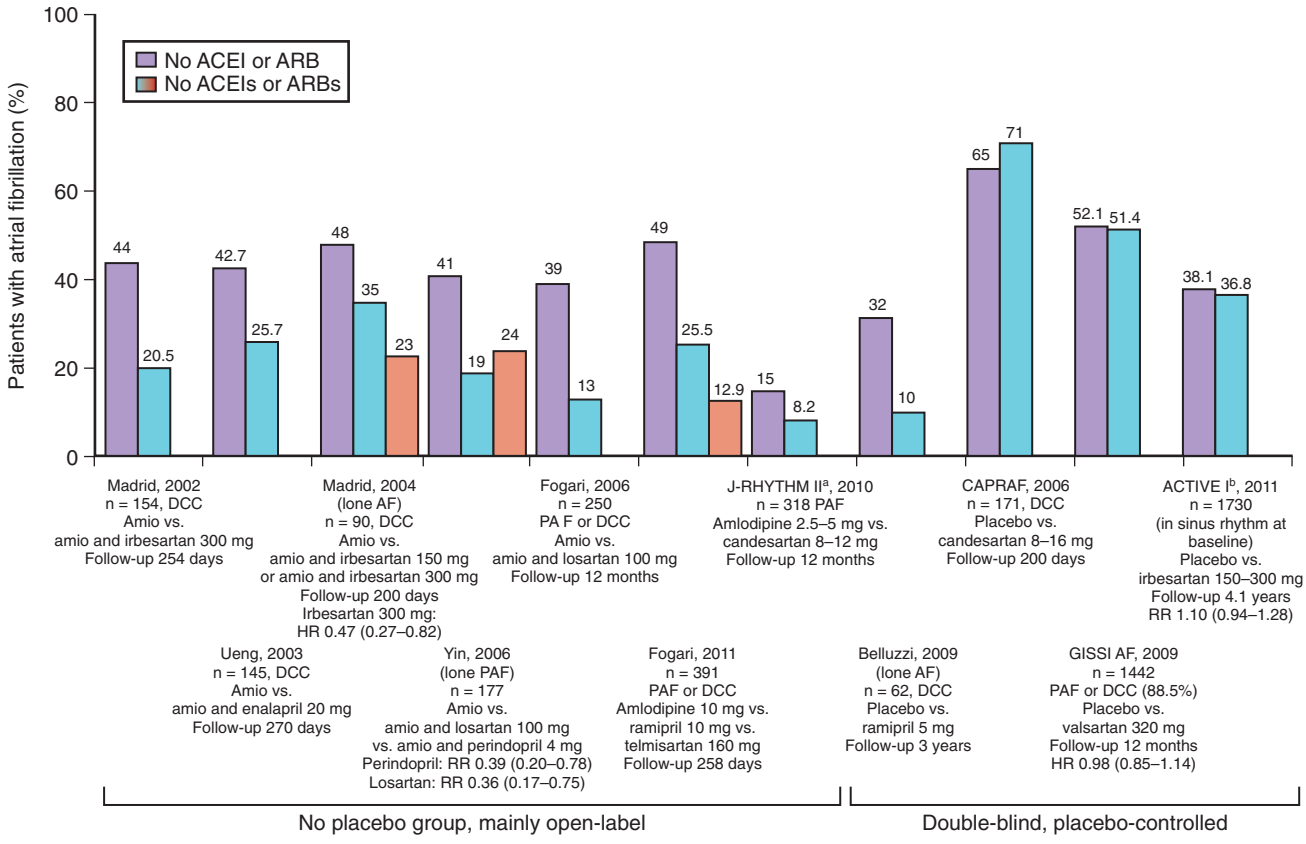


FIGURE 42-53 Freedom from recurrent atrial fibrillation in secondary prevention prospective studies of angiotensin converting enzyme inhibitors (*ACEIs*) and angiotensin receptor blockers (*ARBs*). 95% confidence intervals are given in parentheses. *ACTIVE I*, Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events–Irbesartan; *Amio*, amiodarone; *CAPRAF*, Candesartan in the Prevention of Relapsing Atrial Fibrillation; *DCC*, direct-current cardioversion; *GISSI AF*, Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca Atrial Fibrillation; *HR*, hazard ratio; *J-RHYTHM II*, Japanese Rhythm Management Trial for Atrial Fibrillation; *PAF*, paroxysmal atrial fibrillation; *RR*, relative risk. [a] Patients who developed persistent atrial fibrillation; [b] Recurrence of atrial fibrillation is a secondary endpoint.

Table 42-19 Principles of Initiation of Antiarrhythmic Drug Therapy: Inpatient vs. Outpatient

	UNDERLYING RHYTHM	
DRUG	**ATRIAL FIBRILLATION/ FLUTTER**	**SINUS RHYTHM**
Quinidine	Inpatient	Inpatient
Procainamide	Inpatient	Inpatient
Flecainide	Outpatient*	Outpatient
Propafenone	Outpatient*	Outpatient
Sotalol	Inpatient	Outpatient†
Dofetilide	Inpatient	Inpatient
Azimilide‡	Inpatient	Inpatient
Amiodarone	Outpatient†	Outpatient†

**No known sinus node dysfunction.*
†Preferably with transtelephonic monitoring.
‡An investigational drug.

Rate Control

Rate control is pertinent to all forms of AF and is an essential constituent of its management. Rate control as a primary strategy may be appropriate in (1) patients with a permanent form of the arrhythmia associated with mild symptoms, which can be further improved by slowing heart rate; (2) patients older than 65 years with recurrent AF when the AF is accepted by the patient and the physician; (3) patients with persistent AF and failed repeat cardioversions and serial prophylactic antiarrhythmic drug therapy and in whom the risk/benefit ratio from using specific antiarrhythmic agents leans toward increased risk or those who are ineligible for ablation therapy (Box 42-2).

Constituents of Rate Control

The issue of what constitutes adequate ventricular rate control is still being debated. Consensus has not been reached on what methods need to be employed for effective assessment of ventricular rates either. Adequate rate control probably encompasses more than the mere prevention of fast ventricular rates. The effect

Box 42-2 Preference, Advantages, and Disadvantages of Rate Control for Atrial Fibrillation and Atrial Flutter

FACTORS IMPORTANT IN THE DECISION MAKING
NYHA class heart failure >II
Ejection fraction <40%
AAD and cardioversion refractory (AAD, ≥3; CV, ≥3)
Known proarrhythmic effects of classes I and III AAD
Proarrhythmic risk factors
Intolerance of classes I and III AAD
Left atrial size >5 cm
Symptoms secondary to uncontrolled ventricular rate
Asymptomatic arrhythmia
Sinus node dysfunction
No contraindications for lifelong oral anticoagulation

ADVANTAGES
Reduction of symptoms
Low proarrhythmic risk
Prevention of tachycardia-induced cardiomyopathy
Progression of atrial remodeling
Cost effective

DISADVANTAGES
Need for lifelong anticoagulation
Impaired hemodynamics; loss of atrial contribution
Long arrhythmia duration (>6 months)
Evolution to a permanent form

AAD, Antiarrhythmic drug; CV, cardioversion, NYHA, New York Heart Association.

of excessively irregular rhythm is rarely acknowledged in practice as an important constituent of effective rate control despite some evidence that the rhythm irregularity, per se, may contribute to ventricular dysfunction. Very few studies have specifically addressed these issues, and most of them have only assessed pharmacologic means of rate control.

It is generally assumed that to compensate for loss of atrial contribution, the ventricular rate during AF should probably be about 10% to 20% higher than a corresponding rate during sinus rhythm. Arbitrarily, the rate is generally considered to be controlled when the ventricular response ranges between 60 and 80 beats/min at rest and 90 and 115 beats/min during moderate exercise. The RACE II study in 614 patients with permanent AF has found no significant difference in clinically relevant outcomes such as cardiovascular mortality, hospitalization for CHF, stroke, major bleeding, ventricular tachyarrhythmias, and so on between lenient (resting heart rate <110 beats/min) and strict (resting heart rate <80 beats/min and heart rate during moderate exercise <110 beats/min) rate control (12.9% vs. 14.9%).[271] However, the study was too small, the follow-up was relatively short (up to 3 years), and the difference between the ventricular rates in the two study arms was not sufficient to provide definitive evidence that the degree of rate control is not important, but it is consistent with current evidence which has failed to demonstrate any difference between levels of rate control.

Acute Rate Control

Intravenous nondihydropyridine calcium antagonists (verapamil, diltiazem) and β-blockers (usually esmolol) can accomplish rapid control of the ventricular response rate in the emergency setting (Table 42-20). The decrease in the ventricular rate (approximately 20% to 30%), time to the maximum effect (20 to 30 minutes), the conversion rate (12% to 25%), and the adverse reactions (usually hypotension and bradycardia, although left ventricular dysfunction and high-degree heart block may occur) have been reported to be the same with both classes. β-Blockers are preferable in patients with a history of MI or if thyrotoxicosis is suspected as a cause of the arrhythmia, whereas verapamil and diltiazem are preferred in patients with COPD.

Intravenous digoxin is no longer the treatment of choice when rapid rate control is essential because of the delayed onset of therapeutic effect (more than 60 minutes). Intravenous amiodarone may be effective in rate control when other AV node–blocking agents have no effect on ventricular response or are contraindicated. In patients with pre-excitation syndrome and AF, AV node–blocking agents can improve anterograde conduction in the accessory pathway and produce AF with fast ventricular rates that may degenerate into VF.

Long-Term Rate Control

Digoxin, β-blockers, verapamil, and diltiazem are commonly used. Digoxin is effective in controlling ventricular rates at rest by prolongation of AV node conduction and refractoriness through vagal stimulation, by direct effects on the AV node, and by increasing the amount of concealed conduction in the AV node because of the increased rate at which atria discharge. However, the effect of digoxin is negated during exercise when most of the vagal tone is lost and AV conduction is further enhanced by the increased sympathetic tone. Therefore, digoxin as monotherapy can be effective in older, sedentary patients, but a combination with β-blockers or calcium antagonists is often necessary to achieve rate control in the majority of patients.[272-274]

Nondihydropyridine calcium antagonists and β-blockers and are effective as primary pharmacologic therapy for rate control; however, multiple adjustments of drug type and dosage and a combination of two agents may be needed to achieve the desired effect. For example, in the AFFIRM trial, only 58% of patients in the rate control group achieved adequate rate control with the first drug or combination; drug switches occurred in 37% of the patients, and drug combinations were commonly used. Overall, adequate rate control was ascertained in 80% of patients at 5 years (most frequently on a β-blocker with or without digoxin), but these patients were monitored carefully to assess rate control at each follow-up visit, and frequent drug switches were allowed. Digoxin alone was effective in only 58% of patients.[275]

Atrioventricular Node Ablation and Pacing

Ablation of the AV node followed by implantation of a permanent pacemaker, the "ablate and pace" strategy, can be an alternative strategy to control the ventricular rates in patients with highly symptomatic, intractable AF when poorly controlled, sustained, rapid ventricular rate response is likely to induce or aggravate myocardial dysfunction.[276] A meta-analysis of 21 studies with 1181 patients showed that the ablate and pace strategy significantly improves cardiac symptoms, quality of life, and health care resource utilization in patients with highly symptomatic, drug refractory arrhythmia.[277] However, it is an irreversible procedure rendering a patient pacemaker dependent and should be reserved

Table 42-20 Drugs for Acute Rate Control in Atrial Fibrillation

DRUG	ROUTE OF ADMINISTRATION	DOSE	ONSET	RECOMMENDATION (CLASS)	LEVEL OF EVIDENCE
Esmolol	Intravenous	0.5 mg/kg over 1 min followed by 0.05-0.2 mg/kg/min infusion	5 min	I	C*
Metoprolol	Intravenous	2.5-5 mg over 2 min followed by repeat doses if necessary	5 min	I	C*
Propranolol	Intravenous	0.15 mg/kg	5 min	I	C*
Diltiazem	Intravenous	0.25 mg/kg over 2 min followed by 5-15 mg/h infusion	2-7 min	I	B
Verapamil	Intravenous	0.075-0.15 mg/kg over 2 min	3-5 min	I	B
Digoxin	Intravenous	0.25 mg every 2 h, max 1.5 mg	2 h	IIb†	B
Amiodarone	Intravenous	As for cardioversion‡	6-8 hours	IIb‡	C
Sotalol	Intravenous	1-1.5 mg/kg over 5-10 min	15-30 min	III	B

**For all β-blockers.*
†A class I indication in patients with poor ventricular function and moderately fast ventricular rates; level of evidence B.
‡A class IIa indication in patients with poor ventricular function and moderately fast ventricular rates, level of evidence C.

for patients in whom other means of rate control or rhythm control, including left atrial ablation, is not feasible.

Physiological dual-chamber pacing has been suggested to be more beneficial than ventricular-based pacing in patients who have undergone AV node ablation for paroxysmal AF. DDDR pacing with mode switch can provide AV synchrony during sinus rhythm, and an adequate increase in the ventricular rate during exercise prevents atrial tracking during atrial tachyarrhythmias and delays progression to permanent AF. In patients with evidence of left ventricular dysfunction and interventricular dyssynchrony (e.g., left bundle branch block [LBBB]), implantation of a biventricular pacemaker should be considered.[278,279]

Upstream Therapies

The term *upstream therapy* refers to the use of nonantiarrhythmic drugs that modify the atrial substrate or target specific mechanisms of AF to prevent the occurrence or recurrence of the arrhythmia. These are discussed in detail in Chapter 81. Such agents include ACE inhibitors, angiotensin receptor blockers, aldosterone antagonists, statins, n-3 polyunsaturated fatty acids, and possibly corticosteroids.[280] The key targets of upstream therapy are structural changes in the atria, such as fibrosis, hypertrophy, inflammation, and oxidative stress; however, direct and indirect effects on atrial ion channels, gap junctions, and calcium handling are also applied.

Elevated levels of ACE and angiotensin II and upregulation of profibrotic angiotensin II type I receptors in the atrial myocardium have been reported in animal AF models and in patients with AF.

Inflammation can be a key mechanism for some forms of AF because of the high incidence of AF after cardiac surgery, which is known to induce systemic inflammatory response, and the beneficial effects of drugs with anti-inflammatory properties such as steroids.[281] The anti-inflammatory and antioxidant effects of statins can target specific mechanisms of AF. Statins may protect atrial myocytes during ischemia caused by rapid atrial rates through an increase in the synthesis of nitric oxide in the endothelium. Statins are employed in regulating the variety of matrix-degrading enzymes (matrix metalloproteinases [MMPs]) and thereby may attenuate extracellular matrix remodeling.

Retrospective analyses and reports from studies in which AF was a prespecified secondary endpoint have shown a sustained reduction in new-onset AF with ACE inhibitors and angiotensin receptor blockers in patients with significant underlying heart disease (e.g., left ventricular dysfunction and hypertrophy) and in the incidence of AF after cardiac surgery in patients treated with statins.

However, in the secondary prevention setting, the results with upstream therapies are significantly less encouraging. Although the results of hypothesis-generating small clinical studies or retrospective analyses in selected patient categories have been positive, larger prospective randomized clinical trials have yielded controversial, mostly negative, results (see Figure 42-53). ACE inhibitors, angiotensin receptor blockers, statins, or polyunsaturated fatty acids have not been demonstrated to prevent recurrent paroxysmal or persistent AF.[282]

Nonpharmacologic Therapies

Pulmonary Vein Ablation

Paroxysmal and persistent forms of AF can be treated with pulmonary vein isolation to prevent the induction of AF by rapid repetitive pulmonary vein ectopic activity emanating from the "sleeves" of the atrial myocardium inside the pulmonary veins (Figure 42-54). Current strong evidence suggests that the veins and the antrum are, in fact, critical for maintenance of AF. Following the isolation of all of the veins, about half the patients can no longer sustain AF, suggesting that in significant proportions of patients with paroxysmal AF, the pulmonary veins may also form the substrate maintaining AF. This subject is discussed in detail in Chapter 93.

Recently reported randomized clinical trials have demonstrated substantial advantage of pulmonary vein isolation over pharmacologic rhythm control (Table 42-21).[283-289] The procedure has a success rate approaching 75% to 85% compared with 5% to 35% for antiarrhythmic drug therapy in patients without clinically

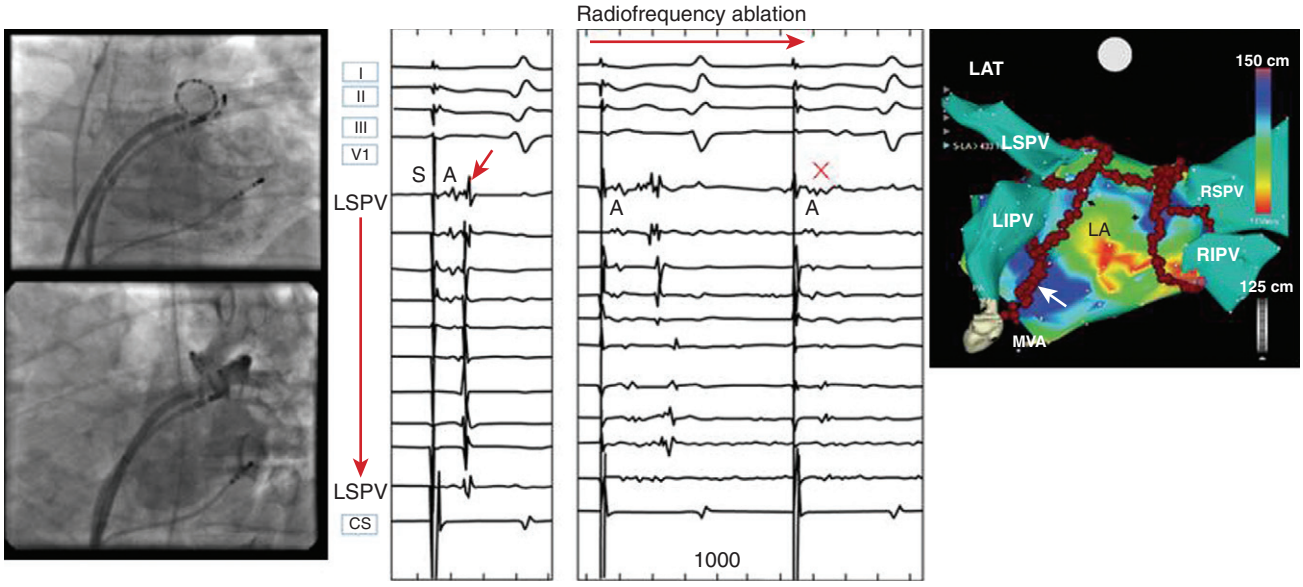


FIGURE 42-54 Paroxysmal and persistent forms of atrial fibrillation (AF) can be treated with pulmonary vein isolation to prevent the induction of AF by rapid repetitive pulmonary vein ectopic activity emanating from "sleeves" of the atrial myocardium inside the pulmonary veins. In general, two different approaches have been adopted: anatomically based pulmonary vein isolation by circumferential ablation at their ostia and segmental isolation of pulmonary veins guided by the detection of high-frequency depolarizations within the ostia (pulmonary vein potentials). The use of a circular mapping catheter (Lasso catheter) allows detection of pulmonary vein potentials and also provides a clear endpoint of complete isolation of the pulmonary veins. The mapping catheter positioned in the left superior pulmonary vein (*LSPV*) (**A**) shows the pulmonary potential (*arrow*) following the atrial potential (*A*) during pacing (*S*) in the coronary sinus (CS) (**B**). **C,** After radiofrequency ablation, complete isolation is achieved as confirmed by the disappearance of the pulmonary vein potential. **D,** Three-dimensional electroanatomic map of the left atrium (*LA*) after pulmonary vein isolation. The *red zones* correspond to the earliest electrical activation of the tissue; *dark red dots* indicate linear lesions made by radiofrequency energy. *LIPV*, Left inferior pulmonary vein; *RIPV*, right inferior pulmonary vein; *RSPV*, right superior pulmonary vein.

Table 42-21 Randomized Controlled Studies of Pulmonary Vein Ablation vs. Antiarrhythmic Drug Therapy in Atrial Fibrillation

STUDY	NO. PATIENTS	TYPE OF AF	PREVIOUS USE OF AAD	CROSSED TO ABLATION IN THE AAD GROUP	AF FREE AT 1 YEAR	
					ABLATION	AAD
Krittayaphong, et al (2003)	30	Paroxysmal, persistent	≥1	Not stated	79%	40%
RAAFT (2005)	70	Mainly paroxysmal	No	49%	87%	37%
CACAF (2005)	137	Paroxysmal, persistent	≥2	57%	56%	9%
Oral, et al (2006)	146	Persistent	≥1 (mean, 2.1 ± 1.2)	77%	74%	4%
APAF (2006)	198	Paroxysmal	≥2 (mean, 2 ± 1)	42%	86%	22%
A4 study (2008)	112	Paroxysmal	≥1	63%	89%	23%
Forleo, et al (2008)	70	Paroxysmal, persistent	≥1	Not stated	80%	43%
Wilber, et al (2009) (Thermocool)	167	Paroxysmal	≥1 (mean, 1.3)	59%[i]	66%	16%
STOP-AF (2010)	245	Paroxysmal	≥1	79%	69.9%	7.3%

AAD, *Antiarrhythmic drugs;* AF, *atrial fibrillation;* APAF, *Ablation for Paroxysmal Atrial Fibrillation study;* A4, *Atrial fibrillation Ablation versus AntiArrhythmic drugs;* CACAF, *Catheter Ablation for the Cure of Atrial Fibrillation study;* RAAFT, *Radiofrequency Ablation Atrial Fibrillation Trial;* STOP-AF, *Sustained Treatment of Paroxysmal Atrial Fibrillation.*
From Camm AJ, Savelieva I: Atrial fibrillation: A4 study: Proof of concept? Nat Rev Cardiol *6:332–334, 2009.*

significant structural heart disease. Accumulating evidence suggests that pulmonary vein ablation can improve left ventricular function in patients with moderate CHF (Table 42-22).[290-293]

However, randomized studies of ablation are relatively small, have used relatively soft endpoints such as the recurrence of AF, and have been undertaken only in the most highly specialized centers. About one quarter to one third of patients required antiarrhythmic drug therapy to prevent recurrences. A significant proportion of patients (25% to 30%) require repeat procedures. Although limited promising experience in patients with AF and

Table 42-22 Long-Term Results of Pulmonary Vein Ablation for Atrial Fibrillation

STUDY	STUDY TYPE	NO. PATIENTS	ABLATION STRATEGY	FOLLOW-UP (MO) (±SD)	ARRHYTHMIA-FREE SURVIVAL (%)	COMPLICATIONS (%)
Gaita (2008)	Randomized 1:1 to PVI vs. PVI + LL	204	PVI/PVI + LL	41.4 ± 6.2/39.7 ± 5.5	41	2%
Fiala (2008)	Randomized 1:1 to segmental PVI vs. circumferential PVI	110	PVI	48 ± 8	56	1%
Bertaglia (2009)	Observational	177	PVI/PVI + LL	49.7 ± 13.3	58	Not reported
Bhargava (2009)	Observational	1404	PVI/PVI + LL	59 ± 16	73	3%
Tsou (2010)*	Observational	123	PVI	71 ± 18	71	Not reported
Wokhlu (2010)	Observational	774	PVI/PVI + LL	36 ± 22.8	64	Not reported
Ouyang (2010)	Observational	161	PVI	57.6	47	2%
Weerasooriya (2011)	Observational	100	PVI/PVI + LL	60	32	6%

**Only patients free from AF 1 year after ablation were included; in a total of 239 patients who underwent AF ablation, the success rate after 71 ± 18 months was only 36.4%.*
LL, *Left lines;* PVI, *pulmonary vein isolation.*

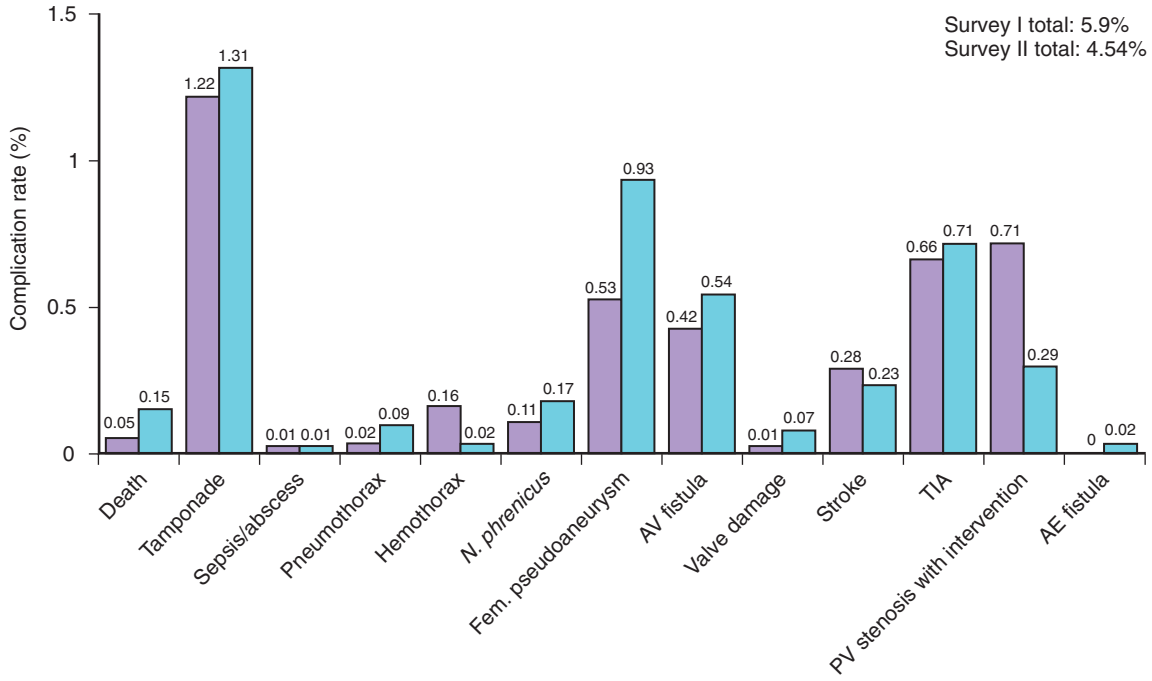


FIGURE 42-55 Safety of pulmonary vein ablation in worldwide surveys I and II. *AV*, Atrioventricular; *TIA*, transient ischemic attack; *PV*, pulmonary vein; *AE*, aortoesophageal. *(From Cappato R, Calkins H, Chen SA, et al: Worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation,* Circulation *111:1100–1105, 2005; and Cappato R, Calkins H, Chen SA, et al: Prevalence and causes of fatal outcome in catheter ablation of atrial fibrillation,* J Am Coll Cardiol *53:1798–1803, 2009.)*

congestive heart failure does exist, the mechanisms of persistent AF are more complex, and ablation procedures must often include additional modification of the substrate by some degree of atrial compartmentalization, for example, lines of block connecting the two upper pulmonary vein orifices along the roof of the left atrium, a line joining the left lower pulmonary vein to the mitral annulus, or both.

Furthermore, in patients with grossly dilated atria and extensive structural abnormalities, even extensive left atrial ablation may not be effective. Left atrial ablation is not free from fatal complications such as stroke (1%) and, rarely, perforation of the esophagus (0.1%). The safety of ablation has significantly improved with an increasing number of procedures performed worldwide (Figure 42-55).[294-298]

Surgical Maze Procedure

The first curative approach to AF was the surgical Maze procedure which was originally conceived to modify the substrate for the arrhythmia by creating lines of conduction block to interrupt all possible re-entrant circuits responsible for maintenance of AF.[297] Although it was initially performed to cure lone AF, it is presently used in association with mitral valve or coronary artery bypass grafting (CABG), with success rates of 74% to 90% at 2 to 3 years postoperatively and a perioperative mortality rate less than 1%.

In a recent meta-analysis of four randomized prospective trials and retrospective studies in patients with AF undergoing mitral valve surgery, a simultaneous Maze procedure increased the likelihood of sinus rhythm by two thirds and reduced the risk of stroke by 56% compared with mitral valve surgery alone.[299] Currently available techniques and prospects of further development and refinement of ablation options and pacing strategies for the

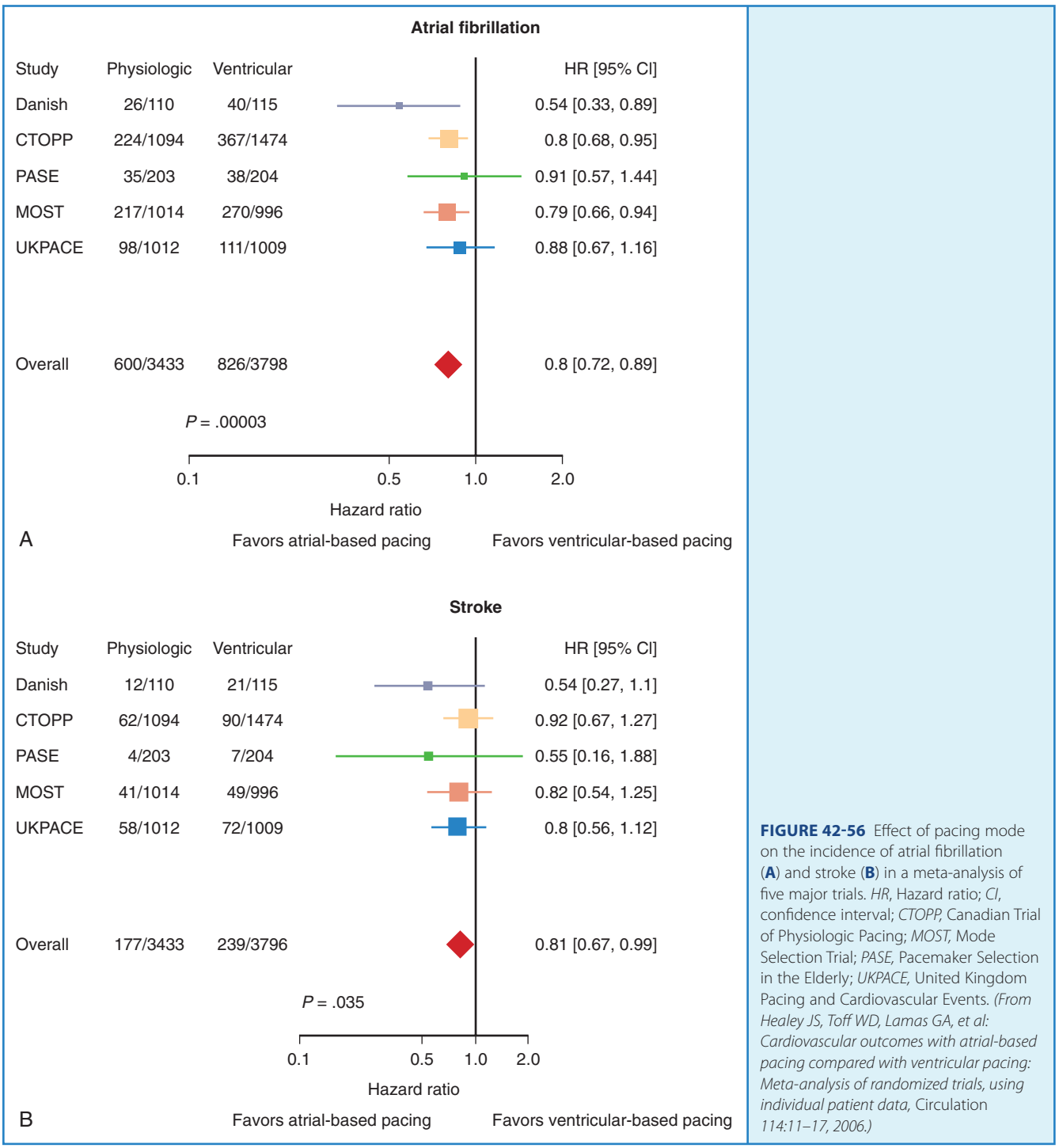


FIGURE 42-56 Effect of pacing mode on the incidence of atrial fibrillation (**A**) and stroke (**B**) in a meta-analysis of five major trials. *HR*, Hazard ratio; *CI*, confidence interval; *CTOPP*, Canadian Trial of Physiologic Pacing; *MOST*, Mode Selection Trial; *PASE*, Pacemaker Selection in the Elderly; *UKPACE*, United Kingdom Pacing and Cardiovascular Events. *(From Healey JS, Toff WD, Lamas GA, et al: Cardiovascular outcomes with atrial-based pacing compared with ventricular pacing: Meta-analysis of randomized trials, using individual patient data,* Circulation *114:11–17, 2006.)*

prevention and termination of atrial tachyarrhythmias are discussed in detail in Chapters 89 and 97.

Preventive Atrial Pacing

Although theoretically very attractive, preventive atrial pacing for the treatment of AF remains a debatable indication because limited data exist to provide sufficient evidence for definitive management guidelines.[300] Atrial pacing can reduce the incidence of AF by (1) eliminating the triggers, modifying the substrate of the arrhythmia by capturing the areas with consistently prolonged activation times (e.g., coronary sinus ostium and Bachmann's bundle), or both; or (2) recognizing and suppressing potential triggers for AF by using specific algorithms such as dynamic atrial overdrive pacing or anti-tachycardia pacing. Several ongoing studies will explore the role of preventive atrial pacing in selected patient populations as an additive to other therapies such as cardiac resynchronization and antiarrhythmic drug therapy. This is discussed in more detail in Chapter 89.

Patients with sinus node dysfunction but with preserved AV conduction obtained substantial benefit from atrial or dual-chamber pacing in terms of progression to permanent AF compared with ventricular pacing.[300] Meta-analysis of five major pacing mode selection trials, which included a total of 35,000 patient-years of follow-up, has shown a statistically significant 20% reduction in AF with atrial-based pacing and a 19% decrease in stroke that was of borderline significance (Figure 42-56).[301]

Excessive right ventricular stimulation during dual-chamber pacing may worsen left ventricular function and thus may negate the physiological advantage of AV synchrony and preservation of sinus node control over heart rate.[302-305] The use of specific algorithms to minimize unnecessary ventricular stimulation in dual-chamber pacemakers has had no significant beneficial effect on mortality or CHF but has further reduced the risk of AF, in particular persistent AF, by 40% compared with conventional dual-chamber pacing. In the Search AV Extension and Managed Ventricular Pacing for Promoting Atrioventricular Conduction (SAVE PACE) trial, the incidence of AF after 1.7 years was 12.7% in the group treated with conventional dual-chamber pacing and 7.9% in the group treated with dual-chamber pacing plus an algorithm reducing unnecessary ventricular pacing.[303]

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CHAPTER 43

Nonsustained Ventricular Tachycardia

Demosthenes G. Katritsis, Wojciech Zareba, and A. John Camm

Nonsustained ventricular tachycardia (NSVT) has been recognized as a usually asymptomatic rhythm disorder detected in an extremely wide range of conditions, from asymptomatic, apparently healthy, young individuals to patients with significant heart disease. Because of its brevity, NSVT does not produce symptoms in most instances; it derives its clinical importance from the fact that its detection may have important prognostic implications, depending on the underlying pathology. In several clinical settings, NSVT is a marker of increased risk for subsequent sustained tachyarrhythmias and sudden cardiac death (SCD), whereas it may have no prognostic significance in a healthy individual, although evidence for occult pathology or an inherited channelopathy in apparently normal subjects who develop ventricular arrhythmia not related to physical exercise continues to accumulate.[1-3] The main task of the physician is to detect the apparently healthy individuals in whom NSVT represents a sign of occult disease and to risk stratify patients with known disease who present with this arrhythmia. This, however, is not an easy task. The patient with NSVT still represents a clinical challenge with regard to proper management, and several crucial questions remain unanswered.

Definition

Traditionally, the term *tachycardia* (from the Greek words *tachy,* meaning fast, and *cardia,* meaning heart) is used to describe conditions in which the heart rate exceeds the conventional number of 100 beats/min for more than three consecutive beats, either in response to metabolic demand or other stimuli or because of disease.[4] *Sustained tachycardia* is defined as tachycardia that lasts for more than 30 seconds (unless requiring termination because of hemodynamic collapse), whereas nonsustained tachycardia terminates spontaneously within 30 seconds.[4] Thus, NSVT has been defined as three (sometimes five) or more consecutive beats arising below the atrioventricular (AV) node with an R-R interval of less than 600 ms (>100 beats/min) and lasting less than 30 seconds.[5]

This definition is by no means a universally accepted one. In the recent Cardiac Arrhythmias and Risk Stratification After Acute Myocardial Infarction (CARISMA) study,[6] NSVT was detected by registering runs of 16 beats or more, with a rate of 125 beats/min, whereas a rate of 120 beats/min or more has been used by the Marburg trial and other studies.[7,8] The period of a tachycardia run to qualify for NSVT has also varied. In the Electrophysiologic Study Versus Electrocardiographic Monitoring (ESVEM) study, the time cut-off was 15 seconds as opposed to the conventional number of 30 seconds, which has been used both by the Multicenter Automatic Defibrillator Implantation Trial (MADIT) and the Multicenter Unsustained Tachycardia Trial (MUSTT) .[9-11] This implies that NSVT cases according to the MADIT and MUSTT criteria might well have been dealt with as sustained ventricular tachycardia (VT) episodes in the ESVEM cohort. In other studies, the terms *ventricular ectopy* or *NSVT* are often used without strictly defined diagnostic criteria.[12]

Epidemiology

Reliable epidemiologic data on NSVT are difficult to obtain. Usually, although not invariably, most patients remain asymptomatic, and the reproducibility of NSVT recordings is documented in only half of the patients with this arrhythmia. In the MADIT, NSVT was defined as reproducible when found in at least two recordings of three consecutive Holter electrocardiograms (ECGs) performed in weekly intervals. Reproducible NSVT was identified in only 50% of the patients with NSVT and did not seem to be an independent risk factor for future arrhythmic events.[13] The reported prevalence of NSVT in various clinical conditions is presented in Table 43-1. Previous studies were based on Holter monitoring, thus reporting NSVT occurring within a short period. The advent of implantable permanent pacemakers, defibrillators, and monitoring devices with extensive ECG monitoring capabilities has allowed for a more accurate estimation of the incidence of NSVT in patients with heart disease. Evidence is now available from implantable cardioverter-defibrillator (ICD) data that NSVT is a distinct tachyarrhythmia that may cause syncope without causing death in patients with heart disease and that the incidence of polymorphic NSVT relative to sustained arrhythmia is greater than previously believed.[14]

In asymptomatic, apparently healthy persons, Holter recordings in older studies revealed a frequency of NSVT ranging from 0% to 3%.[5,15,16] In non–ST-segment elevation acute coronary syndromes, NSVT is detected in 18% to 25% of patients 2 to 9 days after admission.[17] In *acute myocardial infarction* (MI), NSVT during the first 24 hours is frequent (43% in patients without thrombolysis and up to 75% in re-perfused patients).[5,18] In the first 7 days after MI, NSVT is detected in approximately 6.8% to 13.4% of patients in the reperfusion era, which is not much different from that reported in the pre-thrombolytic era (12%; Multicenter Postinfarction Research Program).[18-23] NSVT can be detected in approximately 2% of patients with ischemia and preserved left ventricular function.[24] Recently, the CARISMA study group reported on long-term cardiac arrhythmias recorded by a cardiac

Table 43-1 Reported Prevalence of Nonsustained Ventricular Tachycardia in Different Cardiac Conditions

CONDITION	PREVALENCE
Apparently healthy individuals	0%-3%
Non-ST ACS (2 to 9 days after admission)	18%-25%
Acute MI (early phase)	45%-75%
Reperfused acute MI (later than 1 week)	7%-13%
Heart failure (LVEF <30% to 40%)	30%-80%
DCM	40%-50%
HCM	25%-80%
Significant valve disease	≤25%
Hypertension	8%
Hypertension and left ventricular hypertrophy	12%-28%

DCM, *Dilated cardiomyopathy;* HCM, *hypertrophic cardiomyopathy;* LVEF, *left ventricular ejection fraction;* MI, *myocardial infarction;* Non-ST ACS, *non–ST-segment elevation acute coronary syndrome.*

monitor implanted 2 to 5 days after MI in patients with left ventricular ejection fraction (LVEF) of 40% or less. The detected incidence of NSVT over a 2-year period was 13%.[6]

In patients with *heart failure* and LVEF less than 30% to 40%, the reported prevalence of NSVT is 30% to 80%.[25,26] It seems that ischemic heart failure carries a higher risk for NSVT. In the Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA) trial, in which only one third of patients had ischemic heart disease, the prevalence of NSVT was 33%. Whereas in the Congestive Heart Failure: Survival Trial of Antiarrhythmic Therapy (CHF-STAT) trial, in which the ischemic patients comprised two thirds of the whole cohort, the prevalence was 80%.[25,26] In *dilated cardiomyopathy* (DCM), NSVT has been detected in 40% to 50% of patients.[27-29] In *hypertrophic cardiomyopathy* (HCM), 20% to 30% of patients may have NSVT, whereas in patients with a history of cardiac arrest, this proportion approaches 80%.[30-32] These estimations may not reflect the true incidence of NSVT in HCM, since they are based on highly selected referral populations. In patients with *valvular disease*, the incidence of NSVT is considerable (up to 25% in aortic stenosis and in significant mitral regurgitation) and appears to be a marker of underlying left ventricular pathology.[33,34] In patients with *arterial hypertension*, NSVT is correlated to the degree of cardiac hypertrophy and subendocardial fibrosis.[35,36] Approximately 12% to 28% of patients with hypertension and left ventricular hypertrophy present with NSVT as opposed to 8% of patients with hypertension alone.[35,36] Ventricular extrasystolic activity can be detected with Holter monitoring in up to 50% of patients with repaired *tetralogy of Fallot*, and recent studies have detected a 4% to 14% prevalence of sustained VT.[37-39]

Clinical Electrocardiography

NSVT represents an electrocardiographic diagnosis based on resting or exercise ECG and Holter monitoring recordings. Two major methodology problems may interfere with the recognition as well as interpretation of this condition. First, a universally accepted, established definition does not exist. Second, morphologic criteria such as those used in the description of sustained VT have not been adopted. The nature of the short-lived episodes of arrhythmia may not allow a clear distinction between monomorphic and polymorphic ventricular rhythms. Thus, in most published studies, the terms *NSVT episodes* or *complex ventricular ectopy* are used in a general way without any attempt to distinguish between regular, monomorphic rhythms and the salvos of ventricular depolarizations of variable morphology. This might have important implications in the assessment of the clinical significance of NSVT in various conditions.

Electrocardiographic Patterns

Nonsustained Ventricular Tachycardia Associated with a "Normal" Heart

In the apparently normal population, NSVT episodes without consistent morphology patterns may be recorded either at rest or after exercise. [15,16,40-44] When NSVT is documented in the context of a history of established monomorphic VT, it may demonstrate the same morphology as clinical sustained arrhythmia. VTs with a left bundle branch block (LBBB) pattern and inferior axis originate in the right ventricular outflow tract (RVOT).[45] Left ventricular outflow tract (LVOT) tachycardias may produce a right bundle branch block (RBBB) morphology with inferior axis or a variable QRS morphology, depending on the site of origin. Tachycardias originating in the left coronary cusp have a QRS morphology consistent with an M or W pattern in lead V1, tachycardias originating in the right coronary cusp have an LBBB pattern, and those from the aortomitral continuity usually result in a qR pattern.[46] Idiopathic left VT may also be caused by re-entry within the Purkinje network and may originate within one of the fascicles of the left bundle branch (*fascicular tachycardias*), and usually the posterior fascicle is involved, resulting in a tachycardia with RBBB and left-axis deviation. However, cases with an inferior axis, that is, of anterior fascicular origin, have also been described.[47,48]

The most systematic attempts to characterize the electrocardiographic pattern of NSVT have been reported to be successful in patients with the so-called *repetitive monomorphic VT*, originally described by Gallavardin.[49] This arrhythmia represents a form of the spectrum of idiopathic ventricular outflow tachycardias, which includes *repetitive uniform premature ventricular contractions* (PVCs) and *exercise-triggered paroxysmal VT*. They usually originate in the RVOT and less often in the LVOT and are most probably caused by triggered activity secondary to cyclic adenosine monophosphate–mediated delayed afterdepolarizations.[45] The relatively consistent recording of frequent arrhythmia episodes in patients with repetitive monomorphic VT has made possible the accumulation of useful information on its morphology. Holter studies have revealed that the tachycardia begins with a fusion complex or with an ectopic beat that has the same morphology as the subsequent beats (Figure 43-1).[50] The salvos of VT are generally short (3 to 15 beats) and the coupling interval of the first beat is usually long (>400 ms). The coupling intervals of successive beats may gradually become prolonged.[51-53] Many patients mostly have ventricular premature beats (VPBs) with only occasional episodes of tachycardia, whereas others manifest mainly with short runs of VT, where the tachycardia beats far exceed the number of sinus beats. The rate during tachycardia is generally 110 to 150 beats/min. The arrhythmia is only present within a

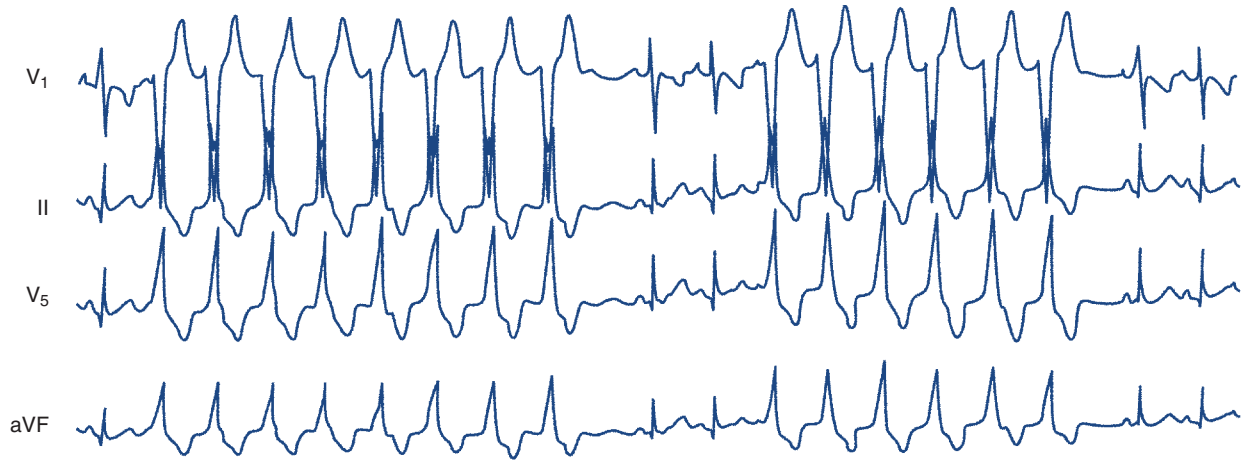

FIGURE 43-1 Repetitive nonsustained episodes of ventricular tachycardia. The left bundle branch block–like QRS complexes suggest that the tachycardia arises from the right ventricle. This patient was asymptomatic, and no evidence of any cardiac pathology was present.

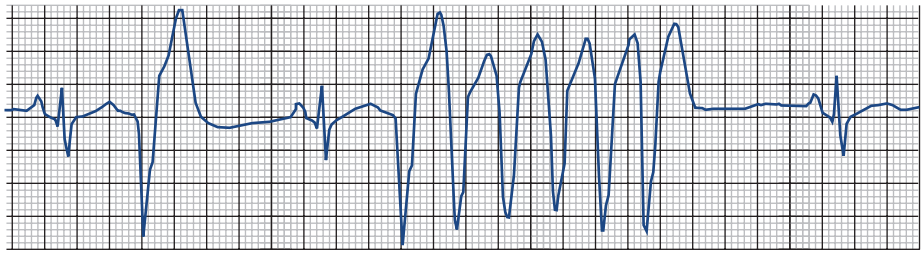

FIGURE 43-2 Nonsustained ventricular tachycardia in a patient with previous myocardial infarction. The morphology of the complexes is similar but not identical.

critical window of heart rates (upper and lower thresholds).[50] Thus, the tachycardia often occurs during exercise but disappears as the heart rate increases and returns during the recovery period following exercise. Some patients develop sustained episodes (>30 seconds) during the recovery phase, and this behavior differentiates repetitive monomorphic VT from the exercise-triggered paroxysmal VT first described by Wilson and others in patients with apparently normal hearts.[54-56] It should be noted, however, that repetitive behavior has been documented in various clinical settings, including cardiomyopathy and previous MI, as well as tachycardias originating in the aortic valve cusps.[51,57]

In *catecholaminergic polymorphic VT*, a familial condition mainly caused by mutations in the genes encoding the cardiac ryanodine receptor channel as well as calsequestrin involved in calcium kinetics, episodes of provoked tachycardia are typically nonsustained.[58] They may originate from the LVOT and less frequently from the RVOT or the right ventricular apex. QRS morphology suggests an outflow tract origin of the initiating beat in more than 50% of patients, and subsequent beats portray a polymorphic or typically bi-directional VT morphology.[59]

Ischemic Heart Disease

Frequent and complex ventricular ectopy as well as NSVT occur more commonly in patients with left ventricular dysfunction. Usually, monomorphic VT is seen in the context of re-entry at the borders of a ventricular scar caused by previous MI, whereas ischemia most of time induces polymorphic VT or ventricular fibrillation (VF).[60,61] The QRS morphology during monomorphic tachycardia may show an RBBB or LBBB pattern or may even be nonspecific (Figure 43-2). Both RBBB and LBBB patterns can be seen in the same patient when the infarct scar involves the interventricular septum (Figure 43-3). Spontaneous reversions to sinus rhythm, thus documenting nonsustained VF, can occur (Figure 43-4), and data from patients with ICDs reveal that up to 40% of all VF episodes are nonsustained.[14]

Cardiomyopathies and Other Conditions

VTs (both sustained and nonsustained) in DCM may present with multiple morphologies or an LBBB or RBBB pattern. In approximately one third of the cases of idiopathic DCM, and probably in a small percentage of ischemic patients, sustained or nonsustained VT is caused by bundle branch re-entry.[62] The necessary condition for bundle branch re-entry seems to be prolonged conduction in the His-Purkinje system, which is reflected in the H-V interval that is prolonged during sinus rhythm and prolonged or equal to the baseline sinus rhythm during VT.[63] The circuit involves the right and left branch bundles, with antegrade conduction occurring most of the times through the right branch. As a rule, AV dissociation is present. These tachycardias are usually unstable; the 12-lead ECG, when obtainable, may show an LBBB

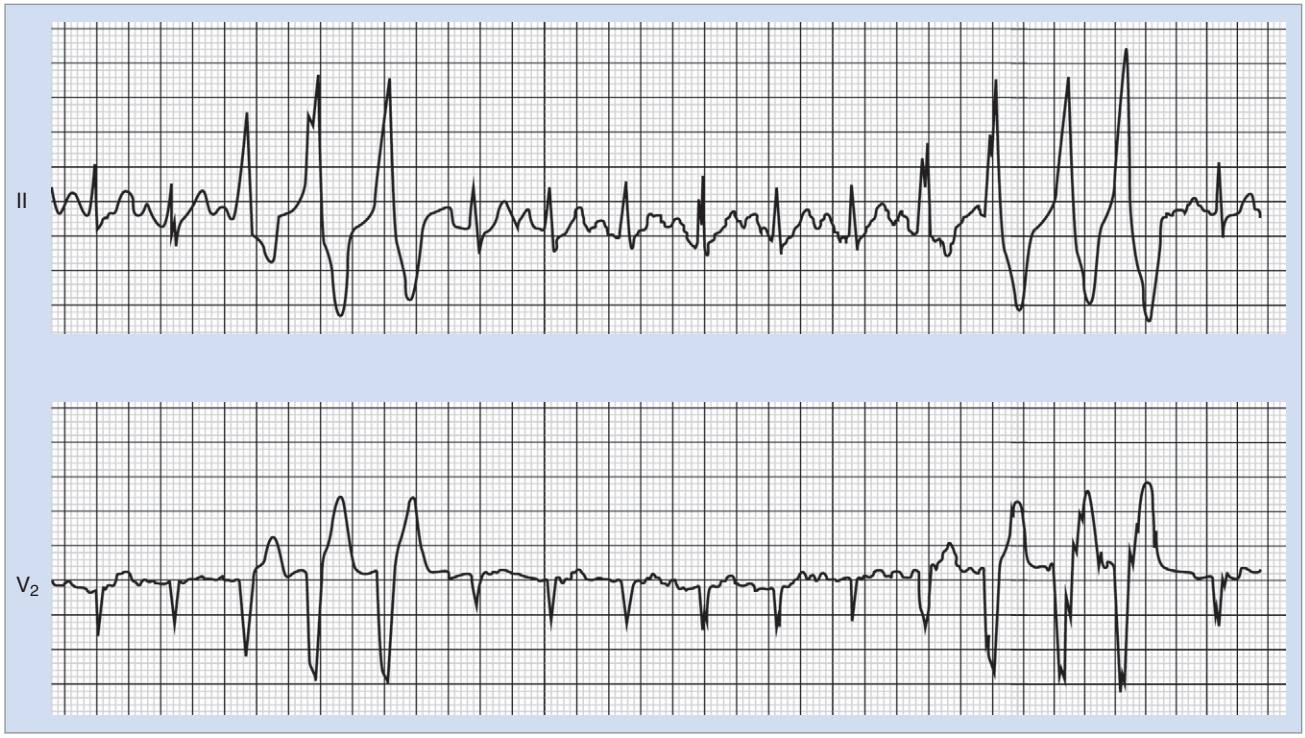

FIGURE 43-3 Two runs of nonsustained ventricular tachycardia from a patient with a previous myocardial infarction. The first beat of tachycardia in the two runs probably represents fusion with sinus beats.

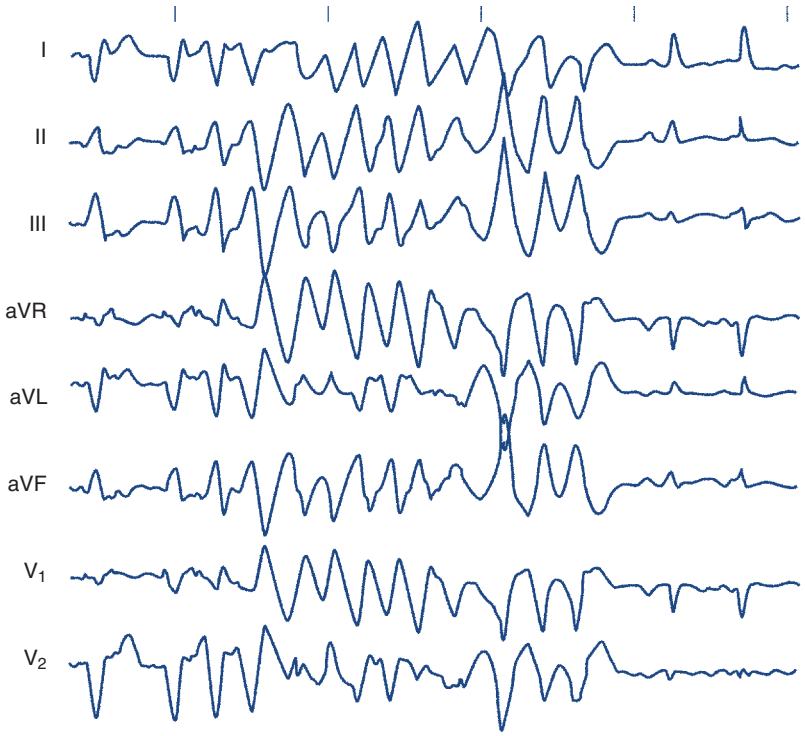

FIGURE 43-4 During electrophysiology testing in a patient with ischemic heart disease and nonsustained ventricular tachycardia on Holter monitoring, an episode of nonsustained polymorphic ventricular tachycardia or ventricular fibrillation is induced.

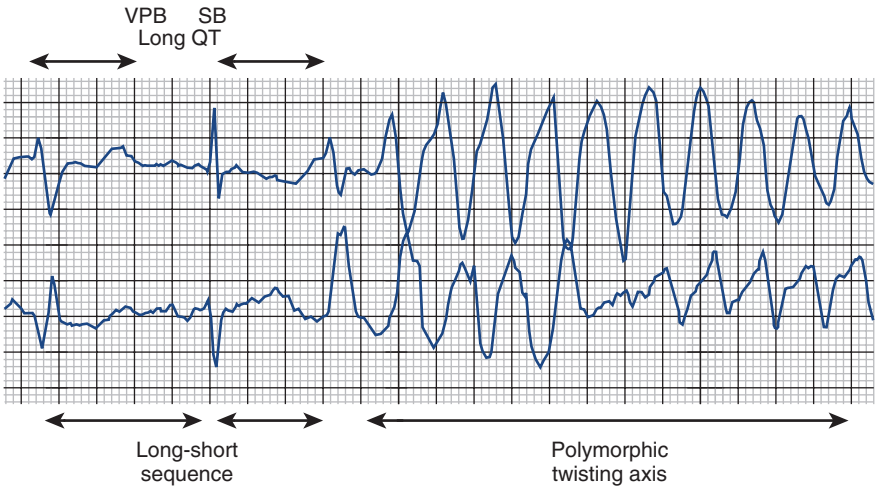

FIGURE 43-5 This is an example of torsades de pointes. Note the relatively rapid but variable rate, continually changing QRS morphology, and variable QRS axis. A polymorphic ventricular tachycardia is usually diagnosed as torsades de pointes when conducted QRS complexes (between episodes of tachycardia) have a prolonged Q-T interval or the tachycardia is initiated after a preceding pause or, as in this case, a (short-) long-short sequence of QRS complexes. *SB*, Sinus beat; *VPB*, ventricular premature beat.

or RBBB pattern, depending on the orientation of activation of the bundle branches.

No characteristic electrocardiographic morphology of NSVT exists in patients with HCM. Relatively slow, often asymptomatic nonsustained episodes of monomorphic VT may be documented on prolonged ambulatory recordings. When nonsustained or sustained VT is induced by programmed stimulation, it is more often polymorphic (60% of patients) than monomorphic (30%).[32,64,65]

In other conditions such as *valvular disease* and *systemic hypertension*, ventricular arrhythmias are common but less well characterized and usually represent polymorphic rhythms.[34-36] Most of the reported patients with *mitral valve prolapse* demonstrate LBBB morphology during tachycardia, which raises the possibility that the mitral valve prolapse might be an incidental finding or that the arrhythmia is caused by other mechanisms not directly related to the mechanical stress imposed on the ventricle by the valvular apparatus.[66,67]

The tachycardias in *arrhythmogenic right ventricular dysplasia* (ARVD) arise from the right ventricle and typically present with LBBB morphology with a left- or even right-axis deviation.[68]

Long QT Syndrome

The typical morphology of recorded arrhythmias in *long QT syndrome* (LQTS; congenital or acquired) is that of *torsades de pointes*.[69] The term refers to the electrocardiographic appearance of spike-like QRS complexes that rotate irregularly around the isoelectric line at rates of 200 to 250 beats/min (Figure 43-5). Typically, the coupling interval of the initial beat of the torsade is long (600 to 800 ms), whereas the last QRS complex of the episode is larger than the normal QRS during sinus rhythm. This is a VT that is frequently nonsustained and sometimes sustained. The tachycardia, which usually occurs in the setting of bradycardia or long postectopic pauses, is often repetitive and may trigger VF. It is seen primarily in association with prolongation of the Q-T interval that may be appreciable before the onset of arrhythmias or after a pause. Not all patients with the LQTS have polymorphic VT with a characteristic torsades de pointes configuration, and this pattern can be seen in some patients without the LQTS. A variety of torsade initiating with a short coupling interval in patients without any evidence of LQTS has also been described.[70]

Clinical Evaluation

Careful clinical assessment of the patient is the cornerstone of the diagnostic process. Age, general condition, previous medical history, and conditions such as electrolyte disturbances, metabolic imbalance, and proarrhythmic effect of drugs should be considered. A standard 12-lead ECG might indicate potential causes of NSVT, including signs of previous MI or active ischemia, conduction disturbances, prolonged Q-T interval, or other signs of electrical instability suggestive of Brugada syndrome or ARVD. In addition, several other clinical parameters and tests can provide specific information about the potential risk of future arrhythmic events in patients who have presented with nonsustained ventricular arrhythmias.

Trans-thoracic Echocardiography

Trans-thoracic echocardiography may detect signs of cardiomyopathy, ARVD and other structural abnormalities, and impaired left ventricular function. Overwhelming evidence indicates that in patients with heart disease, in general, LVEF is the major determinant of cardiac and total mortality.[1] The results of the MADIT, MUSTT, Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), and the Marburg Cardiomyopathy Study (MACAS) trials have also established the importance of LVEF as the most critical prognostic factor in patients with ischemic heart disease and NSVT.[8,10,11,71] Left ventricular function assessment with echocardiography or radionuclide ventriculography is therefore mandatory for the risk stratification and subsequent management of patients with NSVT. However, LVEF does not always predict ICD intervention in patients with ischemic or nonischemic cardiomyopathy.[72] Analysis of arrhythmic death in 674 patients enrolled in MUSTT showed that patients whose only factor is ejection fraction (EF) of 30% or less have a predicted 2-year arrhythmic death risk of 5% or less.[73] Multiple additional factors influence arrhythmic death in patients with LVEF less than 40% and NSVT such as inducible VT, history of heart

failure, NSVT not discovered within 10 days after coronary artery bypass grafting (CABG), and intraventricular conduction delay or LBBB.[73]

Tests for Myocardial Ischemia

Functional tests such as treadmill exercise electrocardiography, myocardial perfusion, and stress echocardiography are required to demonstrate myocardial ischemia in patients with NSVT. Acute myocardial ischemia is an established cause of polymorphic ventricular rhythms.[61] The association of monomorphic VT, a substrate-dependent arrhythmia, with acute ischemia is less well characterized, but ischemia may induce monomorphic VT in the presence of a myocardial scar.[74-76]

Apart from demonstration of ischemia, exercise tasting may also be helpful in patients with LQTS, exercise-triggered RVOT tachycardia, and cathecholaminergic polymorphic VT. NSVT induced by treadmill exercise testing aimed at evaluating presumed LQTS suggests catecholaminergic polymorphic VT rather than LQTS.[77]

Ambulatory Electrocardiographic Monitoring

Holter monitoring is a valuable diagnostic tool in detecting patients with NSVT, and 7-day Holter monitoring improves detection and allows better characterization of ventricular arrhythmic episodes.[78] Detection of NSVT has been reported to predict SCD in patients with non–ST-segment elevation acute coronary syndromes, thrombolysed MI, DCM, HCM, and arrhythmogenic right ventricular dysplasia.[17,18,25,31,79-81] However, whether NSVT provokes arrhythmia or is simply a surrogate marker of a more severe underlying cardiac condition is not known. In patients with revascularization of most infarct-related arteries (78%), NSVT early after MI (4 to 16 days) carried a significant but low RR for the composite endpoint of cardiac death, VT, or VF but not for arrhythmic events considered alone.[20] In the Danish Multicenter Randomized Study on Thrombolytic Therapy Versus Acute Coronary Angioplasty in Acute Myocardial Infarction-2 (DANAMI-2) trial, the prognostic value of NSVT was limited regardless of reperfusion strategy, and in the study of Makikallio et al, no Holter variable predicted sudden death among infarct survivors with an LVEF of 35% or less.[22,79] It seems that in the β-blocking era, all common arrhythmia risk variables, including NSVT, have diminished the predictive power in identifying patients with previous MI at risk of SCD.[82]

Both in MACAS and CHF-STAT, in patients with CM or ischemic cardiomyopathy, NSVT was a predictor of arrhythmia in univariate analysis but not in multivariate analysis, as opposed to LVEF.[8,26] In patients with HCM, NSVT was associated with SCD, but a relation between the risk of arrhythmic death and the frequency, duration, and rate of NSVT episodes could not be demonstrated.[31]

The suppression of frequent ventricular ectopy or NSVT runs following β-blockade or amiodarone therapy does not imply a favorable diagnosis. Mortality was increased in the Cardiac Arrhythmia Suppression Trials (CAST and CAST II) despite reduced ectopic activity, whereas mortality was not reduced by amiodarone in the Veterans Administration CHF-STAT despite the elimination of ventricular ectopy.[83-85] Thus, Holter monitoring may be useful for risk stratification purposes by means of detecting episodes of NSVT in certain clinical settings, but its use for the subsequent follow-up and evaluation of treatment is limited.

Assessment of Autonomic Tone

Heart rate variability (HRV) has been used as an independent risk factor for cardiac mortality in patients with previous MI and has been claimed to be a specific predictor of arrhythmic rather than total cardiac mortality.[86-88] In these patients, a depressed baroreflex sensitivity has been associated with increased cardiac mortality and SCD and with a higher predictive power (in values below 3 ms/mm Hg) compared with LVEF, signal-averaged ECG (SAECG), or HRV.[89,90] Analysis of patients in the Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) trial has shown that NSVT, HRV, and depressed baroreflex sensitivity were all significantly and independently associated with increased mortality. Depressed baroreflex sensitivity, in particular, identified a subgroup with the same mortality risk as patients with NSVT and reduced LVEF.[21]

However, the Multiple Risk Factor Analysis Trial (MRFAT) show that in the β-blocking era, the common arrhythmia risk variables, particularly the autonomic and standard ECG markers, have limited predictive power in identifying patients at risk of SCD.[82] In 43 ± 15 months of follow-up in 675 patients, SCD was weakly predicted only by reduced LVEF (<40%), NSVT, and abnormal SAECG but not by autonomic markers or ECG variables. The positive predictive accuracy of these markers (low LVEF, NSVT, and abnormal SAECG), however, was low at 8%, 12%, and 13%, respectively.[82] The smaller Bucindolo Evaluation in Acute Myocardial Infarction Trial (BEAT) study also refuted the predictive value of HRV, the prognostic information of which was found to be contained completely in heart rate.[91] In patients with nonischemic cardiomyopathy, results on the value of HRV have been conflicting.[7,92,93] Heart rate turbulence and deceleration capacity are newer noninvasive measures of cardiac autonomic regulation that are currently under study.[94] More data are clearly needed to establish the clinical usefulness of autonomic markers, particularly in the setting of NSVT.

Signal-Averaged Electrocardiography

The clinical value of SAECG in patients with NSVT by means of determining prognosis and identifying patients in need for an aggressive antiarrhythmic management has not been established yet. In patients presenting with unexplained syncope, the presence of late potentials is a good predictor of induction of sustained VT, and in survivors of MI an abnormal SAECG has been associated with increased risk of arrhythmic and total mortality.[95-98] However, its positive predictive value in this setting is low (<30%) as opposed to its high negative predictive value (90%). Thus, a negative SAECG might obviate the need for further investigations when the suspicion of a ventricular arrhythmia is low, but in the case of a high suspicion of ventricular arrhythmia, a negative SAECG is not sufficient evidence for the exclusion of sustained VT or NSVT as the cause of syncope. Furthermore, in patients treated with thrombolysis or β-blockers, the predictive ability of SAECG is limited.[82,99] In patients with DCM, SAECG does not predict SCD, but in arrhythmogenic right ventricular dysplasia, SAECG can identify those with more extensive disease and a propensity for inducible VT at programmed electrical stimulation, and is now considered a minor diagnostic criterion.[8,81,100]

T-Wave Alternans

T-wave alternans (TWA) is a test that is thought to reflect dispersion of repolarization and has been shown to predict VT inducibility and future arrhythmic events better than SAECG.[101] In patients similar to those in MADIT II, a microvolt TWA (MTWA) test was found to be better than QRS duration at identifying high-risk patients as well as patients unlikely to benefit from ICD therapy.[102] Recently, in patients with reduced LV function (LVEF <40%) and NSVT, MTWA also predicted unstable ventricular tachyarrhythmias better than electrophysiology testing and LVEF less than 30%.[103] However, in a later study, although TWA predicted higher total mortality in a MADIT II–like population, the risk of tachyarrhythmic events did not differ according to TWA results.[104] The Alternans Before Cardioverter Defibrillator (ABCD) study was the first trial to use MTWA to guide prophylactic ICD insertion in patients with LVEF less than 40% and NSVT. Risk stratification strategies using noninvasive MTWA versus invasive electrophysiological study (EPS) were comparable at 1 year, with very low positive predictive values and very high negative predictive values and complementary when applied in combination. Strategies that use MTWA, EPS, or both might identify subsets of patients least likely to benefit from ICD insertion.[105]

Electrophysiology Testing

EPS may be required for the establishment of initial diagnosis in patients presenting with nonsustained ventricular rhythms. Indications include the need for differential diagnosis of NSVT from short runs of AF in the context of an accessory pathway or other forms of aberration, drug testing for the diagnosis of Brugada syndrome, and programmed electrical stimulation for induction of VT.

Induction of sustained arrhythmia by programmed electrical stimulationstill retains a predictive power in patients with ischemia who have impaired left ventricular function. According to a meta-analysis, in patients with ischemia and NSVT, the induction of sustained VT is associated with a two- to three-fold increased risk of arrhythmia-related death in a previous meta-analysis.[106] In NSVT, in the context of reduced LVEF (<40%), inducibility of sustained monomorphic VT at baseline programmed electrical stimulation was associated with a 2-year actuarial risk of SCD or cardiac arrest of 50% compared with a 6% risk in patients without inducible VT.[107] Analysis of patients enrolled in the MUSTT as well as of those in the registry revealed that noninducible patients have a significantly lower risk of cardiac arrest or SCD compared with inducible patients at 2 and 5 years (12% vs. 24% and 18% vs. 32%, respectively).[108] Still, however, as these results indicate, patients with noninducible sustained VT are not free of risk of SCD. The MUSTT investigators have further analyzed the relation of EF and inducible ventricular tachyarrhythmias to mode of death in 1791 patients who were enrolled in MUSTT and did not receive antiarrhythmic therapy. Total and arrhythmic mortality were higher in patients with an EF less than 30% than in those whose EFs were 30% to 40%. The relative contribution of arrhythmic events to total mortality was significantly higher in patients with inducible tachyarrhythmia (58% of deaths in inducible patients vs. 46% in noninducible patients; $P = .004$). The higher percentage of events that were arrhythmic among patients with inducible tachyarrhythmia appeared more distinct among patients with an EF of 30% or greater (61% of events were arrhythmic among inducible patients with an EF ≥30% and only 42% among noninducible patients; $P = .002$). This study therefore suggested that the major usefulness of EPS may be restricted to patients having an EF between 30% and 40%.[109] The prognostic significance of VT inducibility appears to be similar to that of VT induced by one, two, or three extrastimuli.[110] These results should be considered in the context of evidence from analysis of stored ICD data that has shown that little association exists between spontaneous and induced ventricular arrhythmias.[111]

The role of programmed electrical stimulation has not been established in the patient with ischemia and relatively preserved left ventricular function (LVEF >40%), although some evidence indicates that inducibility of sustained VT or VF at programmed electrical stimulation might retain discriminative ability by means of identifying a higher risk patient cohort.[112,113] The prognostic usefulness of programmed stimulation in patients with nonischemic DCM, including those with NSVT, remains controversial.[114-116] Retrospective cohort analysis of 54 patients from the Mayo Clinic showed that programmed electrical stimulation did not differentiate patients with and those without appropriate ICD shocks.[114] However, inducibility of polymorphic VT or VF is a much stronger predictor of recurrences of fast VT as opposed to sustained monomorphic VT induction in DCM patients with ICD for secondary prevention.[117] Daubert et al, in the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial, reported that inducibility tested via ICD was found in 29 of 204 patients (VT in 13, VF in 16) and that at follow-up, 34.5% of the inducible group (10 of 29) had ICD therapy for VT or VF or arrhythmic death versus 12% (21 of 175) of noninducible patients (hazard ratio [HR], 2.60; $P = .014$).[118] Thus, inducibility of ventricular arrhythmias, especially polymorphic VT or VF, indicates increased likelihood of subsequent ICD therapies and might be considered a useful risk stratifier.

Programmed ventricular stimulation is of diagnostic as well as prognostic value in risk stratifying patients with repaired tetralogy of Fallot.[119] In multivariate analysis of a study on 252 patients with repaired tetralogy, inducible sustained monomorphic or polymorphic VT was an independent risk factor for subsequent events (RR, 4.7; 95% confidence interval [CI], 1.2–18.5; $P < .0268$).[119]

Little evidence exists for benefit from EPS in patients with HCM and NSVT. In patients with a history of cardiac arrest, polymorphic VT that deteriorates into VF was induced in approximately half only.[32,64,65]

Cardiac Magnetic Resonance Imaging

In patients with previous MI, necrotic myocardium and viable myocardium coexisting within the same wall segments, as detected by delayed enhancement cardiac magnetic resonance imaging (CMRI), predicts the occurrence of NSVT in patients without left ventricular dilation, whereas left ventricular mass and end-systolic volume are predictors of NSVT in those with left ventricular dilation.[120] In patients with HCM, the presence of delayed enhancement on contrast-enhanced CMRI is associated with increased likelihood of NSVT compared with those without this finding (28% vs. 4%), and the presence of two-dimensional strain, which is used to identify myocardial fibrosis, in more than three left ventricular segments is an independent predictor of NSVT.[121,122]

Clinical and Prognostic Significance

The physician who cares for a patient presenting with an episode of NSVT has two tasks. First, he or she needs to establish whether the underlying occult pathology is responsible for the arrhythmia; second, in a case of diagnosed heart disease, the patient should be risk stratified to determine the appropriate management and therapy. The clinical approach to the patient with NSVT should therefore always be considered within the particular clinical context in which the arrhythmia occurs. In several settings, the patient with NSVT represents a clinical challenge with regard to proper management, and several crucial questions remain unanswered.[123] The occurrence of an abrupt ventricular arrhythmia is a multi-factorial process involving a continually changing complex substrate of myocardial scarring, ischemia, and adrenergic and genetic factors. We are therefore dealing with a probabilistic event in which each of the currently considered risk factors such as NSVT identifies only a small fraction of the risk process.

Subjects with episodes of NSVT before 40 years of age should be evaluated primarily to rule out nonischemic causes of arrhythmia, including HCM, LQTS, idiopathic DCM, and arrhythmogenic right ventricular dysplasia. Episodes of polymorphic NSVT may indicate the presence of genetic arrhythmia disorders (e.g., LQTS, catecholaminergic polymorphic VT) or drug-induced repolarization abnormalities. ECG testing, history of SCD and syncopal episodes in family members, and current medication history may lead to a proper diagnosis. NSVT at 40 years of age and older requires that the rare causes mentioned earlier should be ruled out, but the main focus is ischemic heart disease.

In patients with known heart disease, the main task of the physician is the risk assessment of the patient; that is, the estimation of the probability that the patient will have future morbid arrhythmic events. Risk stratification attempts to identify the specific mechanisms of further morbidity to predict clinical outcomes and eventually propose clinical strategies for their prevention.

The independent prognostic significance of NSVT depends on the underlying condition (Table 43-2). It currently is not known whether NSVT bears a cause-and-effect relationship with sustained ventricular tachyarrhythmias or if it is merely a surrogate marker of left ventricular dysfunction and electric instability. Even when it does hold prognostic significance, NSVT does not necessarily imply the mechanism of death. Certain patient groups have a high mortality rate because of the progression of their disease. Death in these patients may be arrhythmic, but this does not imply that mere prevention of NSVT will unconditionally prolong life significantly. The cardiac mortality rate at 2 years in MADIT was still 11% despite the use of defibrillators.[10] Furthermore, reduction of arrhythmic death does not necessarily imply a concomitant reduction in total mortality, and even a nonsignificant increase in mortality has been demonstrated despite the reduction of SCD by using amiodarone in patients with acute MI.[124-126]

Table 43-2 Clinical Significance of Nonsustained Ventricular Tachycardia

CLINICAL SETTING	SIGNIFICANCE
APPARENTLY NORMAL HEART	
Random finding	No adverse prognostic significance in the absence of occult pathology
During or after exercise	May predict IHD and increased cardiac mortality
Valvular disease, hypertension	Prognostic significance unknown
ISCHEMIC HEART DISEASE	
Acute MI <13–24 h	No adverse prognostic significance
Acute MI >13–24 h	Adverse prognostic significance
Chronic IHD with LVEF >40%	Unknown. No adverse prognostic significance(?)
Chronic IHD with LVEF <40%	Adverse prognostic significance
DCM	Independent prognostic significance not established as opposed to LVEF
HCM	Adverse prognostic significance, especially in the young
Long QT syndrome, CPVT, repaired congenital abnormalities	**Adverse prognostic significance**
ARVC, Brugada syndrome	**Probably adverse prognostic significance**

ARVD, Arrhythmogenic right ventricular cardiomyopathy; CPVT, *catecholaminergic polymorphic ventricular tachycardia;* DCM, *dilated cardiomyopathy;* HCM, *hypertrophic cardiomyopathy;* IHD, *ischemic heart disease;* LVEF, *left ventricular ejection fraction;* MI, *myocardial infarction;* VF, *ventricular fibrillation.*

Apparently Healthy Individuals

Early reports from longitudinal community-based studies indicated that the presence of complex ventricular ectopy and NSVT increase the risk of heart disease subsequently observed.[15] In other studies, NSVT was not found to adversely influence prognosis, with cardiac event rates not exceeding those detected in age-matched populations without the arrhythmia.[16,40] Polymorphic NSVT, as opposed to monomorphic NSVT, may indicate an increased risk.[127] Thus, recording of spontaneous NSVT in apparently healthy individuals does not imply an adverse prognosis, provided that occult cardiomyopathy and genetic arrhythmia disorders have been excluded. These conditions, however, may remain latent for several years, and although apparently healthy individuals presenting with NSVT can be reassured about their prognosis, long-term follow-up is advisable.

NSVT originating from the RVOT may occasionally cause syncope, although the risk of death is very low. Short cycle length during NSVT and a history of syncope are predictors of the coexistence of VF and polymorphic VT.[128] Subjects with RVOT VT might have subtle structural and functional abnormalities of RVOT as detected by CMRI.[129] Detection of NSVT in patients with ARVD indicates intermediate risk for future arrhythmic events.[130] The diagnosis of RVOT VT needs to be differentiated from the diagnosis of ARVD or cardiomyopathy, which can be accomplished by a series of noninvasive ECG and imaging studies

such as Holter monitoring, SAECG, CMRI and, if needed, endomyocardial biopsy.[81]

Exercise-Induced Nonsustained Ventricular Tachycardia

The occurrence of premature ventricular demoralizations during exercise in apparently healthy subjects has not been associated with an increase in cardiovascular mortality and was considered to be a normal response to exertion.[41,42] However, the Paris Prospective Study, in agreement with earlier data, reported that runs of two or more consecutive ventricular depolarizations during exercise or at recovery may occur in up to 3% of healthy men and indicated an increase in cardiovascular mortality within the next 23 years by a factor of more than 2.5.[43,131] This increased RR persisted even after adjusting for other characteristics and known factors predisposing to coronary artery disease (CAD). Interestingly, among subjects with a positive exercise test for ischemia, only 3% had ectopy, whereas among subjects with exercise-induced ectopy, only 6% had a positive exercise test for ischemia. Thus, although the precise mechanism of arrhythmia is unknown in this setting and various forms of occult cardiomyopathy cannot be excluded, it does not appear to be a direct consequence of ischemia. This study argues that exercise-induced nonsustained ventricular arrhythmia may predict CAD, even in the absence of evidence of ischemia in asymptomatic individuals. These results were also verified in a later study on patients who had been referred for symptom-limited exercise testing without a history of heart failure, valve disease, or arrhythmia. Frequent ventricular ectopy during recovery after exercise is a better predictor of an increased risk of death than ventricular ectopy occurring only during exercise.[44] Exercise testing may also induce catecholaminergic polymorphic VT. When recognized, this condition requires aggressive management.[59]

Ventricular tachyarrhythmias and NSVT commonly occur in trained athletes during ambulatory Holter electrocardiography and are usually associated with a benign course, and resumption of training is safe.[132]

Ischemic Heart Disease

In non–ST-segment elevation acute coronary syndromes, NSVT is common after admission, and even short episodes of VT lasting 4 to 7 beats are independently associated with the risk of SCD over the subsequent year. In the Metabolic Efficiency With Ranolazine for Less Ischemia in Non–ST-segment Elevation Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 36 (MERLIN-TIMI 36) trial on 6300 patients who had 7-day continuous ECG monitoring, a greater than twofold increase in the risk of SCD was seen in patients with both short (4 to 7 beats) and longer (>8 beats) episodes of VT occurring greater than 48 hours after admission compared with patients with no VT (Figure 43-6).[17] This relationship was unchanged after adjustment for clinical characteristics, including LVEF and natriuretic peptides. No increased risk of SCD was observed in patients with ventricular triplets. In several subgroups (history of heart failure, depressed ventricular function, QTc >450 ms), the presence of VT was associated with a greater than 10% incidence of SCD at 1 year. Earlier episodes within 48 hours after admission did not carry the same risk. Thus, extended continuous ECG monitoring beyond 48 hours after admission for non–ST-segment elevation acute coronary syndrome to detect the presence of even short episodes of VT may potentially identify patients at higher risk for SCD.

In acute MI, NSVT during the first 13 to 24 hours does not carry a prognostic significance.[18,133] Following this period, NSVT after MI predicted higher mortality in earlier studies. In the Multi-Center Postinfarction Research Program (MPIP) study in the pre-thrombolytic era, the presence of NSVT was associated with a twofold increase in total and arrhythmic deaths, independent of LVEF.[134,135] A similar relationship between repetitive forms and mortality, and the joint predictive value of NSVT and low EF was noted in the Multicenter Investigation of Limitation of Infarct Size (MILIS).[136] Evidence from the reperfusion era suggests that in the patient with ischemic heart disease, NSVT no

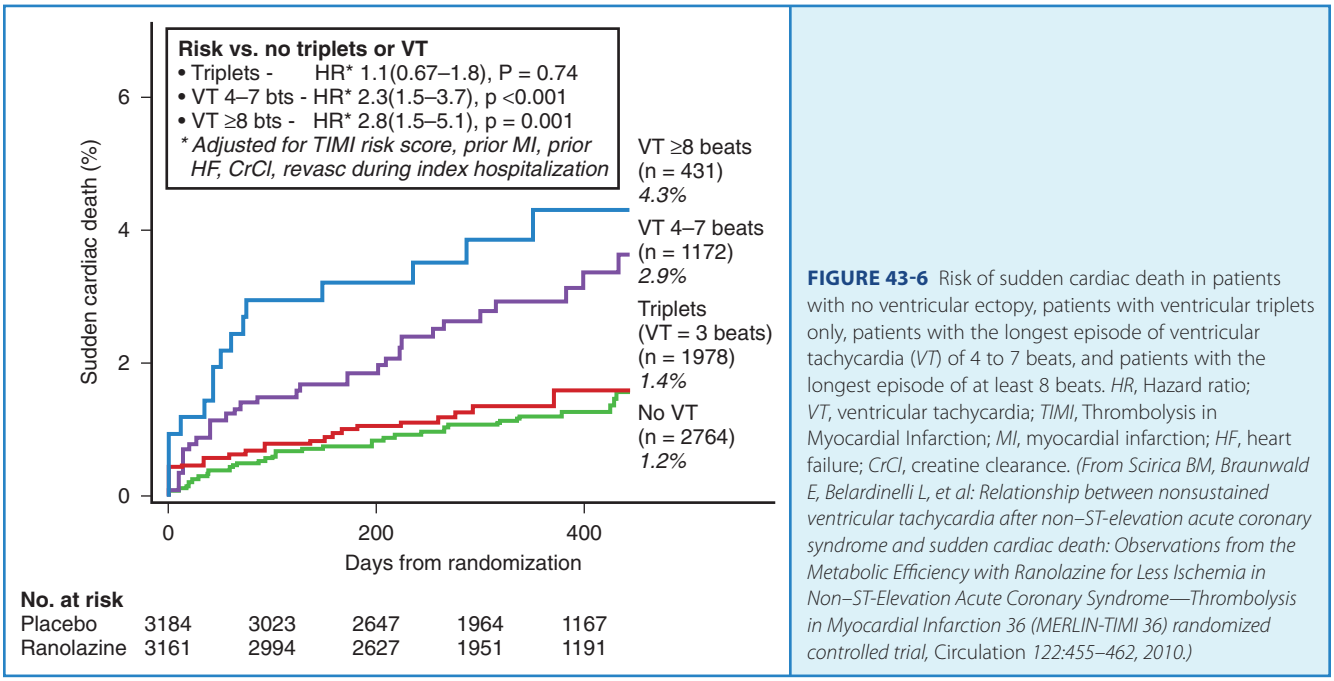

FIGURE 43-6 Risk of sudden cardiac death in patients with no ventricular ectopy, patients with ventricular triplets only, patients with the longest episode of ventricular tachycardia (*VT*) of 4 to 7 beats, and patients with the longest episode of at least 8 beats. *HR*, Hazard ratio; *VT*, ventricular tachycardia; *TIMI*, Thrombolysis in Myocardial Infarction; *MI*, myocardial infarction; *HF*, heart failure; *CrCl*, creatine clearance. *(From Scirica BM, Braunwald E, Belardinelli L, et al: Relationship between nonsustained ventricular tachycardia after non–ST-elevation acute coronary syndrome and sudden cardiac death: Observations from the Metabolic Efficiency with Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndrome—Thrombolysis in Myocardial Infarction 36 (MERLIN-TIMI 36) randomized controlled trial,* Circulation *122:455–462, 2010.)*

longer appears to be an independent predictor of death if other factors such as the EF are taken into account. In the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico 2 (GISSI-2) trial, NSVT was a significant predictor of mortality in univariate analysis, but not independently in multivariate analysis involving other clinical variables.[19] Similarly, in ESVEM, although univariate analysis suggested an association between the presenting arrhythmia and the outcome, multivariate analysis failed to establish the predictive value of the presenting arrhythmia. LVEF was the single most important predictor of arrhythmic death or cardiac arrest in patients with life-threatening arrhythmias who were treated with antiarrhythmic drugs.[9] NSVT has not been found to be an independent predictor of arrhythmic or total mortality in the studies of Hohnloser et al (325 patients with MI) and DANAMI-2 (501 patients with fibrinolysis and 516 patients with primary angioplasty).[20,22] In a study on 2130 infarct survivors, Makikallio et al reported that NSVT predicted SCD only in patients with LVEF greater than 35%. No Holter variable was predictive of outcome in the presence of an LVEF of 35% or more.[79] In the modern era, only ATRAMI has found NSVT to be an independent predictor of adverse prognosis.[21] It seems that it is important not only how often but under what circumstances NSVT occurs. MUSTT data have shown prognostic differences in patients with in-hospital, as opposed to out-of-hospital, identified NSVT.[137] Overall mortality rates at 2-year and 5-year follow-up were 24% and 48%, respectively, for inpatients and 18% and 38%, respectively, for outpatients (adjusted $P = .018$). In patients subjected to surgical coronary revascularization, the occurrence of NSVT within the early (less than 10 days) post-revascularization period portends a far better outcome than when it occurs later after CABG (10 to 30 days) or in non-postoperative settings. Indeed, the approximate 2-year mortality rates for patients with early post-revascularization NSVT, late post-revascularization NSVT, and non-postoperative NSVT were 14%, 23% and 24%, respectively.[138] When, however, sustained VT is inducible in patients with early postoperative NSVT, the outcome is worse compared with noninducible patients.[139] In the MUSTT, racial differences were also shown to influence the outcome of patients with NSVT and reduced left ventricular function.[140]

Recently, CARISMA reported on long-term cardiac arrhythmias recorded by a cardiac monitor implanted 2 to 5 days after MI in patients with an LVEF of 40% or less.[6] Clinically significant bradyarrhythmias and tachyarrhythmias were documented in a substantial proportion of patients, most of them asymptomatic, within the next 2 years. The most significant arrhythmia was intermittent high-degree AV block (10% incidence), which was associated with a very high risk of cardiac death (>30% within the next 2 years), and the most frequent was atrial fibrillation (28%). Nonsustained VT (VT ≥125 beats/min for ≥16 beats lasting <30 seconds) was the most frequent ventricular arrhythmia recorded in the study (incidence of 13%) and was associated with cardiac death over the next 2 years only in univariate analysis (Figure 43-7). It seems, therefore, that with reperfusion and use of β-blockers, NSVT after MI may not be an independent predictor of mortality, especially after EF is taken into account, and its prognostic significance is ambiguous. In patients with non–ST-segment elevation acute coronary syndrome, NSVT occurring beyond 48 hours after admission may indicate an increased risk for SCD.

Not much data on patients with stable ischemic heart disease and an LVEF over 40% exist. In an older trial, NSVT was reported in approximately 2% of patients with ischemia and preserved left ventricular function, apparently excluding previous MI, and did not appear to carry a significant predictive ability.[24]

Heart Failure

No convincing data exist in patients with heart failure. Although the GESICA–Grupo de Estudios Multicentricos en Argentina (GEMA) investigators identified NSVT as an independent predictor of total mortality in patients with heart failure (35% to 40% ischemic heart disease) and an LVEF of 35% or less, in CHF-STAT (70% to 75% ischemic heart disease), after adjusting other variables, especially for LVEF, NSVT was not an independent predictor of SCD or total mortality in patients with heart failure and an LVEF less than 35% to 50%.[26,85] Similar results were published by the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) investigators.[12] Only during the recovery period after exercise, frequent ventricular ectopy has been found to carry an adverse prognostic significance in patients with heart failure.[141] However, in the study by Verma et al, in 421 primary prevention patients with both ischemic and nonischemic cardiomyopathy undergoing ICD implantation, 79 (19%) had received appropriate ICD therapies.[72] NSVT detected on Holter monitoring and no β-blocker use, but not LVEF, was predictive for ICD-derived arrhythmias in patients with either ischemic or nonischemic cardiomyopathies.

Cardiomyopathies

Reports investigating the association between NSVT and cardiac mortality in patients with nonischemic DCM are not consistent. MACAS has reported on noninvasive arrhythmia risk stratification in patients with DCM.[8] On univariate analysis, nonsustained VT and frequent VPBs showed a significant association with a higher arrhythmia risk, but on multivariate analysis, only LVEF was found to be a significant predictor of major arrhythmic events with an RR of 2.3 per 10% decrease of EF. SAECG, baroreflex sensitivity, HRV, and TWA were not helpful in arrhythmia risk stratification. Patients with NSVT in the context of LVEF less than 30% had an eightfold arrhythmia risk compared with patients with LVEF greater than 30% without nonsustained VT.[8] In a recent study on 179 patients with DCM, multivariate analysis detected LVEF, NSVT, and QT dynamicity (QTe slope assessed by dedicated software) as significant predictors of arrhythmic events. Among the patients with a low LVEF, NSVT, steeper QTe-slope, or both identified a subgroup at highest arrhythmic risk.[142] In another study, after medical stabilization with an angiotensin-converting enzyme inhibitor (88%) and a β-blocker, NSVT did not increase the risk of major ventricular arrhythmias in patients with DCM and LVEF of 35% or greater. Conversely, the number and length of NSVT runs were significantly related to the occurrence of major ventricular arrhythmias in the patients with an LVEF greater than 35%.[143] The frequency and complexity of ventricular arrhythmias increase with decreasing function of the left ventricle and with the presence of symptoms of congestive heart failure in patients with nonischemic DCM. However, cardiac death in patients with nonischemic DCM and functional class IV heart failure is more frequently caused by bradyarrhythmia or electromechanical dissociation rather than by ventricular tachyarrhythmias.[4,29]

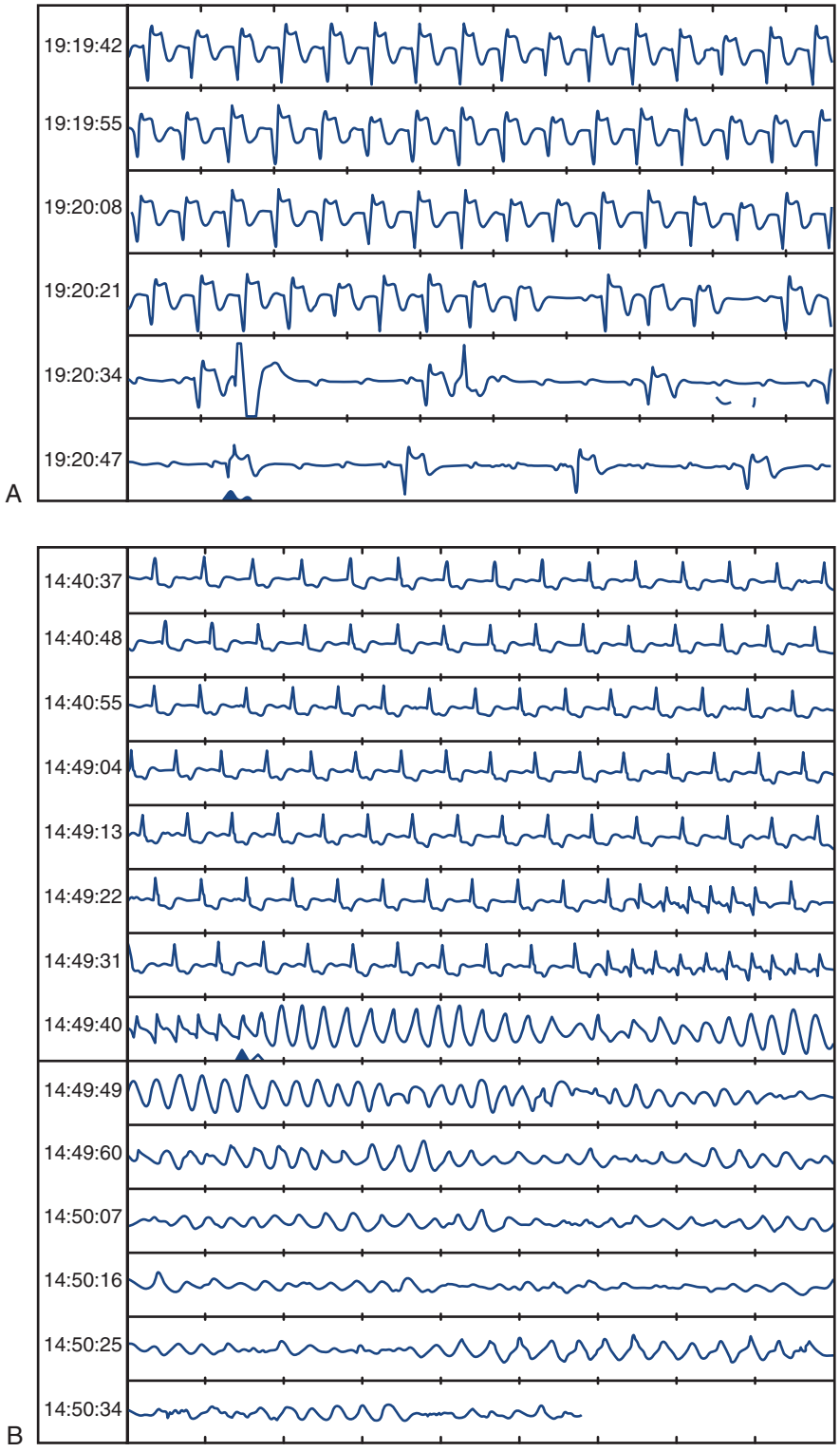

FIGURE 43-7 Electrograms of arrhythmias recorded with an implantable cardiac monitor in a patient with previous myocardial infarction. **A,** Paroxysmal second-degree to third-degree atrioventricular block. **B,** Two episodes of nonsustained ventricular tachycardia (VT) are recorded; the second episode provokes polymorphic VT degenerating to ventricular fibrillation (VF). The episode is automatically activated at the *arrowhead.* The VF converted back to polymorphic VT, which terminated spontaneously (not shown). The patient subsequently received an implantable cardioverter-defibrillator. *(From Bloch Thomsen PE, Jons C, Raatikainen MJ, et al, Cardiac Arrhythmias and Risk Stratification After Acute Myocardial Infarction (CARISMA) Study Group: 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 *122:1258–1264, 2010.)*

Frequent and prolonged (>10 beats) episodes of NSVT on Holter monitoring most probably indicate an increased risk of SCD in HCM, especially in young patients.[31,144,145] In a study of 531 patients with HCM, a relation between arrhythmic mortality and the frequency, duration, and rate of NSVT episodes could not be demonstrated.[31] However, NSVT was associated with a substantial increase in the risk of SCD in young patients with hypertrophic obstructive cardiomyopathy.[31] Adabag et al reported NSVT in Holter recordings in 31% of 178 patients with HCM, and NSVT was associated with greater left ventricular hypertrophy and more severe symptoms.[146] Over a follow-up of 5.5 ± 3.4 years, 11 (6%) patients died suddenly (annual mortality rate, 1.1%), including 5 patients with NSVT. For SCD, NSVT on Holter ECG had negative and positive predictive values of 95% and 9%, respectively, and sensitivity and specificity of 45% and 69%, respectively. Therefore, NSVT had a low positive predictive value and relatively high negative predictive value for SCD in this HCM population. In another study from the same group, delayed enhancement on contrast-enhanced CMRI (believed to represent myocardial fibrosis) was found as an independent predictor of NSVT (RR, 7.3; 95% CI, 2.6–20.4; $P < .0001$).

Asymptomatic patients with ARVD and NSVT have a propensity for increased arrhythmic risk and a rate of appropriate ICD intervention of 3.7% per year.[80] However, the predictive value of NSVT has not been prospectively assessed in this setting.[147]

Other Conditions

The presence of NSVT in patients with *idiopathic ventricular outflow tract arrhythmias* indicates a higher propensity for inducibility of VT during EPS compared with isolated PVCs (48% vs. 4%). At exercise, the incidence of VT in this group is 10%.[45]

In patients with *tachycardiopathy*, the presence of nonsustained VT, in addition to the PVC burden, longer PVC duration, multi-form PVCs, and right ventricular PVCs may be associated with the development of cardiomyopathy.[148]

The occurrence of NSVT in *hypertensive* patients requires evaluation of ischemic heart disease. However, the prognostic value of NSVT in patients with lone hypertension (without evidence for concomitant ischemic heart disease) remains unclear. Evidence that elimination of NSVT improves survival in patients with hypertension is not available.[35,36] Also, no convincing evidence exists to prove that nonsustained VT is an independent predictor of SCD in patients with *valve disease*, including mitral leaflet prolapse. Initial studies suggested that patients with mitral valve prolapse had an increased incidence of NSVT and other arrhythmias.[149,150] Kilgfield et al estimated the annual risk of SCD in patients with mitral valve prolapse at 1.9 per 10,000 patients, lower than the annual risk of SCD from all causes in the adult population in the United States.[151] Thus, patients with mitral valve prolapse are not at increased risk of SCD. NSVT in patients with mitral valve prolapse is related primarily to coexisting mitral regurgitation and secondarily chronic hemodynamic and myocardial abnormalities, but they do not independently contribute to the risk of death.

Ventricular arrhythmias have an adverse prognosis in patients with *repaired tetralogy of Fallot*, and programmed stimulation carries a prognostic value.[38,39,119]

Patients with *Chagas' cardiomyopathy* presenting with either sustained VT or NSVT have a major risk for mortality in the presence of moderate left ventricular systolic dysfunction (LVEF <40%).[152]

In cases of *LQTS,* detection of spontaneous episodes of torsades de pointes indicate an adverse prognosis.[4]

Management and Evidence-Based Therapy

The management and evidence-based therapy of patients with NSVT depend on the underlying condition. Specific underlying conditions are classified as nonischemic and ischemic. Nonischemic conditions with NSVT may include a structurally normal heart, hypertension, valvular disorders, HCM, nonischemic DCM, LQTS, Brugada syndrome, and other rare genetic disorders. Ischemic disease with NSVT cannot be considered a uniform condition, and its management depends on the presence or absence of MI and the degree of left ventricular dysfunction.

Nonsustained Ventricular Tachycardia in Structurally Normal Heart

Sometimes, episodes of NSVT in patients without structural heart disease may cause symptoms and require treatment. Because RVOT VT does not increase the risk of SCD, asymptomatic patients do not require treatment. In symptomatic patients, treatment should be directed toward relief of tachycardia-related symptoms with β-blockers or calcium channel blockers and adenosine, if needed, in an acute setting. If medication is not effective, radiofrequency catheter ablation is recommended; it is successful in more than 80% of cases with a low risk of relapse during follow-up.[153]

Nonsustained Ventricular Tachycardia in Inherited Channelopathies

β-Blocker therapy is the treatment of choice in catecholaminergic polymorphic VT, and some evidence exists that combination of β-blockers with calcium channel blockers is superior to β-blockers alone.[154] Defibrillator implantation may be necessary in addition to β-blockers in some patients with catecholaminergic polymorphic VT.

Usually, cardiac events in patients with LQTS are caused by prolonged polymorphic NSVT or sustained VT (torsades de pointes) that might degenerate into VF.[155] However, transient, asymptomatic runs of polymorphic NSVT are also common. β-Blocker treatment is the therapy of choice in patients with LQTS (especially LQT1 and LQT2); it is effective in 70% of patients, whereas the remaining 30% of patients continue to have cardiac events despite β-blocker treatment.[156] Those patients with recurrent syncope despite β-blocker therapy and those with cardiac arrest should be considered for ICD therapy, which is successful in preventing death.[157]

Although no systematic studies evaluating prognostic significance of NSVT in *Brugada syndrome* have been conducted, it is generally agreed that symptomatic patients (i.e., those with syncope or cardiac arrest presumably caused by NSVT or sustained VT) should be treated with ICDs.[158]

Patients with ARVD are at high risk of sudden death.[81] These patients may present with asymptomatic NSVT despite only subtle right ventricular abnormalities. The results of antiarrhythmic medications have been disappointing, and ICDs seem to be

the therapy of choice in patients with documented arrhythmias or in those who are symptomatic.[80] Catheter ablation of VT, when feasible, is successful in reducing further episodes but cannot offer absolute protection without ICD backup.[159]

Nonsustained Ventricular Tachycardia in Hypertension and Valve Disease

Aggressive treatment of hypertension (including β-blockers) is the therapy of choice in patients with hypertension and NSVT. The majority of patients with mitral valve prolapse and NSVT do not require extensive diagnostic evaluation or treatment. In symptomatic patients (palpitations, syncope) with NSVT, β-blocker treatment is considered the first-line therapy. Other antiarrhythmic agents may be used in cases refractory to β-blocker treatment. Treatment should be directed primarily at improvement of the overall quality of life while considering the potential adverse (potential proarrhythmic) effects of therapy. NSVT is common in patients with other valvular diseases, particularly *aortic stenosis* and *mitral regurgitation*. The presence of NSVT is usually associated with left ventricular hypertrophy or dysfunction, but no clear evidence exists that these arrhythmias indicate increased risk of mortality after valve replacement.

Nonsustained Ventricular Tachycardia in Hypertrophic Cardiomyopathy

The effects of pharmacologic antiarrhythmic therapy in patients with HCM are disappointing.[64,65] β-Blockers may decrease the risk of SCD; however, the risk of death on β-blocker remains significant. Amiodarone was shown to suppress VT induction in some patients while causing conduction abnormalities and facilitating induction of VT in others.[64,65] Therefore, this drug cannot be considered as therapy of choice in high-risk patients with HCM. Defibrillator implantation is the therapy of choice in the primary and secondary prevention of CD in patients with HCM.[160] Patients with a history of syncope, a family history of SCD, or history of NSVT who had received defibrillators as primary prevention had a 5% per year appropriate discharge rate. In patients resuscitated from cardiac arrest (secondary prevention), the rate of appropriate discharges was 11%. More than one third of the patients who had an appropriate discharge of the defibrillator were taking amiodarone, further emphasizing the limited role of antiarrhythmic therapy in these patients. [160] These observations indicate that presence of high-risk factors, including frequent NSVT accompanied by history of syncope or family history of SCD at a young age, may justify defibrillator implantation as primary prevention in patients with HCM.

Nonsustained Ventricular Tachycardia in Dilated Cardiomyopathy

Two large trials evaluated amiodarone therapy in patients with ischemic and nonischemic cardiomyopathy. In the GESICA trial, amiodarone therapy was associated with decreased mortality, whereas no such effect was observed in the CHF-STAT trial.[25,85] The reasons for the different frequencies of NSVT in both studies (34% and 79%, respectively) and the differences in the effectiveness of amiodarone therapy are not clear and might be related to the varying characteristics of patient populations (with the GESICA trial enrolling patients with more advanced left ventricular dysfunction and a high number of patients with Chagas' disease). Results of SCD-HeFT demonstrated that amiodarone is not effective in preventing mortality in patients with nonischemic DCM (HR 1.07, in 813 patients randomized to amiodarone or placebo).[71] The SCD-HeFT study of 2521 patients with ischemic (52%) and nonischemic (48%) cardiomyopathies (EF <36% and New York Heart Association [NYHA] class II or III) randomized the subjects to amiodarone, ICD therapy, or conventional therapy. A history of NSVT was reported in 23% of patients. During a mean 45-month follow-up, a 7.2% annual mortality was observed in the placebo group. ICD therapy was associated with a 23% reduction in mortality (HR 0.77, $P = .007$) in all patients combined. Patients with nonischemic cardiomyopathy had an HR of 0.73, and those with ischemic cardiomyopathy had an HR of 0.79 (no significant difference existed between the two subgroups). The SCD-HeFT data seem to end the controversy regarding the usefulness of amiodarone for primary prevention of SCD in patients with nonischemic (and also in ischemic) cardiomyopathy. Dronedarone also did not fulfill hopes regarding its prevention of mortality in patients with heart failure; therefore, this drug needs to be taken off the list of medications used in such patients.[161]

The effect of defibrillator implantation as primary prevention of cardiac mortality in patients with nonischemic DCM and NSVT or ventricular ectopy was the subject of the DEFINITE trial.[162] In this study, 458 patients with nonischemic DCM with EF less than 36%, symptomatic congestive heart failure, and NSVT or more than 10 PVCs per hour were randomized to defibrillator versus no defibrillator therapy (229 patients in each arm). The mean age of the patients was 58 years. They were predominantly males (71%; mean EF, 21%). NSVT was present in 23% of the patients. During a mean 29-month follow-up, 68 deaths occurred, 28 in the ICD arm and 40 in the non-ICD arm ($P = .08$ from the log-rank test). Two-year mortality rate was 14.1% in the non-ICD arm and 7.9% in the ICD arm (HR, 0.65; CI, 0.40–1.06). The HR for SCD was 0.20 ($P = .006$). Patients with NYHA class III demonstrated significant benefit from ICD therapy with an HR of 0.37 ($P = .02$). A trend for reduced total mortality was observed with ICD. Thus, results from DEFINITE and SCD-HeFT show that patients with nonischemic cardiomyopathy with EF less than 36% and NYHA class II or III have a high (7%) annual mortality despite optimal pharmacologic therapy and that the risk of mortality could be substantially reduced by ICD therapy.

The purpose of the Amiodarone Versus Implantable Cardioverter-Defibrillator: Randomized Trial in Patients With Nonischemic Dilated Cardiomyopathy and Asymptomatic Nonsustained Ventricular Tachycardia (AMIOVIRT) was to compare total mortality during therapy with amiodarone or ICD in 103 patients with nonischemic DCM and NSVT.[163] The primary endpoint was total mortality. Secondary endpoints included arrhythmia-free survival, quality of life, and costs. The study was stopped when the prospective stopping rule for futility was reached. The percentage of patients surviving at 1 year (90% vs. 96%) and 3 years (88% vs. 87%) in the amiodarone and ICD groups, respectively, were not statistically different ($P = .8$). Quality of life was also similar with each therapy (P = not significant). A trend toward a more beneficial cost profile and improved arrhythmia-free survival was observed with amiodarone therapy. Mortality and quality of life in patients with nonischemic DCM and NSVT treated with amiodarone or ICD are not statistically different. ICD was also not found superior to amiodarone in the Cardiomyopathy Trial (CAT) study on patients with recent onset of DCM ≤9 months) and EF 30% or less.[164]

Current indications for ICD or cardiac resynchronization therapy (CRT) therapy include primary prevention indications beyond those based on syncope or arrhythmic events. In light of the results from the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial and subsequently from the Cardiac Resynchronization–Heart Failure (CARE-HF) trial, CRT has been approved as treatment in patients with an LVEF of 35% or less, NYHA class III or IV, and QRS greater than 120 ms.[165,166] CRT provides benefit in patients with heart failure with wide QRS complex; this benefit is observed in patients with ischemic and nonischemic cardiomyopathies, but it might be higher in patients with nonischemic cardimyopathy.[167,168]

Nonsustained Ventricular Tachycardia in Coronary Artery Disease

The management of patients with previous MI and NSVT should first include modern therapy for ischemic heart disease, including revascularization procedures, the use of β-blockers, statins, and angiotensin-receptor blockers or inhibitors. This therapy is the most effective antiarrhythmic measure in patients with CAD as demonstrated by the Coronary Artery Bypass Graft Patch (CABG-Patch) trial.[169] The CAST and CAST II trials demonstrated that class IC antiarrhythmic agents (encainide, flecainide, and moricizine) confer increased (not decreased) mortality in patients with previous MI.[83,84,170] Subsequently, d-sotalol (class III drug) tested in the Survival With Oral d-Sotalol (SWORD) trial also was associated with increased mortality in comparison with placebo.[171] The European Myocardial Infarct Amiodarone Trial (EMIAT) and the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT) failed to demonstrate beneficial effect of amiodarone on survival.[125,126] Therefore, no antiarrhythmic drug is suitable for the primary prevention of cardiac death, with the exception of β-blockers, which were shown in several studies to reduce total and cardiac mortality in patients with previous MI. However, in low-risk to moderate-risk patients with previous MI and NSVT from the Beta-Blocker Heart Attack Trial, there was no reduction in mortality in patients with NSVT.[172]

In the MERLIN study, among patients assigned to ranolazine, an episode of VT lasting at least 8 beats was not associated with SCD compared with patients with no VT lasting at least 8 beats (2.5% vs. 1.6%; HR, 1.1; 95% CI, 0.3–3.5; $P = .90$), whereas among patients assigned to placebo, VT lasting at least 8 beats was significantly associated with SCD (5.4% vs. 1.5%; HR, 2.9; 95% CI; 1.6–5.3; $P < .001$) (P for interaction = .15).[17] These findings indicate that ranolazine most likely contributed to decreased mortality in patients with NSVT. However, these findings require confirmation in prospective studies.

In the 1990s, the implantable defibrillator became a feasible alternative to pharmacologic antiarrhythmic therapy for primary prevention of SCD in patients with CAD and NSVT. In the MADIT study, 196 patients with previous MI, an EF of 35% or less, a documented episode of NSVT, and inducible and nonsuppressible sustained VT were randomized to receive an implanted defibrillator or conventional (primary amiodarone) non-ICD therapy. Fifteen deaths occurred in 95 patients randomized to ICD therapy and 39 deaths in 101 patients randomized to conventional therapy, yielding a 54% reduction in total mortality associated with ICD during a mean 27-month follow-up. This was the first study demonstrating that ICD therapy is beneficial as primary prevention in high-risk patients with previous MI. Antiarrhythmic therapy guided by invasive EPS has historically been used to treat patients with NSVT and inducible sustained VT. MUSTT used the concept of EPS-guided antiarrhythmics to determine whether this approach can reduce mortality in survivors of MI with EF 40% or less and NSVT.[11] The main study enrolled 704 patients with CAD, asymptomatic NSVT, EF 40% or less, and inducible sustained VT. Patients with induced, sustained VT were randomized to no antiarrhythmic therapy or to EPS-guided therapy. The EPS-guided therapy included pharmacologic antiarrhythmic therapy and implantable defibrillators as indicated, based on EPS. The risk of cardiac arrest or death from arrhythmia among patients who received treatment with defibrillators in MUSTT was significantly lower than that among patients who did not receive ICDs (RR, 0.24; 95% CI, 0.13–0.45; $P < .001$). Patients assigned to EPS-guided therapy who were treated with only pharmacologic antiarrhythmics had a similar rate of death and cardiac arrest as those in the control group who had not been treated with antiarrhythmic therapy. These studies demonstrated that ICDs used in patients with previous MI and depressed EF and NSVT significantly reduce the risk of SCD and total mortality.[173]

Subsequently, MADIT II hypothesized that patients with previous MI and markedly depressed left ventricular function (EF ≤30%)—regardless of the presence or absence of other risk stratifiers, including frequent ventricular ectopy and inducibility of sustained VT—will benefit from ICD therapy.[174] MADIT II enrolled 1232 patients with previous MI (742 randomized to ICD therapy and 490 to the non-ICD arm) and demonstrated that ICD therapy was associated with a significant 30% reduction in total mortality during a 20-month follow-up and a sustained 8-year survival benefit.[175] SCD-HeFT (with 52% of the patients having ischemic cardiomyopathy) confirmed the MADIT II findings, indicating substantial benefit from ICD therapy in patients with a low EF (<36%) and NYHA classes II and III. MADIT II and SCD-HeFT significantly changed the clinical approach to patients with previous MI and NSVT. In light of MADIT II, patients with previous MI and EF of 30% or less should undergo ICD therapy regardless of the presence or absence of NSVT. Based on SCD-HeFT, patients with previous MI and EF of 31% to 35% should undergo ICD implantation if they are in NYHA class II or III. Therefore, on the basis of the MUSTT findings, patients with previous MI and NSVT and EF of 36% to 40% should undergo EPS and, if inducible, they should be treated with ICDs.

Two trials have investigated the optimal timing of ICD in patients with previous MI and reduced left ventricular function and other risk factors. The Defibrillator in Acute Myocardial Infarction Trial (DINAMIT), a randomized trial, compared ICD therapy (in 332 patients) with no ICD therapy (in 342 patients) 6 to 40 days after MI in patients with LVEF 35% or less and impaired cardiac autonomic function (manifested as depressed HRV or an elevated average 24-hour heart rate on Holter monitoring).[176] Prophylactic ICD therapy did not reduce overall mortality during an approximately 3-year follow-up, although it was associated with a reduction in the rate of arrhythmic death. The Immediate Risk Stratification Improves Survival (IRIS) investigators randomized 898 patients with an LVEF of 40% or less and a heart rate of 90 or more beats/min on the first available ECG (602 patients), or NSVT (≥150 beats/min) during Holter monitoring (208 patients), or both criteria (88 patients), 5 to 31 days after MI, to treatment with an ICD (n = 445) and to medical therapy alone (n = 453).[177] During a mean follow-up of 37 months, prophylactic ICD therapy did not reduce overall mortality. Fewer SCDs occurred in the ICD group than in the control group (27 vs. 60; HR, 0.55; 95% CI, 0.31–1.00; $P = .049$), but the number of non-SCDs was higher (68

Table 43-3 Management and Evidence-Based Therapy in Patients with NSVT Depending on Underlying Conditions

NSVT SETTING	MANAGEMENT	EVIDENCE-BASED THERAPY
NONISCHEMIC CONDITIONS		
Asymptomatic, no overt heart disease	Evaluate for ischemic heart disease and other disorders	No treatment necessary
Symptomatic with RVOT morphology of NSVT	EPS	β-Blockers, verapamil, adenosine Differentiate with ARVD Radiofrequency ablation, if needed
Hypertrophic cardiomyopathy	Evaluate additional risk factors: Previous cardiac arrest (although most are lethal) Unexplained syncope Massive left ventricular hypertrophy (≥30 mm) Hypotensive or attenuated blood pressure response to upright exercise	β-Blockers, CCBs (in nonobstructive form), septal myectomy/ablation ICD when frequent and prolonged (>10 beats) episodes of NSVT and additional risk factor
Nonischemic dilated cardiomyopathy	Value of EPS not established	Optimal CCB therapy (medical and CRT, if indicated) Ablation for bundle branch re-entry ICD for syncope or LVEF ≤30% to 35% and NYHA class II/III
ARVC	Value of EPS not established	ICD with sustained VT or VF or left ventricular involvement and/or one or more affected family members
LQTS	Genotype analysis useful	β-Blockers ICD if cardiac arrest with β-blockers (especially in LQT2 and LQT3)
CPVT	Value of EPS not established	β-Blockers ICD, if cardiac arrest on β-blockers
Brugada syndrome	Value of EPS disputed	ICD with syncope
ISCHEMIC CONDITIONS		
Acute MI, NSVT <24 hours	Routine for acute MI	Primary angioplasty, thrombolysis
NSVT >24 hours until predischarge	Routine for acute MI	Optimal CAD therapy* Revascularization
Asymptomatic CAD without MI; or MI with EF >40%	EPS if EF <40%	No need for specific management
Syncope in CAD without MI; or MI with EF >40%	EPS	Optimal CAD therapy* If EPS-inducible: ICD† optimal CAD therapy
MI with EF of 31% to 40%	EPS	Optimal CAD therapy If EPS-inducible: ICD
MI with LVEF ≤35% and NYHA II/III	No further testing needed	Optimal CAD therapy ICD therapy
MI with EF ≤30%	No further testing needed	Optimal CAD therapy ICD therapy

**Optimal CAD therapy defined as administration of aspirin, β-blockers, statins, angiotensin receptor blocker/angiotensin-converting enzyme inhibitor (ARB/ACEI), and revascularization therapy.*
†ICD is recommended if indications exist at least 40 days after MI.
ARVC, *Arrhythmogenic right ventricular cardiomyopathy;* ARVD, *arrhythmogenic right ventricular dysplasia;* CAD, *coronary artery disease;* CCB, *calcium channel blocker;* CPVT, *catecholaminergic polymorphic ventricular tachycardia;* EF, *ejection fraction;* EPS, *electrophysiology study;* ICD, *implantable cardioverter-defibrillator;* LQTS, *long QT syndrome;* LVEF, *left ventricular ejection fraction;* MI, *myocardial infarction;* NSVT, *nonsustained ventricular tachycardia;* NYHA, *New York Heart Association;* RVOT, *right ventricular outflow tract;* VF, *ventricular fibrillation;* VT, *ventricular tachycardia.*

vs. 39; HR, 1.92; 95% CI, 1.29–2.84; $P = .001$). Thus, ICD after MI, when indicated, should be considered at least 40 days later than the event.

Current guidelines for ICDs include MUSTT-based class I indication, formulated as follows: "ICD therapy is indicated in patients with NSVT due to prior MI, LVEF <40%, and inducible VF or sustained VT at electrophysiological study (Evidence level B)."[178] However, this category of patients is very much limited to individuals with LVEF of 36% to 40%, since other (MADIT II and SCD-HeFT based) approved indications that do not require documented NSVT cover patients with an LVEF less than 35%.[4]

No data are available from clinical trials to indicate that NSVT in patients with previous MI and EF greater than 40% should be treated with ICDs. The role of EPS-guided therapy and ICDs in these patient populations remains to be determined.

Summary

NSVT can be recorded in an extremely wide range of conditions, from apparently healthy individuals to patients with significant heart disease. The prognostic significance of NSVT is strongly influenced by the type and severity of underlying heart disease. The current evidence-based therapy in patients with NSVT is summarized in Table 43-3. ICD therapy remains the mainstay of current antiarrhythmic regimen in high-risk conditions complicated by NSVT.

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CHAPTER 44

Sustained Ventricular Tachycardia with Heart Disease

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Clinical Electrophysiology: William G. Stevenson
Management: Robert J. Myerburg, Paul Dorian, and Sanjeev Saksena

Sustained ventricular tachycardia (VT) degenerating to ventricular fibrillation (VF) and asystole is the most common cause of premature cardiac death in the Western world. It is difficult to definitively establish from epidemiologic studies whether VT or VF more often causes sudden cardiac death (SCD). However, the identification, immediate treatment, and long-term prevention of sustained VT in patients with pre-existing heart disease will likely have a significant impact on overall cardiac morbidity and mortality.

The definition of sustained VT has undergone evolution. Although no formal definition has been adopted for spontaneous sustained VT compared with VT induced by programmed stimulation, two versions are in common use. In the Electrophysiologic Study Versus Electrocardiographic Monitoring (ESVEM) trial, a 15-second duration was considered sustained VT.[1] Alternatively, many physicians prefer to use 30-second duration or evidence of hemodynamic compromise warranting earlier termination to define VT, as in the case of induced VT. This chapter provides an overview of the epidemiology, pathology, electrophysiology, and management of sustained VT in patients with structural heart disease. In such patients, VT can be conveniently divided into (1) VT caused by, or related to, a "fixed arrhythmogenic substrate" and (2) VT in which the substrate is present intermittently during transient abnormalities in cardiac electrophysiological structure and function (e.g., with changes in the neurohormonal milieu).

Etiology and Pathologic Anatomy

In general, the majority of hearts in patients with a previous history of VT reveal varying types of pathologic changes, with areas of healthy myocardium interspersed among the pathologic processes.[2-4] The most common cause of VT is coronary artery disease (CAD), in either its acute phase or chronic phase. During the acute phase, VT is believed to be caused by altered physiologic, biochemical, or metabolic states. In the chronic phase, a re-entry circuit is created at the junctional areas of the healthy myocardium and scar tissue. The infarct zone is surrounded by varying degrees of border zone with surrounding but damaged myocardial fibers. In general, the infarct size is quite large in these patients and may be related to the development of a ventricular aneurysm.[2-4]

VT also frequently occurs in cardiomyopathy. Any disease state that affects the heart in a chronic process can eventually lead to a cardiomyopathy. Thus VT is expected to occur in advanced cardiomyopathy during the end stage of heart diseases such as CAD, myocarditis, valvular disease, hypertensive heart disease, familial types of cardiomyopathy, and in many other disease states. This cardiomyopathy can have several etiologies; however, the most common type is an idiopathic form. In some patients, "idiopathic" cardiomyopathy may be the end result of previous viral myocarditis. Pathologically, in most cases of cardiomyopathy, the ventricular myocardial cells show varying types of histologic features such as hypertrophy of cells and varying stages of degenerative changes in the cells and fibrosis, with or without the presence of chronic inflammatory cells. Varying degrees of myocardial fiber damage can provide a substrate for a re-entry circuit at the junctional areas with the healthy myocardium.[3]

Myocarditis of any type, in the acute phase or the chronic phase, may cause VT that may result in SCD. The heart may be normal at the gross anatomic level, but microscopic examination may reveal an interstitial type of a myocarditis in the ventricular myocardium, including the bundle branches. In many patients, clinical history may be essentially unremarkable, or a history of a mild attack of influenza several weeks before death may be present.[2-4]

Fibrotic scars in the ventricular myocardium are often seen in young victims of SCD who otherwise have a normal heart. They may be associated with pathologic changes in the peripheral conduction system such as the branching atrioventricular (AV) bundle and bundle branches. The focal scars in the ventricular myocardium, surrounded by healthy myocardium, may form an anatomic substrate for ventricular arrhythmias that promotes re-entry or abnormal automaticity. The etiology of the fibrotic

scars in the ventricular myocardium and the beginning of the bundle branches currently is unknown. One hypothesis is that these may represent the end result of an autoimmune reaction or an allergic state that may or may not be related to a silent form of a previous myocarditis.[2-4]

Uncommon Types of Cardiomyopathy

Less commonly, VT is seen in mitral valve prolapse. Several pathologic abnormalities in cases of mitral valve prolapse are associated with VT.[2-5] A variety of pathologic findings such as a right-sided AV bundle, fibrotic scars in the ventricular septum, degenerative changes in the conduction system, and arteriolosclerosis, may be seen in these patients.

In arrhythmogenic right ventricular dysplasia, the anterior wall of the right ventricle can be partially or completely replaced by fibro-fatty tissue. Some intact myocardial cells may be scattered within the fatty tissue. Similar findings extend to the ventricular septum and the left ventricular myocardium. This often is associated with necrosis of cells and mononuclear cell infiltration. Varying amounts of degenerative changes in the myocardium are present in the right and left ventricles. A segmented and looping left-sided AV bundle has been reported. Small-vessel disease of the ventricular septum may also be present. Thus, in addition to acquired pathologic changes, congenital abnormalities of the conduction system in the sinoatrial, AV node, and AV bundle also occur.[2-4,6]

In hypertrophic cardiomyopathy, the heart is hypertrophied and enlarged. Hypertrophy of the interventricular septum is seen in varying degrees. The AV node may be partly or mostly situated within the central fibrous body and occasionally partly embedded in the tricuspid valve annulus or at the aortic-mitral annulus. The AV nodal artery is usually thickened and narrowed. The sinoatrial (SA) and AV nodes frequently are infiltrated with fat. The AV bundle may be on the right side of the ventricular septum with loop formation and fibrosis of the branching bundle. Focal, fibrotic scars in the ventricular myocardium are associated with myocardial fiber disarray and arteriolosclerosis in the summit of the ventricular septum.[2-4,7]

Infiltrative Diseases of the Myocardium

VT may occur in sarcoidosis and amyloidosis. An infiltrative disease of the myocardium such as sarcoidosis may affect the branching AV bundle and the bundle branches as well as the ventricular myocardium. Likewise, amyloidosis, in either the primary or the secondary form, may involve the ventricular myocardium, including the bundle branches. In 70% of cases of primary amyloidosis, the heart is involved, often with disruption to the entire conduction system. The infiltration of amyloid in the heart eventually results in a restrictive cardiomyopathy, and SCD is commonly seen.[2-4,8] The heart is affected in approximately 13% to 25% of cases of sarcoidosis. Cardiac involvement often is associated with lymph node and lung involvement. Sarcoidosis has a predilection to affect the posterior wall of the left ventricle with aneurysm formation. Sarcoid granulomas may be present in the conduction system and the surrounding myocardium (Figure 44-1). In general, infiltrative lesions can cause conduction disturbances and provide a substrate for re-entrant or automatic VT.[2-4,8]

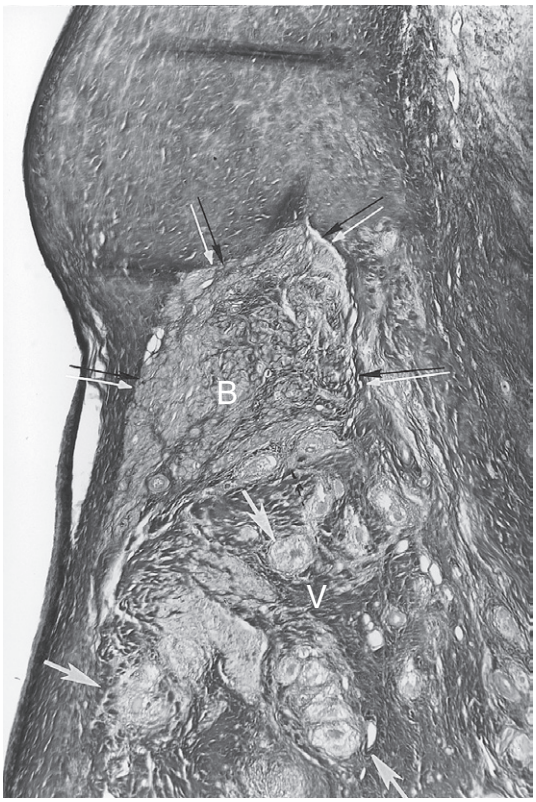

FIGURE 44-1 A 34-year-old male of Italian ancestry died suddenly. He was diagnosed to have right bundle branch block with first-degree and intermittent third-degree atrioventricular (AV) block and recurrent unifocal paroxysmal ventricular tachycardia. During electrophysiological studies with extrastimulus technique, repetitive ventricular tachycardias were induced. Photomicrograph demonstrates sarcoid granulomas of the ventricular myocardium and branching AV bundle (Weigert-van Gieson stain ×45). *B*, Branching AV bundle with sarcoid granulomas; *V*, summit of the ventricular septum with sarcoid granulomas. *Thin white and black arrows* point to sarcoid granulomas in the branching AV bundle; *thick arrows* point to the ventricular septum with granulomas.

Primary Electrical Diseases

Supraventricular arrhythmias are well known to occur in preexcitation syndrome. However, ventricular arrhythmias also can occur in this entity. Pathologically, the accessory pathway is obvious on either the left or right side, associated with cardiomyopathy and fibroelastosis of the left ventricle, along with hypertrophy and degenerative changes of the myocardium.[2-4,9]

Familial Q-T interval prolongation is predominantly an autosomal dominant disorder associated with syncopal episodes, VT, and SCD. Recently, abnormal genes have been identified on several chromosomes in patients with congenital prolonged Q-T interval. Genetic heterogeneity has been documented in linkage studies, in which loci on several chromosomes have been identified. Furthermore, mutations in ion channel genes on chromosomes 3, 7, and others have been identified as related to other forms of long QT syndrome.[2-4,10] Pathologically, there are marked fatty infiltration in the approaches to the AV node; a lobulated AV bundle with or without loop formation; arteriolosclerosis; and focal fibrosis of the summit of the ventricular septum seen

predominantly on the right side. In addition, fibrotic changes are seen to a varying degree in the AV bundle and bundle branches with chronic inflammatory cells in the ventricular myocardium. Of note, pathologic findings do exist in congenital long QT syndrome leading to SCD.[2-4,10]

Skeletal Muscle Disorders

The conduction system frequently is affected in congenital myotonic dystrophy. This progressive, generalized disease is characterized by typical atrophy of skeletal muscles with associated myotonia. Various types of arrhythmias are known to occur in this disease. Pathologically, degenerative changes in the smooth muscles of the cardiac vessels in the left atrium and the aorta with fatty infiltration in the approaches to the AV node, fibrosis of the bundle branches, summit of the ventricular septum, and varying degenerative changes in the myocardium are present. These could form a substrate for AV block and VT.[3,11]

Kearns-Sayre syndrome is characterized by progressive external ophthalmoplegia, retinitis pigmentosa, and AV block rather than VT. Progressive, degenerative changes affect the entire heart. The conduction system is replaced by fibrotic destruction of the bundle branches with fibro-fatty replacement. Some muscle cells may reveal hypertrophy; others become atrophied with perineural and perivascular fibrosis, eventually leading to cardiomyopathy. Although AV block frequently occurs in this disease, electrophysiological studies have demonstrated that the disease affects the entire His-Purkinje system. These findings in the conduction system and ventricular myocardium may form an anatomic basis for VT.[3,12]

Tumors and Parasitic Diseases of the Heart

Any tumor, either primary or secondary, can produce ventricular arrhythmias, as can parasitic infiltration. Hydatid cyst infiltration can result in fibrosis in the perimeter tissues around the cyst. This can permit re-entry and may result in VT.[3,13]

Aneurysm and Diverticulum of the Heart

Aneurysm and diverticulum of the heart may occur in either the right or left ventricle of an otherwise normal heart, and VT may be the first clinical manifestation.[3,13] Pathologic anatomy reveals a large, wide-mouthed aneurysm, but its microscopic appearance can vary with the etiology.

Ventricular Tachycardia in Postoperative Patients with Congenital Heart Disease

Ventricular arrhythmias are known to occur in postoperative patients with congenital heart diseases such as tetralogy of Fallot, aortic stenosis, or other congenital cardiac anomalies. VT can appear many years after the surgery. Fibrotic scars along with healthy myocardium are seen, for example, at the outflow tract of the right ventricle or in any other area in the heart. This substrate can result in re-entry circuits leading to VT.[2-4,14,15] In aortic stenosis, cardiomegaly may occur with myocardial fibrosis.[16]

Iatrogenic Disorders

Antiarrhythmic drugs may alter the physiological, metabolic, and biochemical states of the myocardium, the conduction system, or both and give rise to VT, which may or may not be transient. Likewise, the various resuscitative techniques used and catheter ablation of the myocardium may alter myocardial tissue, leading to formation of fibro-fatty scar and chronic inflammation. This may become a future substrate for VT.[2-4,13,17]

Familial Ventricular Tachycardia

Pathologically, the conduction system and the ventricular myocardium may show degenerative changes with mononuclear cell infiltration and fat to varying degrees. In other individuals, atrophy of the branching part of the AV bundle, with almost complete absence of both right and left bundle branches, may be present. These findings suggest a genetic abnormality of the conduction system that leads to degenerative changes, inflammatory phenomena, and susceptibility to ventricular arrhythmias that cause SCD.[18,19] The anatomic substrate may originate from the myocardial disarray that can be present in either the ventricular septal myocardium or the conduction system. Left or right ventricular septal hypertrophy may also cause degeneration of the AV node, AV bundle, and the main left bundle branch (Figure 44-2).[3,4,20]

Changes on the Right Side of the Ventricular Septum Related to Premature Aging

Premature aging occurs in the summit of the ventricular septum in some individuals, with degenerative changes of the branching bundle and the right bundle branch. These changes are usually associated with arteriolosclerosis of the summit of the ventricular septum and often are seen in SCD in teenagers.[3,4,21]

Idiopathic Ventricular Tachycardia Caused by Congenital Abnormalities of the Conduction System

VT may occur in many disease states involving the conduction system, the myocardium, or both. Diseased myocardial fibers usually are surrounded, at least in part, by healthy myocardial fibers, thereby creating a substrate for re-entry, abnormal automaticity, or slowed conduction. Thus varying types of congenital abnormalities of the conduction system—such as a right-sided AV bundle; left-sided AV bundle; genetically abnormally formed conduction system; and altered metabolic, biochemical, or physiologic states—may result in VT.

Chronic recurrent right VT with QRS morphology of a left bundle branch block (LBBB) pattern in a normal heart, normal coronary arteries, and normal cardiac catheterization findings has been well documented, especially in young patients. However, an anatomic substrate for this abnormality has only been occasionally reported.[22] In one report, a 13-year-old boy with a history of recurrent VT died suddenly. A right-sided, markedly septated AV bundle was found at autopsy. The AV node formed the AV bundle, and the node-bundle junction was ill defined (Figure 44-3). The penetrating AV bundle cells were not well defined as typical cells of the AV bundle, and the latter remained on the right side and eventually became the right bundle branch. In addition, patchy fibrotic scars were present in the right ventricular myocardium. A right-sided, markedly septated, undifferentiated AV bundle that eventually continues as the right bundle branch has been hypothesized to cause recurrent right VT in an otherwise normal heart.[2,3,22]

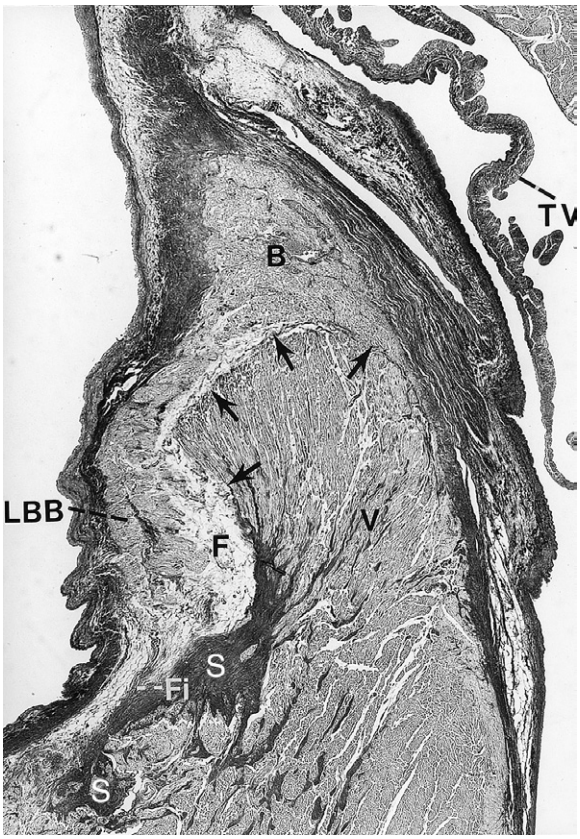

FIGURE 44-2 Nonsustained ventricular tachycardia of familial etiology. A 15½-year-old boy with a history of exercise-related syncope died suddenly while swimming. He had a family history of sudden cardiac death involving three consecutive generations, including a brother. The electrocardiogram and cardiac catheterization results were normal. During electrophysiological studies, with extrastimulus testing, he had polymorphic nonsustained ventricular tachycardia; during stage 5 of the Bruce protocol, he had a run of nonsustained ventricular tachycardia. Photomicrograph of the branching atrioventricular bundle being compressed by the right ventricular septal muscle at the region of the posterior radiation of left bundle branch (Weigert-van Gieson stain ×22.5). *B*, Branching bundle; *F*, fatty metamorphosis; *Fi*, fibrosis and linear change of left bundle branch; *LBB*, posterior radiation of left bundle branch; *S*, increased sclerosis on the mid-septal area on the left; *V*, summit of the ventricular septum. *Arrows* point to the pressure of the right ventricular septal hypertrophy on the atrioventricular bundle at the level of the posterior radiation of left bundle branch. *(From Brookfield L, Bharati S, Denes P, et al: Familial sudden death, report of a case and review of the literature,* Chest *94:989–993, 1988.)*

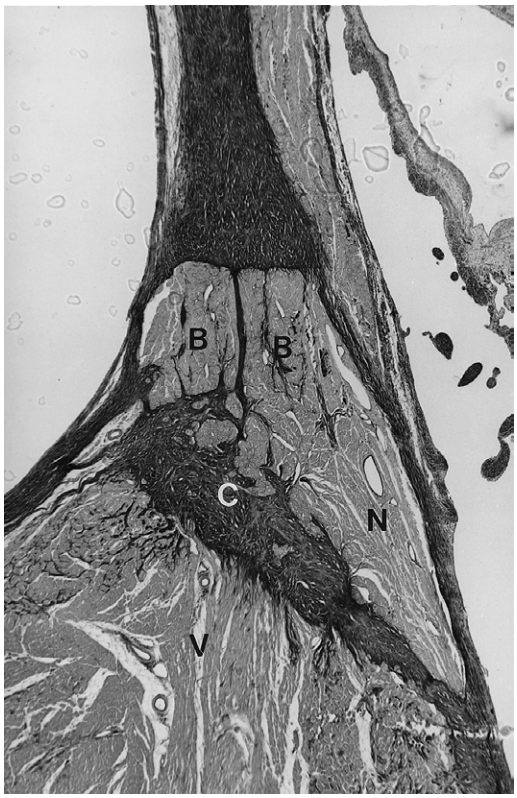

FIGURE 44-3 Idiopathic ventricular tachycardia in an otherwise normal heart. A 13-year-old boy with a history of recurrent ventricular tachycardia died suddenly. Photomicrograph demonstrating a right-sided atrioventricular (AV) node and AV bundle with no sharp line of differentiation between the AV node partly engulfed in the central fibrous body and the markedly septated AV bundle (Weigert-van Gieson stain × 30). *B*, AV bundle; *C*, central fibrous body; *N*, AV node; *V*, ventricular septum. *(From Bharati S, Bauernfeind R, Scheinman M, et al: Congenital abnormalities of the conduction system in two patients with tachyarrhythmias,* Circulation *59: 593–646, 1979.)*

Basic Electrophysiology

VT occurs in different disease substrates. The most common and most widely studied experimental models include healed myocardial infarct, myocardial hypertrophy, and myocardial failure. The origins of VT in each of these substrates are specific mechanisms that provide insight into clinical VT.

Ischemia and Ventricular Tachyarrhythmias

The ventricular arrhythmias caused by myocardial ischemia and infarction occur in several distinct phases. A ventricular arrhythmia can be induced by acute ischemia and reperfusion. It usually occurs between 2 and 30 minutes after acute coronary artery occlusion, when the changes caused by ischemia are still reversible. Arrhythmias associated with the development of myocardial infarction can be categorized as delayed arrhythmias, usually occurring between 5 and 48 hours, late arrhythmias occurring after days to weeks, and chronic arrhythmias occurring months to years later.[23,24] Delayed arrhythmias such as slow VT and accelerated idioventricular rhythms rarely degenerate into VF and are caused by abnormal automaticity of Purkinje fibers overlying the infarct.

Data obtained in 4- to 5-day-old canine infarcts show that the healing infarct undergoes structural and functional changes. The surviving epicardial cells overlying the infarct have abnormal action potentials with diminished upstrokes with loss of the plateau and shorter action potential duration. The density and kinetics of a number of ion channels are altered, and sodium ion and calcium ion currents are reduced, as are transient outward potassium ion currents and the delayed and inward rectifying potassium ion currents.[25] During this stage, re-entrant VT in the so-called *epicardial border zone* (the layer of surviving cells

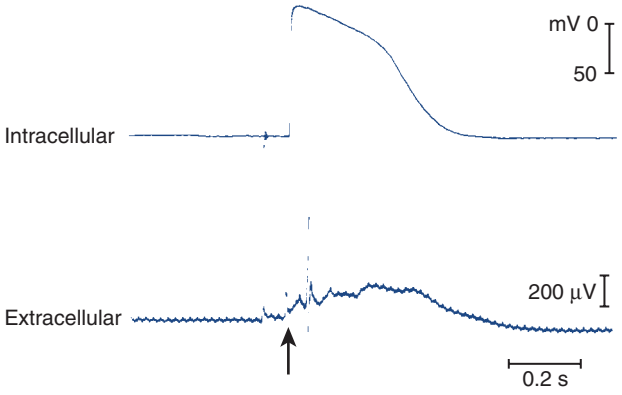

FIGURE 44-4 Transmembrane potential and extracellular electrogram recorded from a resected endocardial preparation from a patient with ventricular tachycardia and a chronic myocardial infarction. The electrogram shows fragmentation. The action potential is close to normal. *(From de Bakker JMT, Coronel R, Tasseron S, et al: Ventricular tachycardia in the infarcted, Langendorff-perfused human heart: Role of the arrangement of surviving cardiac fibers,* J Am Coll Cardiol *15:1594–1607, 1990.)*

overlying the infarct) can easily be induced by premature stimuli. Both the cellular abnormalities, as well as a re-distribution of intercellular gap junctions, play a role in determining the "substrate" for re-entry.[26] These VTs may degenerate into VF, especially in the presence of a high sympathetic tone, but this is uncommon.[24]

In the following few weeks, transmembrane action potentials of the surviving cells gradually return to normal as most of the ion channels recover; by 2 months, action potential configuration in both canine and human infarcts is completely normal (Figure 44-4).[27,28] When the healing phase of myocardial infarction is over and when the fully healed phase begins are difficult points to ascertain. The electrophysiological substrate for VT likely develops gradually over several weeks and remains stable from several months to 15 to 20 years.[29]

Most of the electrophysiological data have been obtained from canine models with healing infarcts. Although many similarities exist between canine arrhythmias and those in humans, some important differences are also present. In dogs with infarcts, arrhythmias can be easily induced during the first week, but inducibility decreases thereafter. In humans, VTs can only be induced in a small minority after 5 days, and inducibility increases after 3 weeks. In dogs, the re-entrant circuit responsible for the tachycardia is located in the epicardial border zone. In humans with healed infarcts, the re-entrant circuit usually is located subendocardially, and only approximately 20% of VTs are caused by re-entry in the subepicardium.

The Substrate for Re-entrant Tachycardia in the Human Heart with a Healed Infarct

In the prethrombolytic era, the incidence of sustained monomorphic VT after discharge from the hospital in patients surviving a myocardial infarction (MI) has been reported to be approximately 3% and that of nonsustained VT as 10% to 20%.[30] Although thrombolysis has drastically reduced arrhythmic events early after MI, with an incidence of sustained VT lower than 1%, post-infarction arrhythmias have certainly not become irrelevant.[31] With improved therapy in the acute stage of MI, more patients survive, but many survivors have left ventricular dysfunction. Ventricular dysfunction is known to be the most important risk factor for SCD, as verified in the European Myocardial Infarct Amiodarone Trial (EMIAT). The combination of arrhythmic death and resuscitated cardiac arrest occurred in 8.6% of patients.[32] How many of these patients developed sustained VT that degenerated into VF is unknown, as is how many had an episode of acute ischemia that induced the lethal arrhythmia. Still, despite intensive therapy, arrhythmic events in patients who have had MI, especially in the presence of ventricular dysfunction, remain an important cause of death.

Reconstruction of the re-entrant circuits and the mechanism of slow conduction in the human heart with a healed infarct is based on observations made during mapping-guided surgery in patients with infarct-related VT as well as on studies on isolated, Langendorff-perfused human hearts and isolated papillary muscles from patients with infarcts undergoing cardiac transplantation.[28,33-35] Figure 44-5 shows the activation map of one beat of a VT induced by programmed electrical stimulation in an isolated, Langendorff-perfused heart. The endocardial surface of the left ventricle is schematically depicted with the left ventricle folded out by making a vertical cut along the left anterior descending artery. The black zone indicates the infarcted area.

Selected extracellular electrograms, recorded simultaneously from the endocardium by a balloon electrode inserted into the ventricular cavity, are shown in Figure 44-5 as well. The cycle length of this tachycardia was 264 ms. The site of earliest activation during this tachycardia was in a small area near the apex, on the border of the septum and the posterior wall, at the margin of the infarcted region (the area encircled by the 0-ms isochrone). Activation spread from this area to the left in the figure (from *a* to *b*) and continued to the anterior wall (from *b* to *c* to *d* to *e*) to reach the other margin of the infarct after 192 ms (near site *e*). Although activation at this margin seems to have died out, because of the slow positive deflection recorded at site *e*, the presence of small deflections indicated by the arrows over the infarcted zone suggests that the spread of activation continued via tracts of surviving muscle within the infarct, through sites *f*, *g*, and *h*, to reach the opposite side of the infarct after 258 ms, re-exciting the area of the 0-ms isochrone and completing a large re-entrant circuit around the circumference of the ventricle.

Subsequent histologic studies of this region confirmed the presence of surviving myocardial muscle bundles, several millimeters below the endocardial surface that connected both margins of the infarct, completing the re-entrant circuit. Figure 44-6 shows superimposed drawings of many histologic sections of this region, where viable muscle is in black and connective tissue in white. Similar tracts were found in other hearts, embedded within the scar of the healed infarct. Such tracts could be localized in the subendocardium, the subepicardium, and intramurally. The myocardial fibers were sometimes arranged in a parallel fashion along the long axis of the tract, allowing relatively rapid transmission of the re-entrant impulse from one side of the infarct to the other. However, in other hearts the fibers were oriented transverse to the direction of impulse propagation; in these cases, transmission through the infarct was very slow.

Figures 44-7 and 44-8 show the mechanism of such "slow" conduction. Figure 44-7 shows selected electrograms from an infarcted human papillary muscle to illustrate the highly fragmented waveforms, typical when connective tissue is

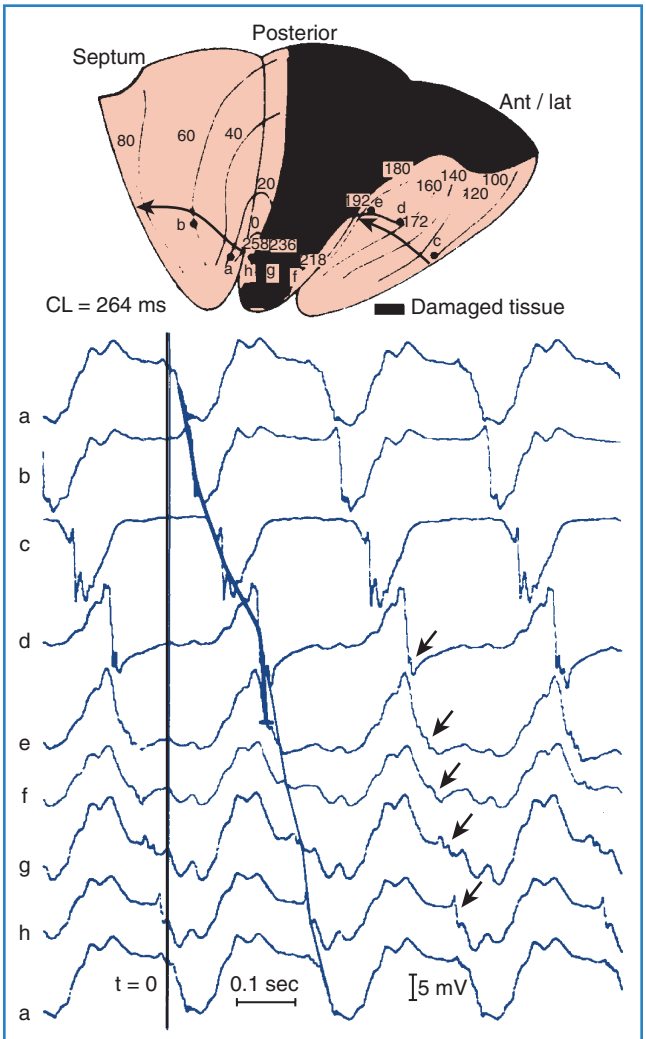

FIGURE 44-5 Endocardial activation pattern of one cycle of sustained ventricular tachycardia induced in a Langendorff-perfused human heart with extensive inferoposterior infarction. Isochrones are in milliseconds with respect to a time reference ($t = 0$) in the bottom panel. *Thick arrows* on the map indicate main spread of activation. In the *bottom panel,* endocardial electrograms recorded at sites indicated in the *top panel* are shown. The *thick line* connects times of activation of subendocardial tissue at the sites *a* to *e*. At site *d*, the main deflection is followed by a second response of small amplitude (*arrow*). At sites *e* to *h*, large signals reflect remote activity, but in all signals small deflections are present (*arrows*). The timing of these small deflections is indicated by the *thin line*. *CL,* Cycle length; *Ant/lat,* anterior/lateral. *(From de Bakker JMT, Coronel R, Tasseron S, et al: Ventricular tachycardia in the infarcted, Langendorff- perfused human heart: Role of the arrangement of surviving cardiac fibers,* J Am Coll Cardiol *15:1594–1607, 1990.)*

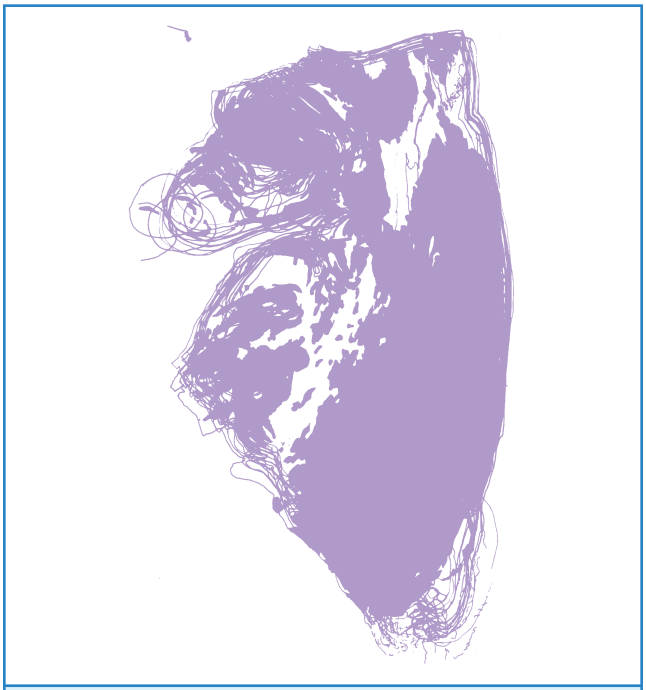

FIGURE 44-6 Superimposed drawings of selected serial sections from the infarcted part of the left ventricle taken from an isolated human heart in which sustained ventricular tachycardia was induced. Viable myocardial tissue is in purple and scar tissue is in *white*. A bundle of surviving myocardium runs through the infarct, connecting the noninfarcted tissue on both sides of the infarct. *(Courtesy Jacques M.T. De Bakker and S. Tasseron.)*

intermingled with viable myocardium. In this muscle, the delay between the deflections at the extreme electrode terminals of the multiple electrode (distance, 1.4 mm) was 45 ms, which would correspond to an overall conduction velocity on the order of 3 cm/sec. As illustrated in Figure 44-8, this apparent slow conduction was caused by "zigzag" conduction in small muscle bundles separated by collagenous septa. Activity in the muscle tracts proceeded both toward the site of stimulation *A* and away from it. Many tracts were dead-end pathways. The actual pathway of activation is plotted in panel *B*. Although the shortest distance between *A* and *B* was 1.2 mm, the length of the zigzag pathway was 25.2 mm. In 10 papillary muscles, conduction velocity parallel to the fiber orientation was, on average, 79 cm/sec, which indicates that both the active electrical properties (action potential amplitude and upstroke velocity) and passive electrical properties (longitudinal coupling resistance) were normal. Conduction velocity at the bifurcation points was only 49 cm/sec, indicating that in addition to the pathway length, impedance mismatch at bifurcations also contributed to activation delay.

Thus, in the human heart with a healed infarct, the substrate for re-entry is formed by the surviving fibers within the infarct. In addition to a substrate, a trigger is needed to initiate the tachycardia. This trigger likely occurs in the myocardium remote from the infarct. In the presence of progressive left ventricular dysfunction, these myocardial zones can undergo arrhythmogenic remodeling. Furthermore, the properties of the noninfarcted myocardium can determine whether VT degenerates into VF. Dispersion of refractoriness in the noninfarcted myocardium is three times larger in patients who have had an MI and subsequently develop VF than in those in whom the VT remains monomorphic and hemodynamically stable.[36]

Role of Cardiac Remodeling in Ventricular Tachycardia

The heart may respond to a variety of abnormal environmental stimuli by altering gene expression or the functional properties of proteins. This ultimately leads to both functional and structural cardiac alterations that may be arrhythmogenic. These processes are referred to as *cardiac remodeling*. Common to all studies on

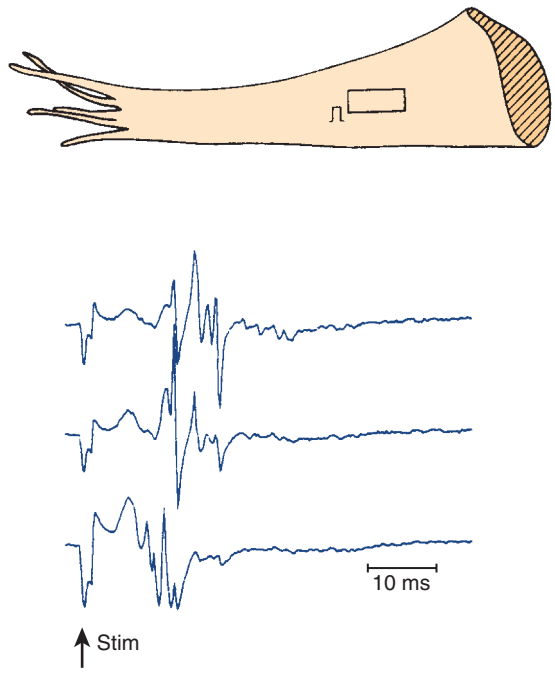

FIGURE 44-7 Selected electrograms recorded at distances of 200 μm in an isolated, superfused infarcted human papillary muscle. The recording area is indicated by the *rectangle*; the site of stimulation (*Stim*) is noted by the *square wave*. Note the high degree of fragmentation of the electrograms. *(Modified from De Bakker JMT, van Capelle FJL, Janse MJ, et al: Slow conduction in the infarcted human heart: "Zigzag" course of activation,* Circulation *88:915–926, 1993.)*

the hypertrophic and failing ventricular myocardium is a prolonged action potential, especially at slow heart rates.[37] This may be considered an adaptive process. In the setting of a prolonged action potential, the intracellular calcium transport is increased, causing enhanced force of myocardial contraction. It can be argued that a prolonged action potential may also protect the heart against re-entrant excitation. However, prolonging repolarization may be arrhythmogenic. Drugs, both cardiac and noncardiac, can prolong the action potential. A risk of development of early afterdepolarizations (EADs) and torsades de pointes (TdP) does exist in this situation.[38] An EAD-induced premature beat generally causes re-entry only in the presence of a marked increase in dispersion of repolarization.[38] In the hypertrophic and failing myocardium, increased dispersion in repolarization (or refractoriness) has been reported.[36,39-41] In hearts with a healed infarct, repolarization of normal, lateral border and infarct-zone cells is nonuniform, with myocardial cells showing different degrees of action potential disturbance and prolongation. Many of these cells, especially those close to the infarct border, show post-repolarization refractoriness.[25] Several reasons for the increased dispersion in repolarization exist: unequal distribution of remodeled ion channels, decreased expression of gap junctional connexins and an altered distribution of gap junctions with the development of fibrosis, and changes in autonomic innervation.[41-46]

Changes in ionic currents contributing to repolarization are seen. The most consistent finding is a reduction in the transient outward current, It_o.[37,42,43] Although this current is very important in determining action potential duration in small mammals such as the rat, its downregulation probably does not have much effect on action potential duration in the hearts of large mammals. It does change the level of the plateau phase of the action potential, and it can affect other currents activated later during the action potential. Both rapid and slow components of the delayed rectifier, Ik_r and Ik_s, are reduced in rabbits with pacing-induced heart failure.[47] The inward rectifier current, I_{K1}, can decrease, remain unchanged, or increase.[37] If I_{K1} is reduced, it will lead to an unstable resting potential; when it is unregulated, pacemaker activity could result.[48,49] The L-type calcium current is either unchanged or decreased, and it is unlikely that this current contributes to action potential prolongation.[50] A role may exist for the late sodium current, which is increased.[51] For most of these remodeled currents, data on regional differences are insufficient. However, in the presence of enhanced β-adrenergic activity, transmural dispersion in repolarization increases because of augmentation of residual Ik_s in the epicardial and endocardial layers, resulting in action potential shortening.[52] But this does not occur in mid-mural M cells, in which Ik_s is intrinsically weak.[52] A decrease in electrical cell-to-cell coupling, either by a decrease in expression of connexins or by the development of microscopic fibrosis in hypertrophied myocardium, reduces electronic current flow and will unmask intrinsic differences in action potential duration. The well-coupled myocardium will attenuate these differences.

Ischemia and infarction result in both afferent and efferent parasympathetic and sympathetic dysfunction in regions apical to the area of infarction. The denervated but otherwise normal myocardium develops adrenergic supersensitivity, and therefore the response to circulating catecholamines is exaggerated.[45] The hypothesis of nerve sprouting in ventricular arrhythmias and SCD states that myocardial infarction results in nerve injury followed by sympathetic nerve sprouting and regional, heterogeneous myocardial hyperinnervation, which, together with electrical remodeling, leads to heterogeneous distribution of repolarization and ventricular arrhythmias.[46]

It is generally agreed that intracellular calcium handling is compromised in heart failure, but reports on virtually all components involved in calcium homeostasis are contradictory.[37,53-55] It is generally accepted that adenosine triphosphate–dependent calcium accumulation by the sarcoplasmic reticulum is decreased. In the presence of a prolonged action potential and altered calcium homeostasis, both EAD and delayed afterdepolarization may occur.[43,49] In hearts with an infarct, in which an anatomic re-entrant circuit may be present, either premature ventricular depolarizations caused by these afterdepolarizations or salvos of triggered activity may initiate sustained re-entrant tachycardias. In hypertrophied and failing hearts without an infarct, with fibrosis and increased dispersion of repolarization, these triggers may equally initiate re-entrant tachycardias. In animal models of heart failure (e.g., rabbits), combined volume and pressure overload resulted in nonsustained VT developing in more than 50% of animals, and SCD was common.[56] However, it is not certain whether SCD is always caused by VT degenerating into VF. In humans with end-stage heart failure as well as in rabbit models of heart failure, bradycardia, asystole, and electromechanical dissociation have been documented to cause SCD.[57-59]

Clinical Presentation

The symptoms associated with sustained VT can range from an asymptomatic patient to cardiovascular collapse resulting in

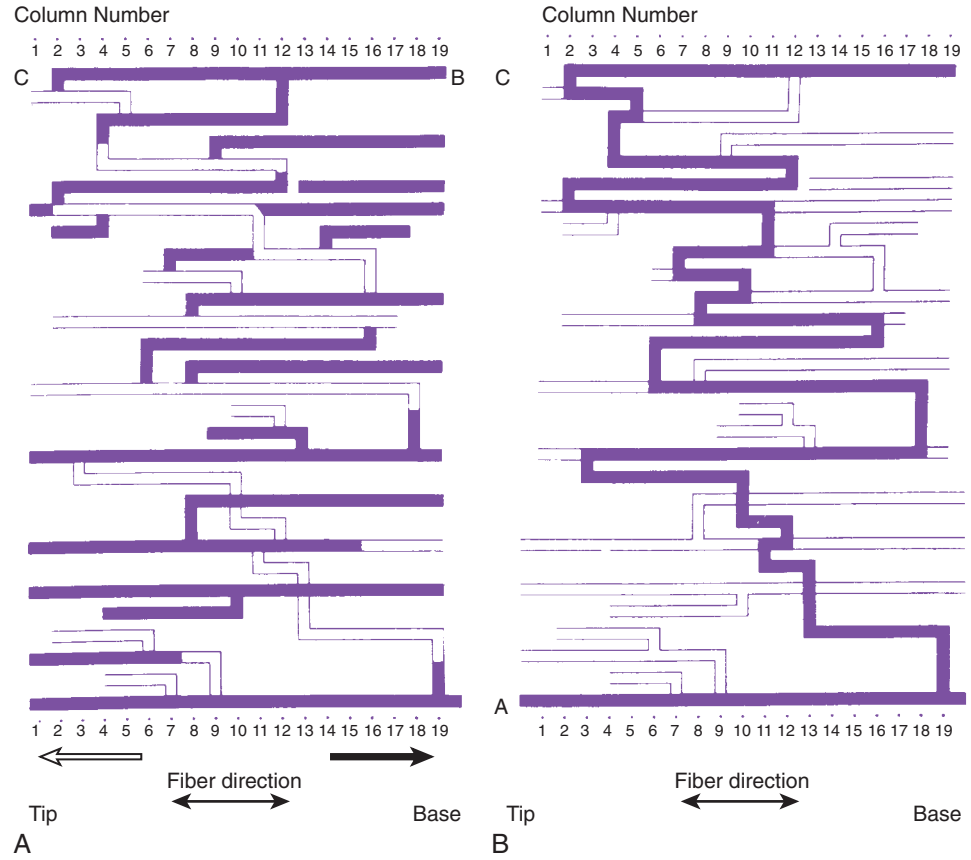

FIGURE 44-8 Map illustrating the spread of activation of the rectangular area shown in the inset of Figure 44-4. In the solid tracts of **A,** activation moves away from the site of stimulation (*site A*); in the open tracts, activation moves toward the site of stimulation. **B,** The tortuous route that activation followed to reach *site B. (Modified from De Bakker JMT, van Capelle FJL, Janse MJ, et al: Slow conduction in the infarcted human heart: "Zigzag" course of activation,* Circulation *88:915–926, 1993.)*

circulatory arrest and unconsciousness. Clinical literature dating to the early twentieth century has documented case reports of sustained VT without symptoms or minimal symptoms. Remarkably, some of these episodes may last weeks or even months. These patients may have only minimal or no palpitations, that, when present, can be regarded as an insignificant symptom. Figure 44-9 shows a patient with incessant VT who, in 1981, had palpitations with mild dyspnea during a single sustained slow VT episode that lasted 1 week, despite the presence of severe left ventricular systolic dysfunction. The most common symptoms of sustained VT are palpitations, dyspnea, angina, hypotension, and near or frank syncope. The severity of symptoms is related to several factors, including tachycardia rate, morphology, severity of left ventricular dysfunction, preload, and coexisting diseases such as CAD. The symptom complex often is defined by the hemodynamic impact of the arrhythmia. In an early study, Saksena and colleagues proved that VT resulted in impaired left ventricular relaxation and subsequently systolic dysfunction and decline in negative and positive dP/dt.[60] Tachycardia rate and pre-existing LV dysfunction were important variables, as was preload. Faster VT rates and low preload predisposed to hypotension and syncope. Hamer noted similar associations with syncope during VT.[61] In a study of defibrillator recipients, presyncope or syncope preceding delivery of implantable cardioverter defibrillator (ICD) therapy was determined by faster events in the "ventricular fibrillation" zone.[62] However, the absence of hemodynamic compromise does not exclude the diagnosis of VT. An axiom holds that wide QRS tachycardia in the presence of history or electrocardiogram (ECG) evidence of myocardial infarction is due to VT until proven otherwise by subsequent investigation.

Electrocardiography

A 12-lead ECG during sustained VT is an important and essential investigational tool for the management of the patient with VT. It should be obtained during the tachycardia and compared with a prior recording in sinus rhythm, if possible. Careful evaluation can confirm the diagnosis, exclude other tachycardias, and help establish its mechanism. The QRS morphology during VT can also help determine its site of origin.

Electrocardiographic Diagnosis of Ventricular Tachycardia

Twelve-lead ECGs are particularly useful to differentiate supraventricular tachycardia (SVT) from VT. Distinguishing these arrhythmias is more difficult when aberrant intraventricular conduction occurs during SVT, but several criteria have been

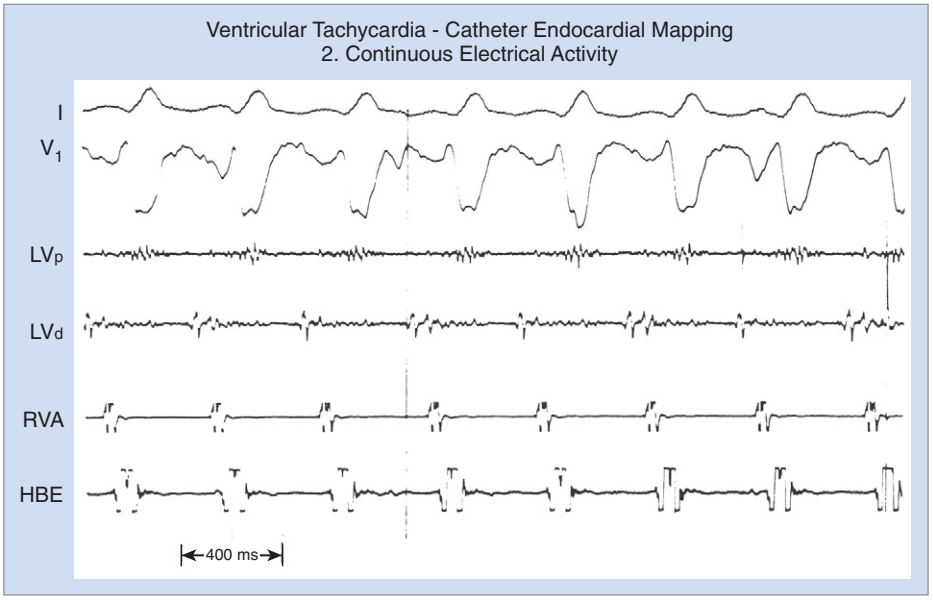

FIGURE 44-9 Incessant ventricular tachycardia (VT) in a patient with coronary artery disease, large left ventricular (*LV*) aneurysm, estimated left ventricular ejection fraction of 15%, and congestive heart failure. The patient was in sustained VT for days with minimal symptoms and a slow VT rate. Catheter endocardial mapping was performed during the episode. *HBE*, His-bundle electrogram; *RVA*, right ventricle electrogram.

proposed to improve diagnostic accuracy.[63-69] AV dissociation is the most specific ECG criterion for the diagnosis of VT in recordings of wide QRS complex tachyarrhythmias. Certain rare types of SVT (e.g., AV node re-entry with retrograde block, junctional tachycardia using a nodo-ventricular fiber with retrograde atrial block) may mimic this finding. AV dissociation is seen in only 21% of ECG recordings with VT and may be difficult to identify with absolute certainty.[65] When AV dissociation is not apparent, other criteria that depend on whether the QRS resembles LBBB or RBBB must be used.

When the ventricles are structurally normal, QRS morphology is an excellent marker of the arrhythmia origin. VT with an LBBB configuration in lead V1 can have its origin in the right ventricle or the intraventricular septum (either right or left side of the septum) (Figure 44-10). A QRS frontal-plane axis directed inferiorly (dominant R waves in leads II, III, and aVF) indicates an origin in the cranial aspect of the heart (e.g., anterior wall of the left ventricle or the right ventricular outflow tract). A QRS frontal plane axis directed superiorly (dominant S waves in leads II, III, and aVF) indicates initial depolarization arising in the inferior wall of the left or right ventricle. Dominant R waves in leads V3 to V4 favor a location of the focus nearer the base of the heart than the apex. Dominant S waves in these leads favor a more apical location. VT with a typical LBBB or RBBB QRS configuration suggests bundle branch re-entry as a mechanism. When areas of ventricular scarring are present, the QRS morphology is less reliable and is sometimes quite misleading.

Kindwall observed several characteristic patterns found in patients with VT complexes resembling LBBB and evaluated four criteria to distinguish VT with LBBB pattern from SVT with aberrant conduction.[66] All patients in the study had a predominantly negative QRS in V1 and a QRS duration greater than 120 ms. Four electrocardiographic criteria were evaluated in this study: (1) R wave in lead V1 or V2 of greater than 30-ms duration, (2) any Q wave in lead V6, (3) a duration of greater than 60 ms from the onset of the QRS to the nadir of S wave in lead V1 or V2, and (4) notching on the downstroke of the S wave in those leads. Table 44-1 summarizes the sensitivity and predictive accuracy of these criteria. None of the criteria, by itself, was very sensitive, but all patients with VT had at least one of these criteria. The specificity remained high (89%) when the combined criteria were used, and the predictive accuracy was excellent (Figure 44-11). Left-axis deviation was of no value in distinguishing VT from SVT in this study. These criteria are easily measured and provide a practical approach to differentiating VT from SVT.

Table 44-1 Sensitivity and Predictive Accuracy of Electrocardiographic Criteria to Distinguish VT Resembling LBBB from SVT with LBBB Aberration

PREDICTIVE CRITERIA*	SENSITIVITY (%)	ACCURACY (%)
R > 30 ms in lead V1 or V2	36	100
Any Q in V6	55	98
Duration >60 ms from QRS to S nadir in lead V1 or V2	63	98
Notched downstroke S wave	36	97
Any of the above present	100	96

**Diagnostic criteria for VT with a morphology resembling left bundle branch block.*
LBBB, *Left bundle branch block;* SVT, *supraventricular tachycardia;* VT, *ventricular tachycardia.*
From Kindwall KE, Brown J, Josephson ME: Electrocardiographic criteria for ventricular tachycardia in wide complex left bundle branch block morphology tachycardias, Am J Cardiol *61:1279–1283, 1988.*

Brugada prospectively analyzed a series of wide QRS tachycardias that included morphologies resembling both LBBB and RBBB.[67] The criteria used to differentiate VT from SVT included

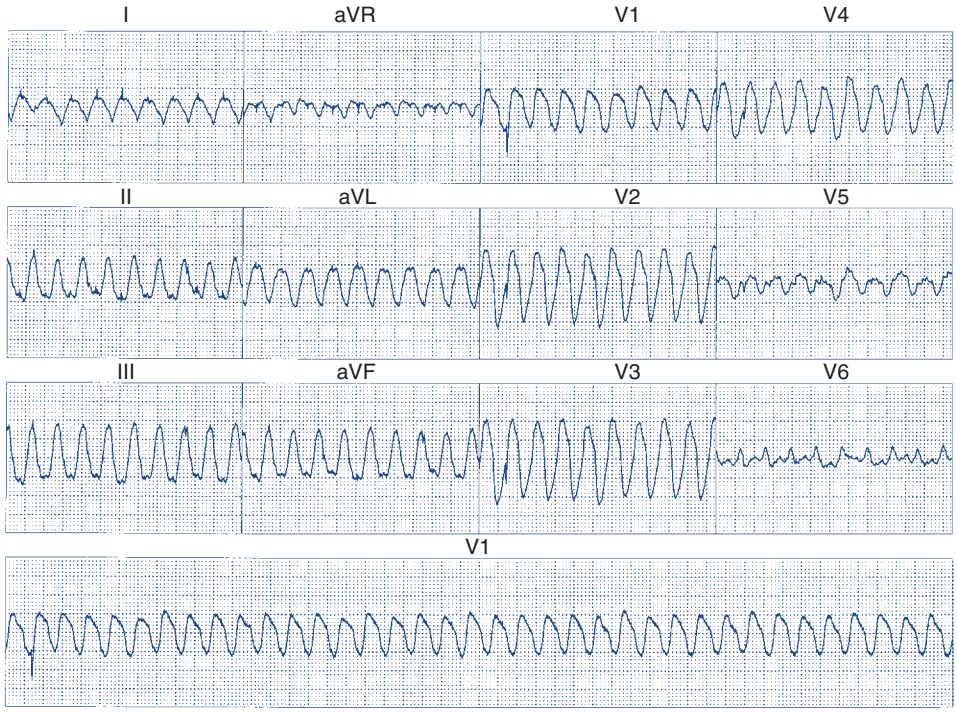

FIGURE 44-10 Twelve-lead electrocardiogram of sustained ventricular tachycardia in an older man with coronary artery disease and inferoposterior myocardial infarction. The tachycardia cycle length is 280 ms; a left bundle branch block–like morphology and an inferior axis are present in lead V1. Prominent R waves are seen in leads V3 and V4.

(1) the presence of an RS complex in at least one precordial lead, (2) an R-S interval in any precordial lead greater than 100 ms, (3) the detection of AV dissociation, and (4) morphology criteria for VT present in leads V1 to V2 and V6. The morphology criteria used for the diagnosis of VT are summarized in Table 44-2. These criteria were present in leads V1 to V2 and V6 in 61% of patients with VT. Unfortunately, only one third of VT recordings fulfill these criteria because of discordance in the morphology criteria in different ECG leads. An RS complex was present in at least one precordial lead in all SVT recordings, but only 26% of the VT recordings did not have an RS complex in any precordial lead. None of the SVTs had an R-S interval greater than 100 ms, but this criterion was met only in 52% of VTs. From these observations the authors concluded that an RS complex in all precordial leads or an R-S interval greater than 100 ms in any precordial lead was highly specific for VT.

To address the sensitivity and specific concerns, Brugada[7] used a stepwise approach to differentiate SVT from VT and prospectively tested this algorithm (Figure 44-12).[67] The algorithm was both sensitive (99%) and specific (96%). The advantage of the stepwise approach is that it guides the analyst to the correct diagnosis. If an RS complex is not present in any precordial lead, the diagnosis of VT is confirmed without the need for further analysis. If an RS complex is present and the longest R-S interval in any precordial lead exceeds 100 ms, then the diagnosis of VT is confirmed. If the R-S interval is less than 100 ms, then an examination for AV dissociation must be performed. The presence of this criterion helps diagnose VT. If AV dissociation is not detected, then the diagnosis of VT depends on the presence of morphology criteria in both leads V1 and V6.

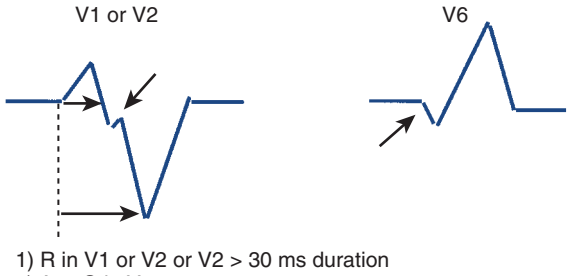

FIGURE 44-11 Four electrocardiographic criteria for ventricular tachycardia with QRS morphology resembling left bundle branch block. *(From Kindwall KE, Brown J, Josephson ME: Electrocardiographic criteria for ventricular tachycardia in wide complex left bundle branch block morphology tachycardias,* Am J Cardiol *61:1279–1283, 1988.)*

Of note, in the presence of structural heart disease, especially in older individuals, most wide-complex tachycardias are caused by VT rather than SVT with aberrant conduction.

Electrocardiographic Localization of the Origin of Ventricular Tachycardia

The morphology of monomorphic VT documented by a 12-lead ECG is also useful in predicting the exit site of re-entrant VT on the basis of studies in patients being considered for catheter

Table 44-2 Morphology Criteria for Ventricular Tachycardia

	SN (%)	SP (%)	+PV (%)	−PV (%)
TACHYCARDIA WITH RBBB QRS				
Lead V1, monophasic R	60	84	78	69
QR or RS	30	98	95	60
Triphasic	82	91	90	83
Lead V6				
R/S ratio <1	41	94	87	63
QS or QR	29	100	100	60
Monophasic R	1	100	100	52
Triphasic	64	95	93	71
R/S ratio >1	30	76	58	81
TACHYCARDIA WITH LBBB QRS				
Leads V1 or V2 and V6				
Any of the following:	100	89	96	—
V1 or V2				
R > 30 ms*				
>60 ms to nadir S*				
Notched S				
Q wave in lead V6				
Lead V6				
QR or QS	17	100	100	52
Monophasic R	100	17	51	100

**Diagnostic criteria for analysis of RS width in precordial leads.*
SN, *Sensitivity;* SP, *specificity;* +PV, *positive predictive value;* +PV, *negative predictive value;* RBBB, *right bundle branch block;* LBBB, *left bundle branch block.*
From Brugada P, Brugada J, Mont L, et al: A new approach to the differential diagnosis of a regular tachycardia with a wide QRS complex, Circulation *83:1649–1659, 1991.*

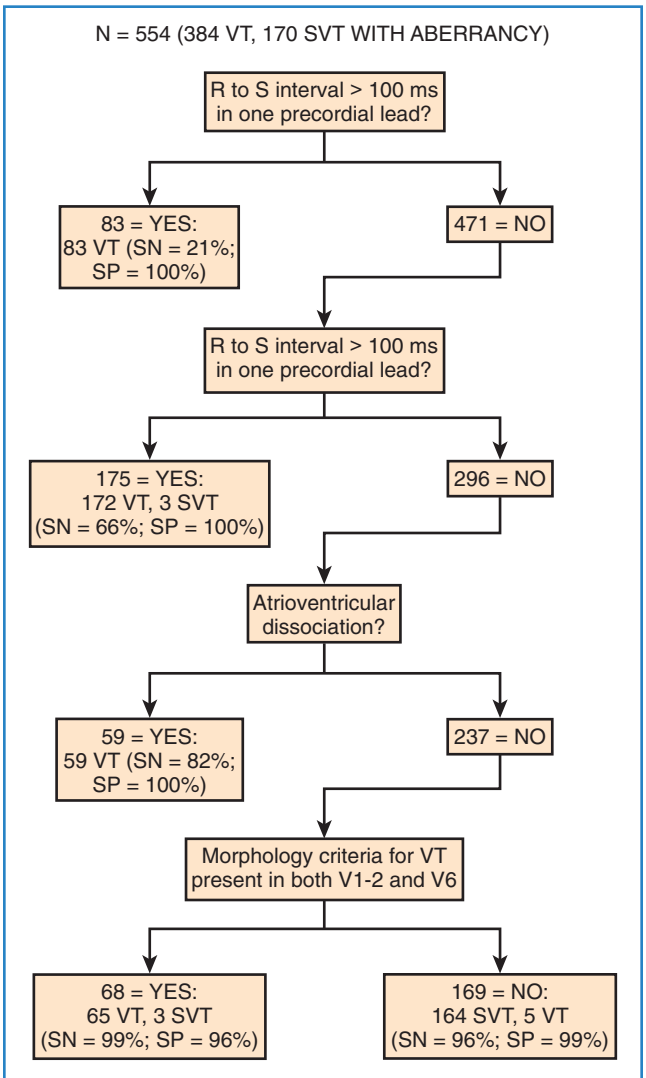

FIGURE 44-12 Algorithm developed by Brugada for diagnosis of ventricular tachycardia. *(Modified from Brugada P, Brugada J, Mont L, et al: A new approach to the differential diagnosis of a regular tachycardia with a wide QRS complex,* Circulation *83:1649–1659, 1991.)*

ablation or surgical excision of their arrhythmias. Josephson analyzed the QRS morphology during VT in patients selected for electrophysiological mapping.[68] VT morphologies can be separated into RBBB and LBBB patterns on the basis of the QRS morphology in lead V1 (Figure 44-13). The RBBB pattern includes monophasic, biphasic, or triphasic R waves in lead V1 or a qR complex in that lead. The LBBB pattern was defined by a QS, rS, or qrS recorded in lead V1. Sixteen VTs with LBBB pattern were studied in patients with CAD. The QRS morphology in lead V1 showed an rS pattern in 10, QS pattern in 4, and qrS pattern in 2. All but one of these arose from sites on or immediately adjacent to the intraventricular septum. Gross electrocardiographic features such as the bundle branch block pattern or QRS axis did not reliably localize the origin of the tachycardia.

Tachycardias were also analyzed according to their site of origin. VT arising from the inferior aspect of the anterior septum was characterized by a superior, leftward axis. In five of the six tachycardias originating from this region, a QS pattern was observed in leads V1 to V4. The one exception was less apical in origin. None developed substantial R waves in the precordial leads, and all had Q waves in leads I and V6. Four tachycardias arose from the superior aspect of the mid-septum to the apical septum. These were characterized by normal or rightward axis and an rS, Qs, or qrS pattern in lead V1. They all developed prominent R waves in the lateral precordial leads. Five instances of tachycardia arose from the posterobasal region, all with rS complexes in leads V1 to V2 and progressive R-wave development in the lateral leads. None had a Q wave in lead I or V6. Four of the tachycardias had a superior, leftward axis. In summary, the presence of Q waves in lead I or V6 and a superior, leftward axis was characteristic of the inferior aspect of the anterior septum. Those arising from the superior aspect of the anterior septum had an inferior, rightward axis. VT arising from the posterobasal region exhibited larger R waves in leads I, V2, V3, and V6.

The instances of tachycardia with a right bundle branch pattern all arose from the left ventricle and were grouped according to

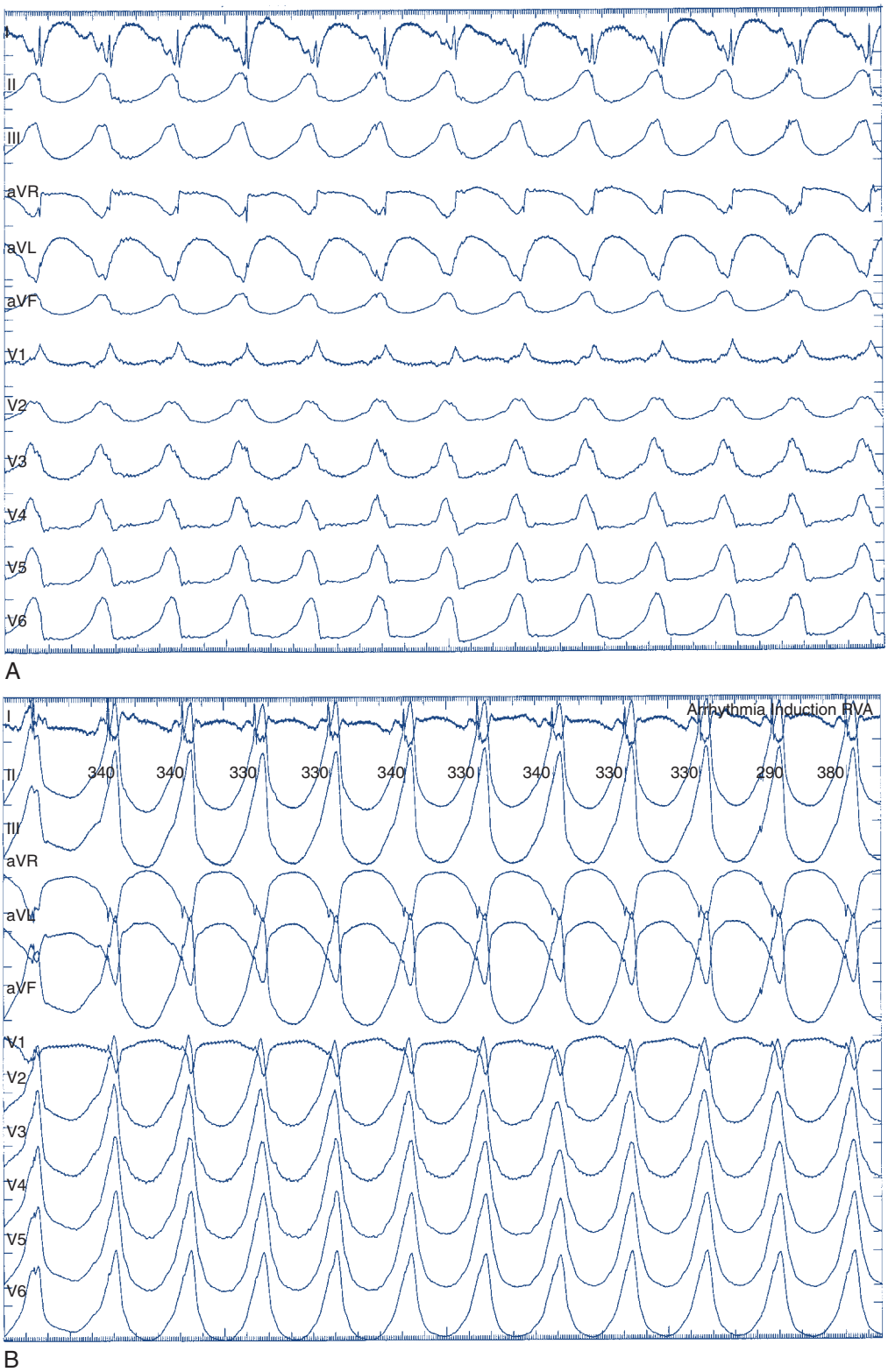

FIGURE 44-13 Twelve-lead electrocardiograms of two clinical morphologic conditions of ventricular tachycardia (VT) in a patient with ischemic cardiomyopathy caused by posterobasal left ventricular aneurysm associated with multi-vessel coronary artery disease. The two hemodynamically stable VT morphologies were mapped to different exit points on the margin of the ventricular aneurysm. **A,** Sustained VT with a right bundle branch block–type morphology in lead V1 with an inferior axis and cycle length of 315 ms. Note the positive R wave in leads V1 to V6. **B,** Sustained VT with a left bundle branch block–type morphology in lead V1 with an inferior axis and cycle length of 330 ms.

their origin from anteroseptal, anterolateral, or basal sites. The electrocardiographic patterns recorded from these sites showed substantial overlap and did not reliably distinguish septal origins from more lateral origins. Anterior and basal origins were distinguished by lead I and the precordial leads. A qR or QS pattern in lead I and a Q wave in leads V1, V2, and V6 suggested an anterior origin. Those arising from basal regions exhibited prominent R waves in leads V1 to V6.

Kuchar analyzed QRS configurations observed during left ventricular pacing in 22 patients to construct an algorithm to localize the origin of VT, which was then prospectively tested in a second group of 44 episodes of VT.[67] As shown in Figure 44-14, apical sites versus basal sites were differentiated by QRS configurations in leads V4 and aVR; anterior sites versus inferior sites were differentiated by QRS configuration in leads II, II, and V6; and septal sites versus lateral sites were distinguished by QRS configuration in leads I, aVL, and V1. Anterior sites were correctly identified in 83%, inferior sites in 84%, septal sites in 90%, and lateral sites in 82%. Apical and basal sites were accurately distinguished in 70%, but the algorithm was not reliable for intermediate sites. Overall, the site of origin was localized in 39%, and in an additional 36% the site of origin was immediately adjacent to the predicted site.

Sippensgroenewegen compared 62-lead body surface QRS integral maps and scalar 12-lead ECGs obtained during pacemapping in patients with prior MI and VT to determine the accuracy of localizing the origin of VT with these two methods.[70] An evaluation of the localization results obtained during pacemapping was performed to compare 12-lead ECGs with body surface mapping. The site of origin, as determined by endocardial mapping, was compared with the location suggested by pacemapping. With pacemapping used in combination with body surface maps, the site of origin was identified within 2 cm of the origin in 80% of VTs. The remaining 20% were localized to an adjacent (2 to 4 cm) or disparate (>4 cm) site. Results obtained with standard 12-lead ECGs were less accurate. Correct localization (<2 cm) was achieved in only 18%. The localization site was adjacent to the site of origin in 55% and disparate in 27%. The size of the corresponding endocardial area was much smaller with body surface mapping (6.0 ± 4.5 cm) than with the 12-lead ECG (15.1 ± 12.0 cm). These results are concordant with a study by Josephson, which showed that pacemapping with a 12-lead ECG allows localization to a relatively large area of 20 to 25 cm.[2,71]

Further study is needed to determine the usefulness of body surface mapping for ablation of VT; however, results obtained by Sippensgroenewegen indicated that this approach is relatively accurate.[72] QRS integral maps (62 leads) were compared with activation mapping data acquired in 64 episodes of VT. The maps were compared with a previously generated infarct-specific reference database of paced QRS integral maps. Each pattern of the database corresponded to 1 of 18 to 22 segments of the left ventricle. Electrocardiographic localization was compared with intraoperative or catheter endocardial activation mapping. Body surface mapping identified the correct segment of origin in 62%, an adjacent segment in 30%, and disparate segments in 8%.

These studies show that the QRS morphology, recorded during VT or ventricular pacemapping, provides an estimate of the site of origin, but major disparities frequently exist between the origin and the site estimated from 12-lead ECGs. Body surface mapping appears to be more accurate but is no substitute for the additional information gained during an electrophysiological study, which provides detailed information about specific components of the re-entrant circuit needed for an ablation procedure.

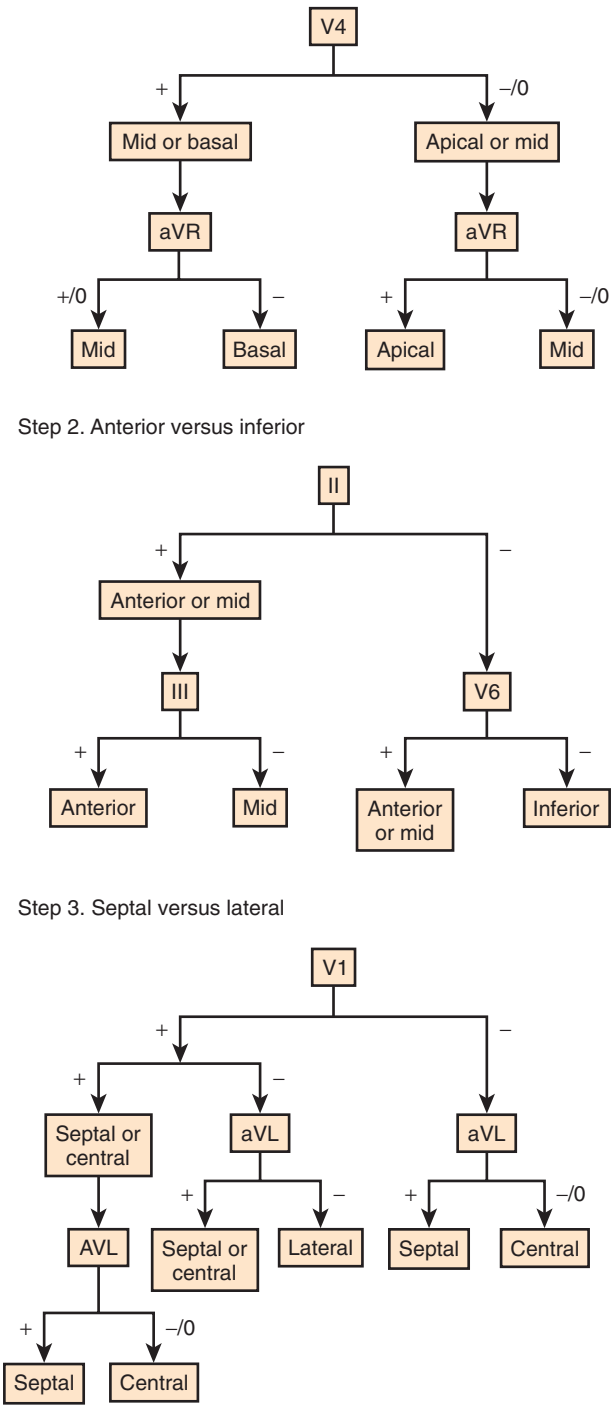

FIGURE 44-14 Algorithm for the localization of the origin of ventricular tachycardia. *(Modified from Kuchar DL, Ruskin JN, Garan H: Electrocardiographic localization of the site of origin of ventricular tachycardia in patients with prior myocardial infarction,* J Am Coll Cardiol *13:893–903, 1989.)*

Clinical Electrophysiology

The majority of ventricular tachycardias associated with heart disease are caused by re-entrant mechanisms and can usually be initiated and terminated by critically timed ventricular stimuli. This finding allows evaluation in the electrophysiology laboratory under controlled conditions. Induced arrhythmias are classified on the basis of duration and morphology. Arrhythmias that last 30 seconds or longer or that require earlier termination because of hemodynamic consequences are referred to as *sustained VT*. Sustained VT can be either monomorphic or polymorphic, depending on QRS morphology.

Programmed Stimulation for Initiation of Ventricular Tachycardia

Most laboratories proceed through a stepwise stimulation protocol for initiation of sustained VT. After ventricular pacing for 8 to 15 beats, a single extrastimulus is used to scan electrical diastole until it encounters refractoriness or reaches a very short coupling interval (<200 ms). Second, third, and, in some cases, fourth stimuli are then added. Two or more different basic pacing rates (drive cycles) typically are used (e.g., 100 and 150 beats/min) before premature stimulus delivery. If pacing at the right ventricular apex fails to induce VT, pacing at a second right ventricular site (e.g., the right ventricular outflow tract) generally is used. Some laboratories also use pacing from the left ventricle. The number of stimuli, basic drive cycles, and ventricular pacing sites varies among laboratories. In general, pacing with up to three extrastimuli at two cycle lengths and two sites induces VT in approximately 90% of patients who have had this arrhythmia spontaneously after MI.[73] The addition of rapid burst pacing, left ventricular stimulation, and programmed stimulation during isoproterenol infusion further increases sensitivity.

As the number of extrastimuli increases, the risk of initiating nonspecific, polymorphic VT (Figure 44-15) or VF increases. Limiting the closest coupling interval to greater than 200 ms reduces the risk of initiating ventricular fibrillation.[73] Although stimulation protocols are relatively sensitive for detecting an inducible VT, the precise number of required stimuli and stimuli-coupling intervals often varies over time such that a change in the number of extrastimuli required for initiation of VT is not necessarily a reliable indication that susceptibility to VT has changed.[74,75] VT initiated by isoproterenol infusion or with rapid burst pacing during isoproterenol administration, but not in response to coupled extrastimuli, is believed to be more likely caused by abnormal automaticity rather than by re-entry. Rarely, monomorphic VT may be induced by such measures in genetically based cardiac arrest syndromes.

Confirming the Diagnosis

In contrast to ECGs, in which atrial activity may be difficult to detect, direct recordings from the atrium always allow clear delineation of whether AV dissociation is present (Figure 44-16). When AV dissociation is present, the diagnosis is VT, with the rare exception of junctional ectopic tachycardia with ventriculoatrial (VA) block or rare forms of SVT without atrial tissue participation. The former arrhythmia, which occurs most commonly in the early postoperative period after repair of congenital heart disease in children, is rare in adults. When AV dissociation is present and depolarization of the bundle of His does not precede each QRS complex, the diagnosis of VT is unequivocal (see Figure 44-16). However, diagnostic dilemmas occasionally are encountered. If each QRS complex is followed by an atrial depolarization, VT with 1:1 conduction in a retrograde manner through the His-Purkinje system and the AV node must be distinguished from antidromic AV re-entry using an accessory pathway (see Chapters 25 and 43).

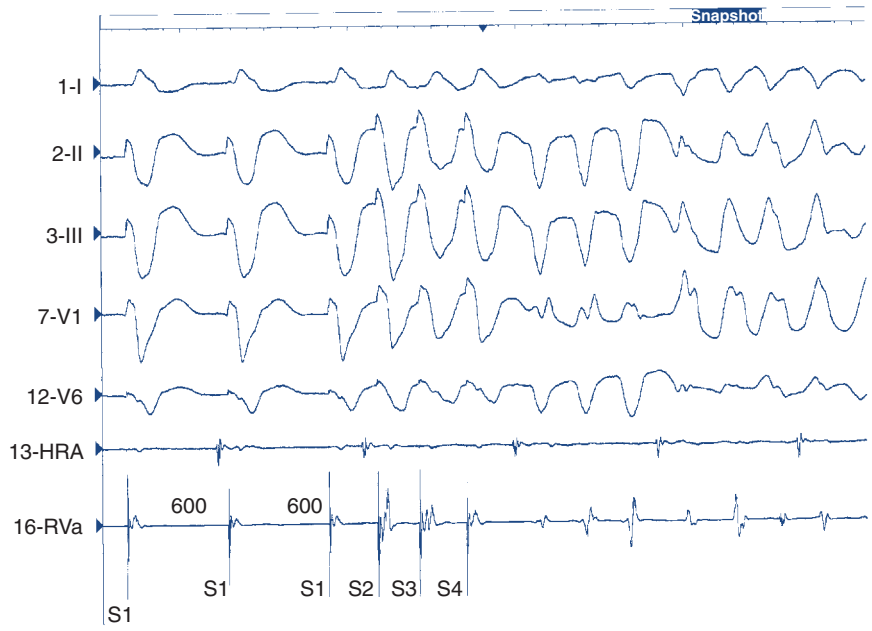

FIGURE 44-15 Initiation of polymorphic ventricular tachycardia by programmed stimulation from the right ventricular apex. From the top are surface electrocardiogram leads I, II, III, V1, and V6 followed by intracardiac recordings from the high right atrium (*HRA*) and right ventricular apex (*RVa*). From the left, the last two stimuli (*S1*) of a stimulus train at a cycle length of 600 ms (100 beats/min) followed by three consecutive premature stimuli (*S2, S3, S4*) are shown. This initiates polymorphic ventricular tachycardia.

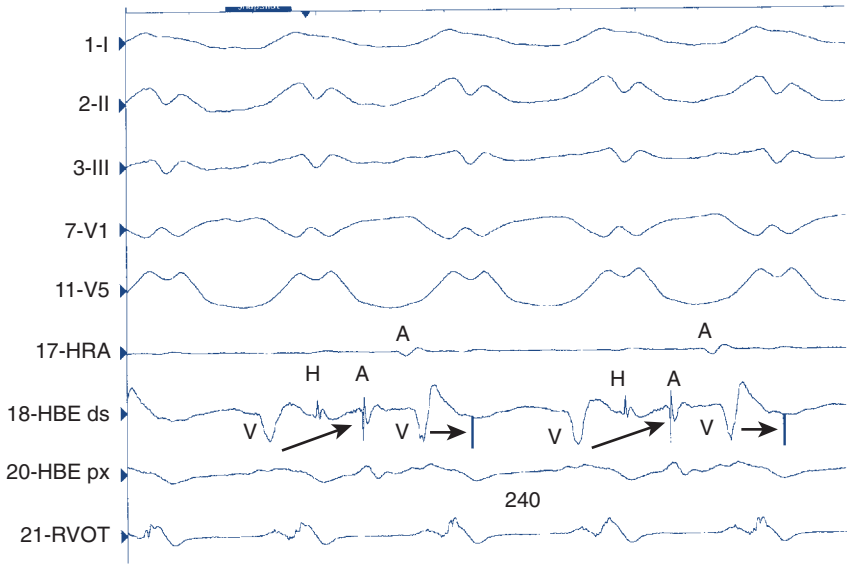

FIGURE 44-16 A tracing from the electrophysiology laboratory during sustained monomorphic ventricular tachycardia (VT). From the top are surface electrocardiogram leads I, II, III, V1, and V5 followed by intracardiac recordings from the high right atrium (*HRA*) and His bundle electrograms (*HBE*) catheters. The VT has a cycle length of 240 ms (250 beats/min) and a left bundle branch block, inferior axis QRS configuration. During VT, a 2:1 ventriculoatrial block is present; every other ventricular beat conducts in a retrograde manner into the bundle of His (*H*) and then to the atrium (*A*). Thus the atria and the bundle of His are not involved in causing the VT. *RVOT,* Right ventricular outflow tract.

Polymorphic Ventricular Tachycardia

Polymorphic VT (see Figure 44-15) indicates a continually changing ventricular activation sequence. Spontaneous polymorphic VT is most commonly caused by myocardial ischemia or TdP associated with Q-T interval prolongation. TdP is not reproducibly inducible in the electrophysiology laboratory, and electrophysiological studies are not warranted in the presence of active ischemia. Polymorphic VT also occurs in idiopathic VF, Brugada syndrome, and hypertrophic cardiomyopathy as well as other cardiomyopathies.

During ventricular stimulation, the significance of initiating polymorphic VT is often difficult to interpret. When sustained, polymorphic VT usually quickly deteriorates to VF. Nonsustained polymorphic VT is a nonspecific response to programmed stimulation that can be observed in patients who do not have a susceptibility to arrhythmias. Sustained polymorphic VT (lasting >30 seconds or requiring termination) is initiated less commonly in normal hearts and usually requires aggressive stimulation (three or more extrastimuli and relatively short stimulus coupling intervals of <200 ms). Initiation of polymorphic VT may be a marker of electrical instability in some situations. It is induced in approximately one third of patients who have been resuscitated from VF associated with depressed ventricular function and CAD.[76] In patients with prior infarction and inducible polymorphic VT, sustained monomorphic VT may become inducible after administration of IV procainamide.[74] Stabilization of a re-entry circuit by an antiarrhythmic drug is a possible mechanism, but the clinical relevance of this observation is unclear.

Initiation of polymorphic VT is of possible relevance in patients with suspected Brugada syndrome. Polymorphic VT, often induced with two or fewer extrastimuli, is induced in approximately 80% of patients with Brugada syndrome who have been resuscitated from cardiac arrest.[77] In a patient with other features of the syndrome, inducible polymorphic VT further supports the diagnosis. In patients with hypertrophic cardiomyopathy, sustained VT (usually polymorphic) is inducible in 66% of those who had a prior cardiac arrest compared with 23% of patients without a history of cardiac arrest or syncope.[78] The prognostic significance of inducible polymorphic VT in hypertrophic cardiomyopathy and other cardiomyopathies is controversial.[79]

Sustained Monomorphic Ventricular Tachycardia

During sustained monomorphic VT, each QRS complex resembles the preceding and following QRS (see Figure 44-16). The ventricles are repetitively depolarized in the same sequence. In contrast to polymorphic VT, which can occasionally be induced in the absence of a cardiac abnormality, spontaneous or inducible sustained monomorphic VT indicates the presence of either an abnormal region supporting re-entry or a focus of automaticity. Re-entry through regions of ventricular scar from MI is the most common cause. Other causes of scar-related VT include arrhythmogenic right ventricular cardiomyopathy, sarcoidosis, scleroderma, Chagas disease, ventricular incisions after cardiac surgery, or other cardiomyopathic processes.[78] Areas of scarring can often be identified as regions of low electrogram voltage during catheter mapping (Figure 44-17). On occasion, an incessant, idiopathic VT consistent with automaticity will cause tachycardia-induced cardiomyopathy.[80]

Bundle Branch Re-entry Ventricular Tachycardia

A bundle of His deflection is consistently present before each QRS during an uncommon type of VT caused by re-entry through the bundle branches (Figure 44-18). The re-entry wavefront circulates

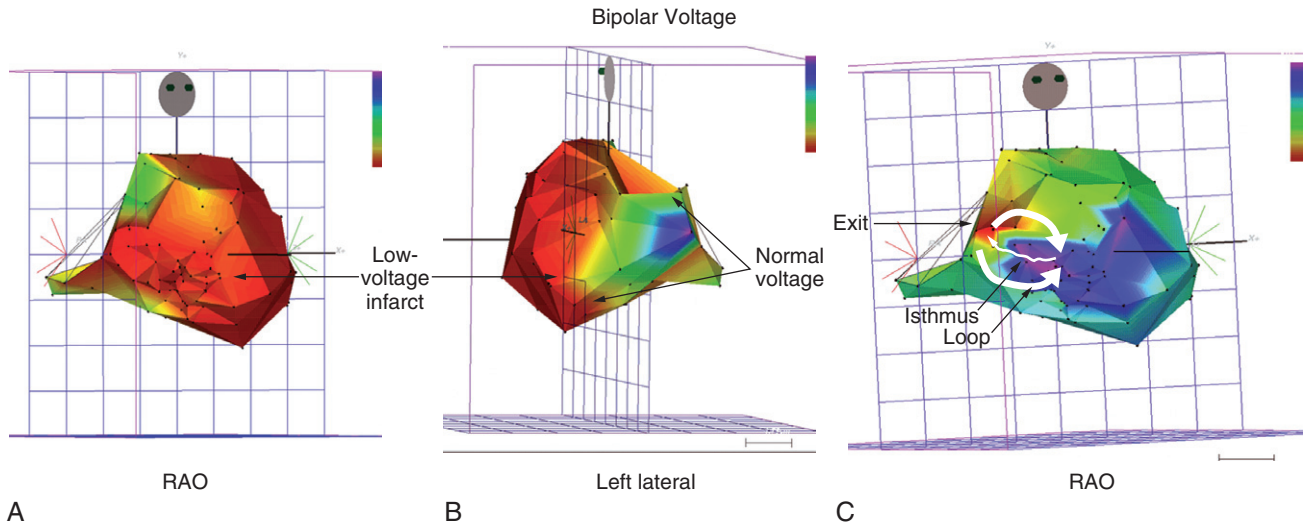

FIGURE 44-17 Mapping data from a patient with prior anterior wall infarction and ventricular tachycardia. **A** and **B,** Map of the left ventricle in right anterior oblique (*RAO*) and left anterior oblique projections obtained by moving a mapping catheter from point to point. The color coding indicates electrogram voltage; low-voltage areas are red, yellow, and orange; normal voltage is green, blue, and purple. A very large area of low voltage, identifying the infarct region, occupies the septum, apex, and anterior wall. **C,** Ventricular activation sequence map obtained during ventricular tachycardia. The color coding indicates the sequence of activation, and the circuit is indicated by the *white arrows*. The ventricular tachycardia circuit isthmus is located on the septum. The re-entry wavefront travels from apical to basal along the septum exiting near the base (*red*), then divides into two wavefronts that propagate superiorly and inferiorly and back to the isthmus.

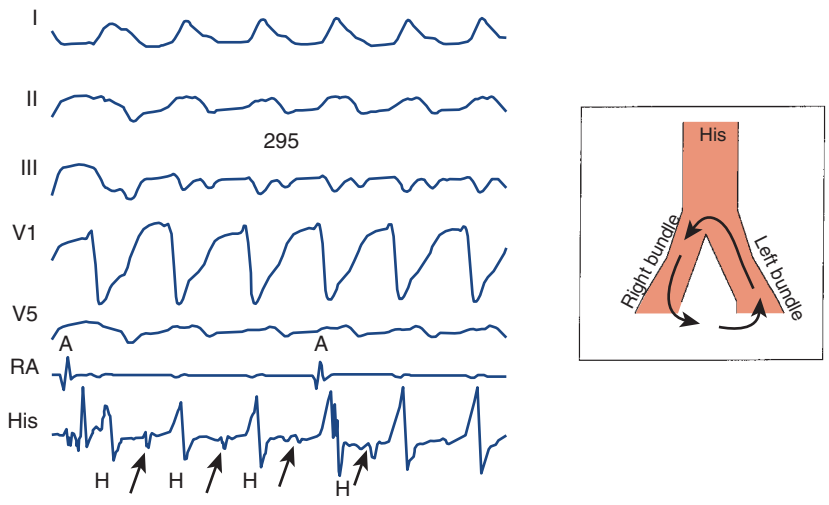

FIGURE 44-18 Bundle branch re-entry ventricular tachycardia. In the tracing at the left, surface electrocardiogram leads I, II, III, V1, and V5 are followed by recordings from the high right atrium (*RA*) and bundle of His, respectively. Tachycardia with a cycle length of 295 ms (203 beats/min) with a left bundle branch block–like configuration in lead V1 is present. Atrioventricular dissociation is present as indicated by the slower rate of atrial depolarization (*A*) in the right atrial tracing. Although the atria are dissociated, a bundle of His deflection (*H* followed by *arrow*) precedes each QRS complex. The mechanism is shown at *right*.

up the left bundle branch, down the right bundle branch, and then through the intraventricular septum to re-enter the left bundle.[81] Ventricular depolarization proceeds from the right bundle, giving rise to a tachycardia with an LBBB configuration. Rarely, the circuit revolves in the opposite direction (down the left bundle and back up the right bundle) or is confined to the fascicles of the left bundle branch system, giving rise to a tachycardia with an RBBB configuration. The diagnosis is confirmed by showing that the atria can be dissociated but that the bundle of His depolarization is closely linked to the circuit. Bundle branch re-entry should be particularly suspected when sustained monomorphic VT occurs in the absence of a large region of ventricular scar or infarction, such as in patients with valvular heart disease, cardiomyopathy, or muscular dystrophy and in association with

evidence of His-Purkinje system disease (intraventricular conduction delay) during sinus rhythm.[82,83] Most patients have an LBBB QRS pattern on the resting ECG during sinus rhythm and a history of dilated cardiomyopathy.

QRS Morphology of Induced Ventricular Tachycardia

The QRS morphology reflects the ventricular activation sequence and often provides an indication of the likely location of the arrhythmogenic region (Figure 44-19). For automatic or focal VT, activation spreads away from one arrhythmia focus; the QRS morphology is an excellent indicator of the location of the focus. The QRS morphology is less reliable as an indicator of the circuit location for scar-related VT but is still useful.

Scar-related re-entry circuits can be modeled as having surviving bundles of myocytes in the region of the scar. The depolarization of these strands is not detected in the surface ECG (Figure 44-20; also see Figure 44-17). These bundles may form narrow isthmuses in the re-entry circuit that are desirable targets for ablation. Recordings from these regions often reveal multiple low-amplitude potentials (Figure 44-21). During VT, the QRS is inscribed after the re-entry wavefront emerges from an isthmus at its exit and propagates across the ventricles. The QRS morphology indicates the location of the re-entry circuit exit (see Figure 44-20). Patients with scar-related VTs often have multiple morphologies of inducible VT; typically three or more are observed in patients referred for catheter ablation (Figure 44-22; also see Figure 44-20).[84] VT that has been observed to occur spontaneously is often referred to as *clinical VT*. Other VTs may arise from the same region of the scar or from anatomically separate regions. Some "nonclinical" VTs are subsequently observed to occur spontaneously or are initiated by anti-tachycardia pacing from an implanted defibrillator during an attempt to terminate a clinical VT.

Pacing for Ventricular Tachycardia Termination

Monomorphic VT can be reliably terminated by electrical cardioversion, which presumably depolarizes the re-entry circuit in advance of the circulating wavefront, which then collides with refractory tissue, extinguishing re-entry. Many monomorphic VTs can also be terminated by pacing that is faster than the tachycardia (overdrive pacing). The stimulated wavefront propagates to the re-entry circuit and then splits into wavefronts traveling in the same direction as the re-entry circuit wavefronts (orthodromic) and a second wavefront traveling in the opposite direction (antidromic). The antidromic wavefront collides with the next re-entry wavefront, and both are extinguished. The stimulated orthodromic wavefront continues through the circuit and may reset the circuit so that tachycardia continues (known as *resetting* or *entrainment*). If the orthodromic wavefront encounters refractory tissue and is extinguished, the tachycardia terminates. Pacing during tachycardia also has the possibility to accelerate the tachycardia or initiate VF (see Figure 44-22). Thus the capability for prompt defibrillation must be present when anti-tachycardia pacing is used.

Catheter Mapping of Ventricular Tachycardia

When VT is caused by increased automaticity, the source of the tachycardia often can be identified by activation sequence mapping (i.e., recording the activation sequence of the ventricle during VT). At the tachycardia focus, ventricular activation preceding the QRS onset is identified. Pacing at this site during sinus rhythm will produce a QRS morphology strikingly similar to that of the VT. Thus comparing the QRS morphology produced by ventricular pacing at different sites (pacemapping) can also localize the VT focus.

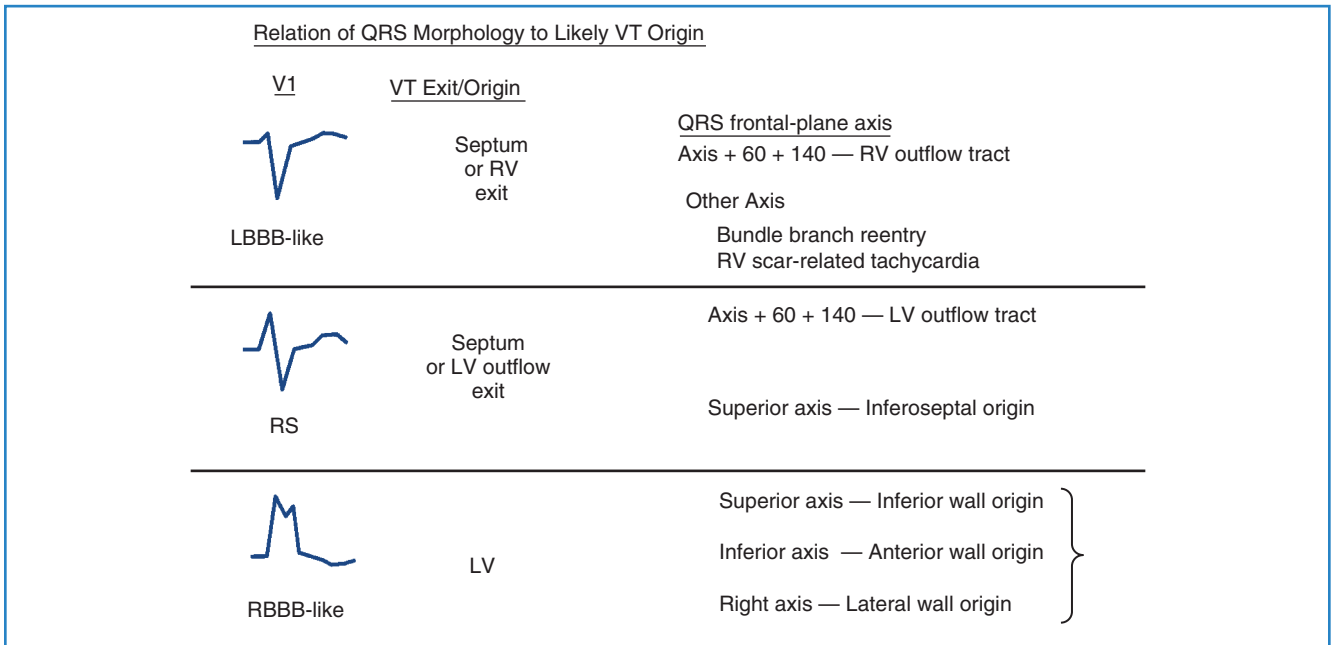

FIGURE 44-19 The QRS morphology suggests the likely origin and often the type of heart disease and ventricular tachycardia (VT). The morphology of lead V1 provides an initial indication of the likely ventricle of origin. Further refinement is based on the frontal-plane QRS axis, as shown at *right*. *LBBB*, Left bundle branch block; *LV*, left ventricle; *RBBB*, right bundle branch block; *RV*, right ventricle. See also Figure 44-14.

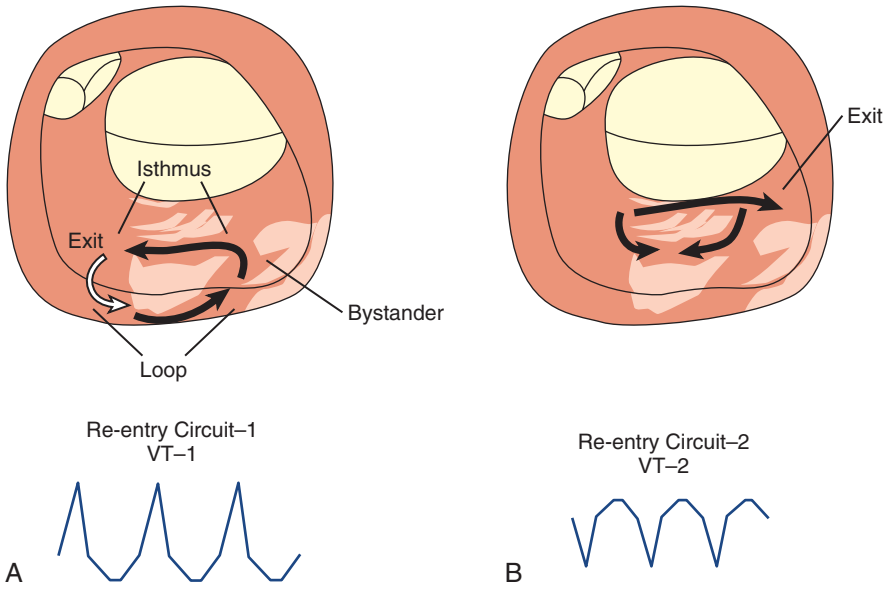

FIGURE 44-20 Schematic of the left ventricle with re-entry circuits in an inferior wall region of infarction. **A,** The re-entry wavefront propagates through a narrow isthmus and exits at the margin of the infarct to propagate across the ventricles, producing the QRS complex. After exiting, the circulating wavefront propagates along the margin of the infarct, then into the infarct, and to the proximal portion of the isthmus. The tissue along the infarct border forms a broad loop in the re-entry circuit. Bystander areas are adjacent to the infarct but not in the re-entry circuit, often giving rise to abnormal signals that misleadingly appear to be in the circuit based on timing and characteristics. **B,** Illustration of how the same infarct can give rise to a different re-entry circuit from that shown in **A**, creating multiple morphologies of monomorphic ventricular tachycardia (*VT*).

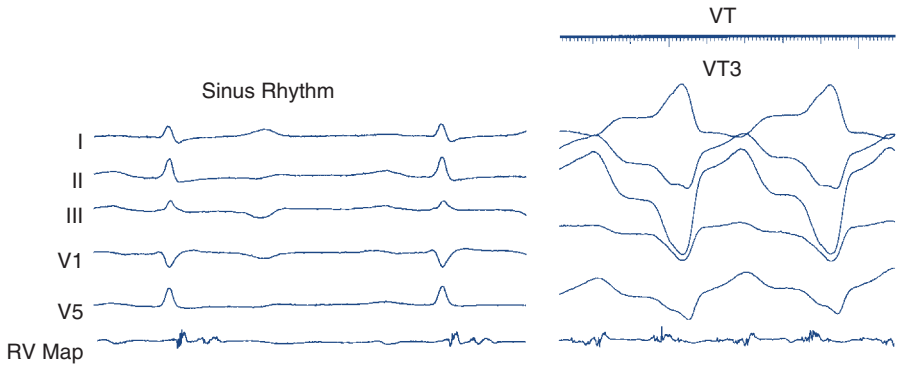

FIGURE 44-21 Recordings from a patient with arrhythmogenic right ventricular cardiomyopathy and ventricular tachycardia (*VT*). From the top are surface electrocardiogram leads I, II, III, V1, and V5 and an intracardiac recording from the mapping catheter positioned at the anterobasal right ventricle near the tricuspid annulus (*RV Map*). During sinus rhythm, the right ventricular electrograms recorded from this area are low amplitude and fractionated (multiple deflections), consistent with an area of scar with surviving myocyte bundles. Induced VT (*right*) had a rate of 150 beats/min. Fractionated potentials are recorded preceding the QRS complex, consistent with an isthmus in the re-entry circuit.

Activation sequence mapping is more difficult for re-entrant VTs. The area of activation before QRS onset usually identifies an area that is near the re-entry circuit exit. Low-amplitude signals are often recorded from sites in the circuit that are proximal to the exit. Often, only portions of the circuit are located in the endocardium because other segments are deep to the endocardium or epicardial in location and cannot be sampled by an endocardial catheter.

Pacing during tachycardia can be used to determine the re-entry circuit location (entrainment mapping). Pacing trains that capture, but have no effect on, tachycardia often indicate that the pacing site is not in the tachycardia circuit. Stimulated wavefronts that propagate to the circuit, enter the circuit, and propagate through the circuit will reset the re-entry circuit in a characteristic manner. Whether this occurs depends on the timing of the stimulus relative to activation in the circuit. The wavefront must reach a portion of the circuit after that area has recovered excitability from the preceding wavefront. A single pacing stimulus may reset the tachycardia while a train of several stimuli continually resets the tachycardia, a response known as *entrainment*.[84]

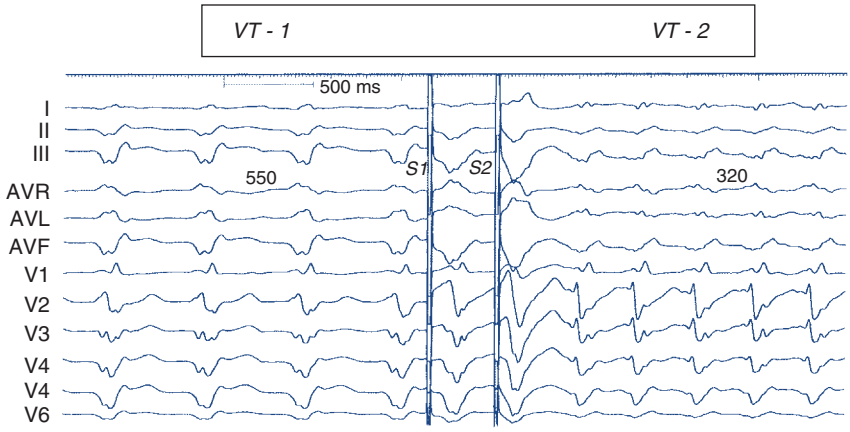

FIGURE 44-22 Twelve-lead electrocardiogram recording two morphologies of ventricular tachycardia (*VT*) in a patient with prior infarction. The initial VT (*VT-1*) has a cycle length of 550 ms. Two premature ventricular stimuli (*S1, S2*) initiate monomorphic *VT-2*, which is substantially faster (cycle length of 320 ms) with a different QRS morphology.

Management

Principles of Practice

It is convenient to divide sustained VT in patients with structural heart disease into "syndromes," which usually can be identified by examining the ECG recorded at the initiation of tachycardia (usually recorded as a single-lead rhythm strip), the 12-lead ECG recorded shortly after treatment of the acute rhythm disturbance, and by considering the clinical context in which this arrhythmia arises.

Sustained monomorphic VT occurs in patients with prior left ventricular scarring (most commonly from prior MI); most often arises without a specific predisposing event, often at rest or with modest activity; and generally is not preceded by symptomatic, electrocardiographic, or enzymatic evidence for myocardial ischemia or MI.[85] Sustained VT is observed in a circadian pattern similar to that of SCD and MI, with a predilection for the morning hours (at least in patients with implanted defibrillators).[86,87] It tends to occur in clusters, suggesting that neurohumoral, in particular sympathetic, activation may contribute indirectly to the instantaneous probability of VT occurring in a susceptible patient.[87,88] On occasion, sustained VT occurs many times within a brief period, a syndrome commonly termed *electrical storm.* It is often arbitrarily defined as more than two or three episodes of sustained VT in a 24-hour period. Patients with this syndrome are perceived to have a very poor prognosis, although aggressive therapy, particularly β-blockers and amiodarone, may allow a prognosis similar to that for patients who do not develop electrical storm, as has been shown in observational studies.[88,89] A related syndrome is that of polymorphic VT in patients with severe ventricular scarring, occurring most often in the setting of a generalized cardiomyopathy such as dilated idiopathic cardiomyopathy, or that associated with hypertrophic cardiomyopathy, valvular disease, or hypertensive cardiomyopathy. Although the precipitating events for this type of VT are also not clearly understood, they may be more likely to occur during physical exercise, elevated sympathetic tone, or episodes of worsening heart failure. The management of these patients, in addition to antiarrhythmic therapy, may also be aggressively directed toward improving myocardial function and decreasing sympathetic tone, for example, with afterload reduction, preload reduction, and sympathetic blockade.

A particular pattern of sustained ventricular arrhythmias can be observed in patients with myocardial ischemia, acute MI, or severe CAD. In these patients, VT arises more frequently under conditions of physical or psychological stress; it may be preceded by chest pain or other symptoms of myocardial ischemia; and the ECG before or after treatment of the VT frequently shows sinus tachycardia, ST-segment depression, or signs of MI. The *electrocardiographic signature* of this arrhythmia (Figure 44-23) typically involves a relatively short Q-T interval as well as the initiating beat of tachycardia being closely coupled to the last normal beat, which immediately ushers in polymorphic VT that may rapidly degenerate to VF. Patients observed to have this pattern should be immediately and thoroughly investigated for myocardial ischemia; treatment directed at ischemia, rather than only at the arrhythmia, is often sufficient to prevent recurrence.[90,91]

The syndrome of polymorphic VT associated with prolonged repolarization is discussed in detail in other sections of this book. However, it should be noted that sustained VT in association with delayed repolarization (TdP) may manifest as relatively monomorphic VT, especially at its outset (Figure 44-24). The electrocardiographic clues to the etiology as being related to abnormal and delayed repolarization rather than to an underlying "arrhythmogenic scar" are also to be found in the initiating sequence of tachycardia. Delayed repolarization–related VT is generally associated with Q-T interval prolongation, a pause-dependent initiating sequence, and a relatively long coupling interval between the last normal beat and the first beat of tachycardia. This beat typically falls on the late portion of the T wave or T-U complex of a beat with prolonged repolarization. These arrhythmias should be carefully distinguished from those caused by an arrhythmogenic scar because they can be effectively treated with IV magnesium and by repletion of potassium, as indicated, by increasing the heart rate, and by treating the underlying disturbance leading to prolonged repolarization, which is often drug therapy that prolongs repolarization, causes bradycardia, or both. In patients with structural heart disease, the precipitating causes are usually antiarrhythmic drugs that prolong repolarization, hypokalemia or hypomagnesemia, or bradycardia.

Acute Treatment of Sustained Ventricular Tachycardia

The acute management of VT should first be directed at restoring effective circulation, as outlined in the International Guidelines

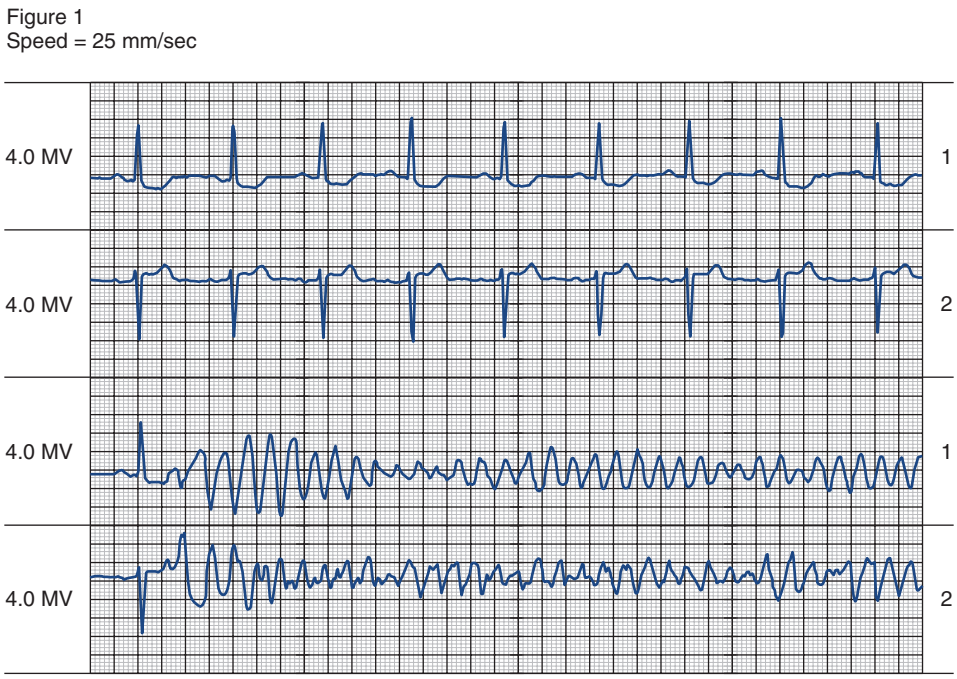

FIGURE 44-23 "R on T" ventricular premature beat inducing ventricular fibrillation from a 70-year-old man with severe triple-vessel coronary disease. Note that the Q-T interval is relatively short and that the premature ventricular contraction inducing tachycardia has a short coupling interval to the last normal beat.

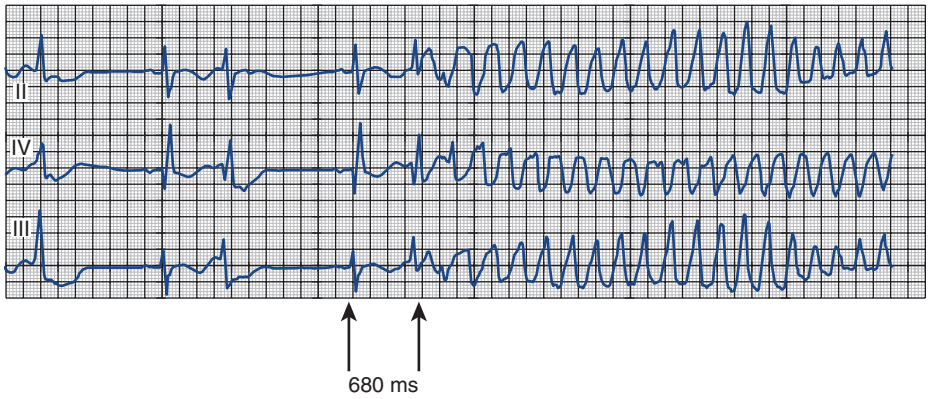

FIGURE 44-24 Electrocardiographic signature of polymorphic ventricular tachycardia (VT) with delayed repolarization from a patient taking sotalol and with hypokalemia. Note the pause-dependent onset of VT with a prolonged Q-T interval on the beat initiating tachycardia.

for Advanced Cardiac Life Support.[92] In brief, all patients with substantial hemodynamic compromise, including diminished level of consciousness, hypotension, and clinical signs suggesting cerebral or vital organ hypoperfusion, heart failure, or signs or symptoms of myocardial ischemia, should be treated with urgent synchronized cardioversion. Of note, carefully performed electrical cardioversion is almost completely effective for the treatment of VT, if it can be provided promptly, and is associated with extremely low risk. The perceived need for anesthesia is often seen as a limitation to acute cardioversion but can generally be performed by conscious sedation without intubation or serious anesthetic risk. If drug therapy is chosen either as initial treatment of VT or therapy to prevent recurrences immediately after electrical cardioversion, IV procainamide and IV amiodarone are recommended.[92] Careful monitoring for hypotension and bradycardia, which may be caused by the antiarrhythmic drug therapy, is required.

A large evidence base of randomized clinical trials is not available to assist the clinician in the treatment of patients immediately following successful conversion from sustained VT to sinus rhythm. The immediate risk of recurrence will vary with the clinical context and be generally relatively low in patients with stable CAD and left ventricular dysfunction with monomorphic VT. It is higher in patients with acute hemodynamic compromise independent of the tachycardia; ongoing myocardial ischemia; or other metabolic disturbances found in postoperative states,

sepsis, pneumonia, or hypoxia. In patients with nonischemic cardiomyopathies, therapy specifically directed at blunting the effects of sympathetic activation on the heart with intravenous β-blockers, or stellate ganglion block, is an often neglected but important aspect of therapy.[89] Limited, controlled clinical trials suggest that IV amiodarone and bretylium are likely effective at preventing recurrent VT.[93] Bretylium, however, is no longer commercially available. In a randomized, multi-center trial in patients with electrical storm (defined as more than two episodes of sustained VT in a 24-hour period [mean, 4.93 episodes] resistant to treatment with IV lidocaine and procainamide), patients were randomized to blinded treatment with IV amiodarone (1000 mg/day), IV bretylium (2.5 g/day), and low-dose amiodarone (125 mg/day).[93] Although interpretation of this study has been complicated by the fact that many patients in the low-dose amiodarone group and the bretylium group received open-label treatment with unblinded IV amiodarone, the results suggest that IV amiodarone is efficacious at reducing the likelihood of recurrent VT. The median number of episodes was 0 in the first 12 hours after treatment with amiodarone and 0.48 during the entire study period. The median time to termination of incessant VT was 4.23 hours after the initiation of IV amiodarone therapy. No comparable trials of class I drugs or sotalol in electrical storm have been conducted so far. Extrapolation from clinical trials of prophylactic therapy suggests that class I drugs (sodium channel blockers) should be avoided in patients with frequently recurring VT or VF.[92]

In the Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients (OPTIC) study in patients with implanted defibrillators, amiodarone was superior to sotalol or β-blockers in preventing appropriate ICD therapies for VT or VF.[94]

Although no randomized clinical trials of sedation in patients with frequently recurring VT have been performed, anecdotal experience suggests that vigorous sedation is an important adjunct in the treatment of this syndrome. As an acute therapy, IV sotalol, IV flecainide, and IV procainamide have all been reported to be effective in the acute termination of sustained VT.[92] Given the negative inotropic and proarrhythmic risks of drugs with sodium channel–blocking activity, it seems prudent to use such drugs with great care, if at all, in patients with structural heart disease and sustained VT, especially in the context of CAD.

Once patients have been stabilized with respect to the acute event, attention can be turned to investigating the underlying cardiac pathology and assessing and optimizing therapy for left ventricular dysfunction and myocardial ischemia.

Impact of Clinical Trials

A recent explosion of epidemiologic insights and information from randomized trials has changed clinical practice in the treatment of VT (Box 44-1). For several years, the similarity of patient profiles (stratifying by left ventricular ejection fraction [LVEF], previous MI) and risk for sudden cardiac death and sustained VT has been apparent.[85] In 1975, Schaffer et al reported on 234 patients after successful resuscitation of cardiac arrest. Over a follow-up period of 51 months, 89 episodes (approximately 38%) of recurrent cardiac arrest or death occurred.[95] A similar rate of recurrence was noted by Myerburg et al in 1984—the recurrence rate for cardiac arrest was 10% the first year after arrest and 5% per year in each of the following 3 years.[96] In 1993, the Cardiac Arrest in Seattle: Conventional versus Amiodarone Drug Evaluation (CASCADE) study reported an improvement in out-of-hospital cardiac arrest survival in patients randomized to amiodarone (versus conventional antiarrhythmic therapy) of 78% at 2 years and 52% at 4 years.[97] Therapeutic options drastically shifted in the 1980s with the emergence of ICDs. Several recent trials have compared the efficacy of antiarrhythmic therapy and ICDs for overall mortality in patients who have sustained a VT event.

In 1995, Dutch investigators randomized 60 patients with previous MI, cardiac arrest secondary to VT or VF, and inducible ventricular arrhythmia at electrophysiological study to conventional therapy (class IA, IC, and III drugs) or the ICD.[98] The LVEF was approximately 30% in each group. Drug efficacy was assessed by serial drug testing, and nonresponders were given an ICD. An imbalance of coronary revascularization occurred in the conventional therapy group (10%) and the ICD group (26%). Although the numbers of clinical endpoints (death, prolonged syncope with circulatory arrest, and congestive heart failure requiring transplantation) were small, the outcome favored treatment with an ICD ($P < .02$).

The Cardiac Arrest Study Hamburg (CASH) began enrollment in 1987 and randomized patients to antiarrhythmic therapy (propafenone, metoprolol, or amiodarone) or ICD.[99] Entry criteria included survivors of cardiac arrest secondary to VT (83%) or VF (16%). All patients underwent electrophysiological testing. The primary endpoint was total mortality, with secondary endpoints of VT recurrence, need to discontinue medical therapy, recurrence of cardiac arrest, and need for cardiac transplantation. In 1992, the CASH Safety and Monitoring Board discontinued the propafenone randomization arm because of an excess of SCD, recurrent cardiac arrest, and recurrent VT (all secondary endpoints) in the patients taking class Ic drugs compared with the ICD arm ($P < .05$) despite no differences in the total mortality rate. LVEF averaged for all four groups was more than 40%. The other three treatment arms continued to recruit patients. The final results showed a 36.4% mortality rate in the ICD group and a 44.4% mortality rate in the metoprolol and amiodarone groups combined. A one-sided t test (which would have amplified any benefit of the ICD) had a P value of .081 as the reported significance value.

Two larger studies, having slightly more heterogeneous populations, also address the issue of ICD versus antiarrhythmic therapy in patients with symptomatic VT. The Canadian Implantable Defibrillator Study (CIDS) randomized 659 patients with documented VF, out-of-hospital cardiac arrest, symptomatic VT, or syncope with inducible VT at electrophysiology study to ICD or amiodarone therapy.[100] Entry criteria in approximately 50% of each group were VF or cardiac arrest. Mean LVEF was 33% in each group. The primary endpoint was all-cause mortality. An intention-to-treat analysis was used to analyze the data in a one-sided t test. On treatment analysis showed 94% of those randomized to ICD actually received an ICD, and 85% of patients randomized to amiodarone were still on therapy at their 5-year follow-up. Although β-blocker use was a potential confounder (23% in the amiodarone group, 53% in the ICD group), the overall mortality rate (10.2% per year) in the amiodarone group was not significantly higher than that in the ICD group (8.3%, $P = .142$).

The largest study to date has been the Antiarrhythmics versus Implantable Defibrillator (AVID) study, which randomized 1016 patients with resuscitated VF, sustained VT with syncope, and sustained VT with hemodynamic compromise to antiarrhythmics or to ICD implantation.[101] The 6035 patients were screened, with 17% randomized. Of the randomized patients, 45% had VF and

Box 44-1 Indications for Implantable Cardioverter Defibrillator Therapy for Patients at Risk of Sustained VT

CLASS I

1. ICD therapy is indicated in patients who are survivors of cardiac arrest due to VF or hemodynamically unstable sustained VT after evaluation to define the cause of the event and to exclude any completely reversible causes. *(Level of Evidence: A)*
2. ICD therapy is indicated in patients with structural heart disease and spontaneous sustained VT, whether hemodynamically stable or unstable. *(Level of Evidence: B)*
3. ICD therapy is indicated in patients with syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced at electrophysiological study. *(Level of Evidence: B)*
4. ICD therapy is indicated in patients with LVEF <35% due to prior MI who are at least 40 days post-MI and are in NYHA functional class II or III. *(Level of Evidence: A)*
5. ICD therapy is indicated in patients with nonischemic DCM who have an LVEF ≤35% and who are in NYHA functional class II or III. *(Level of Evidence: B)*
6. ICD therapy is indicated in patients with LV dysfunction due to prior MI who are at least 40 days post-MI, have an LVEF <30%, and are in NYHA functional class I. *(Level of Evidence: A)*
7. ICD therapy is indicated in patients with nonsustained VT due to prior MI, LVEF <40%, and inducible VF or sustained VT at electrophysiological study. *(Level of Evidence: B)*

CLASS IIA

1. ICD implantation is reasonable for patients with unexplained syncope, significant LV dysfunction, and nonischemic DCM. *(Level of Evidence: C)*
2. ICD implantation is reasonable for patients with sustained VT and normal or near-normal ventricular function. *(Level of Evidence:C)*
3. ICD implantation is reasonable for patients with HCM who have one or more major risk factors for SCD. *(Level of Evidence: C)*
4. ICD implantation is reasonable for the prevention of SCD in patients with ARVD/C who have one or more risk factors for SCD. (Level of Evidence: C)
5. ICD implantation is reasonable to reduce SCD in patients with long QT syndrome who are experiencing syncope and/or VT while receiving β-blockers. *(Level of Evidence: B)*
6. ICD implantation is reasonable for non-hospitalized patients awaiting transplantation. *(Level of Evidence: C)*
7. ICD implantation is reasonable for patients with Brugada syndrome who have had syncope. *(Level of Evidence: C)*
8. ICD implantation is reasonable for patients with Brugada syndrome who have documented VT that has not resulted in cardiac arrest. *(Level of Evidence: C)*
9. ICD implantation is reasonable for patients with catecholaminergic polymorphic VT who have syncope and/or documented sustained VT while receiving β-blockers. *(Level of Evidence: C)*
10. ICD implantation is reasonable for patients with cardiac sarcoidosis, giant cell myocarditis, or Chagas disease. *(Level of Evidence: C)*

CLASS IIB

1. ICD therapy may be considered in patients with nonischemic heart disease who have an LVEF of ≤35% and who are in NYHA functional class I. *(Level of Evidence: C)*
2. ICD therapy may be considered for patients with long QT syndrome and risk factors for SCD. *(Level of Evidence: B)*
3. ICD therapy may be considered in patients with syncope and advanced structural heart disease in whom thorough invasive and noninvasive investigations have failed to define a cause. *(Level of Evidence: C)*
4. ICD therapy may be considered in patients with a familial cardiomyopathy associated with sudden death. *(Level of Evidence: C)*
5. ICD therapy may be considered in patients with LV noncompaction. *(Level of Evidence: C)*

CLASS III

1. ICD therapy is not indicated for patients who do not have a reasonable expectation of survival with an acceptable functional status for at least 1 year, even if they meet ICD implantation criteria specified in the class I, IIa, and IIb recommendations above. *(Level of Evidence: C)*
2. ICD therapy is not indicated for patients with incessant VT or VF. *(Level of Evidence: C)*
3. ICD therapy is not indicated in patients with significant psychiatric illnesses that may be aggravated by device implantation or that may preclude systematic follow-up. *(Level of Evidence: C)*
4. ICD therapy is not indicated for NYHA class IV patients with drug-refractory congestive heart failure who are not candidates for cardiac transplantation or CRT-D. *(Level of Evidence: C)*
5. ICD therapy is not indicated for syncope of undetermined cause in a patient without inducible ventricular tachyarrhythmias and without structural heart disease. *(Level of Evidence: C)*
6. ICD therapy is not indicated when VF or VT is amenable to surgical or catheter ablation (e.g., atrial arrhythmias associated with the Wolff-Parkinson-White syndrome, RV or LV outflow tract VT, idiopathic VT, or fascicular VT in the absence of structural heart disease). *(Level of Evidence: C)*
7. ICD therapy is not indicated for patients with ventricular tachyarrhythmias due to a completely reversible disorder in the absence of structural heart disease (e.g., electrolyte imbalance, drugs, or trauma). *(Level of Evidence: B)*

VT, *Ventricular tachycardia;* ICD, *implantable cardioverter-defibrillator;* VF, *ventricular fibrillation;* LVEF, *left ventricular ejection fraction;* MI, *myocardial infarction;* NYHA, *New York Heart Association;* DCM, *dilated cardiomyopathy;* LV, *left ventricular;* HCM, *hypertrophic cardiomyopathy;* SCD, *sudden cardiac death;* ARVD/C, *arrhythmogenic right ventricular dysplasia/cardiomyopathy;* CRT-D, *cardiac resynchronization therapy/defibrillation;* RV, *right ventricular.*

Modified from Epstein AE, DiMarco JP, Ellenbogen KA, et al: ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: American College of Cardiology/American Heart Association Task Force on Practice Guidelines developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons, J Am Coll Cardiol *51:1–62, 2008.*

55% had VT at entry. The patients randomized to antiarrhythmics could be further randomized to electrophysiology-guided treatment with sotalol or empiric amiodarone at the discretion of the investigator. LVEF was similar in each group (31% and 32%). An on-treatment analysis showed that 98% of the ICD group received an ICD. In the antiarrhythmic group, 85% received empiric amiodarone, 11% received amiodarone after not responding to sotalol, and 2.6% were treated with sotalol. The study was terminated early in April 1997 because of the recommendation of the Data and Safety Monitoring Board; unlike the CIDS study, the ICD group showed a significant improvement in total mortality rate over an average follow-up of 18 months (15.8% in the ICD group, 24% in the antiarrhythmic group; $P = .02$).

In summary, the available epidemiologic and clinical trial data evoke several principles applicable to patients with sustained symptomatic VT. The ICD prevents arrhythmic death only. The majority of participants in these trials with low LVEF and structural heart disease have competing modes of death. Antiarrhythmics may have some positive effect on congestive heart failure (amiodarone) or actually worsen arrhythmic death via proarrhythmia (propafenone in the CASH study). Investigator and subject bias is unavoidable in a trial that is not blinded to the treatment arm. Furthermore, a heterogeneous study population (as in the AVID and CIDS studies) may not have the same treatment effect across all strata in the group. Domanski et al reported a differential effect of antiarrhythmics and ICD therapy from the AVID database based on strata of left ventricular EF.[91,102] In patients with LVEF greater than 35%, the two therapies showed no difference in survival, suggesting that all the treatment effects came from enrolled patients with LVEF less than 35%. Despite the inherent limitations of the published clinical trials, the largest studies favor ICD therapy in patients whose primary mortality risk is from symptomatic ventricular tachyarrhythmia. Box 44-1 lists current indications and contraindications to ICD therapy.

In summary, the long-term management of patients with sustained VT and heart disease is very similar to that for patients resuscitated from cardiac arrest.[103] A retrospective analysis of outcome in patients with "tolerated" VT and VT without cardiac arrest in the AVID trial suggests that their outcome is very similar to that in patients with VF or VT with serious cardiac compromise. It seems reasonable to expect that most patients with sustained symptomatic VT or VF, regardless of the severity of symptoms, have a poor prognosis and should be managed as outlined in the section on evidence-based therapy in VF. However, patients with relatively preserved LV function (EF > 40%) and symptomatic VT without cardiac arrest were not included in the randomized trials of ICD therapy. Whether such patients would have had improved survival with ICD therapy compared with "best medical therapy" (which should almost certainly include β-blockers and amiodarone) is unknown. Subanalyses of the CIDS and AVID studies suggest that a benefit of the ICD over amiodarone, in the medium term, may not be observed in patients with LVEF greater than 35% and symptomatic VT.[102,104] These latter patients can be reasonably treated with either an ICD or oral amiodarone and a β-blocker.[105] Long-term management of patients with sustained VT without heart disease is detailed in the next section.

Impact of New Device Technology

Concurrent with these important secondary and primary prevention clinical trials have been important technologic advances in device technology.[106] These are discussed in greater detail in Section IX of this text. Of greatest importance for patients with sustained VT and left ventricular dysfunction is the advent of biventricular pacing. Biventricular pacing has shown benefits in patients with drug-refractory congestive heart failure and coexisting intraventricular and interventricular dyssynchronous wall motion.[107] These patients have been largely identified by the presence of prolonged QRS complexes, although other techniques of wall motion analysis are increasingly being applied. Thus patients with bundle branch block, particularly with QRS complexes greater than 0.15 seconds and first-degree AV block, which can further compromise ventricular filling, are candidates for this technique. Atrial fibrillation (AF) has been an important coexisting arrhythmia in many of these sustained VT patients and causes progressive heart failure and increased mortality rates. New AF therapies for prevention and termination are now available in ICD devices. Thus alternative-site pacing such as dual-site atrial pacing, novel preventive pacing algorithms for atrial premature beat suppression, anti-tachycardia pacing for atrial tachycardia termination, and AF therapies are now available. Figure 44-25 shows an ECG from an older patient with refractory persistent AF, sustained VT with syncope, and refractory congestive heart failure. A four-chamber ICD device (Insync III; Medtronic, Minneapolis, MN) with biventricular pacing and dual-site right atrial pacing leads was inserted for the management of these clinical syndromes.

Data from recent trials such as the Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure (COMPANION) study confirms the morbidity and mortality benefits of biventricular pacing. The availability of new technology and supportive evidence that can reduce the risk of competing (i.e., nonsudden) death in the patient with sustained VT and heart disease provide an important impetus to the primary use of ICD devices in patients with left ventricular dysfunction and congestive heart failure.

Impact of Catheter Ablation Techniques

Catheter ablation technologies have been applied for ablation of sustained and hemodynamically stable VT in patients with and without organic heart disease who could undergo catheter mapping.[108,109] Radiofrequency ablation remains the mainstay of this approach. In addition to ECG morphology, catheter mapping with contact catheter and noncontact three-dimensional mapping techniques has facilitated determination of the exact localization of the VT substrate. (The details of these techniques are reviewed in other chapters in this text.) These methods now permit rapid mapping and accurate geometric localization of these diseased tissues in a few or even one tachycardia cycle. Thus increasingly hemodynamically unstable VT episodes can be treated by ablative interventions.[110] Radiofrequency energy delivered by contact electrodes with or without cooled-tip technology can now produce moderate-sized lesions in diseased ventricular myocardium. Thus VT ablation can temporarily suppress, reduce the frequency of, and even eliminate recurrent sustained VT in selected patients. It can reduce the need for ICD therapies.[111]

However, it is not curative, and VT recurrences often occur during long-term follow-up.[112] Thus VT ablation in patients with organic heart disease is a potential management tool in specific clinical scenarios. It is valuable in drug-refractory incessant VT or electrical storm unresponsive to medical therapy. In patients with frequent, recurrent ICD shocks despite antiarrhythmic drug

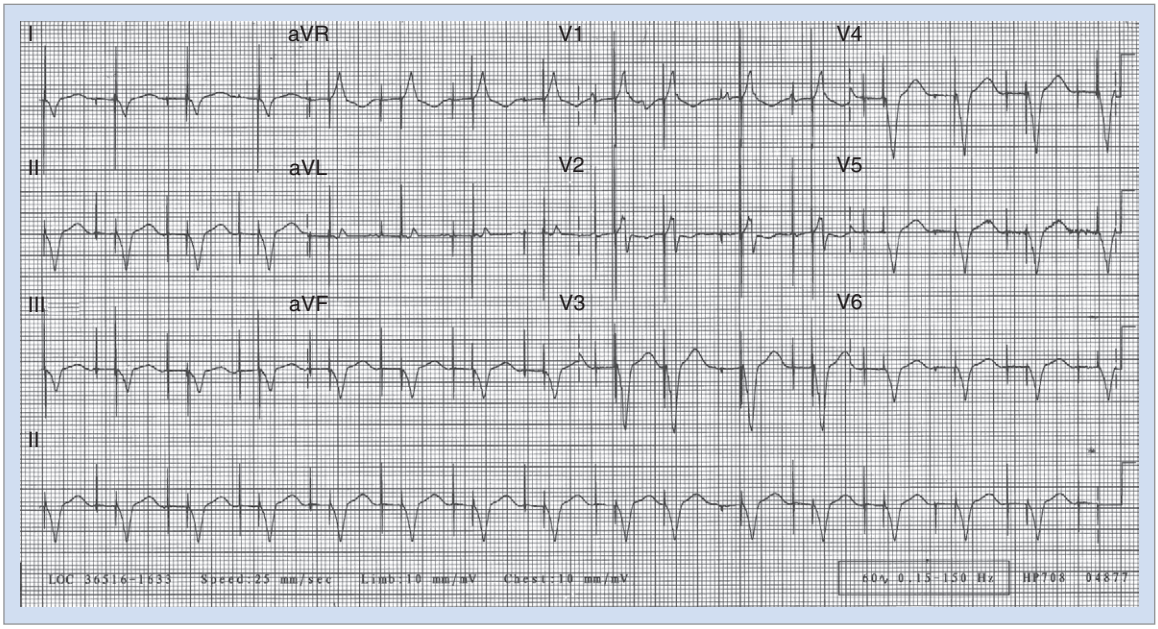

FIGURE 44-25 Twelve-lead electrocardiogram of a patient with refractory congestive heart failure, ventricular tachycardia, and refractory atrial fibrillation who had a four-chamber implantable cardioverter-defibrillator system. Dual-site right atrial and biventricular pacing leads were placed with a Medtronic InSync III (Minneapolis, MN). Control of atrial fibrillation and heart failure improved with device therapy.

therapy, VT ablation will reduce the need for these therapies. Finally, it can be used in a patient who is intolerant to antiarrhythmic drug therapy when frequent VT recurrences must be addressed. However, VT ablation should be used in conjunction with ICD therapy, whenever possible, to provide backup rescue therapies for recurrent VT or VF.

Impact on Patient Selection

The selection of the first line of therapy in VT management is now defined by the clinical disease, intercurrent factors, and arrhythmia characteristics. Management of the underlying disease and associated conditions such as heart failure and ischemia is an integral part of patient management. Arrhythmia frequency is an important consideration. Frequent or incessant VT requires evaluation for intercurrent precipitating factors such as electrolyte abnormalities, enhanced sympathetic tone, hypoxia, or uncontrolled ischemia. Correction of these factors often converts this intolerable VT frequency to "occasional event" status. The hemodynamic impact of the arrhythmia also determines the urgency of the response. Hemodynamic collapse requires urgent use of both pharmacologic and nonpharmacologic therapies. In more stable VT episodes, drug therapy, mapping and ablation, and antitachycardia pacing become competitive options. With reduction of event frequency or in patients with sporadic VT episodes, a longer term management strategy is appropriate for implementation. Prevention of SCD with ICD backup is an essential part of the therapeutic prescription in these patients. Antiarrhythmic drugs and catheter ablation can play a supportive role in this phase of management to reduce VT event rates, make it amenable to pacing therapies, and prevent frequent symptoms related to the arrhythmia and ICD therapies.[113]

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CHAPTER 45

Ventricular Tachycardia and Ventricular Fibrillation Without Structural Heart Disease

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Definition and Classification, Principles of Practice: Kelley Anderson
Epidemiology, Clinical Electrophysiology, Management: Kelley Anderson and Sanjeev Saksena
Electrocardiographic Features: Bruce D. Lindsay

Idiopathic ventricular tachycardia (IVT) and idiopathic ventricular fibrillation (IVF) have been intermittently recognized and reported since the early 1900s. Since Vakil's classic description of ventricular aneurysms and their association with ventricular tachycardia (VT), early literature defined VT as being associated with heart disease.[1-3] The occurrence of paroxysmal VT in young patients and occasionally those with apparently healthy hearts, emerged from time to time.[4,5] The availability of electrocardiographic recordings focused attention on the region of origin of ventricular arrhythmias, including ectopic beats as well as VT.[6,7] In 1974, in a careful review of the literature of the twentieth century, investigators from the Chicago School of Electrophysiology noted that "cardiac stimulatory studies suggest the site of origin of ventricular ectopic beats can be identified by QRS configuration." Ectopic beats were classified according to their bundle branch block–like configuration, with left ventricular origin being ascribed to right bundle branch configurations and right ventricular origin to left bundle branch configurations.[8] The latter were credited with a more favorable outcome. However, occasional reports of deaths in young patients existed, disputing a uniform benign prognosis. With advances in the evaluation and management of ventricular arrhythmias, there now exists a far greater body of knowledge regarding these conditions. IVT and IVF have been studied for anatomic substrate, clinical electrophysiology, and outcomes with and without therapy. This chapter summarizes the current understanding of this constellation of conditions.

Definition and Classification

In current-day parlance, IVT refers to VT of unknown cause that occurs in the absence of significant structural heart disease or transient or reversible arrhythmogenic factors (e.g., electrolyte disorders, myocardial ischemia). IVF may include polymorphic VT evolving to VF or may initiate directly as VF. In practice, one cannot categorically exclude patients with evidence of structural heart disease because advances in diagnostic tests demonstrate structural changes in some patients with classic IVT syndromes.[9-11] Magnetic resonance imaging (MRI) has shown subtle wall motion disturbances that may represent structural disease.[12-15] In addition, a patient could have structural disease caused by a coexisting cardiac disorder. The term *idiopathic* is sometimes inappropriate given the depth of understanding that now exists for a few of the disorders. For the purposes of this discussion, the syndromes listed in Box 45-1 are assumed to be distinct IVT syndromes. However, it must be acknowledged that these syndromes consist of heterogeneous subtypes, and some share characteristics with other IVT syndromes so that clear distinctions are not always possible. Moreover, reports of "new" IVTs arise frequently.[16,17] Some of these may be previously unrecognized syndromes, whereas others may be variants of established forms.

Epidemiology

Epidemiologic data on IVT syndromes are scarce because of difficulties in recognizing the syndrome and its demographics. The demographics of the clinical syndrome of IVT derived initial impetus from clinical and later electrophysiological studies (EPSs). Pietras et al analyzed 27 patients with chronic recurrent VT classified according to the electrocardiogram (ECG) classification and examined their clinical, ECG, and hemodynamic features.[8] They further tabulated 73 reported cases in the then-existing literature. They noted that the mean age of right-sided VT was lower (32 years) than that of left-sided VT (43 years), with a similar trend in the previously reported data (36 vs. 53 years). Females predominated in the case of right-sided VT (52% and 66% in the two series, respectively) compared with left-sided VT (33% and 15% in the two series, respectively). Organic heart disease was almost invariably present with left-sided VT (100% and 85%, respectively) and absent or uncommon in right-sided VT (25% and 48%, respectively). Mortality rates were significantly lower in right-sided VT, with no deaths in their series and a 12% incidence in the reported literature. Chapman et al reported electrical and hemodynamic correlates in a series of patients with "idiopathic VT" in 1975.[18] Subsequently, EPSs in this syndrome have defined

Box 45-1 Idiopathic Ventricular Tachyarrhythmia Syndromes

POLYMORPHIC VT OR VF SYNDROMES
Long QT syndrome
Brugada syndrome
Short-coupled torsades de pointes
Catecholamine-induced polymorphic VT
Other idiopathic polymorphic VT or VF syndromes

MONOMORPHIC VT SYNDROMES
Right ventricular outflow tract VT*
Left ventricular outflow tract VT
Left ventricular fascicular tachycardia
Adrenergic monomorphic VT
Other idiopathic monomorphic VT syndromes (e.g., pulmonary artery, bundle of His, aortic sinuses of Valsalva, coronary sinus and cardiac veins, mitral and tricuspid annuli and epicardial origin)

**And other adenosine-sensitive VTs.*
VT, Ventricular tachycardia; VF, ventricular fibrillation.

the arrhythmia mechanisms, subgroups, novel clinical therapies, and their outcomes.[9,19]

Formal epidemiologic data are lacking, but IVT is considered rare. IVT syndromes arising in the right ventricular outflow tract (RVOT) or the left ventricular outflow tract (LVOT) are the most common forms of IVT. The RVOT origin predominates, accounting for more than 70% of referred patients, although LVOT origin is being increasingly recognized.[20-22] Aortic cusp IVT has been reported to account for 17% to 21% of outflow tract IVT.[23,24] Analysis of multiple-center experiences suggests that IVT constitutes approximately 10% of all VT referrals to electrophysiologists, but the true incidence in the community remains unclear.[23] IVF is believed to represent 5% to 10% of sudden cardiac death (SCD) victims and implantable cardioverter-defibrillator (ICD) recipients.[25-27] IVF populations are still being defined. Commonly recognized genetic syndromes include the long QT syndrome (LQTS), Brugada syndrome, and the more uncommon short QT syndrome (SQTS). Information regarding their prevalence is emerging and is discussed below. One important subgroup is associated with an early repolarization abnormality.[28] Haissaguerre et al described an early repolarization abnormality in 31% of patients with IVF compared with 5% in control groups in a case-control study. Patients with this finding had a higher 5-year mortality rate. These early repolarization abnormalities have now been classified under the term *J-wave syndromes*.

Population data exist for some genetically based IVT or IVF syndromes. It has been estimated, for instance, that Brugada syndrome accounts for 4 to 10 cases of SCD per 10,000 inhabitants per year in Thailand and Laos, countries with an apparently high incidence. Nevertheless, the problem may be much larger. Autopsy series suggest that in 5% to 15% of cases of SCD, no evidence of heart disease or other likely cause exists.[29-31] These observations raise the possibility that the IVT and IVF syndromes are common but insufficiently recognized. IVF syndromes with early repolarization have been studied in both IVF survivors and population studies. Tikannen et al studied more than 10,684 middle-aged subjects and noted that the early-repolarization pattern of 0.1 mV or more was present in 5.8% (3.5% in inferior leads and 2.4% in lateral leads).[32] J-point elevation of at least 0.1 mV in inferior leads was associated with an increased cardiac mortality risk (relative risk [RR], 1.34; $P = .03$); J-point elevation of more than 0.2 mV in inferior leads occurred in 0.3% of patients, who had a markedly elevated risk of death from cardiac causes (RR, 2.98; $P < .001$) and from arrhythmia (adjusted RR, 2.92; 95% confidence interval [CI], 1.45 to 5.89; $P = .01$). Long Q-T interval and left ventricular hypertrophy were actually weaker predictors of this outcome. Juntila and Myerburg noted variations in the frequency of early repolarization ranging from 10% to 42% based on ethnicity in healthy athletes.[33] Antzelevitch has proposed three subtypes of J-wave syndrome on the basis of these data.[34] *Type 1*, an early repolarization pattern present predominantly in the lateral precordial leads, is common in healthy male athletes and is rarely seen in IVF survivors; *type 2*, which has the ECG pattern predominantly in inferior or inferolateral leads, has a higher risk; and *type 3*, which displays global findings and is associated with the highest IVF risk, is often associated with incessant VF.

A recent retrospective multi-center study evaluated the profile of pediatric patients with IVT. Mean age at first manifestation of the arrhythmia was 5.4 years, with a range of 0.1 to 15 years, and 27% of patients manifested the disorder in infancy.[35]

Mechanisms and Clinical Presentation

Focal VTs are currently believed to have enhanced or triggered automaticity as the underlying mechanism, although micro–re-entry cannot be often definitively excluded. VT may appear to be focal with micro–re-entrant circuits or if a focal breakout occurs endocardially from an epicardial circuit. Triggering can be caused by early afterdepolarizations (EADs) or delayed afterdepolarizations (DADs). The former may underlie the initiation of polymorphic tachycardias in LQTS. DADs can be mediated by intracellular calcium overload, which activates the transient inward current I_{ti}. This is enhanced by β-adreneregic stimulation, increased pacing rates, and digoxin. This mechanism is likely to mediate IVTs arising in the RVOT. Enhanced automaticity that is not triggered is often stress related or promoted by isoproterenol. It can be suppressed by β-blockade. This mechanism may exist in some catecholamine-sensitive, focal-origin VTs or IVFs originating from abnormal automaticity from damaged Purkinje fibers.

The clinical presentation of patients with IVT is highly variable. IVT arising in the outflow tract most often manifests in the third to sixth decade of life and has a female preponderance.[36-38] Palpitations in an otherwise healthy young individual are a classic description in this entity. These can be exercise induced or may occur at rest. Salvos of nonsustained VT (NSVT) are common. Hormonal triggers have been reported, and more frequent arrhythmic events, ventricular ectopic beats, or VT events are seen during exercise or increased activity. These can culminate in near syncope or syncope, dysthymia and, on occasion, cardiac arrest. Cardiac arrest can be the primary presentation in some individuals, particularly if a family history of SCD exists. Others seek medical attention in the asymptomatic state with a family history of SCD or for an electrocardiographic abnormality such as LQTS or Brugada syndrome. Increasing awareness of the familial forms of the arrhythmia and symptomatic high-density ventricular ectopy or NSVT can lead to medical evaluation.

Electrocardiographic recordings and exercise testing frequently assist in the classification of IVT and should be routinely performed. These are discussed in the next section and more extensively in Chapters 53 and 70.

The typical morphology of ventricular premature beats (VPBs) has been extensively analyzed and can provide clues to the origin

or arrhythmia in the monomorphic forms of IVT. For outlflow tract VT, QRS duration is generally less than 140 ms, and arrhythmogenic right ventricular dysplasia is a differential diagnosis with wider QRS complexes. The initiation of the VT is often with long-coupled extrasystoles and is monomorphic. Multiple different morphologies should raise suspicion of structural heart disease with VT. In general, outflow tract VT has a benign course, but more malignant forms are seen in Brugada syndrome or LQTS, polymorphic VT, catecholaminergic VT, and IVF.

Electrocardiographic Features of Idiopathic Ventricular Tachyarrhythmias

Analysis of the surface ECG morphology is an essential aspect of localization of the origin of IVT. The ECG during sinus rhythm is often normal, although a right bundle branch block (RBBB) morphology has been described with outflow tract VT in 10% of patients.[20] The primary forms of IVT include arrhythmias arising from the RVOT or LVOT, the aortomitral continuity, and intrafascicular re-entry. These four types of IVTs can be distinguished by characteristic ECG patterns that reflect the origin or mechanism of the arrhythmias. The electrocardiographic features of the RVOT and LVOT reflect the anatomic proximity of these structures. As shown in Figure 45-1, the RVOT is anterior to the right and left aortic cusps. Accurate ECG lead placement is essential to distinguish electrocardiographic features from these areas. Because of the proximity of these anatomic sites, small changes in lead position may have a substantial impact on the ECG morphology of arrhythmias arising from this region. In addition, the close anatomic relationships of the outflow tracts and the great arteries and coronary vasculature make exact localization potentially problematic. Other factors include the exact position of the aortic cusps relative to the RVOT, the axis of the heart, and the precise connections of muscle fibers connecting the tissue above the aortic cusps to the left ventricle.

Right Ventricular Outflow Tract

The clinical features and the general ECG characteristics of VT arising from the RVOT were described by Buxton in 1983.[19] The ECG exhibits a morphology resembling left bundle branch block (LBBB) with an inferior axis. These arrhythmias are associated with exercise, and in many patients the arrhythmias are nonsustained and repetitive. Others may simply have frequent monomorphic ventricular ectopy. Figure 45-2 was recorded from a patient with repetitive VT arising from the RVOT. Jadonath determined the usefulness of the 12-lead ECG in localizing the origin of RVOT tachycardia in patients who underwent ablation of arrhythmias.[39] They divided the RVOT into nine segments and assessed the QRS morphology recorded by pacing at each segment. A QS pattern in lead aVR and monophasic R waves in leads II, II, and aVF were noted in all patients at all nine sites. Pacing at anterior sites produced either a dominant Q wave or qR pattern in lead I, but a monophasic R or Rs complex was never observed. Conversely, a dominant R wave was observed in lead I during pacing from posterior sites. The QRS exhibited a QS pattern in lead aVL during pacing from anterior sites, but the R wave became progressively larger in lead aVL with more posterior sites. Early R-wave transition in the precordial leads was likely to be observed during pacing from the posterosuperior aspect of the septum. Similar results were reported by Yoshida and colleagues.[40] Coggins observed that VT arising from the septal side of the RVOT had a negative QRS complex in aVL, whereas VT arising

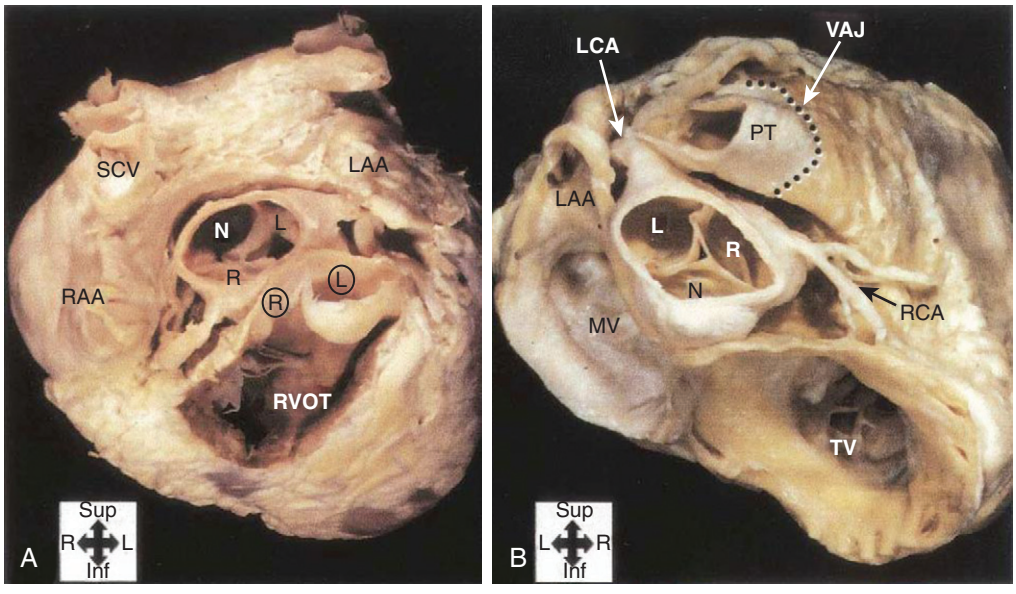

FIGURE 45-1 Heart specimens illustrating the anatomic arrangement between the right ventricular outflow tract (RVOT) and the aortic sinuses. **A**, Viewed anteriorly, the RVOT passes leftward and superior to the aortic valve. **B**, The posterior view shows the left (*L*) and right (*R*) coronary aortic sinuses adjacent to the pulmonary infundibulum. The noncoronary (*N*) aortic sinus is remote from the RVOT but is related to the mitral valve (*MV*) and the central fibrous body. The *dotted line* marks the ventriculoatrial junction (*VAJ*) between the wall of the pulmonary trunk (*PT*) and right ventricular muscle. *LAA*, Left atrial appendage; *LCA*, left coronary artery; *LV*, left ventricle; *RAA*, right atrial appendage; *RCA*, right coronary artery; *SCV*, superior vena cava; *TV*, tricuspid valve. *(From Ouyang F, Fotuhi P, Ho SY, et al: Repetitive monomorphic ventricular tachycardia originating from the aortic sinus cusp: Electrocardiographic characterization for guiding catheter ablation,* J Am Coll Cardiol *39:500–508, 2002.)*

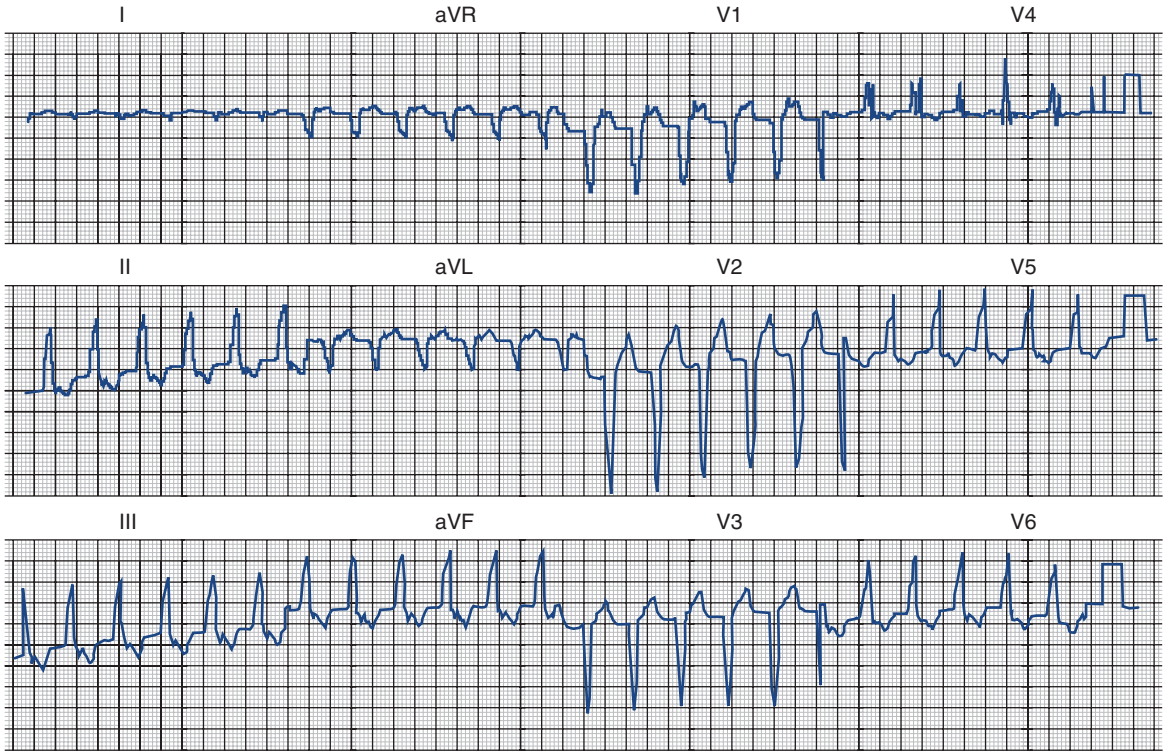

FIGURE 45-2 Twelve-lead electrocardiogram of ventricular tachycardia arising from the right ventricular outflow tract. The QRS exhibits a morphology resembling right bundle branch block with an inferior axis.

from the lateral aspect of the RVOT was associated with a positive QRS in aVL.[21]

Electroanatomic mapping shows border regions as a low-voltage region in the RVOT at the breakout point or origin of the VT.[41] An analysis by Dixit categorized RVOT arrhythmias as arising anterior and leftward on the septal side, as opposed to posterior and more rightward, and distinguished the electrocardiographic features of these arrhythmias from those arising on the free wall. Figure 45-3 displays the scheme used in this analysis.[42]

The electrocardiographic features corresponding to these sites are shown in Figure 45-4. As noted by other authors, the amplitude of the R wave in limb lead I depends on the origin being anterior or posterior. They observed that arrhythmias arising from the free wall of the RVOT show more delayed R-wave transition in the precordial leads and notching in the inferior leads.

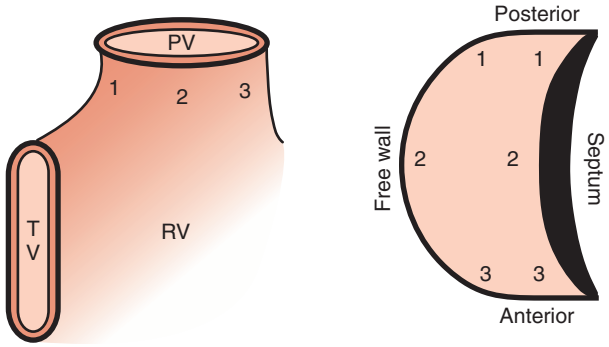

FIGURE 45-3 Schematic representation of the right ventricular outflow tract (RVOT), in which the most superior (*sites 1, 2, and 3*) septal and free wall site targeted in the study are identified. *Left*, Location of sites 1 through 3 along the superior septal RVOT as seen in the right anterior oblique fluoroscopic projection. *Right*, RVOT viewed coronally from above the pulmonic valve (*PV*). Sites 1 (most posterior) through 3 (most anterior) along the septum and free wall are shown. *RV*, Right ventricle; *TV*, tricuspid valve. *(From Dixit S, Gerstenfeld EP, Callans DJ, Marchlinski FE: Electrocardiographic patterns of superior right ventricular outflow tract tachycardias: Distinguishing septal and free-wall sites of origin,* J Cardiovasc Electrophysiol *14:1–7, 2008.)*

Left Ventricular Outflow Tract

Ventricular arrhythmias arising from the LVOT are distinguished from RVOT arrhythmias by several differences in the QRS morphology. Earliest ventricular activation may arise in the sinus of Valsalva, below the aortic valve, or on the epicardium. Figure 45-5 was recorded from a patient with repetitive VT whose arrhythmia origin was just below the anterolateral aspect of the aortic valve. Callans et al described four patients with monomorphic VT mapped to the LVOT.[43] Two patients, whose arrhythmias originated above the mediosuperior aspect of the mitral annulus, had VT that exhibited a right bundle, inferior-axis VT with a dominant R wave in lead V1. The ECGs of these patients resembled those recorded from the five patients studied by Lamberti; in

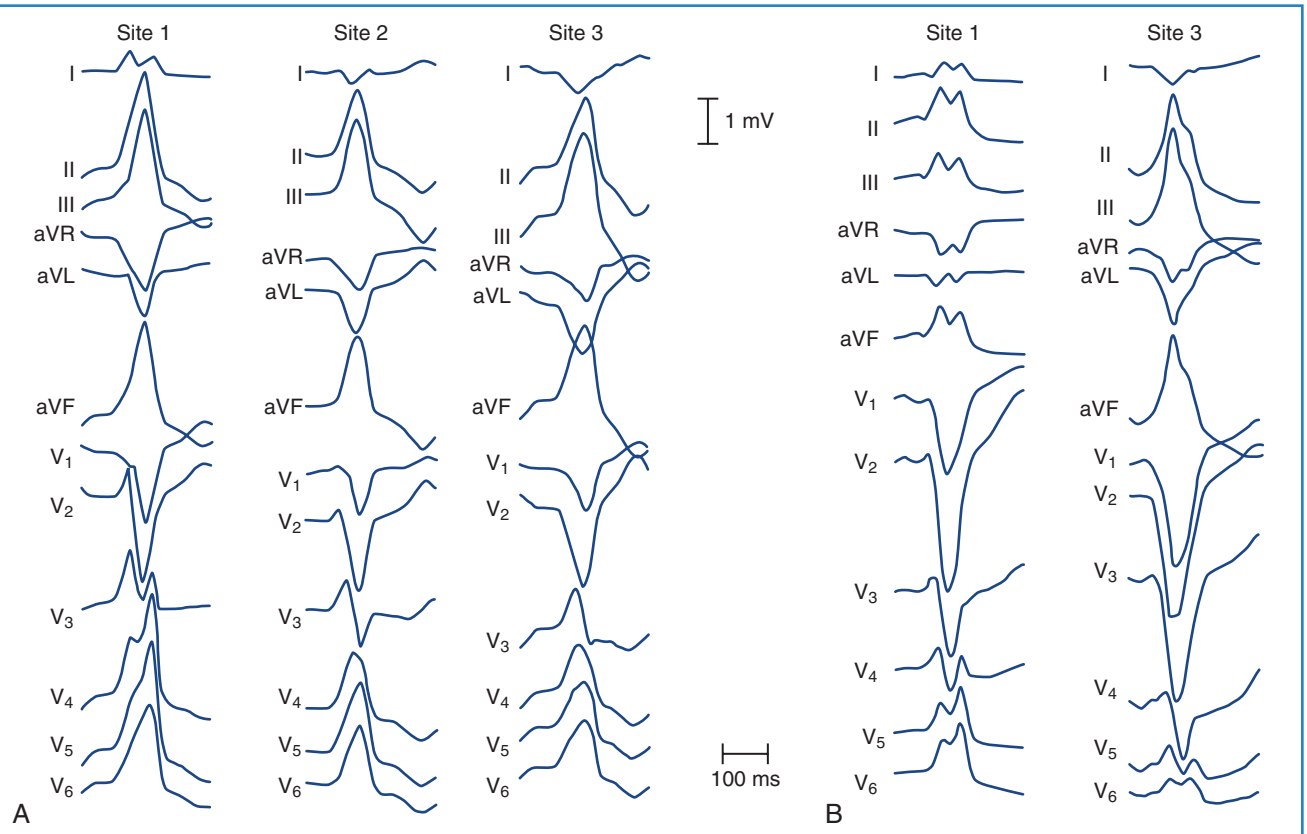

FIGURE 45-4 Unique electrocardiographic morphologies that help to distinguish site of origin of the clinical arrhythmia in the superior right ventricular outflow tract. **A,** ECG morphologies of spontaneous arrhythmias from septal sites 1, 2, and 3. **B,** ECG morphologies of spontaneous arrhythmias from free-wall sites 1 and 3. All the free wall sites show notching in the inferior leads and late precordial transition (≥V4). In comparison, all the septal sites lack both notching of inferior leads and late precordial transition. For both the septal and free wall locations of the clinical arrhythmias, lead I helps distinguish anterior and leftward location (site 3, negative polarity) from posterior and rightward location (site 1, positive polarity). Site 2, which lies between sites 1 and 3, manifests multiphasic polarity in lead I. *(From Dixit S, Gerstenfeld EP, Callans DJ, Marchlinski FE: Electrocardiographic patterns of superior right ventricular outflow tract tachycardias: Distinguishing septal and free-wall sites of origin,* J Cardiovasc Electrophysiol *14:1–7, 2008.)*

these patients, intracardiac echocardiography had been used to demonstrate that in all of them, VT arose close to the left coronary cusp in the area of atriomitral continuity.[44] The other two patients described by Callans had VT that arose from the basal aspect of the superior left ventricular septum. The ECGs recorded from these patients had a left bundle, inferior-axis QRS mapped to the LVOT. The ECGs recorded from these patients were distinguished from the ECGs of those with arrhythmias arising from the RVOT by an earlier precordial R-wave transition (median lead V3 vs. lead V5), more rightward axes, taller R waves inferiorly, and small R waves in lead V1. Absence of an R wave in lead V1 and late precordial transition suggested an origin in the RVOT. These results are similar to those reported by Kamakura and Krebs, who found that if the R/S ratio in lead V3 was 1 or more, the origin was likely to be in the LVOT.[45,46] Kanagaratnam described a variant of LVOT VT in 12 patients whose arrhythmias arose from the aortic sinus of Valsalva.[47] Two characteristic QRS morphologies were observed. ECGs recorded from all patients had (1) a left-bundle, inferior-axis, tall monophasic R waves inferiorly and (2) early precordial lead transition with rS or RS in lead V1 and Rs pattern in leads V2 or V3. Those in whom the tachycardia was ablated from the noncoronary sinus were distinguished by a notched R in lead I.

The use of intracardiac echocardiography and radiographic imaging has helped refine the origin of LVOT arrhythmias and their relationship to the coronary cusps and aortomitral continuity.[48,49] Pacemapping from the aortic cusps can be difficult because of catheter stability and high thresholds; Figure 45-6 shows characteristic ECG patterns associated with this region. Recordings from the right coronary cusp typically exhibit notching in the downstroke of lead V1 and an R in limb lead I. A W pattern in lead V1 is observed near the commissure of the right and left coronary cusps. Arrhythmias arising from the left coronary cusp exhibit a qrS pattern and either a QS or rS in limb lead I. Each of these locations is associated with a prominent R wave in the inferior leads and an R-wave transition in leads V2 or V3.

Ventricular arrhythmias arising from the aortomitral continuity are characterized by a qR complex in lead V1 and an RS or rs complex in limb lead I. The relationship between aortic and mitral valves is shown in Figure 45-7. The R wave in lead V1 becomes more monophasic as the origin moves more leftward across the superior aspect of the mitral annulus. Figure 45-8 illustrates the differences among the paced or spontaneous beats arising from the RVOT, the left coronary cusp, the aortomitral continuity, and the superior aspect of the mitral annulus.

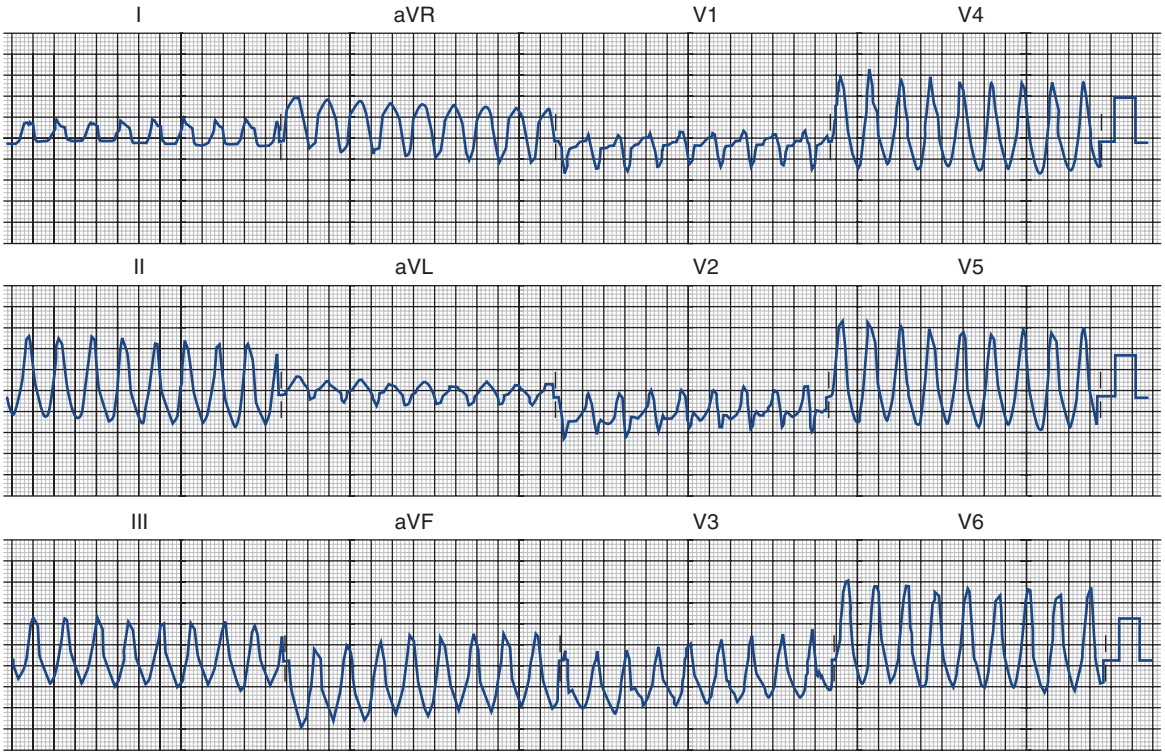

FIGURE 45-5 Twelve-lead electrocardiogram of ventricular tachycardia that arose from the left ventricular outflow tract. Note the RS configuration in lead V1 and the prominent R wave in lead V2. The axis is inferior, and a prominent R wave is seen in lead I.

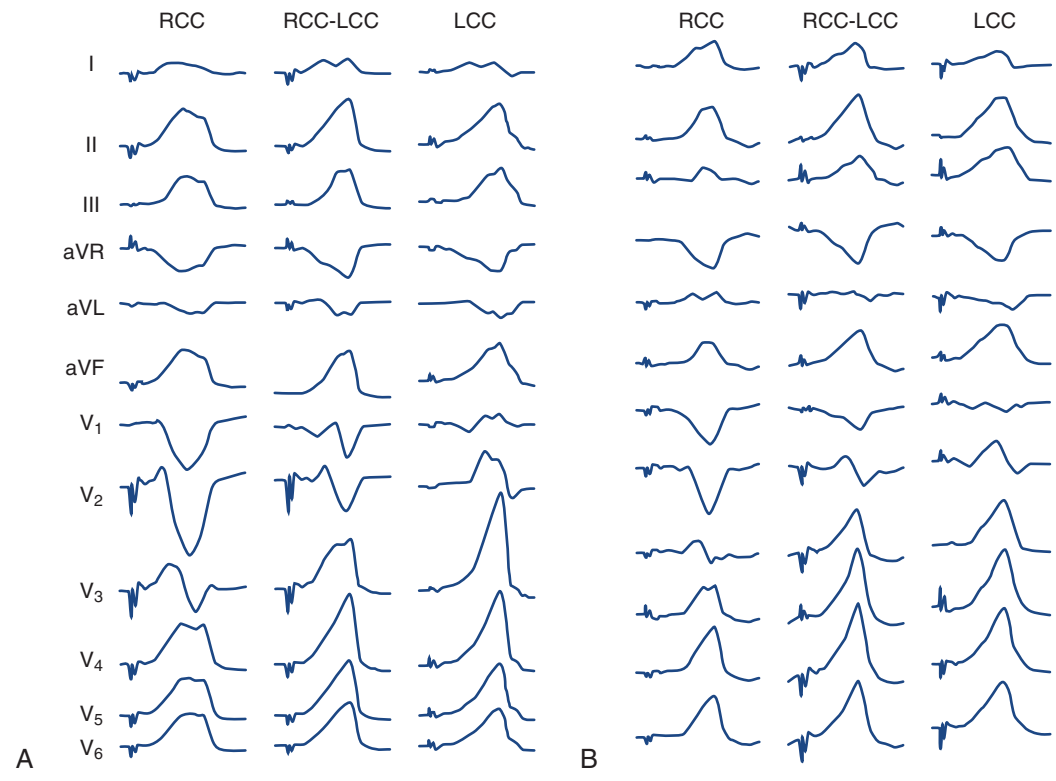

FIGURE 45-6 Detailed pacemaps from the right/left coronary cusp (RCC-LCC) region guided by intracardiac echocardiography imaging in two study patients. Pacemaps from the individual RCC and LCC cusps show a QS and multiphasic or W-shaped morphologies, respectively, in lead V1. The pacemaps from the RCC-LCC commissure show a W morphology (**A**) or a characteristic notch in the downward deflection in lead V1 (**B**) with precordial transition at lead V3. *(From Bala R: Electrocardiographic and electrophysiologic features of ventricular arrhythmias originating from the right/left coronary cusp commissure,* Heart Rhythm *7:312–322, 2010.)*

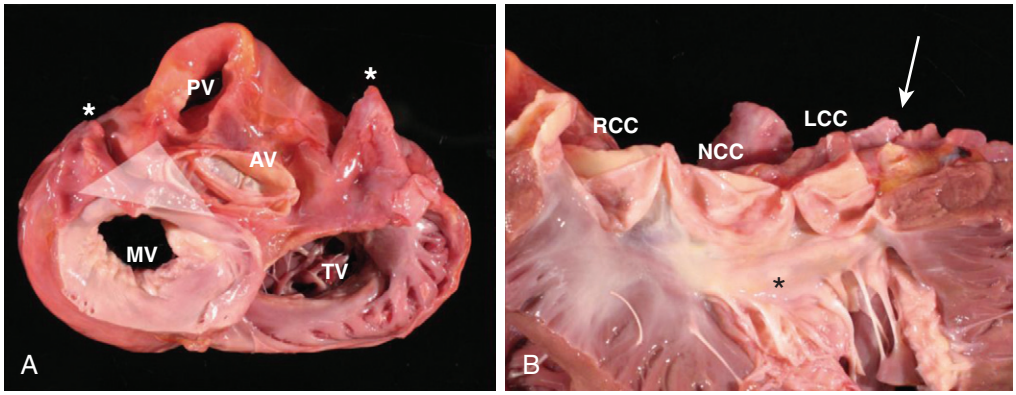

FIGURE 45-7 Gross anatomy of the heart. **A,** View from the atria toward the valvular apparatus showing the anatomic relationship between the aortic valve (*AV*), mitral valve (*MV*), pulmonary valve (*PV*), and tricuspid valve (*TV*). *Asterisks* indicate the left and the right atrial appendages, respectively. The *white triangle* represents the area of the aortomitral continuity corresponding to Figure 45-2. **B,** View of the anterior leaflet of the mitral valve (*asterisk*) after opening of the left ventricle and the aortic valve, showing the close relationship of the aortic valve and the anterior leaflet of the mitral valve. The *arrow* indicates the left main artery. *LCC*, Left coronary cusp; *NCC*, noncoronary cusp; *RCC*, right coronary cusp. *(From Steven D: Ventricular tachycardia arising from the aortomitral continuity in structural heart disease: Characteristics and therapeutic considerations for an anatomically challenging area of origin,* Circ Arrhythm Electrophysiol *2:660–666, 2009.)*

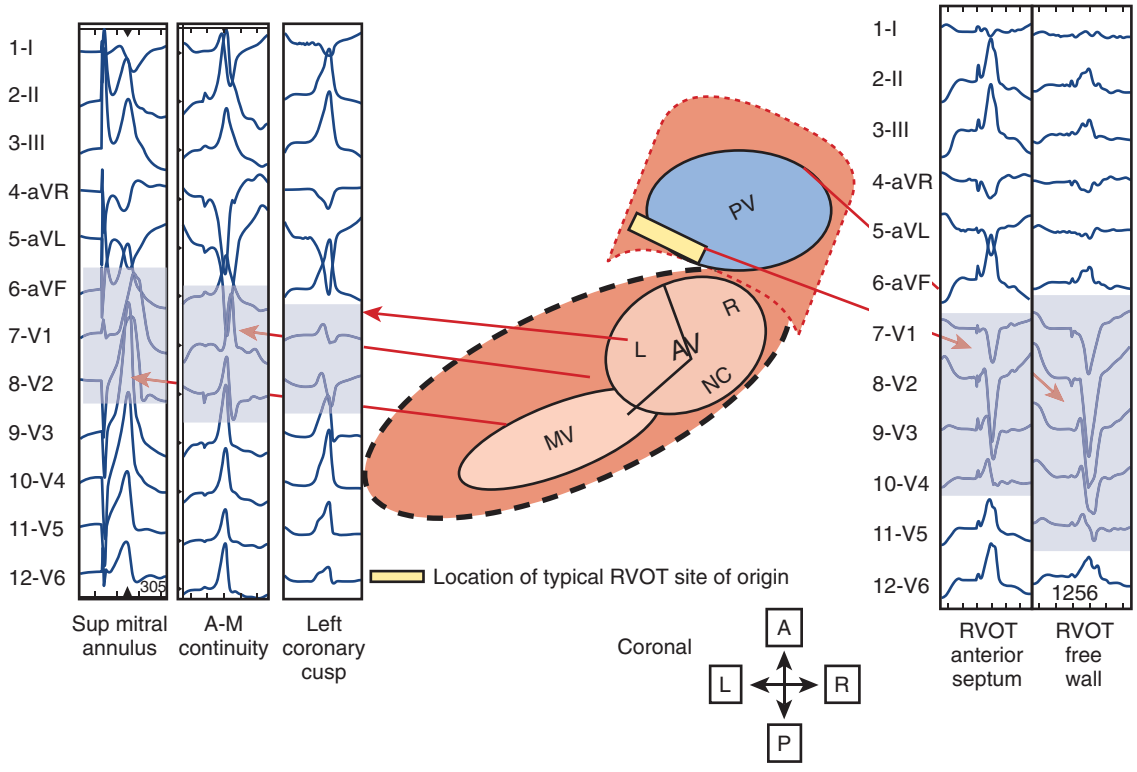

FIGURE 45-8 Electrocardiogram (ECG) patterns associated with selected outflow tract locations. Twelve-lead ECG pacemaps or ventricular tachycardia (VT) from the free wall of the right ventricular outflow tract (*RVOT*), anteroseptal aspect of the RVOT (typical RVOT VT origin), left coronary cusp, aortomitral (*A-M*) continuity, and superior mitral annulus are shown. Moving from right to left from the RVOT free wall to the anterior septum and across the left ventricular outflow tract, it is clear that the precordial transition becomes earlier, with an eventual monophasic R wave in lead V1 from the superior mitral annulus. Note the signature W shape in lead V1 of the left coronary cusp VT and the qR in lead V1 from the aortomitral continuity pacemap. *AV*, Aortic valve; *MV*, mitral valve; *NC*, noncoronary cusp; *PV*, pulmonic valve. *(From Bala R: Electrocardiographic recognition and ablation of outflow tract tachycardia,* Heart Rhythm *4:366–370, 2007.)*

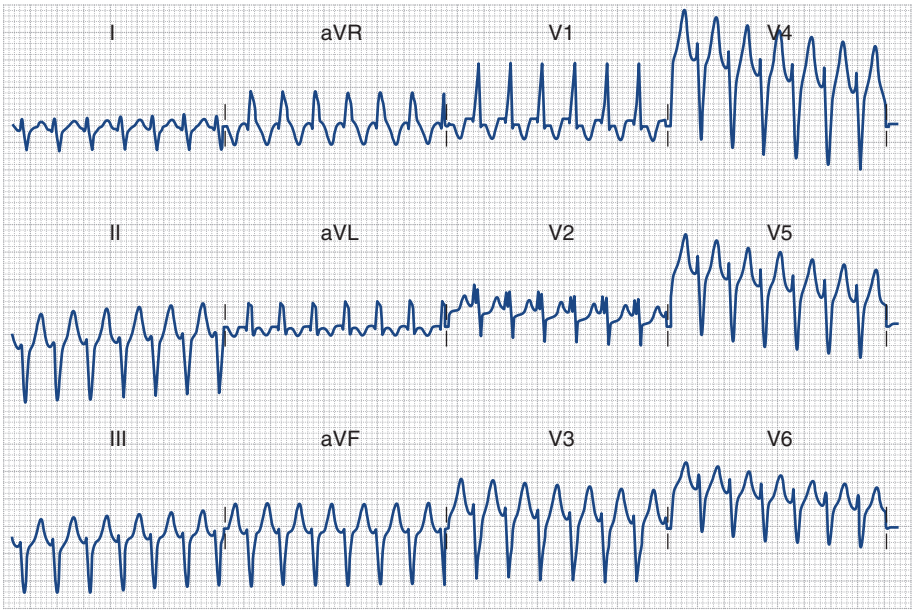

FIGURE 45-9 Twelve-lead electrocardiogram of idiopathic VT caused by intrafascicular re-entry. The QRS morphology resembles right bundle branch block, and the axis is leftward and superior.

Idiopathic Verapamil-Sensitive Left Ventricular Tachycardia

Idiopathic verapamil-sensitive VT that has a QRS pattern of RBBB and left-axis deviation was described by Lin in 1983.[50] This is typically seen in adolescents and young adults up to the age of 40 years, with a male preponderence.[23] ECG morphologies can include a small r–deep S configuration in some precordial leads. Subsequent studies, which focused on the electrophysiological basis of the arrhythmia and ablation techniques, demonstrated that the QRS axis is usually leftward and superior, although it could be indeterminate or rightward. Electrophysiological data demonstrate that re-entry either is intrafascicular or involves abnormal Purkinje tissue with decremental conduction properties and is sensitive to verapamil.[51-58] The exact QRS morphology depends on which branches of the fascicles provide the exit points, and unsuccessful attempts to ablate the arrhythmia have shown changes in QRS morphology that suggest the potential for multiple exit points. Re-entry in and exit points from the left bundle branches predominate, with more than 80% involving the left posterior fascicle as an exit. Anterior left fascicular exit has also been observed. Slowly rising " rounded" ventricular potentials have been reported during VT, suggesting verapamil-sensitive regions. Sharp potentials have also been seen at exit points, possibly from Purkinje network cells.[23] These have been targeted for catheter ablation. Figure 45-9 demonstrates idiopathic left-sided VT caused by fascicular re-entry that was ablated by applying radiofrequency (RF) energy at the site of a presystolic "fascicular" potential on the inferior aspect of the septum approximately 2 to 3 cm from the apex.

Polymorphic Ventricular Tachycardia and Idiopathic Ventricular Fibrillation

Polymorphic VT (PMVT) has been observed in clinical conditions in patients without structural heart disease. Genetically based disorders have been associated with PMVT and are detailed in Chapters 62 to 65. Initially described by Belhassen, IVF has been the focus of increased investigation in the last decade.[26,59] Abnormalities in the early phase of repolarization have been reported in survivors of IVF. Haissaguerre et al observed notching of the S wave, QRS slurring, and ST-segment elevation with T-wave inversion, especially in inferior and lateral leads (Figure 45-10). Early repolarization was more frequent in patients with IVF than in control subjects (31% vs. 5%; $P < .001$). Among these patients, those with early repolarization were more likely to be male and have a history of syncope or sudden cardiac arrest during sleep than those without early repolarization. Ventricular ectopics that initiated ventricular arrhythmias could be mapped to sites concordant with the localization of repolarization abnormalities. The incidence of recurrent VF was greater in those with a repolarization abnormality than in those without such an abnormality (hazard ratio [HR], 2.1; $P = .008$). Triggering premature beats arising from the Purkinje network have been incriminated as the initiators of PMVT or IVF in some patients. In IVF, these triggers may arise in the right ventricle (RV) or the left ventricle (LV), with the former having longer QRS durations than the latter and prominent S waves rather than R waves in lead V1.[23] Triggering premature beats are often prominent after resuscitation from an episode of IVF (see Figure 45-10). J-point elevation, especially in inferior leads, has been associated with increased risk.[60] QRS slurring may also be associated with increased risk.[61]

Clinical Electrophysiology

Remarkable advances have been made in understanding congenital LQTS and Brugada syndrome. These disorders are described in detail elsewhere in this text, but because they may provide insights into other IVT syndromes, certain aspects are discussed here. The mechanism of VT (usually torsades de pointes) in patients with LQTS is not known with certainty. However, one

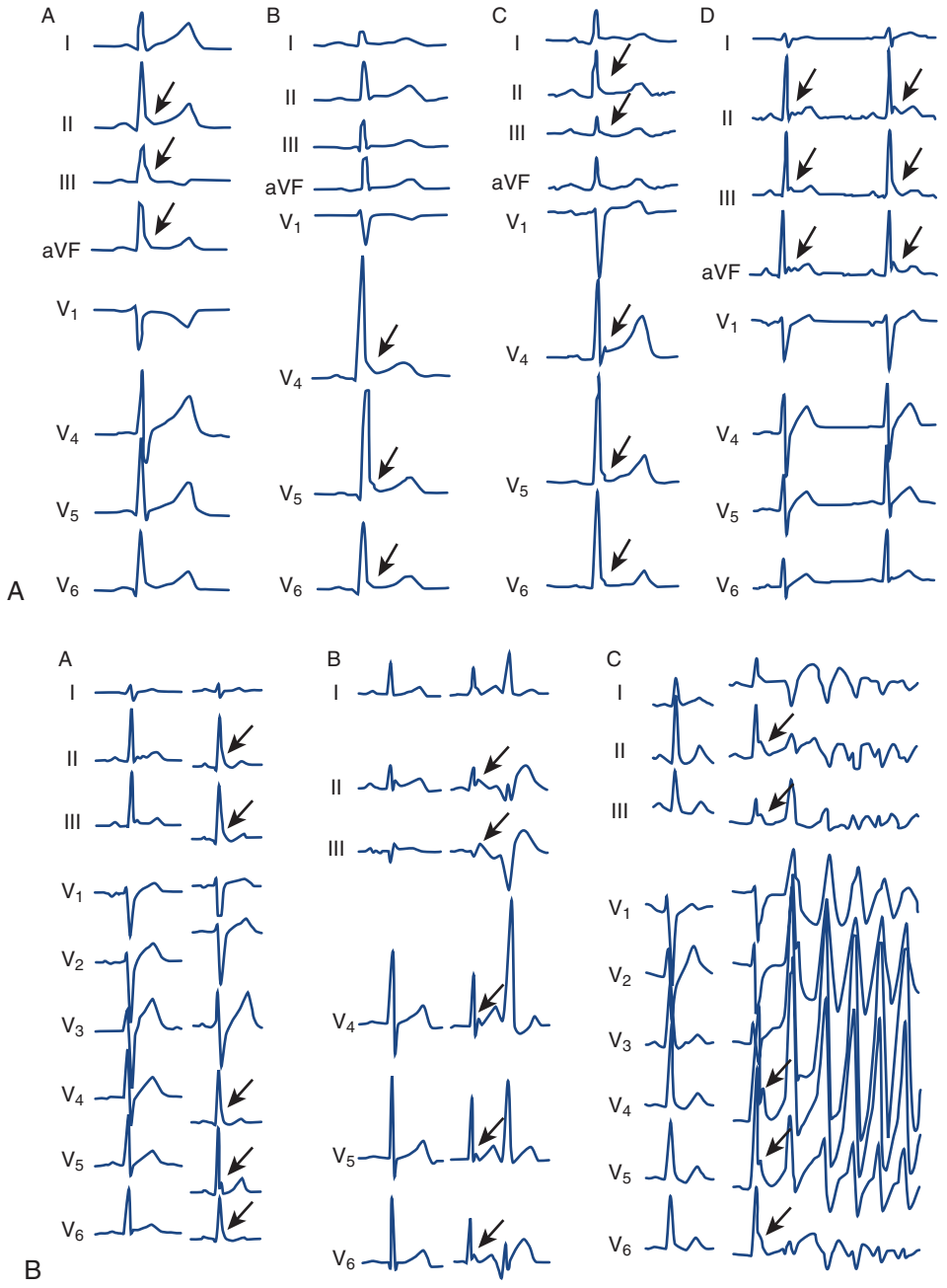

FIGURE 45-10 Three-dimensional noncontact mapping of ventricular tachycardia (VT) arising in the right ventricular outflow tract (RVOT). **A,** Sinus rhythm. **B,** VT arising from RVOT. The noncontact map of the outflow tract is seen as an elliptical oblong chamber, with the VT wavefront shown in sequential images. Note the focal origin with centrifugal propagation. Timing is shown in milliseconds after onset.

theory is that the mechanism is re-entry resulting from increased dispersion of repolarization caused by differential prolongation of action potential duration (APD) in myocardial cells with particular lengthening in M cells.[62,63] Re-entry may be triggered by EADs caused by abnormal calcium kinetics that result from delayed repolarization. This could explain why different mutations producing action potential prolongation by distinct mechanisms result in similar VTs. However, differences exist between the circumstances under which arrhythmias arise. In a model of LQTS, sympathetic activity had different effects in the three subtypes. In LQT1, sympathetic activity was necessary for increased dispersion of repolarization, and torsades de pointes did not develop without it. In LQT2, dispersion of repolarization and tendency for torsades de pointes varied with the level of sympathetic activity, whereas in LQT3, enhanced sympathetic activity reduced dispersion of repolarization and was protective against torsades de pointes.[63]

The mechanism of VT in Brugada syndrome has also been hypothesized to be re-entry as a consequence of increased dispersion of repolarization. In this case, the increased dispersion

of repolarization is thought to result from differential action potential abbreviation, with the greatest effect occurring in epicardial cells.[64] Re-entry could be triggered by phase 2 re-entry. Several mutations may produce the Brugada syndrome phenotype. This may account for the differences in clinical characteristics seen in some nocturnal death disorders encountered in Southeast Asia. Little is known about the short-coupled variant of torsades de pointes and catecholaminergic polymorphic VT (CPVT) syndrome.[65-69] On the basis of the appearance of the tachyarrhythmias, re-entry caused by dispersion of repolarization is a possible mechanism. However, the mechanism by which this occurs and the factors that produce it are unknown.

The usefulness of clinical EPS in IVT syndromes associated with PMVT or VF is limited. First, ventricular tachyarrhythmias cannot be induced in all IVT syndromes, notably LQTS. Second, when induced, it is difficult to confirm that the induced VT is the same as the spontaneous arrhythmia. Third, the induced VTs are difficult to study in a systematic fashion because they are rapid, polymorphic, poorly tolerated, and often require countershock. In contrast to LQTS, VT or VF is often inducible in patients with Brugada syndrome. In addition, a provocative test is available. The characteristic ECG pattern of RBBB and ST elevation may not be present at rest, but it may be provoked by administration of ajmaline, flecainide, pilscainide, or procainamide. VT cannot usually be induced in patients with the short-coupled variant of torsades de pointes. Isoproterenol infusion can be used to provoke VT in patients with CPVT syndrome. Adenosine can suppress IVT in patients with RVOT VT.[68] IVF has been studied in the electrophysiology laboratory and is described in detail in Chapter 95. Triggering premature ventricular beats can have a uniform morphology, and localization by mapping and catheter ablation may be effective in selected patients.

The clinical electrophysiology of the monomorphic forms of IVT differ considerably from the forms associated with VF and PMVT. The most common form of monomorphic IVT is RVOT VT. It has been shown to result from cyclic adenosine monophosphate–mediated triggered activity, which depends on DADs.[9] The underlying pathophysiological basis for this abnormality remains unclear, particularly why it arises from localized areas of the heart. A genetic abnormality for a variant form of RVOT VT has been reported, but a familial distribution is not usually observed.[69] EPS has been very useful in the investigation of this syndrome. RVOT VT is often induced by rapid pacing or isoproterenol infusion. In some cases, infusions of aminophylline, atropine, epinephrine, or very high-dose isoproterenol (up to 14 μg/min) may be required.[70] RVOT VT usually presents with a single QRS morphology, typically a LBBB pattern and inferior axis consistent with an RVOT origin. It cannot be entrained. It usually terminates in response to adenosine, verapamil, β-blockers, or vagal maneuvers. Multiple configurations in individual patients have been reported.[71]

Mapping of RVOT VT can localize this tachycardia to virtually all regions of the outflow tract. Figure 45-10 is a three-dimensional map of the propagation of a single VT wavefront. Note that the site of origin in the outflow tract is focal in nature and well defined by the mapping technique. Noncontact mapping can define the focus in a single cycle, but sequential mapping with magnetic electroanatomic techniques may be used in stable, sustained VT. Tachycardias arising from the LVOT and epicardial sites have many features in common with RVOT VT, including a response to adenosine,[42,72] which suggests a common mechanism and justifies the designation "adenosine-sensitive VTs." Sites of origin can often be predicted by careful examination of the configuration in the 12-lead ECG.[42,44]

Left ventricular fascicular tachycardia is another important monomorphic IVT syndrome. It is less common than RVOT VT, although it is more prevalent in series arising from Asian countries than from Western countries. This arrhythmia is believed to result from re-entry. Although previously thought to result from micro–re-entry, recent investigations suggest a macro–re-entrant circuit.[73-79] Characteristic features include induction and termination with programmed stimulation, a relatively narrow QRS, the presence of a Purkinje system potential, and entrainment. Left ventricular fascicular tachycardia is more commonly associated with the left posterior fascicle and has an RBBB–left axis configuration. The RBBB–right axis configuration of this VT is associated with the anterior fascicle.[80-82] Termination with verapamil is usual. Rarely adenosine may terminate this VT if catecholamines were required for its induction.[83] Incessant forms of left ventricular fascicular VT can result in a tachycardia-induced cardiomyopathy.[84]

Adrenergic monomorphic VT can present with a left or right bundle branch QRS pattern. Clinical and electrophysiological characteristics of this VT are poorly defined. This form of VT has electrophysiological properties that would be expected with enhanced automaticity as its basis. It is often initiated by catecholamine infusion and exercise, but it cannot be induced, entrained, or terminated by programmed stimulation. Verapamil has no effect on this form of VT, whereas adenosine has been reported to result in transient suppression.[82,83] It is terminated and suppressed by β-blockers.

Monomorphic IVT with both LBBB and RBBB morphologies is observed in infants and children.[84] These arrhythmias may be incessant, which can result in a tachycardia-induced cardiomyopathy. More often, they have a good prognosis and may also resolve spontaneously. The extent to which these arrhythmias have similar mechanisms to RVOT VT, left ventricular fascicular VT, and adrenergic monomorphic VT is uncertain. Other forms of monomorphic VT may be encountered in patients without significant structural heart disease in clinical practice. Often, these cannot be classified as one of the common forms detailed earlier.

Principles of Practice

The first clinical objective in evaluating a patient who presents with possible IVT is to estimate the immediate risk of arrhythmic death. If the risk is high or uncertain, the patient must be hospitalized and continuously monitored until definitive treatment is established or the risk of death is determined to be low. IVT syndromes are usually considered after common arrhythmic conditions and underlying heart disease are excluded. However, laboratory studies cannot definitively exclude the presence of an IVT syndrome. Therefore, even when the etiology of VT appears clear, the practitioner must always be cognizant of the possibility that an IVT syndrome may coexist. The goal of the clinical evaluation process is also to identify all potential arrhythmogenic factors. This permits the most precise estimation of the risk of SCD and appropriate choice of therapy. Thus, evaluation is a process of both positive identification and exclusion of arrhythmogenic factors.

Two classes of conditions associated with VT must be excluded before a presumptive diagnosis of IVT is made (Box 45-2). Extrinsic proarrhythmic factors (e.g., conditions that cause electrolyte

Box 45-2 Disorders that Mimic Nonstructural Ventricular Tachyarrhythmia Syndromes

EXTRINSIC DISORDERS
Epilepsy
Substance abuse
Extreme diets
Hyperaldosteronism
Hypercoagulation
Pulmonary embolism
Bradyarrhythmias
Supraventricular tachyarrhythmias

UNDETECTED STRUCTURAL HEART DISEASE
Right ventricular dysplasia
Sarcoidosis
Hypertrophic cardiomyopathies
Dilated cardiomyopathies
Myocarditis
Coronary artery spasm
Anomalous coronary artery
Coronary artery disease
Accessory atrioventricular connections

disturbances or drugs that prolong repolarization) may be associated with VT in the presence of normal cardiac structure and function and are discussed elsewhere in this text. In addition, VT may exist with undetected cardiac disease and can mimic IVT syndromes. A comprehensive evaluation that attempts to exclude all potential conditions that could contribute to arrhythmogenesis requires invasive procedures for definitive diagnosis. This is essential in the patient who presents with cardiac arrest or a hemodynamically compromising VT, but the extent to which it should be applied to patients with less symptomatic presentations or suspected IVT must be judged individually.

EPS can provide information in some cases where the history, ECG, and other tests results are inadequate to guide therapy. EPS has at least three potential indications. First, it is used to screen for various forms of IVT in patients without documented arrhythmias. Various forms of programmed stimulation (extrastimulus testing and rapid pacing) before and during catecholamine infusions are used to initiate VT. Induction of a sustained VT is generally considered an abnormal response. However, the induced VT and the hemodynamic response should be consistent with the clinical presentation. Identification of fractionated potentials during sinus rhythm might be taken as evidence of substrate for re-entrant arrhythmias. Induction of PMVT or VF is considered a risk factor for spontaneous ventricular arrhythmias in patients with IVF or Brugada syndrome. However, failure to induce VT or VF does not indicate a low risk. Unfortunately, the sensitivity of EPS for nonspecific screening is low because many forms of IVT cannot be reliably induced. In addition, if the pretest probability of an IVT is low, as for common symptoms such as syncope, the yield of EPS will be exceedingly low. Moreover, the likelihood of a false-positive response is increased. The advantages of EPS are that the results can be obtained quickly and used immediately if the test result is positive. It is hoped that new methods of provocation will be developed to expand the usefulness and enhance the value of EPS. Provocative testing by administration of ajmaline, flecainide, or procainamide has been advocated for patients at increased risk for Brugada syndrome. However, flecainide has also been suggested as a therapy for LQT3. A recent study demonstrated that changes in the ECG suggestive of Brugada syndrome occurred in patients with the LQT3 genotype, raising concerns about the role of flecainide both as a treatment and as a provocative test. Thus, the optimal use of this drug test has not yet been defined.

The second function of EPS is to confirm IVT and refine clinical diagnostic possibilities. This is exemplified by the patient who presents with monomorphic IVT. If the arrhythmia can be induced, it can often be characterized by the mode of induction (extrastimulus technique, rapid pacing, requirement for catecholamines), the electrocardiographic pattern (bundle branch pattern and axis), the presence of multiple configurations, the response of tachycardia to pacing maneuvers (entrainment, resetting, termination), and the response to drugs (e.g., adenosine, verapamil, and β-blockers) and vagal maneuvers. EPS may provide critical data needed to distinguish monomorphic IVTs, which are usually associated with a good prognosis, from VT associated with life-threatening disorders. The most common clinical dilemma is to distinguish between RVOT VT and VT caused by arrhythmogenic right ventricular dysplasia. VT arising from these two disorders may have similar QRS configurations and response to programmed stimulation, including sensitivity to catecholamines. The most useful differential finding is sensitivity to adenosine, which is rarely observed in other forms of VT.

The third function of EPS in patients with IVT is therapeutic. EPS has been reported to be useful for guiding antiarrhythmic drug therapy in patients with IVF, although this approach is now not widely recommended. RF catheter ablation is widely used in the monomorphic IVT syndromes after mapping of the IVT origin at EPS. Figure 45-10 is a noncontact three-dimensional map of catheter ablation of the RVOT focus. Note that individual lesions are marked at the site of application relative to the focal origin and propagation of the arrhythmia. Catheter ablation may be the therapy of choice for many patients with IVT syndromes.

Genetic testing can provide a more precise diagnosis if a specific mutation is detected. It is limited in that many key genetic abnormalities have not yet been defined. Currently, another major problem is that this test is still not as widely available as desired, though commercially available testing is being disseminated. Nevertheless, little doubt exists that genetic testing will become routine, as it will improve risk assessment and treatment of the patient, living relatives, and future generations of the family.

Evidence-Based Therapy

No clinical trials have addressed therapeutic options in patients with IVT and IVF syndromes. Retrospective and prospective registries have produced data that are used to guide therapy. The reliability of the results and their applicability to future patients are uncertain because databases are small and biases created by the referral process may exist. Nevertheless, they provide the best available evidence. Consensus statements from professional societies have leaned heavily on these resources.[23,25,35,59] The largest registry exists for patients with LQTS. Results from this database support the use of β-blockers as a mainstay of therapy but report a persistently high risk despite β-blocker therapy in patients with a history of cardiac arrest or syncope.[85] A report from an international registry suggests that medical therapy with β-blockers, sodium channel blockers, and amiodarone are ineffective for

IVF. This contradicts a prior study from Belhassen et al, which reported success in EPS-guided treatment with certain sodium channel blockers, especially quinidine.[86]

Management of Idiopathic Ventricular Tachycardia and Ventricular Fibrillation

Prevention of SCD is the first priority in patients with IVT and IVF syndromes. Affected individuals are often young and have normal cardiovascular function. They have few competing risks, and long-term survival may depend on the risk of arrhythmic death and complications resulting from therapy. Unfortunately, precise arrhythmic risk assessment for IVT syndromes is difficult. First, data for reliable outcome prediction are scarce. Second, heterogeneity exists within the IVT population. Arrhythmic risk may be affected by a particular genotype and by variations among a particular genotype. Penetrance for a given genotype has been found to vary unpredictably.[87] Inadequate diagnoses in families pose another challenge that is often encountered during the evaluation of living members of a family in which multiple SCDs have occurred. Affected living family members are assumed to carry the "malignant" genotype, and prophylactic therapy is often considered. However, it is often not possible to determine the genotype if it is an ambiguous phenotype and because genetic testing is often not available. In such instances, the individual is either at very high risk or very low risk. Fortunately, risk assessment should continue to improve as IVT registries collect more data, diagnostic methods improve, and genetic testing becomes a widespread clinical tool.

The potential for SCD, uncertainty of arrhythmic risk, and limitations of existing therapeutic options complicate the management of IVT and IVF syndromes. It is widely assumed that the ICD is an acceptable therapy for IVF and malignant forms of IVT. Results from clinical trials support the use of ICDs over amiodarone for reduction of all-cause mortality in survivors of cardiac arrest and patients with certain forms of VT.[88] However, available clinical trial evidence has been largely obtained from cardiac arrest or VT populations with heart disease and multiple competing mortality risks. These trials may be poor guides to selection of therapy in patients with IVT syndromes. Long-term data on ICD efficacy are now available from some registries and observational studies.[89-92] These data suggest that long-term prevention of SCD is achieved with ICD therapy, with an acceptable complication rate. Recently, catheter ablation of triggering VPBs has been performed in patients with IVF and the Brugada syndrome at specialized centers. Evidence to support reduction in arrhythmic event rates exists, but no large clinical study or comparative evaluation of catheter ablation versus the ICD is available. As such, this therapy must be considered adjunctive to ICD implantation at this time. This is discussed further in Chapters 94 and 95.

Patients with IVT are often children or adolescents. ICDs may have a significant advantage in these patients in that they ensure therapeutic compliance. In this group of patients, compliance with medications is often difficult, especially in the absence of symptoms. Devices also offer female patients protection during pregnancy without the need for antiarrhythmic drug therapy. However, young patients face numerous replacements of the ICD generator and leads and a long period of exposure to the complications of ICD therapy. Furthermore, quality of life may be adversely affected by concern about body image, isolation and ridicule from peers, and dependence on medical services.[93] ICD shocks, whether appropriate or inappropriate, may diminish quality of life still further.

Despite reasons for considerable concern with regard to the effects of ICD therapy on quality of life in the young population and the risks of long-term ICD therapy, no alternatives are likely to provide more reliable protection against arrhythmic death. ICDs are therefore recommended if the risk of arrhythmic death is high. Survivors of cardiac arrest or rapid ventricular tachyarrhythmias are usually assumed to be at high risk. This fact is borne out by results from the Unexplained Cardiac Arrest Registry of Europe (UCARE), which estimated the rate of recurrence of cardiac arrest or syncope in patients with idiopathic VF to be about 30%.[25]

Decisions regarding the use of ICDs in groups of patients with higher risk/benefit ratios are more difficult (e.g., patients who present with syncope, affected asymptomatic family members of cardiac arrest survivors, and asymptomatic members of "high risk" families whose genotype is unknown).

LQTS may be a prototype for IVT syndromes in that it demonstrates how progress improves care but also creates new areas of uncertainty. Only approximately 70% of LQTS carriers have unequivocal QT prolongation, and approximately 12% have a normal Q-T interval. In addition, SCD is the first manifestation of the syndrome in at least 10% of affected persons. Several genetic defects and sporadic mutations that cause this disorder are probably still undiscovered. Moreover, the types of provocative factors, the risk of sustained VT, and the response to therapy vary with the specific genetic defect. Despite the effectiveness of the therapy itself, failure of medical therapy may result from several sources, including incomplete compliance, inadequate drug dose, or exposure to proarrhythmic drugs. Patients who present with VT or syncope, those with symptoms despite β-blockers, and other individuals at high risk are candidates for ICD therapy. Left cervico-thoracic ganglionectomy and permanent pacing probably prevent SCD in some individuals, but failures have been reported. They may be useful adjuncts or alternatives in patients who are intolerant of β-blockers or in those who are not able to comply with drug therapy. Experimental therapies include administration of supplemental potassium chloride for *HERG* mutations, potassium channel openers for LQT1 and LQT2, and mexiletine or flecainide for LQT subtypes 3, 2, and possibly 1.[92,93]

In contrast to LQTS, widely accepted treatment alternatives to the ICD for preventing arrhythmic death in other IVT syndromes associated with PMVT or VF are not yet available. In Brugada syndrome, sodium channel blockers are used to provoke characteristic ECG abnormalities and may provoke VT.[92] Other drugs such as β-blockers and amiodarone have not provided adequate protection. Likewise, as noted earlier, the UCARE database results indicate failure of treatment with amiodarone, β-blockers, and sodium channel blockers in patients with IVF.[25] In contrast, treatment with class I antiarrhythmic drugs, mostly quinidine, guided by EPS was reported to be effective in one small series.[86] It is possible that the distinctive effects of quinidine on the transient outward current were responsible for the excellent protective effect that was observed. However, this approach has not been widely embraced, although certain subgroups of LQTS and short QT syndrome have been shown to respond to type 1 drugs. Verapamil and amiodarone may inhibit VT in the short-coupled variant of torsades de pointes but have not been shown to prevent SCD.[94] β-Blockers are reportedly effective in patients with CPVT,

but the experience may be too limited to adopt this approach with confidence. As yet, no well-defined role exists for surgical intervention (other than left cervicothoracic sympathectomy in LQTS) for polymorphic IVT and IVF syndromes.

The risk of arrhythmic death is believed to be low in monomorphic IVT syndromes such as RVOT VT and its variants. Unless features are present to suggest a malignant potential, such as syncope or very rapid tachycardia, ICD therapy is not indicated. Instead, the goal is to relieve symptoms or prevent the detrimental effects of incessant tachycardia.[59,91] If symptoms are absent or minimal and tachycardia is infrequent, no treatment may be necessary. Pharmacologic therapy with β-blockers or calcium antagonists, alone or in combination, is usually safe and often effective.[59] Amiodarone, sotalol, encainide, and flecainide may be effective. Nicorandil, a potassium channel opener, has been reported to terminate and suppress adenosine-sensitive VT.[93] If adequate control is obtained with well-tolerated and presumably safe pharmacologic therapy (e.g., with β-blockers or calcium channel blockers), then this therapy may be preferred in many individuals. If symptoms are intermittent, then drugs could also be used on an "as needed" basis.

Nonpharmacologic therapy should be considered for patients with disease refractory to drug therapy or who are intolerant of drug therapy, those who prefer it to a lifelong need for drugs, and those who wish to become pregnant. Many patients prefer to discontinue all medications when pregnant, a time when therapy should not be withdrawn because changes in cardiovascular function due to pregnancy could exacerbate some forms of VT or cause more severe symptoms. Catheter ablation offers the possibility of permanent correction, with a high probability of success (Figure 45-11). The techniques of mapping and ablation are described in Chapters 94 and 95. In brief, contact catheter mapping or noncontact mapping is used to identify the site of earliest ventricular activation. Presystolic potentials are usually present at this site, and repetitive firing can usually be demonstrated at this location, often after isoproterenol administration.[94] RF contact catheter ablation lesions are delivered at this site and in adjoining areas. Occasionally, more than one site may be seen. Efficacy rates can exceed 80% to 90% in RVOT VT, with a 5% VT recurrence rate. Predictors of failure with catheter ablation include failure to induce and map the arrhythmia at EPS, multiple VT morphologies, a δ wave–like beginning of the QRS, and a poor match between the 12-lead ECG during VT and during pacing at the ablation site.[95] Left heart catheterization is not required for most cases of RVOT VT, which minimizes the risk of complications estimated at less than 2%. Cardiac perforation and tamponade have been reported, and ablation of foci near the bundle of His region can result in heart block. High-power irrigated ablation could injure the posterior regions of the RVOT artery trunk and the coronary ostia and pulmonary arterial trunk. Risks may also be greater if lesions are delivered in the LVOT VT or in the epicardial regions. Thromboembolism, coronary arterial injury, and aortic valve injury may occur during LVOT VT ablation. Heart block, aortic valve injury, and coronary artery injury are potential risks with ablation of aortic cusp VT and mitral annulus VT. Specialized technical approaches and multi-modality imaging are often needed to avoid complications with these arrhythmias. See Chapter 94 for more detailed technical considerations.

Drug therapy is associated with a low initial risk but greater risk of failure because of ineffectiveness or intolerance and potential for unknown, long-term adverse reactions. Moreover, the cost difference may be minimal because of the long-term need for drugs and the possibility that catheter ablation will be necessary at a later date. In the absence of a controlled comparison of drug therapy and catheter ablation, each case must be considered individually, and the alternatives discussed thoroughly to determine the most appropriate therapy for the patient. Device therapy (e.g., pacing inhibition or anti-tachycardia pacing) could trigger RVOT VT and therefore would not be a logical first-line choice. However, published evidence that confirms or refutes this is lacking.

Idiopathic fascicular VT is also believed to have a benign long-term outlook, although the extent of experience is less than that for RVOT VT.[59] Treatment is indicated for the prevention or control of symptoms and for protection against the potential deleterious effects of incessant tachycardia. Calcium antagonists have been shown to be effective in many patients, as have β-blockers. Drug therapy or catheter ablation are both reasonable approaches. Probably, many types of monomorphic IVT do not have characteristics of left ventricular fascicular VT or RVOT VT. The prognosis of such arrhythmias cannot be assumed to be as

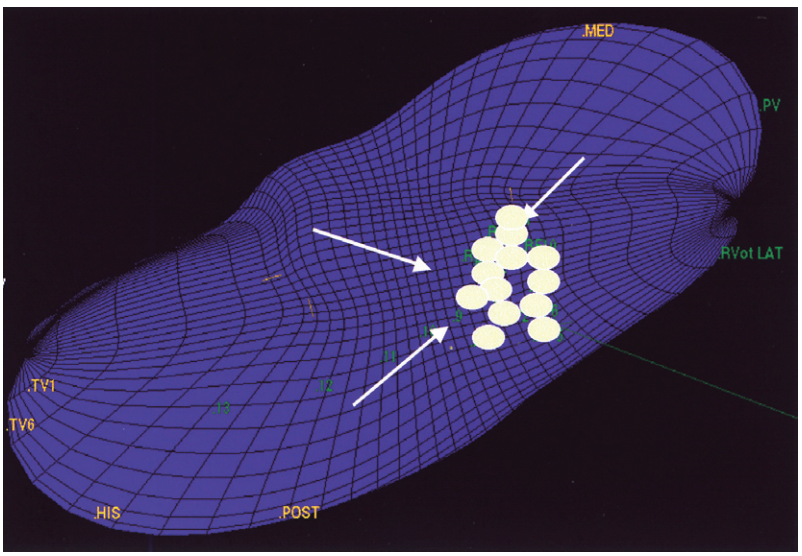

FIGURE 45-11 Catheter ablation guided by three-dimensional noncontact mapping in the same patient with ventricular tachycardia arising from the right ventricular outflow tract shown in Figure 45-4. Ablation lesions (*circular markers*) are shown individually at the focal origin and in the surrounding region. Successful ablation was achieved.

benign as these IVTs. Clinical judgment must be used individually to assess the risk-to-benefit ratio of ICD implantation, catheter ablation, or drug trials in these patients.

Summary

Increasingly recognized as being encountered in practice, IVT and IVF syndromes are always in the differential diagnosis of patients who present with known or suspected VT. The diagnosis can be obvious if characteristic ECG findings are present, but these can be occult or absent in many patients. The clinical challenge occurs because no tests or algorithms are capable of excluding IVT syndromes. Finally, IVT and IVF syndromes have proven to be contributors to SCD in the absence of structural heart disease. Substantial effort is now being devoted to discovering the mechanisms of these arrhythmias and to developing tests to identify susceptible individuals, which will eventually lead to clinical trials in these populations.

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CHAPTER 46

Ventricular Fibrillation

Introduction, Principles of Practice: Paul Dorian
Etiology and Pathology: Saroja Bharati
Epidemiology: Robert J. Myerburg
Basic Electrophysiology: David Rosenbaum, Kara J. Quan, and Mariah L. Walker
Clinical Electrocardiography: Bruce D. Lindsay
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Evidence-Based Therapy: Paul Dorian and Michael Domanski

Ventricular fibrillation (VF) is the most serious cardiac arrhythmia and has a primary role in mediating sudden cardiac death (SCD). It leads to immediate circulatory arrest with cardiovascular collapse. A variable period may elapse, but cardiac asystole usually supervenes (Figure 46-1). Spontaneous termination of VF, which is seen in animal experiments, is rare in humans. VF is often preceded by an organized, rapid ventricular tachycardia (VT) of variable duration; recordings from implantable devices have now substantiated this. Ischemic injury may trigger VF. If untreated, this leads to irreversible end-organ damage, including cerebral and myocardial damage after 5 to 7 minutes of VF. Even with optimally performed basic cardiopulmonary resuscitation (CPR), the mortality rate is greater than 95% if defibrillation is delayed by more than 10 minutes. The rule of survival from out-of-hospital VF is that survival decreases by 10% for each minute before defibrillation. The sine qua non of effective resuscitation from VF is thus prompt defibrillation, delivered as early as possible. Importantly, however, a brief period of CPR *before* defibrillation in out-of-hospital cardiac arrest, especially if the arrest is more than 4 minutes in duration, may increase survival rates.

Etiology

VF occurs in many disease states of the myocardium and the conduction system and can be broadly grouped under two categories: (1) genetic/familial and (2) acquired. Genetically based abnormalities of the myocardium or the specialized conduction fibers or both may give rise to the clinical manifestations of familial occurrence of VT and VF. In most cases, the initial arrhythmia is one of various forms of VT (monomorphic or polymorphic VT, which then degenerates to VF). However, acquired cardiac diseases such as coronary artery disease (CAD), hypertensive heart disease, cardiomyopathy of any etiology with or without heart failure, and other miscellaneous disease states (see Chapter 47) are the most common causes of VF and SCD.[1-3] VT leading to VF may occur in acute myocarditis of any etiology. However, intractable VT with recurrent cardiac arrest refractory to medications or defibrillator device implantation may be related to chronic myocarditis (Figure 46-2).[4-6]

Pathology

The anatomic basis for VF in acquired heart diseases is similar to that of VT. In this chapter, emphasis is given to the morphologic findings for VF in athletes or healthy youths who were seemingly living a "normal, asymptomatic" life and died suddenly. In addition, familial occurrences of SCD caused by recurrent VT degenerating to VF is briefly discussed.[1-3,5,6]

Sudden Cardiac Death in Athletes or the Young and Healthy

The conduction system has been carefully studied in several young persons who were living a "normal" life and died suddenly. Routine autopsies are often unremarkable. In the majority, the heart is hypertrophied and enlarged to a mild, moderate, or marked extent; however, at the gross level, no significant abnormalities were seen.[3] A serial section examination of the conduction system and the surrounding myocardium reveals varying types of abnormalities, either of a congenital or acquired nature. Congenital abnormalities can exist in the sinoatrial (SA) node, atrioventricular (AV) node, or the AV bundle and the bundle branches (Figure 46-3). Abnormal formation of the SA or AV nodes, such as a double SA node, a double AV node, or the abnormal location of the SA and AV nodes in unexpected areas, can be seen pathologically. The AV bundle may be considerably fragmented into several components, abnormally located, or both. In addition, acquired pathologic findings exist in the form of focal myocardial disarray, fat, or fibrosis to varying degrees, disrupting or replacing parts of the specialized conduction fibers and the

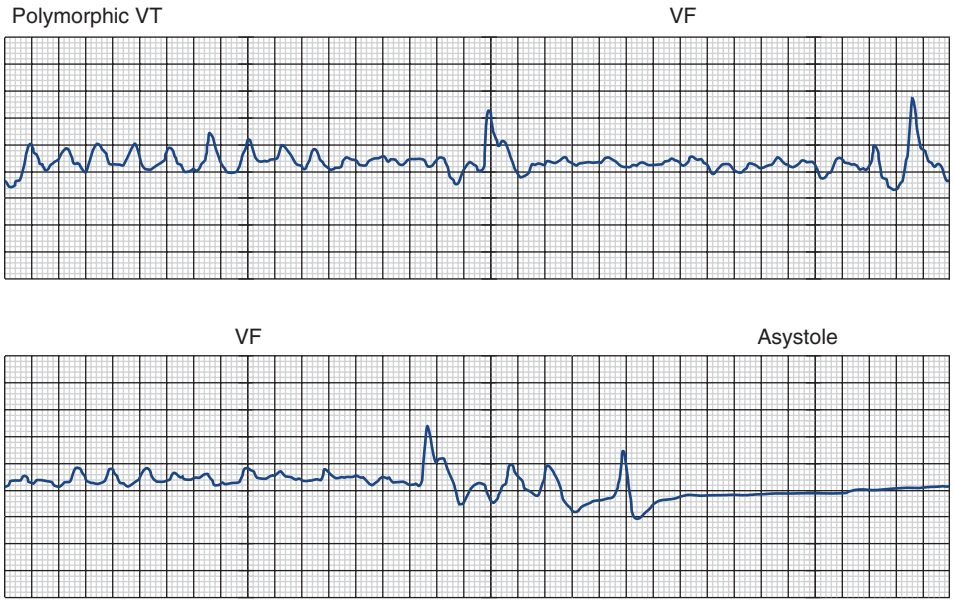

FIGURE 46-1 Evolution of polymorphic ventricular tachycardia (*VT*) into ventricular fibrillation (*VF*) and subsequent development of cardiac asystole.

surrounding myocardium (see Figure 46-3) with arteriolosclerosis (small vessel disease) of the ventricular septum. In general, the findings in the conduction system are accompanied by pathologic findings in the surrounding myocardium. Mononuclear cell infiltration in the approaches to the SA node and in the SA node itself is present.[3]

Despite such pathologic findings in and around the conduction system, these persons were considered to be asymptomatic, and SCD was the first manifestation of the disorder. Clinically, in almost all, VF was the only common denominator observed by the paramedics at the time of resuscitation. It can be hypothesized that varying types of congenital or acquired pathologic findings in and around the conduction system may remain "silent," and these individuals are asymptomatic for long periods. Other disorders (e.g., right ventricular cardiomyopathy, hypertrophic cardiomyopathy, idiopathic dilated cardiomyopathy) can lead to VT degenerating to VF, the first evident manifestation of the disease. During an altered physiological or metabolic state, anatomic findings, pathologic findings, or both may trigger an arrhythmia that progresses to VT, VF, and SCD.[3]

Familial Sudden Cardiac Death

A genetic tendency for the development of an abnormal conduction system, the surrounding myocardium, or both may also lead to VT, VF, and SCD (Figure 46-4).[5,6] Familial occurrence of ventricular arrhythmias may be related to the many genetic mutations associated with congenital long QT syndrome (LQTS) or Brugada syndrome. These disorders of ion channel function may also lead to cellular dysfunction and pathologic changes such as fatty infiltration, fibrosis, and disruption of the conduction system and the adjoining myocardium.[7,8] These disorders are discussed in other chapters in this text and are alluded to in subsequent sections of this chapter.

Of note, in many cases of SCD in young patients, no gross anatomic or histologic abnormalities are identified.

Epidemiology

Ventricular Fibrillation and Sudden Cardiac Death

The epidemiology of VF intertwines with the available data on SCD (or cardiac arrest) and its documentation by emergency medical system (EMS) personnel.[9] In 1998, an epidemiologic prospective study from northeast Italy reported an incidence of cardiac arrest of 95 of 100,000 persons per year.[10] In this study, VF accounted for 30.2% of the initially recorded rhythms, asystole for 48.3%, and pulseless electrical activity for 21.5%. A similar study of out-of-hospital cardiac arrest confirmed VT or VF as the initial rhythm in 59 (30%) of 197 patients of a patient cohort from the Los Angeles area.[11] Although VT and VF were consistently more likely to be associated with return of spontaneous circulation in these two studies, the time dependency of the initial recorded rhythm is still debated. The Ontario Prehospital Advanced Life Support (OPALS) study quoted an annual incidence of 58 out-of-hospital cardiac arrests per 100,000 persons, and in the subgroup of EMS-witnessed cardiac arrests, VT and VF accounted for 34.2% of cases.[12] However, a recent analysis from Sweden estimated that patients with an electrocardiogram (ECG) taken within the first 10 minutes from a witnessed cardiac arrest have an incidence of VF of 50% to 60%. Linear regression further estimated that ECGs taken within the first 4 minutes should have an incidence of 75% to 80%.[13]

Ventricular Fibrillation and Population Considerations

Despite the debate on the true proportion and incidence of VF in prehospital cardiac arrest, event rates range from 250,000 to more than 450,000 per year in the United States.[14] This absolute number is heavily influenced by population dynamics and the defined subpopulation being discussed.

The median incidence of cardiac arrest in 10 large Canadian and U.S. communities is 52 cases per 10,000 annually.[15] The

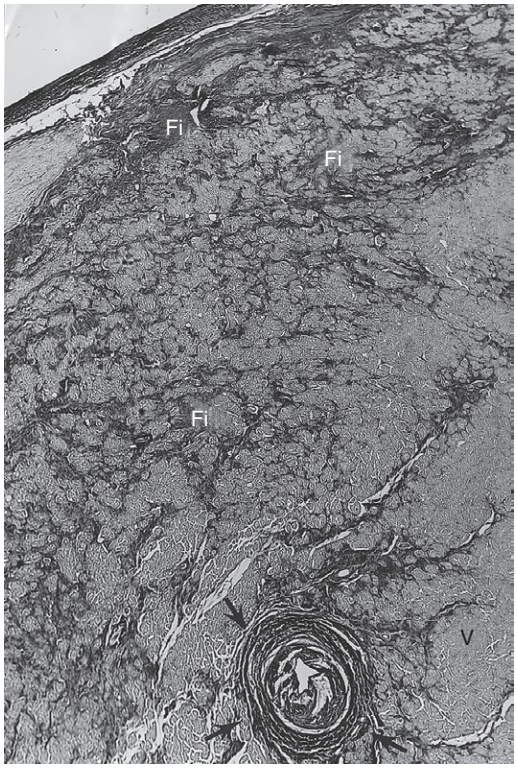

FIGURE 46-2 Chronic myocarditis in a 35-year-old man with polymorphic sustained drug-refractory ventricular tachycardia associated with multiple cardiac arrests, uncontrolled by β-blockers, antiarrhythmic drugs, and defibrillator insertion. The patient underwent heart transplantation. The explanted heart revealed myocarditis of a chronic or smoldering type in the approaches to the atrioventricular (AV) node, the AV node, and beginning of the right bundle branch. The AV bundle revealed fibro-fatty change and was left sided. There was marked fibrosis of the left bundle branch, chronic epicarditis, arteriolosclerosis of the summit of the ventricular septum, and fibrosis on both sides of the septum. (Weigert-van Gieson stain ×45). *Arrows* point to arteriolosclerosis. *Fi*, Fibrosis in the myocardium; *V*, ventricular septum. *(From Bharati S, Olshansky B, Lev M: Pathological study of an explanted heart due to intractable ventricular fibrillation,* J Cardiovasc Electrophysiol *3:437–441, 1992.)*

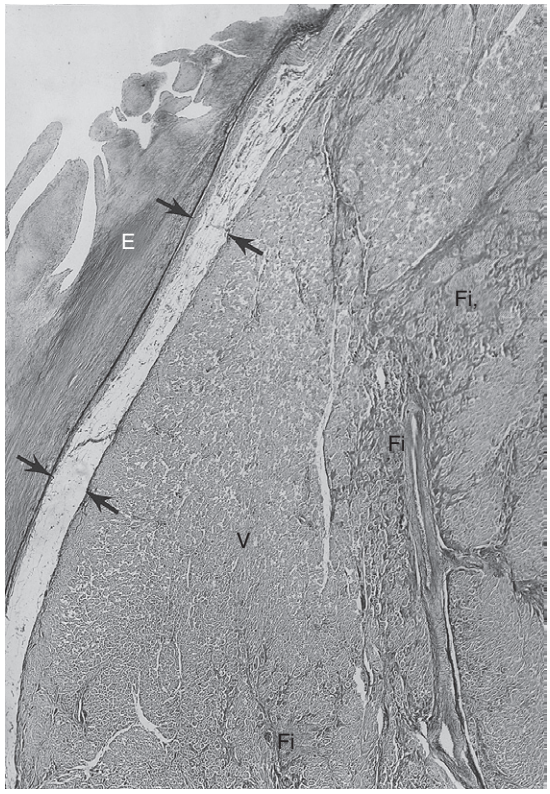

FIGURE 46-3 Conduction system and adjoining myocardial disease in a 25-year-old man who collapsed while playing basketball. He was found to be in ventricular fibrillation and could not be resuscitated. Photomicrograph of the left bundle branch shows falling out of cells. Note the endocardial thickening and numerous focal areas of fibrosis of the ventricular septum (Weigert-van Gieson stain ×30). *Arrows* point to the loss of left bundle branch fibers. *E*, Endocardium; *V*, ventricular septum; *Fi*, fibrosis. *(From Bharati S, Lev M:* The cardiac conduction system in unexplained sudden death, *Mount Kisco, NY, 1990, Futura.)*

well-documented high-risk subgroups (ischemic heart disease with low left ventricular ejection fraction [LVEF], complex ventricular ectopy, prior hospital admission for congestive heart failure [CHF], or previous cardiac arrest) contribute a *minority* of the total number of cardiac arrests, although the subgroup percent incidence per year is the highest (Figure 46-5).

A screening tool or preventative intervention would need to be applied to 999 of 1000 persons to influence the 1 of 1000 previously unidentified persons destined for a cardiac arrest. The Framingham study demonstrated a large disparity from the highest to lowest decile (14-fold increase in risk) for SCD measuring the well-known risk factors such as age, family history, gender, tobacco use, hyperlipidemia, and hypertension.[16] Electron beam computed tomography for the detection of coronary artery calcification has been correlated to coronary event risk.[17] A recent publication compared the Framingham risk index and coronary artery calcification in an autopsy series of SCD victims.[18] The two risk assessment methods had modest correlation with each other (63%). Of the cases, 83.5% had a coronary artery calcification score or Framingham risk index above average for age. The remaining 17.5% highlight the need for exploration of new cardiac risk factors (e.g., fibrinogen, homocysteine, infectious agents, or ion channel abnormalities) that could be applied to the population at large.

The high-risk subpopulations have been targeted in recent publications for epidemiologic analysis. The Worcester Heart Attack Study described a relatively fixed incidence rate of 4.7% for VF in hospitalized patients with validated acute myocardial infarction (MI) over a 22-year period (1975 to 1997).[19] The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2) database reported an incidence of early-onset VF (<4 hours after onset of acute MI) and late VF (>4 to 48 hours) of 3.1% and 0.6%, respectively. In-hospital prognosis was worse in patients with VF than without VF, but the postdischarge to 6-month mortality rate was similar for both VF subgroups and controls.[20] The patient with prior cardiac arrest has a similar "time dependence" of risk of recurrent events, as was presented by Furukawa et al (Figure 46-6).[21]

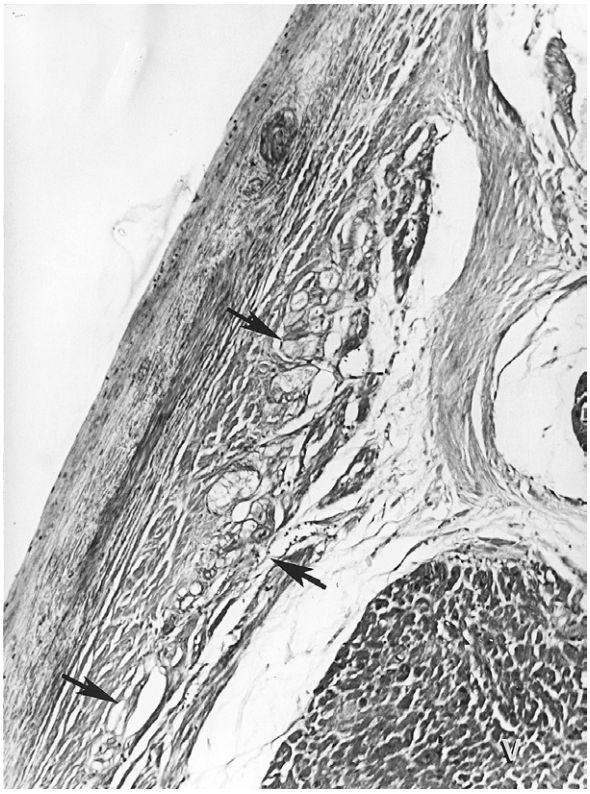

FIGURE 46-4 Cardiac conduction system histology in a 16-year-old girl with a familial history of alternating bi-directional tachycardia who died suddenly. Fatal ventricular arrhythmias occurred in three generations, including two siblings and the mother. The conduction system revealed degenerative changes. Photomicrograph demonstrates vacuolar degeneration of left bundle branch (hematoxylin-eosin stain ×104). *Arrows* point to vacuolar degeneration of main left bundle branch. *(From Gault JH, Cantwell J, Lev M, Braunwald E: Fatal familial cardiac arrhythmias,* Am J Cardiol *29:548–553, 1972.)*

Low LVEF was a strong predictor of the highest risk of recurrence (11% in the first 6 months). Persistent inducibility at electrophysiological study (EPS) was the better predictor for recurrent events from 6 to 42 months, but the subsequent risk fell to 0.8% over the final 6 months of the study period. In the patients who entered the Antiarrhythmics Versus Implantable Defibrillators (AVID) study with VF, the survival curve shows the same early recurrence (<6 months) in the patients treated with antiarrhythmic drugs as those who did not receive this therapy (Figure 46-7).[22]

Clinical trials are assessing the "static" risk of cardiac events outside the setting of acute hospitalization.[23] The Multicenter Automatic Defibrillator Implantation Trial (MADIT-II) trial tested implantable cardioverter-defibrillator (ICD) therapy versus standard medical therapy in patients with ischemic heart disease, an LVEF less than 30%, and previous MI. It showed a 31% relative risk reduction with ICD therapy. The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) trial compared three arms of therapy in patients with congestive heart failure and LVEF less than 30%: best conventional heart failure therapy with placebo, best conventional heart failure therapy with amiodarone, and best conventional heart failure therapy with ICD.[23] In a preliminary report, there was a 23% relative reduction in all-cause mortality with the ICD compared with placebo (7.2% to 5.8% per year), and no reduction in mortality rate with amiodarone compared with placebo. The most recent developments in assessing risk of cardiac arrest have been in the blossoming technology of molecular genetics. The familial types of LQTS and their respective genetic bases have been well described elsewhere. An increasingly recognized syndrome of right bundle branch block (RBBB), ST segment elevation, and aborted SCD (Brugada syndrome) has also been ascribed to a genetic mutation in the gene encoding the cardiac sodium channel. Its prevalence in a European study by ECG screening was estimated at 0.1% of the general population.[24] If the only effective therapy for the syndrome is ICD implantation, the economic impact on the public health budget is obvious.

A trial of the automated external defibrillator (AED) to be used in the home by trained spouses or cohabitants of individuals with prior anterior MI (the Home Automated External Defibrillator Trial [HAT]) was not able to show a reduction in mortality rate, in part because of the unexpectedly low incidence of VF as the initial recorded arrhythmia in these patients.[25]

The epidemiology of VF and SCD are closely aligned. From a public health perspective, the largest number of cardiac arrest survivors will have the well-described cardiac risk factors from the Framingham study (e.g., hypertension, hyperlipidemia). An intervention for the population as a whole, however, will require treatment of a vast majority to prevent a single cardiac arrest. The high-risk subset of pre–cardiac arrest (although a minority of the total number) is currently undergoing research investigating prophylactic ICD implantation and the cost effectiveness of such a practice. New screening tools that are widely applicable, economical, and cost-effective are needed for future progress in SCD prevention.

Basic Electrophysiology

During VF, the myocardium fails to contract effectively and circulate blood. Although certain species such as rats can spontaneously revert from VF to normal sinus rhythm, in humans, VF is lethal if not treated promptly. Thus, analysis of the electrophysiological mechanisms culminating in VF is critical to effective therapy.

Ventricular arrhythmias can develop by three major mechanisms. Abnormal impulses may be initiated by (1) triggered activity (early or delayed afterdepolarizations); (2) abnormal automaticity, which refers to the inherent ability of various regions of myocardium (other than the SA node) to act as pacemakers; and (3) re-entry. Re-entrant excitation is believed to be the primary, and most clinically relevant, mechanism for VF and is therefore the focus of this chapter.

Dynamics of Re-entrant Ventricular Fibrillation

VF is generated by self-sustained re-entrant circuits that turn around regions of conduction block. In some circumstances, the zone of conduction block can be anatomic in nature, such as the site of a healed infarct or a region of fibrosis. In such cases, the re-entrant circuit is anchored to the site of block and results in a stable rotor and monomorphic VT. When the zone of conduction block is functional in nature, the region of refractoriness is transient both spatially and temporally. Re-entrant circuits that form around such zones can therefore meander freely or change

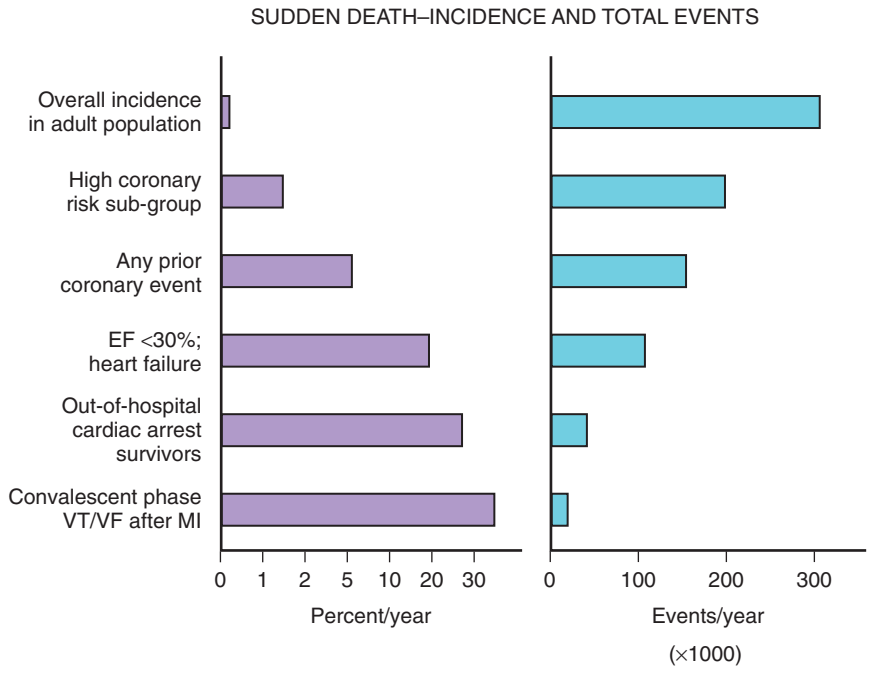

FIGURE 46-5 Risk of sudden cardiac death, with influence of pre-existing heart disease on magnitude of risk in middle-aged and older adults. The prevalent etiologies are a function of age. *EF*, Ejection fraction; *VT/VF*, ventricular tachycardia/ventricular fibrillation; *MI*, myocardial infarction. *(Modified from Myerburg RJ, Kessler K, Castellanos A: Sudden cardiac death: Structure, function and time-dependence of risk,* Circulation *85[suppl I]:2–10, 1992.)*

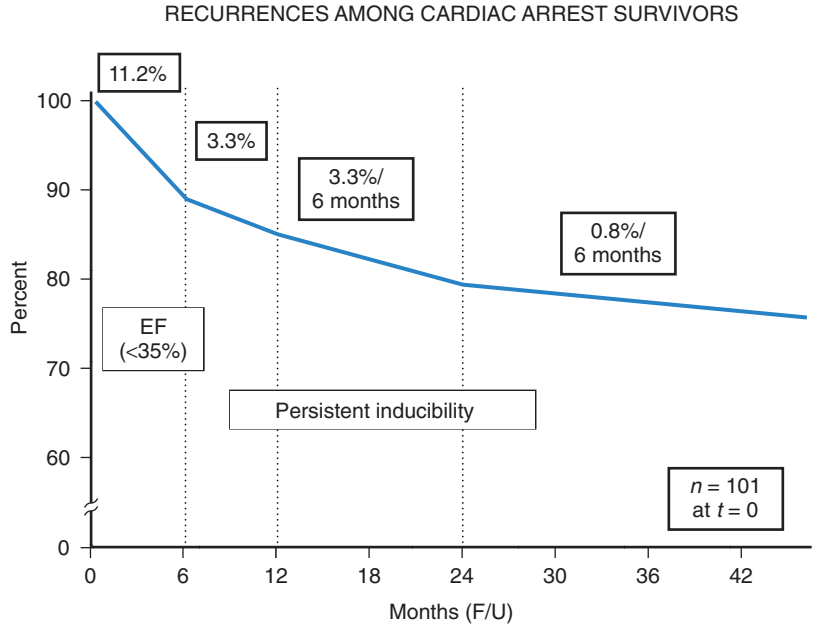

FIGURE 46-6 Risk of recurrent cardiac arrest among survivors of out-of-hospital cardiac arrest. The highest risk of recurrent cardiac arrest is within the first 12 to 24 months. In the earlier part of that period, ejection fraction (*EF*) is the most powerful predictor, whereas persistent inducibility of ventricular tachyarrhythmias during electrophysiological studies becomes an important predictor beyond that period. Nonetheless, EF remains a predictor throughout. *F/U*, Follow-up. *(Modified from Furukawa T, Rozanski JJ, Nogami A, et al: Time-dependent risk of and predictors for cardiac arrest recurrence in survivors of out-of-hospital cardiac arrest with chronic coronary artery disease,* Circulation *80:599–608, 1989.)*

in size, providing an important mechanism for VF. However, the nature of re-entrant waves and the mechanisms by which they lead to VF are still not entirely clear.

Nature of Fibrillatory Wavefronts

Re-entrant excitation is the fundamental mechanism responsible for VF. The precise nature of these wavefronts, their formation, and sustainability are key to understanding VF. Various theories exist regarding the nature of re-entrant waves. One such theory is the *leading circle hypothesis*, originally put forward by Allessie and coworkers to explain atrial fibrillation (AF).[26] This hypothesis states that a re-entrant circuit is the smallest pathway in which the impulse can continue to circulate and that the core is kept permanently refractory (i.e., there is no excitable gap) (Figure 46-8). However, Janse questioned whether the core is truly refractory during re-entry, since membrane potential is relatively normal in this region and diastolic intervals are relatively long.[27] Furthermore, the presence of an excitable gap allows wavefronts (spontaneous or induced) to invade the area and terminate or entrain the re-entrant circuit; Allessie et al were able to terminate tachycardia with premature beats (i.e., anti-tachycardia pacing).[26] It now

appears that in most cases of VF, an excitable gap does exist; however, there may still be room for leading circle re-entry in a subset of arrhythmic phenomena, particularly with regard to AF.[28]

An alternative mechanism for VF is *spiral wave re-entry*. This theory suggests that the wavefront curves, or forms a spiral, because curvature is negatively related to conduction velocity (because of the source-sink relationship). As a result, the wave is highly curved near the core and moves slowly, but at the distal end the wave speed increases, resulting in a spiral shape. Two-dimensional spiral waves may theoretically exist in surviving two-dimensional layers overlying the healed myocardial infarcts, although three-dimensional waves (i.e., scroll waves) are clearly more relevant to cardiac arrhythmias. A scroll wave can be thought of as a stack of spiral waves in which the cores line up to form a "filament" at the center. Simple scroll waves, in which the filament forms a straight line, have been demonstrated during VF.[29] A scroll wave with a core that is perpendicular to the recording surface will appear as a two-dimensional spiral wave, whereas a filament that is parallel to the recording surface will appear as a plane wave. It has been suggested that during VF, scroll waves are usually oriented parallel to the surface, which may explain why mapping studies sometimes fail to detect re-entry during VT or VF. A scroll wave with a ring-shaped filament is called a *scroll ring*. It is interesting to note that the cross-section of such a wave would represent classic figure-of-eight re-entry. Only indirect experimental evidence is available for the existence of scroll rings, probably because of the difficulty of measuring them, because they manifest only transmurally, never on the surface.[30] The shape of a scroll as it is initiated strictly depends on the shape of the inexcitable obstacle encountered by the wavefront. Thus, filaments of varying shape can readily develop in the myocardium. Scroll rings ultimately collapse on themselves, but simple scroll waves can be stabilized and maintained.[31]

Numerous hypotheses have been offered regarding the nature of fibrillatory waves that underlie VF. Three of these theories are illustrated in Figure 46-9: (1) the multiple wavelet hypothesis, (2)

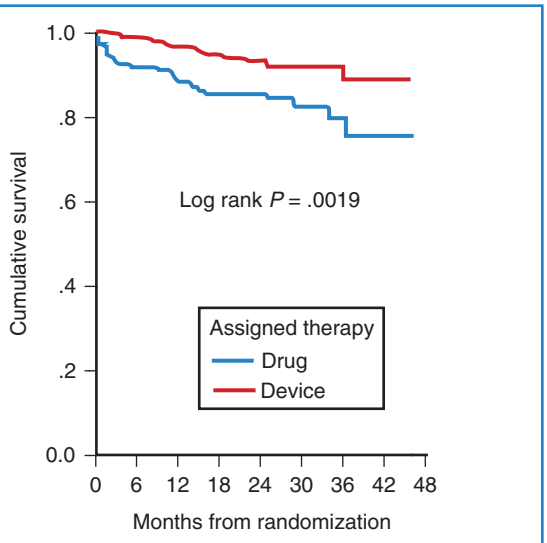

FIGURE 46-7 Survival free of arrhythmic cardiac death in patients with ventricular fibrillation who qualified for the Antiarrhythmics Versus Implantable Defibrillators (AVID) study. Nonarrhythmic cardiac and noncardiac deaths are censored. *(From the AVID Investigators: Causes of death in the AVID study,* J Am Coll Cardiol *34:1552–1559, 1999.)*

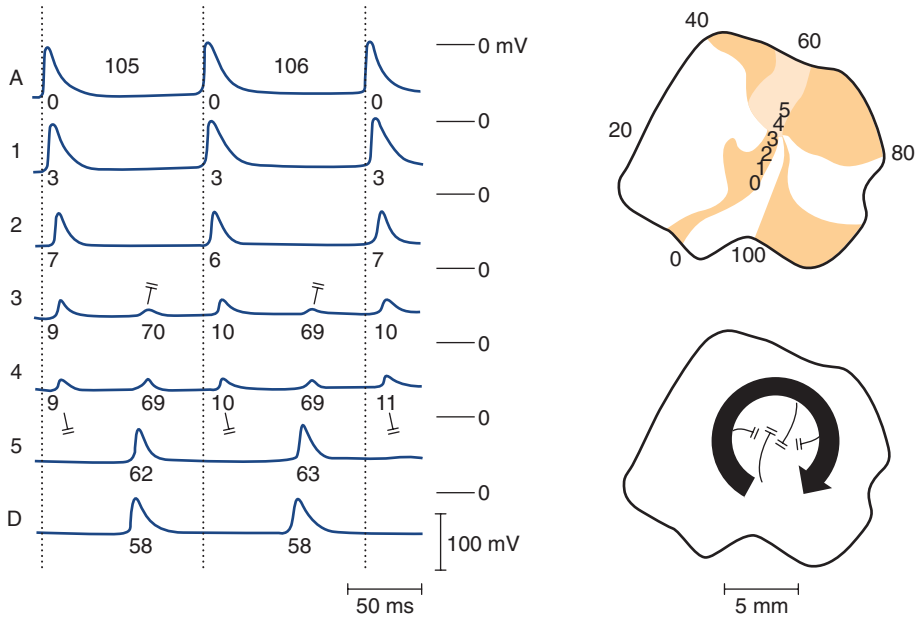

FIGURE 46-8 Leading circle re-entry. Activation map (*right*) and action potential recordings (*left*) obtained during steady-state tachycardia in an isolated rabbit atrial preparation. Cells in the central area of the re-entrant circuit show double potentials of low amplitude (*tracings 3 and 4*). A schematic activation pattern is shown on the *lower right*. *Double bars* indicate conduction block; the black section is absolutely refractory; between the head and tail of the re-entrant wavefront, relatively refractory tissue is present. Characteristics for leading circle re-entry are (1) the core is kept in a permanent state of refractoriness by centripetal wavelets, and (2) the head of the leading circle bites into its own relative refractory tail. *(From 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 *41:9–18, 1977.)*

the meandering spiral wave hypothesis, and (3) the mother-daughter wavelet hypothesis. The *multiple wavelet hypothesis* was put forward in the early 1960s by Moe and describes fibrillation as consisting of multiple, nonstationary wavefronts that continuously form, fractionate, and reform (Figure 46-9, *A*).[32] Spatial dispersion of repolarization was an important condition for initiating multiple wavelet VF. Others have suggested that VF is caused by spiral re-entrant waves that meander around the myocardium (see Figure 46-9, *B*).[33] According to this theory, the chaotic appearance of the ECG in VF is attributable to the meandering of a single spiral wave rotor throughout the ventricular myocardium. Jalife suggested that the mechanism of fibrillation may consist of a stable, periodic re-entrant wave that gives off "daughter wavelets" that meander and fractionate (see Figure 46-9, *C*).[34] According to this hypothesis, unstable daughter wavelets form because of local gradients of refractoriness and give rise to the fibrillatory patterns of the ECG.

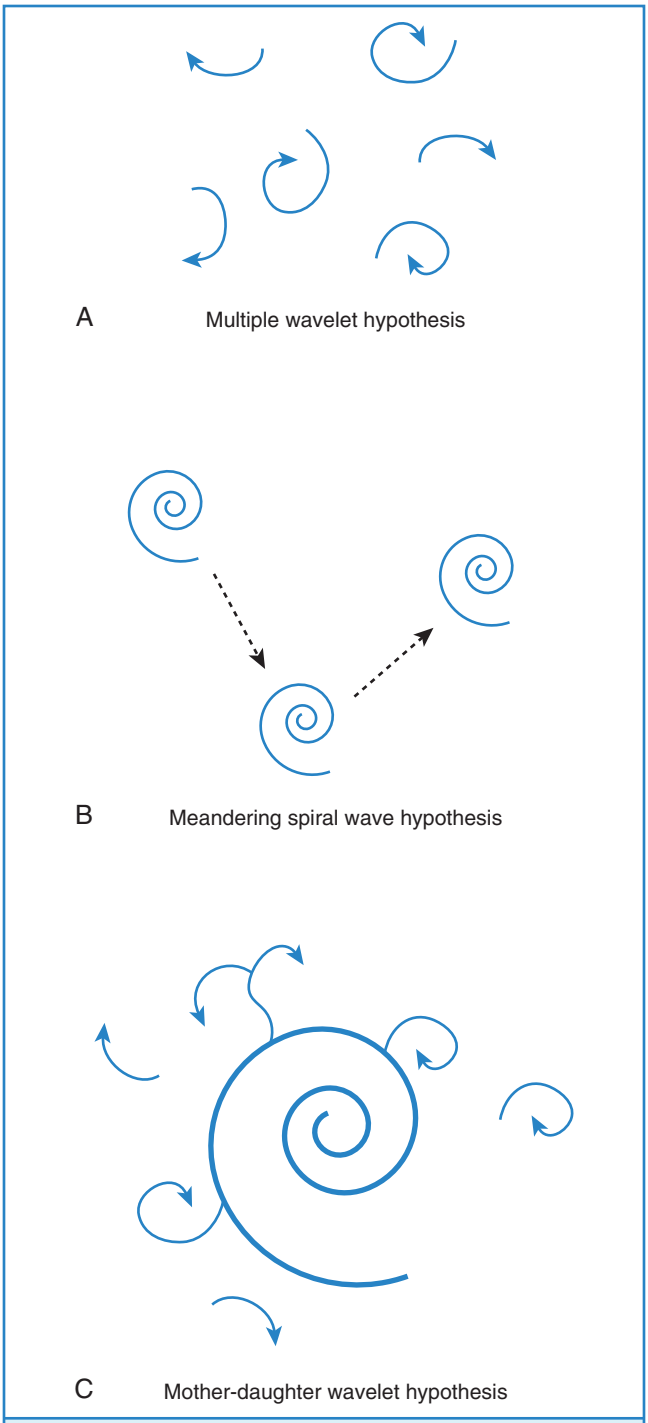

FIGURE 46-9 Various theories of fibrillatory wavefront behavior. **A,** Multiple wavelet hypothesis. **B,** Meandering spiral wave hypothesis. **C,** Mother-daughter wavelet hypothesis.

Substrates for Ventricular Fibrillation: Heterogeneities of Repolarization and Refractoriness

Various anatomic and functional substrates can lead to the development of the fibrillatory dynamics previously described. Early studies of AF suggested that the heterogeneity of refractoriness was a necessary substrate for fibrillation in the heart.[32] Although it was later shown that VF can occur in hearts without large dispersions of refractoriness (i.e., in normal hearts), or in modeling studies using simulations of electrically homogenous tissue, these studies may not be clinically relevant.[35] It is more difficult to initiate VF in a normal heart, and the vast majority of fibrillatory episodes occur in diseased hearts, in which the gradients of repolarization kinetics (and therefore refractoriness) are almost certainly abnormal. The important role of repolarization in the development of re-entrant substrates has recently been emphasized by studies demonstrating the inherent heterogeneities in repolarization properties that exist transmurally.[36] Antzelevitch and others have demonstrated that trans-mural heterogeneities of repolarization are critical in the development of the substrates for re-entry under various drug-induced or disease-induced conditions.[37,38]

Rosenbaum et al recently developed a hypothesis that explains how the critical heterogeneities of repolarization that provide a substrate for re-entry may occur.[39] Beat-by-beat alternation of cardiac action potential duration (APD) has been shown to underlie T-wave alternans, an electrocardiographic indicator that correlates well with the risk of SCD.[39] We have demonstrated that when alternans occurs in various regions of the myocardium in a "discordant" manner (i.e., some regions are on a long-short-long cycle, and others are on a short-long-short cycle), steep gradients of repolarization develop and reverse the direction on a beat-by-beat basis, which can lead to conduction block, re-entry, and VF.[40]

In related work, Laurita et al demonstrated that premature beats modulate the dispersion of repolarization in a manner that has direct effects on vulnerability to VF.[41] As the S_1-S_2 interval is shortened, gradients of repolarization decrease concomitant to a decrease in vulnerability to VF, but then increase with a concomitant increase in VF vulnerability as S_1-S_2 is further shortened (Figure 46-10). Such biphasic modulation of dispersion relates back to the concept of the "vulnerable period," which arose from critical studies by Moe, who described the window of time during the ECG T wave when vulnerability to VF is greatest.[32] Thus, dispersion of repolarization and refractoriness appears to play a major role in the mechanism of re-entrant VF.

Restitution Hypothesis

Restitution is a property of cardiac myocytes that dictates the APDs of a premature action potential after a period of steady-state rhythm. The APD of the extrasystolic beat is determined not

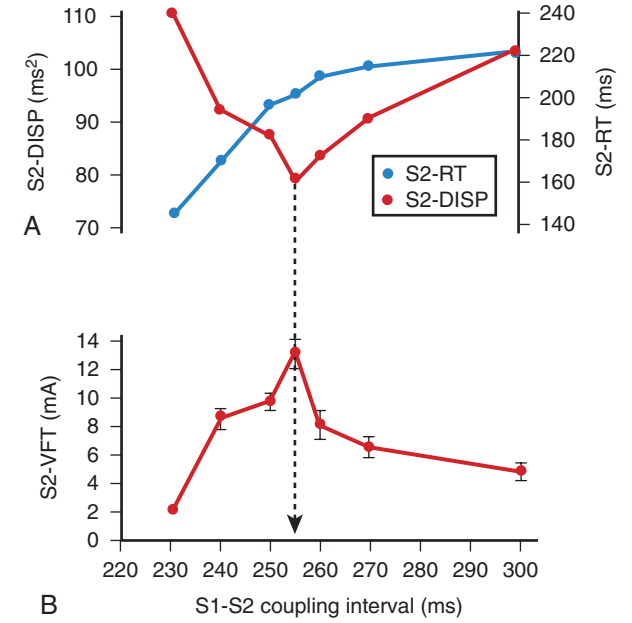

FIGURE 46-10 Modulated dispersion hypothesis and vulnerability to ventricular fibrillation. **A,** Dependence of mean repolarization (*S_2-RT, blue circles*) and dispersion of repolarization (*S_2-DISP, red circles*) on S_1-S_2 coupling interval. **B,** Dependence of arrhythmia vulnerability (*S_2-VFT*) on premature coupling interval. Dispersion of repolarization (**A,** *red circles*) and vulnerability to fibrillation (**B**) were modulated in a similar biphasic fashion, with minimum vulnerability (i.e., maximum S_2-VFT) and minimum dispersion occurring at the same S_1-S_2 coupling interval (255 ms, *dashed arrow*). This inherent mechanism may provide protection against premature stimuli delivered at moderate coupling intervals. *(From Laurita KR, Girouard SD, Akar FG, et al: Modulated dispersion explains changes in arrhythmia vulnerability during premature stimulation of the heart,* Circulation *98:2774–2780, 1998.)*

only by the S_1-S_2 interval but also by the APD of the pre-extrasystolic beat. Furthermore, gradients of restitution kinetics are known to exist across the epicardial surface such that cells in different regions of the heart having equal baseline APDs could have different extrasystolic APDs following the same S_1-S_2 interval.[42] In theory, if gradients of restitution kinetics are steep enough, underlying heterogeneities of repolarization would not be necessary to create dispersions of repolarization following a premature beat.[42] However, cardiac tissue is known to exhibit repolarization heterogeneities across epicardial and trans-mural surfaces, so the role of restitution may be to enhance existing dispersion of repolarization and promote VF.

One possible mechanism to describe the role of restitution in VF is the *restitution hypothesis*, which states that when the restitution curve (a plot of APD vs. diastolic interval) has a slope greater than 1, VF may be initiated. For example, a wavefront encroaching on the tail end of a previous wave creates a gradient of diastolic interval between the two (assuming the degree of curvature is not identical); in regions of tissue where restitution is steep, this will create large dispersions of APD along the second wavefront. Some areas of the wave may have such a short diastolic interval that they fail to propagate, resulting in wavefront fractionation. This was demonstrated by Garfinkel et al, who also used pharmacologic agents to flatten the restitution curve slope and decrease vulnerability to VF. Koller et al showed that elevating extracellular potassium decreases the portion of the restitution curve where the slope is 1 or more and converts VF to a periodic rhythm.[43,44] Other investigators have shown that the biphasic nature of a restitution curve, demonstrated in a number of cardiac tissue types, is also an important determinant of vulnerability to VF.[45] More recently, the restitution hypothesis has been applied to restitution curves for both APD and conduction velocity.[46]

Myocardial Ischemia

VF is commonly caused by acute myocardial ischemia. Under experimental conditions, it is often difficult to provoke VF in normal tissue using premature stimuli; however, in ischemic tissue, premature beats exacerbate dispersion of refractoriness and readily lead to tachyarrhythmias.[47] This is because of the various electrical alterations that occur during ischemia and the consequent formation of various substrates that promote re-entry and VF.

At the cellular level, acute ischemia results in depolarization of the resting membrane potential, decreased maximum rise rate and amplitude of the action potential, and decreased APD, as well as reduced intercellular coupling.[48-53] Depolarization of the membrane is attributed largely to accumulation of extracellular potassium, as is post-repolarization refractoriness.[54,55] Acidosis can produce a small depolarization of resting membrane potential and also decreases gap junction conductance and cell-to-cell coupling.[56] The net result of the electrical changes that occur during ischemia is the formation of various substrates that can lead to re-entry and wavebreak, such as slowed conduction velocity, increased dispersion of refractoriness, and alternans.

Healed Myocardial Infarcts

The process of tissue healing and scar formation after an episode of acute myocardial ischemia involves necrosis of the infarcted region as well as swelling and hypertrophy of the noninfarcted region as it attempts to compensate for the loss of cardiac muscle.[57] Heterogeneity of repolarization may result from the uneven prolongation of APD in the hypertrophied post-MI ventricle, changes in expression of gap junction proteins, or both.[58,59] A healed infarct may also provide an anatomic substrate for arrhythmias. Infarcts vary from simple surviving muscle bundles that form accessory pathways to complex subendocardial sheetlike structures, which are linked to the surrounding myocardium by multiple connecting bundles, creating complex matrices of conductive tissue that may promote multiple re-entrant circuits. In particular, the combined effects of slowed conduction and the presence of structural anomalies is significant because in tissue where excitability is low, a wavefront breaking past an obstacle will curl at the inner ends (where the break occurred) to create figure-of-eight re-entry, whereas in a normally excitable medium, the wave tends to reform on the other side of the obstacle.[60]

Autonomic Modulation of Ventricular Fibrillation

It has been well established that increases in sympathetic tone increase the risk for SCD, whereas vagal reflexes have the opposite effect.[61-63] Studies in dogs have shown that left cardiac sympathetic denervation, or left stellectomy, increases survival and

decreases arrhythmias during acute MI.[64] In contrast, unilateral blockade of the right stellate ganglion by cooling increases the number of arrhythmias after coronary occlusion.[65] Many clinical trials have shown that β-adrenergic receptor blocking drugs have a potential benefit in preventing SCD in patients with MI, whereas anti–α-adrenergic agents have not been shown to be effective.[66-69]

It has been suggested that during acute MI, sympathetic nerves that traverse the myocardial wall are damaged, leading to denervation hypersensitivity.[70] This, in turn, leads to spatially inhomogeneous responses to β-adrenergic stimulation across the ventricle, forming potential substrates for re-entrant excitation. Further investigation is required to elucidate fully the mechanistic role of β-adrenergic stimulation and arrhythmogenesis.

Genetic Substrates for Ventricular Fibrillation

Brugada syndrome is a cardiac disease characterized by an elevated ST segment that is unrelated to ischemia, Q-T interval prolongation, electrolyte abnormalities, or structural heart disease.[71] Patients with Brugada syndrome are at increased risk of SCD from VF. The syndrome is caused by a mutation in the gene encoding the cardiac sodium channel (*SCN5A*) and is common in Southeastern Asia, where it is the second highest cause of death among young men.[72] In Europe, gender specificity is less distinct, although affected women tend to be less symptomatic than affected men. Patients with Brugada syndrome often die in their sleep, and a possible relationship to sudden infant death syndrome has been suggested.[73]

It is believed that the mechanism of VF in patients with Brugada syndrome is related to reduced function of the mutant late inward sodium current, forcing the balance of plateau currents in favor of repolarization. This is why any further impairment of sodium channel function (e.g., by sodium-blocking drugs) can exacerbate the electrocardiographic and arrhythmogenic phenotype in this disorder.[74] Because epicardial, not endocardial, cells possess the transient outward current (I_{to}), they are most susceptible to the repolarizing effect of the sodium channel mutation in Brugada syndrome. Marked and selective shortening of epicardial action potentials relative to endocardial action potentials produces a transmural voltage gradient during the plateau that, in turn, is believed to account for the characteristic pattern of ST segment elevation seen in these patients.[75] Transmural action potential gradients also account for the presumed mechanism of VF (i.e., phase 2 re-entry).

In a recent provocative study, Haisaguerre et al identified a select group of patients with recurrent idiopathic VF that seemed to originate with premature beats emanating from the distal His-Pukinje system; these patients were successfully treated with radiofrequency ablation targeting the originating premature beats, with a low rate of VF recurrence.[76]

In summary, VF is a complex arrhythmia associated with many distinct electrophysiological mechanisms that no doubt highly depend on the disease state in question. Although most often associated with acute ischemia or healed MI, VF can occur in the absence of any structural heart disease, such as heritable disorders (e.g., Brugada syndrome). Greater understanding of these various mechanisms is required to guide the development of novel pharmacologic approaches and targets that can ultimately be used in the treatment and prevention of VF. Until then, clinicians will have to rely on electrical defibrillation, which is highly effective irrespective of the underlying VF mechanism.

Clinical Electrocardiography

The role of electrocardiography has been increasing in patients presenting with VF. Certain ECG features may identify high-risk patients or transient events that can result in VF, which may be preceded by VT (see Chapter 47).

Electrocardiographic Features of Patients at High Risk for Ventricular Fibrillation

Electrocardiographic recordings obtained at the onset of VF provide insight into events that precipitate SCD. Documentation of these events has been obtained by continuous monitoring in hospital telemetry units and by ambulatory monitoring. The patients involved in these studies had a high incidence of CAD, and most had frequent or complex ventricular ectopy. The terminal events were associated with sinus arrest, complete heart block, or ventricular asystole in approximately 10% of patients; in 90%, VF was preceded by VT or ventricular flutter of variable duration.[77-80] ST segment and T-wave changes indicative of ischemia related to acute MI or coronary spasm have also been reported to precede terminal ventricular arrhythmias.[77-80] Other studies indicate that bradycardia and electromechanical dissociation are important causes of SCD in patients with advanced heart failure and nonischemic cardiomyopathy.[81] These observations have significant implications for strategies to reduce mortality rates in patients at risk for SCD.

The diagnostic role of the ECG in identifying patients with genetic disorders associated with SCD from ventricular arrhythmias has continued to evolve over the past decade. The electrocardiographic characteristics of LQTS, Brugada syndrome, and arrhythmogenic right ventricular cardiomyopathy (ARVC) have gained widespread attention. This is vital to the prevention of SCD in young patients with these disorders, particularly if these patients participate in athletics. A recent study has suggested a higher incidence of early repolarization changes in the inferolateral leads (J-point elevation and notching in the terminal portion of the QRS complex) among survivors of cardiac arrest caused by idiopathic VF when compared with control subjects.[82]

The pattern of early repolarization associated with highest risk seems to be global or inferolateral early repolarization with prominent J waves on the resting ECG.[83] It is not clear if a single disorder of repolarization causes at least some of the cases previously labeled "idiopathic VF," or, as seems more likely, a spectrum of disorders is associated with abnormal and heterogeneous repolarization that predisposes otherwise normal individuals to VF. These disorders have been collectively named *early repolarization disease*.[84]

Although the prevalence of repolarization abnormalities in patients resuscitated from VF with no evident structural heart disease is higher than expected, these abnormalities are also common in young, healthy individuals. The sensitivity, specificity, and predictive accuracy of this finding are not clear. The risk of cardiac arrest in asymptomatic patients with early repolarization is likely very low.

Long QT Syndrome

The electrocardiographic manifestations of LQTS include QT prolongation, abnormalities in T-wave morphology, increases in QT dispersion, T-wave alternans, and a relative degree of

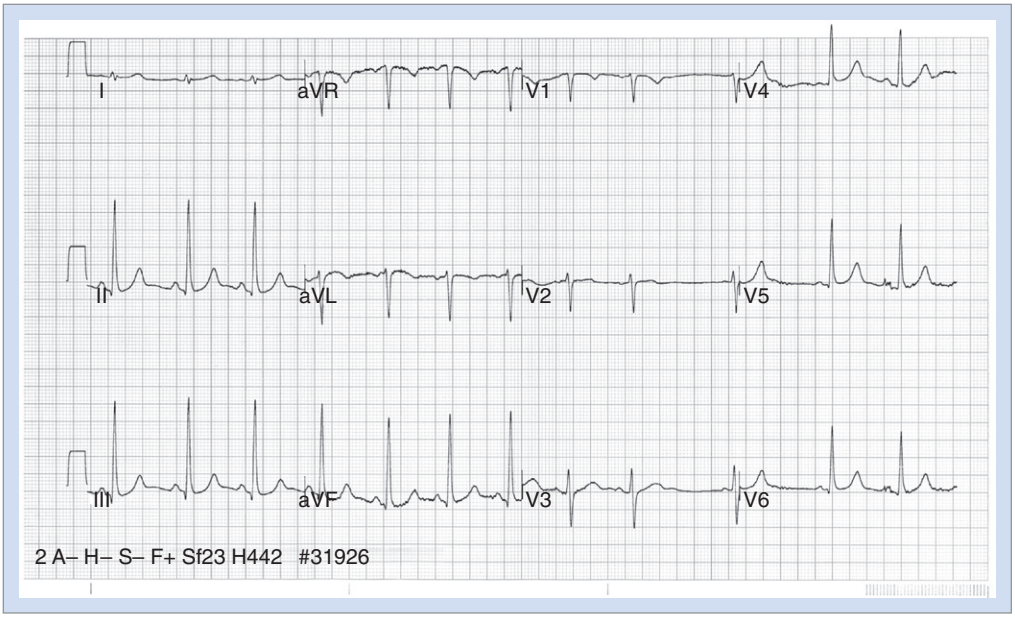

FIGURE 46-11 Twelve-lead electrocardiogram of a patient with familial long QT syndrome. Note the prolonged Q-T interval and T-wave abnormalities.

bradycardia in children (Figure 46-11). The upper limits of normal for the QTc values are 460 to 470 ms for females and 440 to 460 ms for males.[85,86] Longer QT values may be observed in normal women after puberty.[87] The degree of QT prolongation does not directly correspond with the risk of syncope, but malignant ventricular arrhythmias are more frequent when the QTc exceeds 600 ms.[87] A diagnostic dilemma is that the Q-T interval shows temporal variations in patients with this syndrome, and the QTc may fall within the normal range on a random recording.[88] Garson reported that 6% of LQTS patients had a normal Q-T interval, and data from the International Registry showed that 10% of family members with a QTc less than 440 ms had a cardiac arrest.[89,90] Thus, an ECG with a normal QTc does not exclude the diagnosis if strong suspicion exists that a patient has the syndrome, especially if the QTc is on the border of normal.

The effect of exercise increases the QTc in patients with LQTS, but this effect is less apparent in patients with LQT3 than in those with other genotypes.[91] Approximately 62% of patients with LQTS exhibit T waves that are biphasic or notched, and a higher incidence of these abnormalities is seen in patients with cardiac events.[92] The characteristic features are most pronounced in precordial leads V2 to V5. The appearance of notched T waves may be provoked by exercise. The degree of QT dispersion is measured by the difference between the longest and shortest Q-T intervals on the 12-lead ECG and is prolonged in patients with LQTS.[93] It is thought to represent increased dispersion of repolarization. Patients who show no change in the degree of QT dispersion when they are treated with β-blockers appear to be at increased risk for cardiac events.[90,94] T-Wave alternans is a beat-to-beat alternation in the amplitude or polarity of the T wave. It appears to be a marker of electrical instability that may precede torsades de pointes.[94] Children with LQTS often have resting heart rates that are lower than normal and may exhibit a blunted chronotropic response to exercise.[87,95] Torsades de pointes, which is the ventricular arrhythmia associated with LQTS, is characterized by the undulating amplitude of the QRS complex, which gives the appearance of twisting about its axis. The onset is frequently associated with pause-dependent ventricular ectopy that falls on the T wave.[96-98]

Brugada Syndrome

The ECG patterns associated with Brugada syndrome are (1) a terminal R′ in lead V1 with complete or incomplete RBBB; (2) convex downward (coved) ST segment elevation equal to 0.1 mV in lead V1 or leads V1 and V2; convex upward (saddle-shaped) ST-segment elevation equal to 0.1 mV; and (3) J-point elevation followed by a downsloping ST segment ending in a negative deflection (triangular shape).[98] Serial ECGs performed on the same patient may show variation from one pattern of ST-segment elevation to another, normalization, and progressive development of RBBB. Figure 46-12 shows examples of variable Brugada ECG patterns that occurred during an ajmaline test in the same patient.[99,100] The prevalence of the Brugada ECG pattern is reported to be 0.07% to 0.7%, and there is a male predominance that is especially marked in Asians.[101-106] The range in prevalence appears to depend on the criteria used to make the diagnosis. The saddleback ST-segment elevation is more common. The typical coved pattern was found in 0.1% to 0.26% of community-based populations in Japan and Europe.[104-106] In a Japanese study population that underwent ECGs during health examinations, the prevalence of all types of Brugada ECG patterns was 0.7%.[103] The coved-type ST-segment elevation was found in 38% of subjects with the Brugada pattern, and the saddleback-type ST-segment elevation was seen in 62%. In the same study, the rsR′ pattern in lead V1 was observed in 41%, and the Rsr′ pattern was recorded in 59%. The prevalence of the coved pattern was 0.26%, and the typical Brugada ECG pattern with coved ST-segment elevation and the rsR′ pattern in lead V1 was 0.12%. If only male subjects were considered, the criteria for a Brugada ECG pattern was met

in 2.14% of the population, but the typical pattern in males was 0.38%.[104] In a European population studied by Hermida, the prevalence of ST segment elevation was 6.1%; however, only 1 (0.1%) of the 61 subjects who met the study's criteria for the Brugada pattern had the coved pattern. All of the others had the saddleback pattern.[103]

The prognostic significance of the Brugada ECG pattern is difficult to assess. Brugada reported an 8% incidence of arrhythmic events in an asymptomatic hospital-based population.[106] The degree and type of ST segment elevation require further study for risk stratification of asymptomatic individuals in community-based populations. Matsuo evaluated mortality in patients younger than 50 years who had ECGs recorded during biannual examinations from 1958 through 1999.[107] A total of 32 patients were identified with the Brugada ECG pattern. Seven of these patients died suddenly or died of an unexplained accident. Although total mortality was not increased in patients with the Brugada ECG pattern, the mortality rate from unexpected death was significantly higher. No increase in mortality was observed in studies by Miyasaka, Takenaka, or Priori.[104,105,107] In the Osaka population, one SCD occurred among the 98 subjects with the Brugada ECG pattern during a mean follow-up of 2.6 years.[104] A 3-year follow-up reported by Atarashi of patients with a Brugada ECG pattern found cardiac event–free rates of 67.6% in symptomatic patients and 93.4% in an asymptomatic group.[108] Coved-typed ST segment elevation appeared to be related to cardiac events. The higher incidence in hospital-based studies may reflect referral patterns based on a family history of SCD. Differences in criteria or ECG interpretation affect the diagnosis of this pattern, and the follow-up in most studies is too short to draw definitive conclusions about the long-term prognosis.

Arrhythmogenic Right Ventricular Cardiomyopathy

ECG recordings during sinus rhythm in patients with ARVC have several distinctive features (Figure 46-13).[109] The QRS may be prolonged in the right precordial leads to a greater extent than in leads I or V6. The QRS is often greater than 110 ms in lead V1

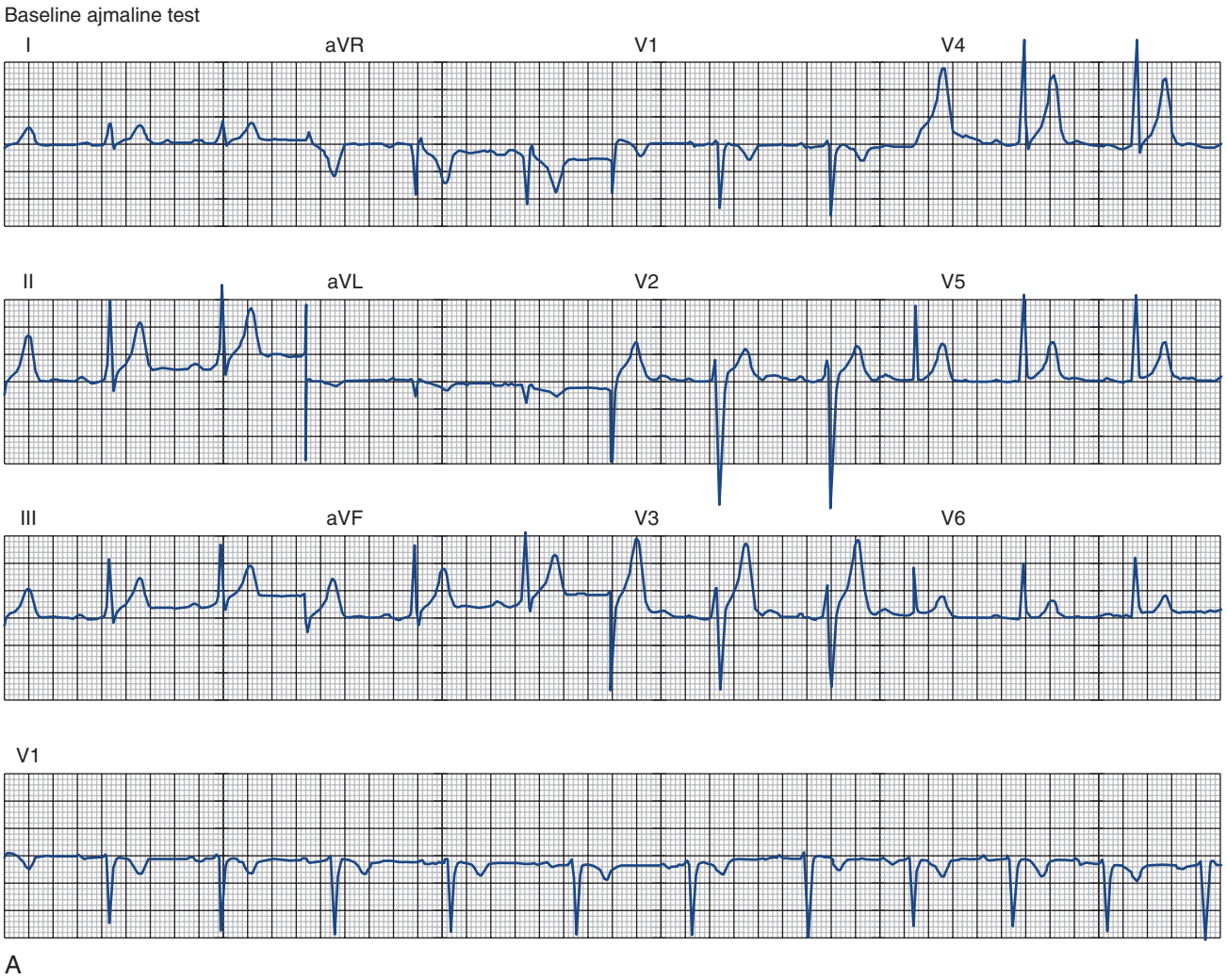

FIGURE 46-12 Serial changes in a Brugada pattern electrocardiogram recorded in a patient during an ajmaline test. Twelve-lead ECGs are recorded at baseline (**A**), followed by ajmaline infusion. At 2 minutes, ST-segment elevation that is coving upward is seen in the right precordial leads (**B**), followed by marked ST-segment elevation in leads V1 to V3 (**C**).

Continued

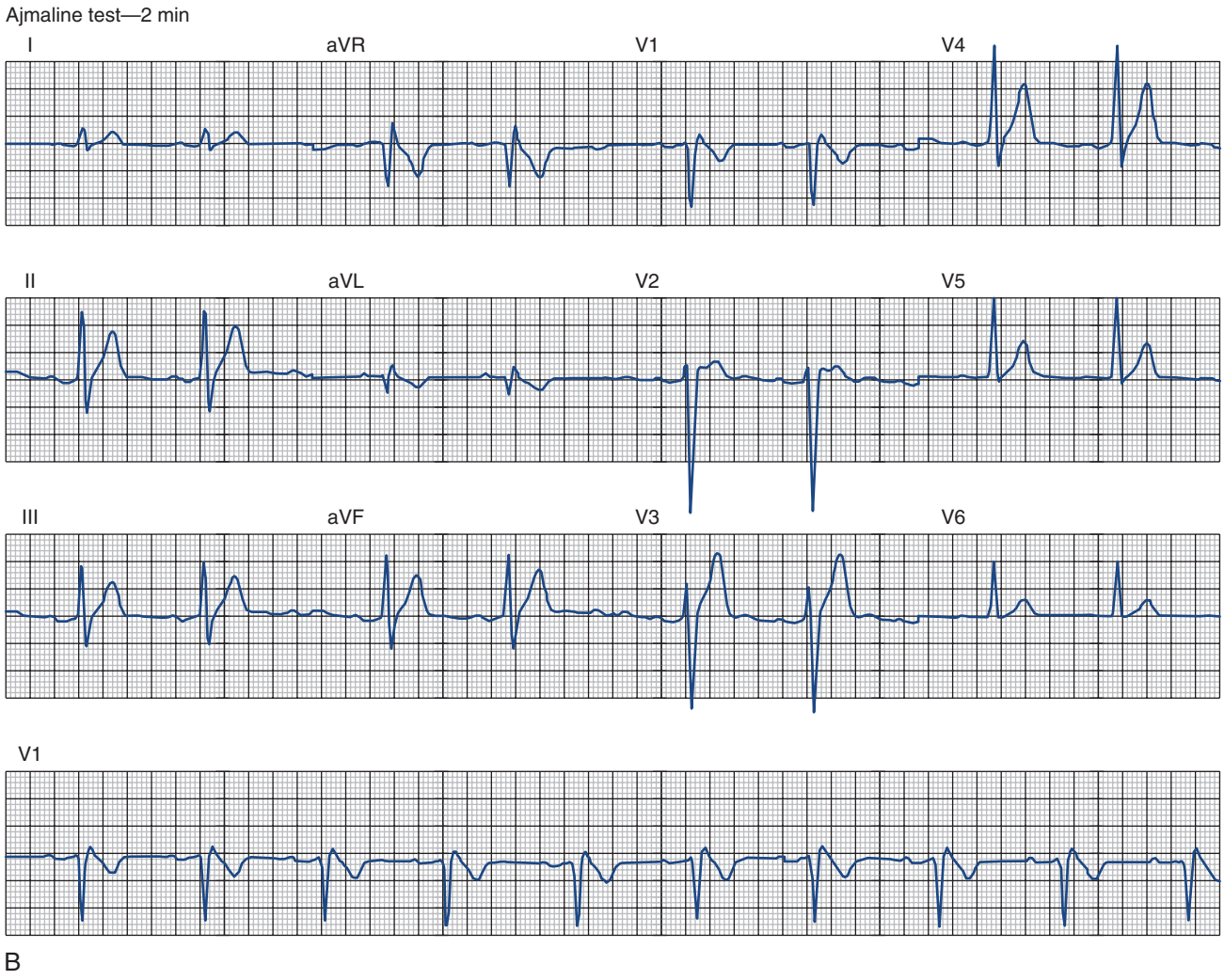

FIGURE 46-12, cont'd

(sensitivity, 55%), and a pattern of incomplete RBBB is observed.[110] In 30% of cases, the delay in conduction over the right ventricle results in a small potential at the terminal portion of the QRS in lead V1 that has been termed an *epsilon* (ε) *wave*, which can be amplified with bipolar recordings over the inferior and superior aspects of the sternum.[109] This can be achieved by repositioning the left arm lead over the xiphoid process, positioning the right arm lead over the manubrium sternum, and applying the left leg lead at the position customarily used for lead V4 or V5.[111] The other major feature of ECGs recorded from patients with ARVC is inversion of the T waves in the precordial leads, which is observed in 42% to 54% of patients.[111,112] Metzger assessed the value of serial 12-lead ECGs in 20 patients to recognize progression of ARVC over a mean of 71 ± 48 months.[113] Abnormalities were detected in 90% of the patients. The most frequent abnormality was T-wave inversion in the precordial leads. No correlation was demonstrated between the ECG and the extent of disease detected by echocardiography. In the 14 patients who had several ECGs recorded over time, no clear progression of electrocardiographic abnormalities was observed.

The ventricular arrhythmias associated with ARVC typically show a morphology resembling left bundle branch block in lead V1 with a variable axis. Nava published a clinical profile and long-term follow-up of 37 families with ARVC that demonstrated a correlation between the severity of echocardiographic findings and the severity of ventricular arrhythmias, which were seen in all patients with the severe form of the disease, in 82% with moderate disease, and in 23% in those with mild disease.[112] Overall, 60 (45%) of 132 affected living members had ventricular arrhythmias. These included VF in 1, sustained VT in 14, nonsustained VT in 8, ventricular couplets and triplets in 16, and frequent ventricular premature depolarizations in 8. Exercise-induced polymorphic VT was observed in 13 patients with no other documented arrhythmias. Only one patient who was judged to have mild disease had a sustained ventricular arrhythmia. Although the data from this study showed a low incidence of VF, the incidence may be higher. In 19 of the 37 families, the proband died at a young age, and the diagnosis was made at autopsy. One may speculate that some of these subjects had VF. Figure 46-14 shows electrograms recorded from an ICD implanted in a teenager (male) with ARVC and frequent nonsustained ventricular arrhythmias. The recording shows the sudden onset and successful termination of VF, which occurred at night while he was asleep. He had no prior history of syncope or sustained ventricular arrhythmias.

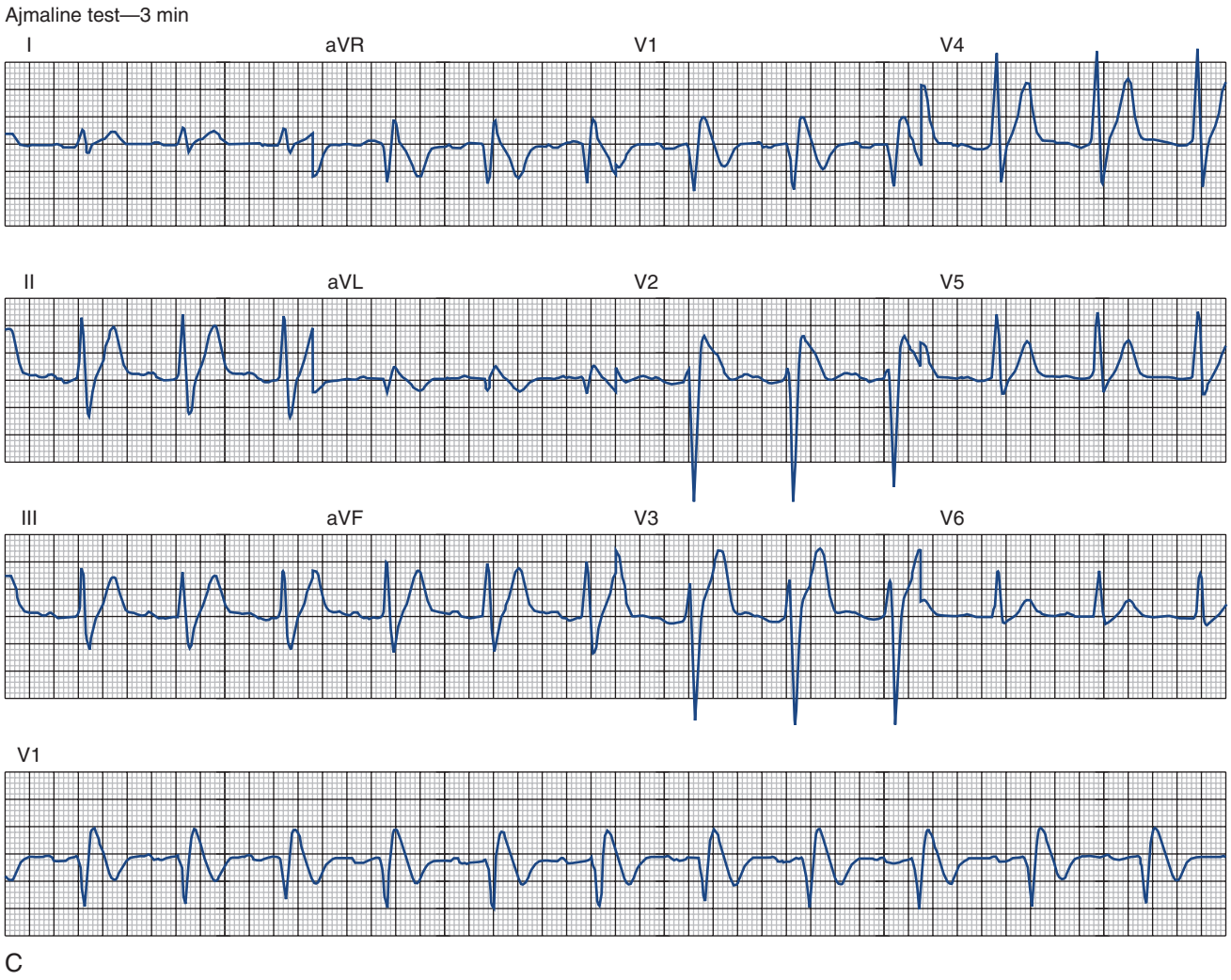

FIGURE 46-12, cont'd

Diagnostic Evaluation

Investigation of patients who have been resuscitated from an episode of spontaneous VF is directed toward determining whether the episode of VF had a transient or reversible cause, identifying the type and extent of underlying structural heart disease, documenting the mechanism of VF, identifying coexisting disease states that may interact with future antiarrhythmic therapies, and assessing and monitoring selected antiarrhythmic therapy. In each instance, the importance of a complete history and physical examination is well established and needs no further discussion.

Evaluation of Transient or Reversible Causes

VF that occurs secondary to a reversible or transient cause may be adequately treated by correction of the reversible cause or by short-term therapy or close observation while awaiting spontaneous resolution of the transient cause.[114] The causes of VF with these characteristics are usually readily identified with a few focused investigations. Electrolyte abnormalities are identified with serum electrolyte testing performed as soon as possible after resuscitation. The most common electrolyte abnormalities leading to VF are hypokalemia, hypomagnesemia, or both. When considering the temptation to ascribe an episode of VF wholly to hypokalemia, hypomagnesemia, or both, one must recall that the adrenergic discharge state during resuscitated VF results in redistribution of extracellular potassium and magnesium into the intracellular compartment. Accordingly, relative hypokalemia, hypomagnesemia, or a combination is very common after VF.[115] Only marked hypokalemia, hypomagnesemia, or both and confidence that future episodes can be prevented should prompt the belief that the episode of VF had a reversible cause.

The early performance of a 12-lead ECG and serum markers of myocardial necrosis (creatine kinase [muscle or brain type], troponin) will permit identification of the patient whose VF has occurred in the acute phase (first 48 hours) of an MI. Evidence that acute MI produces an environment that constitutes only a transient risk of VF is most convincing for a Q-wave MI.[116] Nevertheless, the risk of VF may also be transient in the setting of a

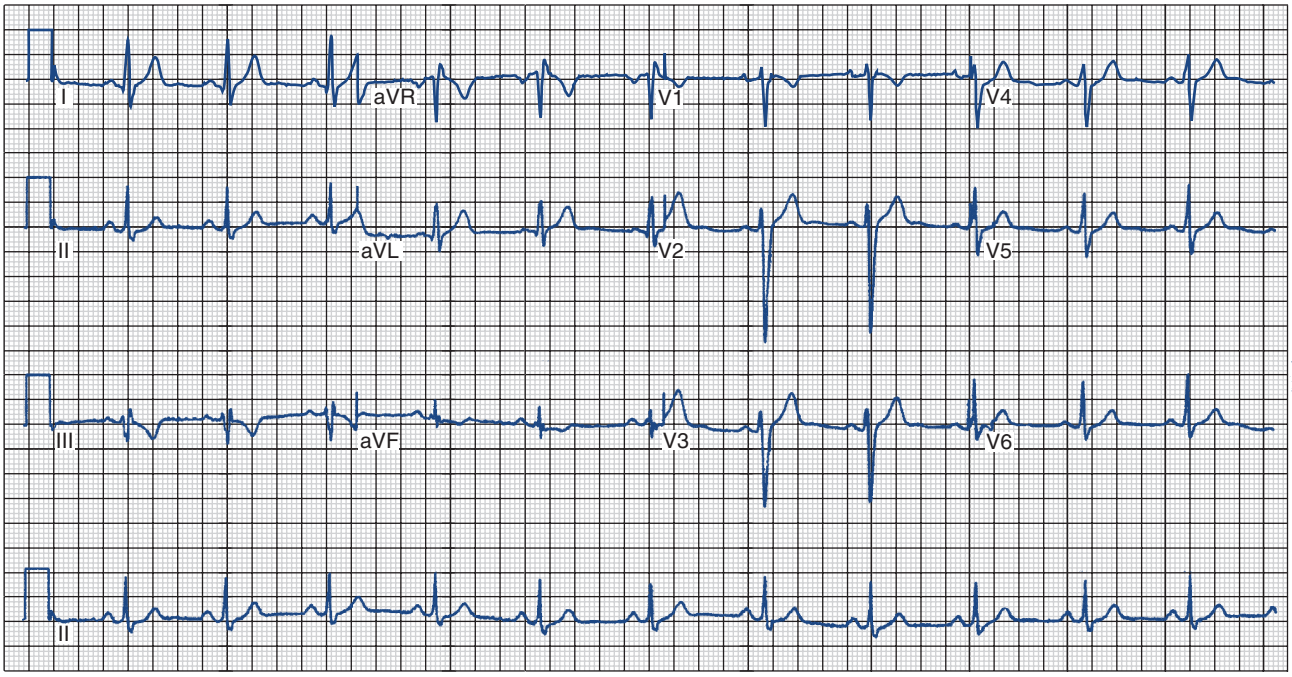

FIGURE 46-13 Twelve-lead electrocardiogram recorded from a 19-year-old man with arrhythmogenic right ventricular cardiomyopathy. An ε wave is present in lead V1 at the end of the QRS.

non–Q-wave MI.[117] However, the practitioner must avoid the temptation to ascribe an episode of VF wholly to an acute MI if the only evidence of acute myocardial necrosis is a marginal elevation in a serum marker of necrosis; such elevations may be secondary to the VF-induced cardiac arrest rather than represent its cause. The diagnosis of MI in the setting of out-of-hospital cardiac arrest from VF is made difficult by the usual absence of a history of chest pain, frequent nondiagnostic ECG abnormalities that may be a consequence of the myocardial ischemia resulting from the global "no-flow or low-flow state" during VF, and the absence of a specific cut-off for the degree of cardiac enzyme elevation that separates MI causing VF from VF causing myocardial necrosis. In general, the presence of a culprit lesion (coronary thrombus or ulcerated plaque) on angiography early after cardiac arrest and well-preserved or normal left ventricular function suggests an ischemic or infarction-related cause.

The other common reversible or transient cause of VF is the use of a proarrhythmic drug: a classic antiarrhythmic drug, other drugs with electrophysiological effects, and recreational drugs, particularly cocaine.[118] Use of these agents is determined from the history. However, if the practitioner believes that a report of such drug use will not be forthcoming from a high-risk individual, a toxicology screen is advised. When therapeutic drug use is reported, early determination of a serum concentration of the agent may be important when toxicity related to that agent has a relationship to serum concentrations (i.e., digitalis).

Finally, an episode of VF may be considered reversible if it accompanies a state of extreme physiological derangement that is not expected to be recurrent. Such states include that seen in the immediate postoperative period, with sepsis, and with hemodynamic instability, especially when the treatment of the physiological derangement required administration of sympathomimetic agents.

Identification of Structural Heart Disease

In most of the world, the most common forms of structural heart disease that precipitate VF are atherosclerotic CAD and either congestive or hypertrophic cardiomyopathy. Accordingly, most patients who have been resuscitated from VF require an echocardiographic examination, an exercise test (with or without myocardial perfusion imaging), and cardiac catheterization with coronary angiography.

The echocardiogram primarily serves as an adjunct to the physical examination for identification of myocardial or valvular structural heart disease. It is particularly suited to the documentation of hypertrophic cardiomyopathy and for the detection of other forms of structural heart disease that have escaped clinical detection. Although the echocardiogram is also useful to quantitate left ventricular systolic function, radionuclide ventriculography, cardiac computed tomography, cardiac magnetic resonance imaging, and contrast ventriculography may provide more accurate determinations of this important prognostic variable. Of importance, the echocardiogram is not very sensitive for the detection of early arrhythmogenic right ventricular dysplasia.

Exercise testing of the patient who has been resuscitated from an episode of VF provides information about the inducibility of both exercise-related myocardial ischemia and exercise-related arrhythmias.[119] The sensitivity, specificity, and spatial localization of reversible myocardial ischemia can be enhanced by coupling the exercise test with radionuclide or echocardiographic imaging techniques.

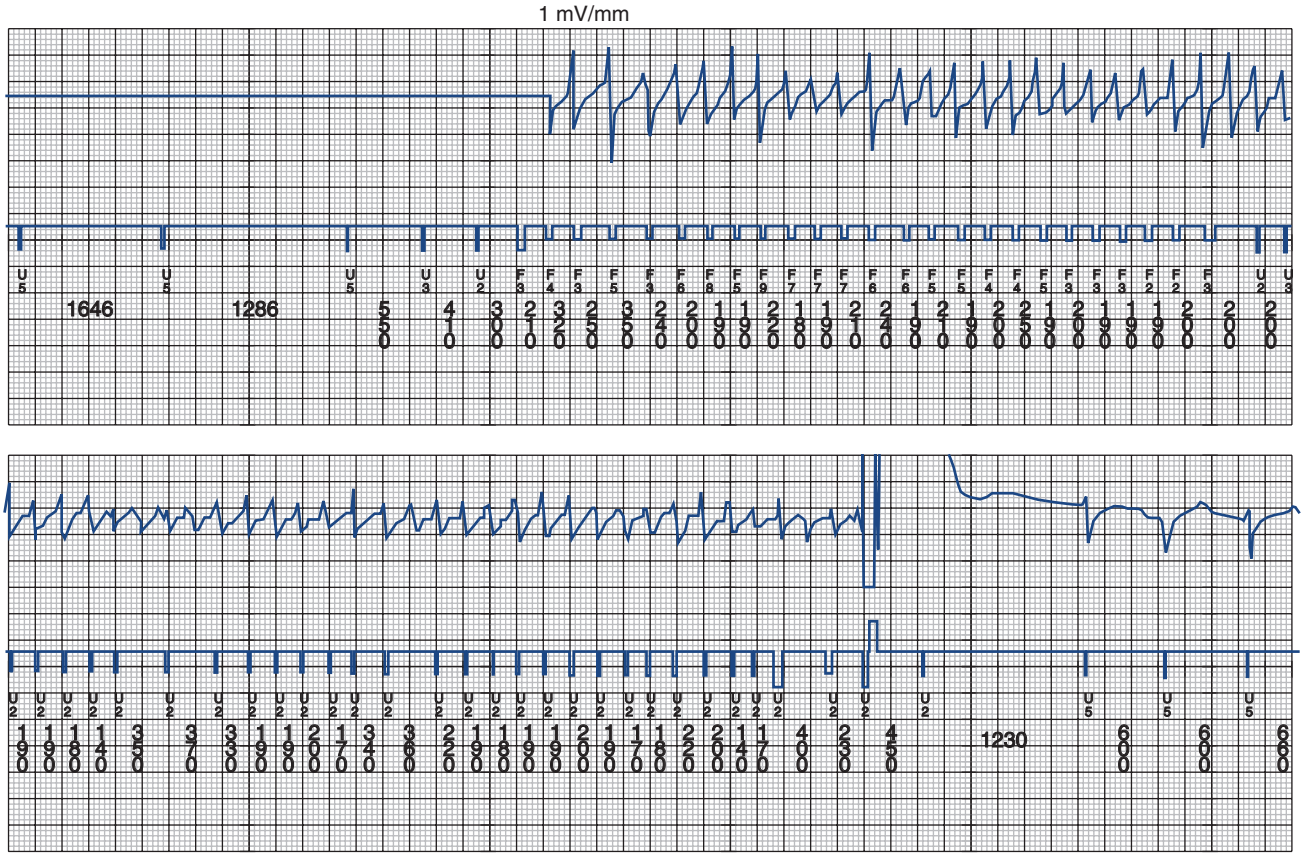

FIGURE 46-14 Electrograms recorded from an implantable cardioverter-defibrillator (ICD) in a patient with arrhythmogenic right ventricular cardiomyopathy. The continuous recordings document the sudden onset of ventricular fibrillation, followed by an ICD shock and conversion to sinus rhythm. The *upper channel* represents the stored intracardiac electrogram. The *lower channel* marks sensed events and displays the cycle length.

Despite the availability of these noninvasive diagnostic procedures, the critical importance of accurate and complete anatomic and functional diagnosis of structural heart disease in a patient who has been resuscitated from VF usually necessitates cardiac catheterization and coronary angiography. Occasionally, the combination of information available from the history of events surrounding the spontaneous episode of VF (especially when preceded by physical or emotional stress accompanied by angina), evidence of reversible myocardial ischemia on exercise testing (especially when associated with evidence of ventricular electrical instability), and documentation of CAD (especially when not associated with severe left ventricular dysfunction) will suggest the possibility that the episode of VF was caused by reversible myocardial ischemia that can be corrected. Although coronary revascularization in this setting has been reported to prevent further episodes of VF in some patients, the effect is not necessarily predictable.[120] Accordingly, it has become customary to either assume that the revascularization procedure was insufficient for the prevention of VF recurrences or document that VT or VF is not inducible by programmed stimulation performed during a transvenous catheter EPS study after the revascularization procedure—preferably after a preoperative catheter EPS documented the inducibility of sustained VT or VF.

On occasion, specialized procedures are required to identify underlying structural heart disease in selected patients for whom a high index of suspicion exists. These procedures include cardiac magnetic resonance imaging, catheter endomyocardial biopsy, or both for the diagnosis of arrhythmogenic right ventricular dysplasia (ARVD), cardiac magnetic resonance imaging, catheter endomyocardial biopsy, or both for the diagnosis of myocarditis; signal averaged electrocardiography for the diagnosis of ARVD; infusion of a class I antiarrhythmic agent for the diagnosis of Brugada syndrome; and infusion of epinephrine for the diagnosis of LQTS. To date, genetic testing has not yet reached the maturity at which it can be recommended for diagnostic purposes in patients with VF. However, the future promise of genetic testing in this regard is high.

Documentation of the Mechanism of Ventricular Fibrillation

The debate on the advisability of offering a baseline transvenous catheter EPS to all patients who have had an episode of VF in the absence of a reversible or transient cause is still ongoing.[121] The major potential advantage of an EPS for patients with VF is the possibility of demonstrating that the VF was caused by another arrhythmia that would be treated in another way. Of course, VF may result from the degeneration of other tachyarrhythmias best treated by trans-catheter ablation procedures such as supraventricular tachyarrhythmias (including AF in the setting of ventricular pre-excitation) and certain VTs (including bundle

branch re-entrant VT). EPS may also help distinguish patients with a permanent VT substrate (typically those with a myocardial scar who have inducible VT) from those without a permanent VT substrate (typically those without a myocardial scar who do not have inducible monomorphic VT). This distinction may assist the practitioner in the selection of treatment modalities. For example, revascularization of CAD is rarely, if ever, useful in the former circumstance. Finally, EPS may also provide information regarding optimal programming of a subsequently implanted ICD. Nevertheless, each of these potential advantages is more likely to be had by the patient who presents with VT.

Identification of Other Disease States

Identification of other disease states that interact with antiarrhythmic therapies to be prescribed for the treatment of VF is an important goal of the investigations performed in this patient population. Screening biochemical investigations for renal or hepatic dysfunction are indicated before the prescription of antiarrhythmic drugs that depend on the renal or hepatic metabolism. Similarly, prescription of those therapies with adverse effect profiles that include interaction with other organ systems should be preceded by screening of the integrity of that organ system (e.g., thyroid function testing and pulmonary function testing in preparation for amiodarone therapy). These screening examinations are then be repeated as necessary during follow-up and can be compared with the baseline evaluations to substantiate change.

Assessment and Monitoring of Selected Antiarrhythmic Therapy

The assessment and monitoring of some forms of antiarrhythmic therapy require other selected investigations. Although now infrequently used, the selection of antiarrhythmic drug therapy by suppressing ventricular premature beats requires a baseline EPS as well as antiarrhythmic drug–free, and drug assessment 24-hour ambulatory ECG examinations along with exercise tolerance tests.[119,122] Similarly, the selection of antiarrhythmic drug therapy using the approach of suppression of ventricular tachyarrhythmias induced by programmed stimulation requires a baseline EPS as well as antiarrhythmic drug–free and drug assessment EPSs.[123,124] Of course, the follow-up of patients with a treated propensity to VF usually requires long-term surveillance—most commonly with repeated 24-hour ambulatory ECG examinations. However, no direct evidence suggests that such surveillance is of value to the patient with VF.

Electrophysiological Study

The role of EPS in the patient with VF depends on the etiology of the arrhythmia. Secondary VF is associated with acute reversible derangement such as ischemia, electrolyte imbalance, or cardiac trauma. In contrast, primary VF is not associated with any acute precipitant. In secondary VF, the best approach is to treat the specific precipitant responsible for VF. The role of EPS is often limited in secondary VF. Therefore, the focus of this section is on the approach to primary VF in the electrophysiology laboratory. In the setting of primary VF, it is imperative to first define the anatomic substrate. Because healed MI is the most common cause of primary VF, echocardiography, stress testing, and cardiac catheterization are all important diagnostic tools. If myocardial ischemia is demonstrated, revascularization (percutaneous or surgical) can improve long-term survival.[125,126]

Induction of Ventricular Tachycardia Versus Ventricular Fibrillation

After defining the underlying heart disease, EPS is important for risk stratification for primary VF. It is believed that VF is often preceded by VT, which degenerates into VF, so the induction of VT in the electrophysiological laboratory is indicative of the clinical rhythm (Figure 46-15). Therefore, the principal goal at EPS is the induction of sustained monomorphic VT. In the setting of a healed MI, VT can be induced at EPS in 20% to 45% of patients. The anatomic and electrophysiological substrate of VT is well described. Areas of healed MI, regions of slow conduction, and inhomogeneities of refractoriness all contribute to the specific responses to programmed stimulation and the induction of VT. As the induction of VT at EPS is already well described (see Chapters 25, 26, and 47), the focus of this section is induction of VF.

The correlation between the induction of VF in the electrophysiology laboratory and the incidence of VF as the presenting arrhythmia is limited, perhaps because of transient factors or prior VT in either situation.[127] Among patients with previous cardiac arrest, 20% to 50% do not have VF induced at EPS. VF is inducible in up to 25% of cardiac arrest survivors compared with 3% of patients who presented with monomorphic VT. This suggests that induction of VF in patients who present clinically with VF may be specifically predictive of spontaneous VF episodes, whereas induction of VF in patients who presented with VT may represent a nonspecific response to programmed electrical stimulation.[128]

In patients with asymptomatic nonsustained VT, CAD, and an ejection fraction less than 40%, VF or polymorphic VT is induced in up to 6% of cases.[129] Clinical variables often fail to distinguish patients with inducible arrhythmias from those without inducible arrhythmias. Ejection fraction is not significantly different in patients with no inducible arrhythmia, inducible nonsustained VT, inducible sustained monomorphic VT, or inducible VF (Figure 46-16). Of the 6% of patients in whom VF or polymorphic VT was induced, 17% died suddenly during follow-up.[126] The presence of inducible sustained ventricular arrhythmias and the persistence of inducible sustained ventricular arrhythmias on therapy were significant univariate predictors of SCD. However, only the persistence of inducible sustained arrhythmias on therapy was an independent predictor of SCD (Figure 46-17).

Electrophysiological Characteristics Associated with Induction of Ventricular Fibrillation

It is not well understood why VF is induced in some patients in the clinical electrophysiology laboratory and not in others. Because VF can be induced in perfectly normal hearts by using either multiple closely coupled premature stimuli or by shocks applied on the T wave, induction of VF by catheter stimulation is not necessarily associated with a poor prognosis. Several potential reasons exist for the nonspecific response of induction of VF at EPS, including local graded response in normal muscle or decremental conduction block caused by short coupling intervals. This appears to have less to do with dispersion of refractoriness or propagation and more to do with local graded responses in

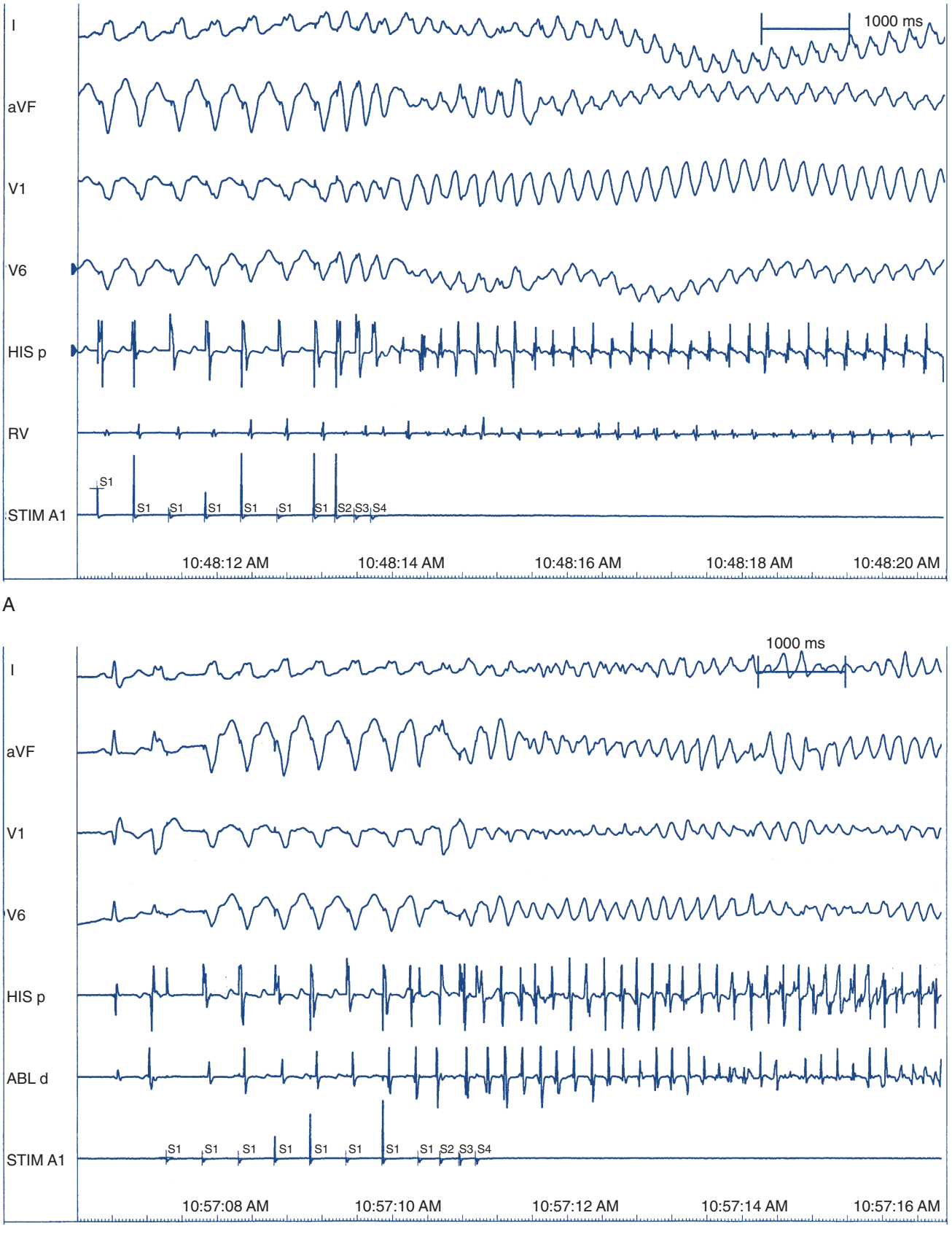

FIGURE 46-15 A, Induction of rapid monomorphic ventricular tachycardia with triple ventricular extrastimuli in a patient with cardiac arrest. **B,** A subsequent induction attempt with triple extrastimuli resulted in induction of ventricular fibrillation.

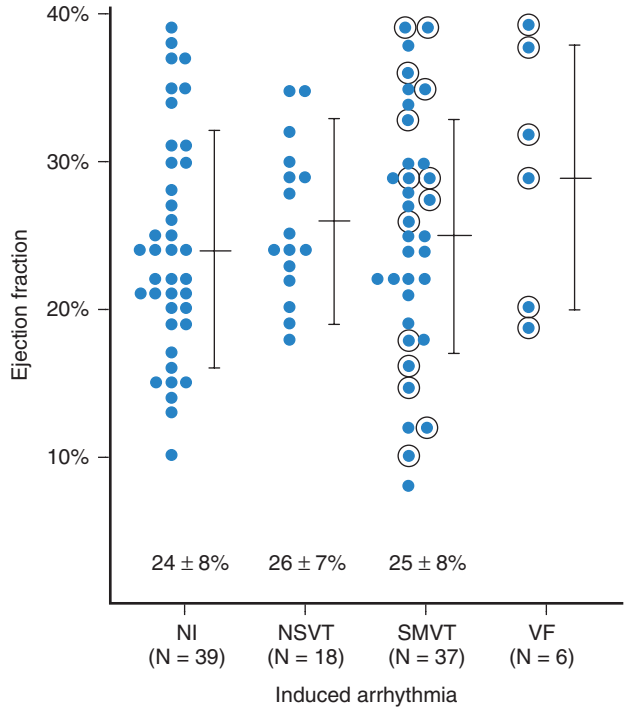

FIGURE 46-16 Scatterplot of left ventricular ejection fraction stratified by baseline-induced ventricular arrhythmia. *Vertical bars* are the mean ± SD of each group. *Circled dots* represent patients in whom inducible arrhythmias were suppressed. *P* = not significant among groups. *NI*, Noninducible; *NSVT*, nonsustained ventricular tachycardia; *SMVT*, sustained monomorphic ventricular tachycardia; *VF*, ventricular fibrillation. *(From Wilber DJ, Olshansky B, Moran JF, Scanlon PJ: Electrophysiological testing and nonsustained ventricular tachycardia: Use and limitations in patients with coronary artery disease and impaired ventricular function, 82[2]:350–358, 1990.)*

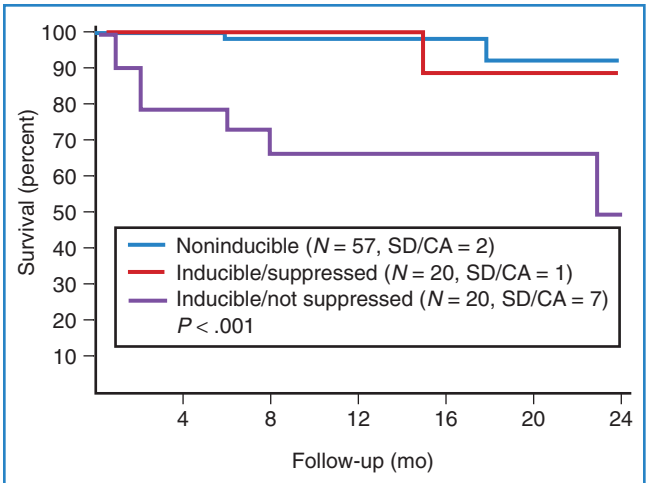

FIGURE 46-17 Actuarial incidence of sudden cardiac death or cardiac arrest in 97 patients, stratified by treatment subgroup. Three patients with cardiac arrest during serial drug testing were not included in analysis. *CA*, Cardiac arrest; *SD*, sudden cardiac death. *(From Wilber DJ, Olshansky B, Moran JF, Scanlon PJ: Electrophysiological testing and nonsustained ventricular tachycardia: Use and limitations in patients with coronary artery disease and impaired ventricular function, 82[2]:350–358.)*

normal muscle. For this reason, premature coupling intervals are usually not shortened below 180 ms to avoid inducing VF that has no diagnostic value.[129] Other causes of nonspecific responses to programmed stimulation and induction of VF include increased conduction latency and prolongation of local activation time in proximity of the stimulus electrode. Induction of VF is preceded by increased latency (Figure 46-18).[130]

Another hypothesis suggesting why VF is induced with closely coupled premature beats during programmed stimulation is *delayed conduction*. Conduction slowing by itself causes dispersion of activation time between sites near the stimulating electrode and distant sites. Also, conduction slowing of a premature beat allows distant sites to have a longer coupling interval of the premature beat compared with that from the pacing site. These factors result in dispersion of refractoriness, with the refractory periods following the premature beat being longer at distant sites than at the pacing site. This, in turn, allows additional premature beats to induce VF. Therefore, the measurement technique itself alters what we are attempting to measure (Table 46-1).[131] In addition, indirect evidence suggests that the mechanism of VF in the setting of a healed MI may be related to areas of slow conduction and stable re-entrant circuits. Occasionally, polymorphic VT or VF can transform to monomorphic VT by type I antiarrhythmic medications.[132] These tachycardias have been mapped in the operating room and have been cured by endocardial resection. These findings have not been observed in patients with a normal heart and inducible polymorphic VT or VF. Therefore, use of a type I antiarrhythmic agent may be helpful in differentiating between a nonspecific finding from a significant one in the electrophysiology laboratory.

Prognosis and Clinical Relevance

The prognostic value of electrophysiological evaluation has been extensively studied in survivors of cardiac arrest. The reproducibility of inducible VF is strongly predictive of recurrent cardiac arrest. However, the failure to induce arrhythmias with programmed stimulation may not necessarily be associated with a benign prognosis. In a specific subset of patients with CAD, LVEF less than 40%, asymptomatic nonsustained VT, and no inducible arrhythmias, the relative risk of death was 1.8.[125]

In addition, several secondary prevention trials have supported the efficacy of defibrillator implantation in out-of-hospital VF survivors irrespective of the outcome of EPS. Results of the Cardiac Arrest Study Hamburg (CASH), AVID, and the Canadian Implant Defibrillator Study (CIDS) support defibrillator placement in cardiac arrest survivors who have no reversible cause of VF.[133,134]

In summary, the usefulness of EPS in patients with VF is evolving. If a clearly reversible cause of secondary VF is identified, correction of the underlying problem is needed. With primary VF, it may be reasonable to consider EPS. The specificity of induction of VF by programmed stimulation varies with the patient's clinical presentation. The induction of VF may be related to areas of slow conduction or healed MI, local graded responses, decremental conduction block caused by short coupling intervals, and increased latency and prolongation of activation time. Defibrillator insertion may be indicated despite a negative EPS result in these patients.

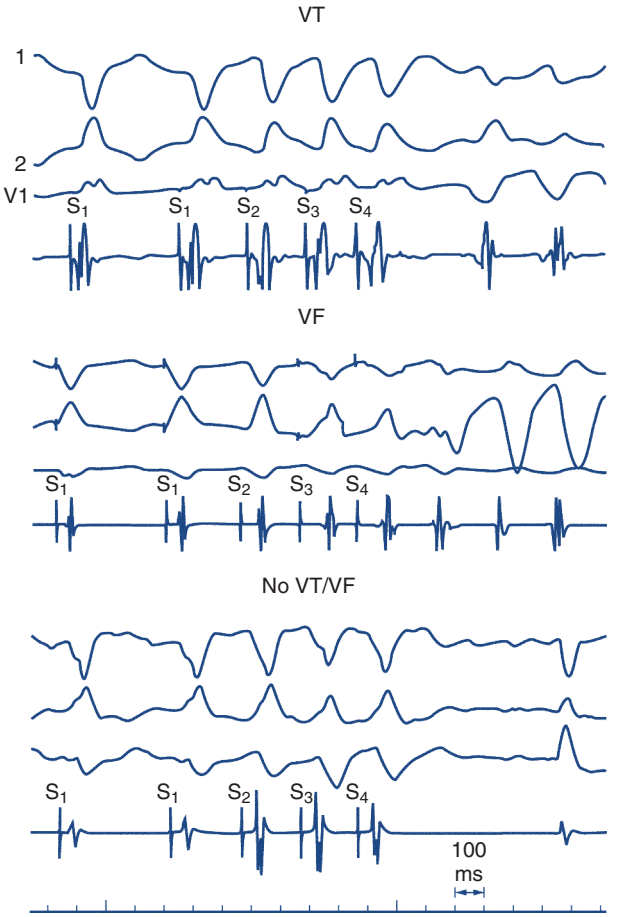

FIGURE 46-18 Tracings of electrocardiogram leads I, II, and V1 and ventricular electrograms. *Top,* Tracing of the last two ventricular stimuli from the drive (S_1) and the triple extrastimuli that result in the induction of sustained monomorphic ventricular tachycardia. *Middle,* Induction of ventricular fibrillation. *Bottom,* No induction of ventricular tachycardia or ventricular fibrillation. *VF*, Ventricular fibrillation, paper speed 100 ms/cm; *VT*, ventricular tachycardia. *(From Avitall B, McKinnie J, Jazayeri M, et al: Induction of ventricular fibrillation versus monomorphic ventricular tachycardia during programmed stimulation: Role of premature beat conduction delay,* Circulation *85:1271–1278, 1992.)*

Principles of Practice

The main strategic approaches to preventing death from VF include prevention and treatment. *Preventive therapies* of proven benefit include β-blocker therapy in patients with MI or heart failure; angiotensin-converting enzyme inhibition in patients with left ventricular dysfunction; spironolactone therapy in patients with moderate or severe heart failure; revascularization (bypass surgery in patients with left main or severe three vessel disease, especially with left ventricular dysfunction); and possibly amiodarone therapy. No other antiarrhythmic drug has been shown in any controlled study to reduce the likelihood of VF, SCD, or overall mortality. *Anticipatory therapy* for VF (i.e., treating those patients at particularly high risk for this arrhythmia) may include the implantation of an ICD; providing family members with a semiautomatic external defibrillator; using "wearable" AEDs; and, from a public health perspective, providing EMS personnel or trained lay rescuers with manually operated semiautomated external defibrillators. These are deployed in locations readily accessible to rescuers in proximity to patients experiencing cardiac arrest. The best and most publicized examples of these anticipatory strategies include the provision of semiautomated external defibrillators and trained lay operators in casinos, airports, and on long-haul airplane flights and sophisticated tiered therapy programs with EMS programs. *Therapy* for VF includes both defibrillation and adjunctive therapies such as measures to support the failing circulation during CPR as well as antiarrhythmic drug therapy to enhance the probability of successful resuscitation from VF.

Evidence-Based Therapy

Rescue of the Patient with Ventricular Fibrillation

Optimal resuscitation from VF requires restoring a perfusing cardiac rhythm as early as possible as well as providing the maximum possible cerebral and coronary blood flow during the resuscitation process. Mechanical aids, which improve cardiac output during CPR, have consistently shown improved outcomes in experimental settings and have shown, in limited human clinical trials, improved early resuscitation and improved survival to hospital admission.[135] However, definitive clinical trials with respect to improving survival to discharge from hospital are lacking although such interventions may be able to improve long-term outcomes in patients with VF, particularly if the interventions are begun relatively early (e.g., at 5 to 10 minutes) after the onset of cardiac arrest from VF.

Mechanical interventions of this type include the active compression-decompression CPR device, interposed abdominal and chest compression devices, the impedance threshold valve, mechanical or pneumatically driven chest compression devices, or devices inserted into the chest cavity to assist in direct cardiac compression.[136] All these devices increase cardiac output by increasing intrathoracic pressure during the compression phase of CPR or by increasing venous return during the decompression phase, either by positive abdominal pressure or by negative intrathoracic pressure during the decompression phase of CPR. The recent Prehospital Resuscitation Using an Impedance Valve and Early vs. Delayed Analysis Impedance Threshold Device (ROC PRIMED ITD) study was stopped at the recommendation of the Data and Safety Monitoring Board; the ITD did not improve survival to hospital discharge (see www.nih.gov/news/health/nov2009/nhlbi-06.htm).

Drug Therapy in Acute Management of Ventricular Fibrillation

The benefit of pharmacologic therapy as an adjunct to defibrillation in out-of-hospital VF is incompletely established. Despite many decades of use and ample laboratory experimental evidence of benefit, controlled clinical trials have not provided any clear evidence that either low-dose or high-dose epinephrine is beneficial in the treatment of patients with out-of-hospital VF.[137] Vasopressin, which appears to be superior to epinephrine in experimental models of cardiac arrest in improving survival from experimental VF, appears to be superior to epinephrine in some studies but not in others.[138-140] However, vasopressin has also not been proven superior to placebo in randomized controlled trials.

Table 46-1 Normalized Latency and Activation Times for S_1-S_2, S_1-S_2-S_3, and S_1-S_2-S_3-S_4 Used to Derive Cumulative Latency and Activation Times

LATENCY			ACTIVATION TIME		
VT	**VF**	**NO VT OR VF**	**VT**	**VF**	**NO VT OR VF**
S_2 4 ± 4*	17 ± 13	1 ± 6*	2 ± 6*	43 ± 27	1 ± 12*
S_2 5 ± 5	10 ± 14	1 ± 6*	6 ± 10*	22 ± 20	1 ± 12†
S_3 4 ± 5*	14 ± 23	5 ± 12*	8 ± 15*	31 ± 32	10 ± 15*
S_2 4 ± 8	8 ± 10	1 ± 6*	4 ± 9†	16 ± 15	1 ± 12†
S_3 12 ± 14	20 ± 20	5 ± 12*	17 ± 17†	37 ± 26	10 ± 15†
S_4 7 ± 18	14 ± 27	7 ± 13	8 ± 22†	33 ± 36	14 ± 17‡

Normalized latency and activation times for S_1-S_2, S_1-S_2-S_3, and S_1-S_2-S_3-S_4 used to derive cumulative latency and activation times (in ms). Sustained monomorphic ventricular tachycardi was initiated with lower latency times than the induction of ventricular fibrillation. Total activation times were longer in the inducible ventricular fibrillation group with single, double, and triple premature stimuli.
VT, Ventricular tachycardia; *VF*, ventricular fibrillation.
**P* < *.01 vs. ventricular fibrillation.*
†*P* < *.001 vs. ventricular fibrillation.*
‡*P* < *.05 vs ventricular fibrillation.*
From Avitall B, McKinnie J, Jazayeri M, et al: Induction of ventricular fibrillation versus monomorphic ventricular tachycardia during programmed stimulation. Role of premature beat conduction delay, Circulation 85:1271–1278.

Similarly, the evidence base regarding antiarrhythmic therapy is incomplete. The standard therapy used to assist electrical defibrillation has been lidocaine; no evidence from controlled clinical trials is available to suggest that lidocaine is superior to placebo or any other agent in improving survival to hospital admission or survival to hospital discharge.[141] In a meta-analysis of prophylactic lidocaine used in the post-infarction period, lidocaine may reduce the incidence of primary VF but appears to increase mortality rate.[142] Lidocaine likely increases defibrillation thresholds and may increase the incidence of asystole. Magnesium is not superior to placebo in in-hospital cardiac arrest caused by VF.[143-145] Bretylium, although studied in VF, is no longer available.

Intravenous (IV) amiodarone for VF resistant to three defibrillation shocks was compared with placebo in a blinded, randomized clinical trial by Kudenchuk et al.[146] The 246 patients with shock-resistant, out-of-hospital VF were randomized to 300 mg amiodarone by IV bolus versus placebo; the primary study endpoint was survival to hospital admission, achieved in 44% of amiodarone-treated patients versus 34% of placebo-treated patients. In a related study, IV amiodarone was compared with IV lidocaine in a blinded, randomized trial of patients with VF persisting after three shocks, IV epinephrine, and a further defibrillation shock. Survival to hospital admission was achieved in 23% of amiodarone-treated patients versus 12% of lidocaine-treated patients ($P = .009$).[147] Although neither of these studies demonstrated statistically significant improvements in survival to hospital discharge, if any antiarrhythmic drug is to be used in out-of-hospital VF, on the basis of these studies it seems reasonable to consider amiodarone as the drug of choice.

It is important to note that resuscitation from VF is a dynamic clinical situation, and many patients will have multiple recurrences of VF in the seconds to minutes after initial defibrillation and also undergo multiple transitions among VF, asystole, pulseless electrical activity, and a perfusing organized rhythm during the course of a protracted cardiac arrest. The use of adjunctive drug therapy can therefore be considered a means to prevent recurrences of VF as much as to assist in defibrillation. In particular, patients with frequent recurrences of VF may benefit from intensive antiadrenergic therapy, IV amiodarone therapy, and occasionally from anti-ischemic therapy, revascularization therapy, or therapy with an intra-aortic balloon pump.[148,149]

"Non-antiarrhythmic" Drugs that Prevent Sudden Cardiac Death

In the setting of heart failure, a cascade of neurohumoral activation initially supports perfusion.[150] Over time, however, the biologically active molecules released in the neurohumoral activation, including the sympathetic nervous system and the renin-angiotensin-aldosterone system, result in progressive left ventricular dysfunction. Pharmacologic antagonism of these two systems has proven to be an effective treatment paradigm.

β-Blockers

Strong evidence for a beneficial effect of β-blocker treatment in patients following an MI was reported in 1981 by the Norwegian Multicenter Study Group.[68] In their study, 1884 patients were randomly assigned to treatment with timolol (10 mg twice a day) or to placebo. Mortality in rate the control group was 16% compared with 10% in the timolol group ($P = .0001$), and a reduction in SCD from 13.9% to 7.7% ($P = .0001$) was observed. In the following year, the Beta-Blocker Heart Attack Trial (BHAT) reported a comparison of propranolol and placebo in patients with prior MI.[66] In that study, 3837 patients were randomized to treatment with propranolol or placebo 5 to 10 days after an MI. The trial was stopped 9 months early after an average follow-up of 25 months because of a highly significant difference in mortality in favor of propranolol (7.2% in the propranolol group vs. 9.8% in the placebo group). These trials, along with a series of subsequent studies, were combined in a meta-analysis confirming that β-blockers reduce both total mortality and SCD.[153]

More recently, two studies investigating treatment of patients with heart failure have suggested the benefit of β-blockers with respect to reduction of total mortality and prevention of SCD.[154,155] The Cardiac Insufficiency Bisoprolol Study II (CIBIS II) trial randomized 2647 patients with an LVEF of 35% or less and New York Heart Association (NYHA) functional class III or IV heart failure to the β_1-selective agent bisoprolol or placebo.[156] All-cause mortality was reduced from 17.3% in the placebo group to 11.8% in the bisoprolol group ($P < .0001$). Significantly fewer SCDs occurred in bisoprolol-treated patients compared with placebo-treated patients (3.6% vs. 6.3%; $P = .0011$). The Metoprolol Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) randomized 3991 patients with LVEF of 40% or less in NYHA functional class II to IV heart failure to treatment with the β_1-selective agent metoprolol, in its controlled release or extended release form, or placebo.[155] All-cause mortality was 7.2% per year in the metoprolol group and 11% in the placebo group ($P = .00009$). A reduction in SCD was seen in metoprolol-treated patients (odds ratio [OR], 0.59; confidence interval [CI], 0.45 to 0.78).

Angiotensin-Converting Enzyme Inhibitors

The survival advantage conferred by angiotensin-converting enzyme (ACE) inhibitors in patients with heart failure has been demonstrated in a number of studies.[156-159] However, only in the Tandolapril Cardiac Evaluation Trial (TRACE) did the reduction in SCD reach statistical significance.[160] A recently published meta-analysis has now clearly demonstrated that ACE inhibitors reduce SCD.[160] In this study, 15,104 patients from 15 trials were studied. The relative risk of SCD in ACE inhibitor–treated patients was 0.80 (95% CI, 0.70 to 0.92).

Aldosterone Antagonism

The effect of spironolactone on survival was studied in the Randomized Aldactone Evaluation Study (RALES).[161] A total of 822 patients on an ACE inhibitor with an LVEF of 35% or less and severe heart failure symptoms were randomly assigned to treatment with spironolactone or placebo. After a mean follow-up of 24 months, the mortality rate was 46% in the placebo group and 35% in the spironolactone group ($P < .001$). The relative risk of SCD in spironolactone-treated patients was 0.71 (CI, 0.54 to 0.95).

Recent studies have confirmed these findings and extended the benefit to patients with mild heart failure, in whom eplerenone, a selective aldosterone inhibitor, reduces all-cause mortality. A total of 12.5% of patients receiving eplerenone and 15.5% of those receiving placebo died (hazard ratio [HR], 0.76; 95% CI, 0.62 to 0.93; $P = .008$).[162] Taken together, the data confirm that antagonizing the various components of the neuroendocrine activation that accompanies heart failure results in a reduction in SCD.

Anti-thrombotic and Anticoagulant Therapy

Accumulated data have suggested that ischemia caused by thrombus formation in stenotic coronary arteries may result in SCD. On the basis of pathologic examinations, greater than 80% of SCD cases in patients with ischemic heart disease may be associated with thrombus formation or plaque fissuring.[163,164] In the Second International Study of Infarct Survival (ISIS-2), aspirin use was associated with a reduction in total mortality and SCD.[165] A multivariate analysis of the 6797 participants in the Studies of Left Ventricular Dysfunction (SOLVD) demonstrated that both antiplatelet and anticoagulant therapies were associated with a reduction in the risk of SCD.[166] This provides a rationale for anti-thrombotic therapy, anti-platelet therapy, or a combination of both in patients with left ventricular dysfunction.

Antiarrhythmic Drugs

The importance of ventricular ectopy as a risk factor for SCD in patients with coronary disease is well established. It was therefore reasonable to hypothesize that suppression of premature ventricular complexes (PVCs) using standard antiarrhythmic agents that block sodium or potassium channels might reduce the risk of SCD.

Class I Agents

The Cardiac Arrhythmia Suppression Trial (CAST) studied patients with a history of MI and frequent PVCs that were suppressible with encainide, flecainide, or moricizine (type IC agents that are sodium channel blockers).[167] More than 90 days after MI, patients were also required to have an LVEF of 40% or less. Despite suppression of PVCs, the encainide and flecainide arms of the trial were stopped early because of increased mortality in patients treated with antiarrhythmic drugs. The moricizine arm was subsequently stopped because it became clear there would be no benefit and because of concern about an apparent early increase in mortality.[168]

The CAST trial provided four important insights: (1) the mechanism causing PVCs was different from that causing the arrhythmia (presumably a ventricular tachyarrhythmia) that provoked SCD; (2) ventricular ectopy is not an appropriate surrogate endpoint for SCD in clinical trials; (3) antiarrhythmic drugs could be proarrhythmic, even months after initiation; and (4) a change in the myocardial substrate, presumably ischemia, could make the antiarrhythmic drug proarrhythmic.

New Class III Drugs

In the Survival with Oral D-Sotalol (SWORD) study, the impact on SCD of d-sotalol, a potassium channel blocker without β-blocker properties, was studied.[3,127,169] Patients with a history of MI and LVEF less than 40% were randomly assigned to d-sotalol or placebo. The study was terminated because of an excess risk of mortality in d-sotalol–treated patients (relative risk [RR], 1.65; $P = .006$). Dofetilide was also evaluated in patients with CHF.[170] In a study of 1518 patients with symptomatic CHF and severe left ventricular dysfunction randomized to dofetilide or placebo, no difference in mortality rate was seen, although dofetilide was successful in converting AF to sinus rhythm. Similar results were obtained in patients with prior MI but without CHF.[171] These data suggest that although dofetilide has no role in the prevention of SCD, it may be a useful treatment option in patients with AF who are also at risk for SCD because it did not increase mortality rate in these patients. A meta-analysis performed by Teo et al of antiarrhythmic trials was reported in 1993. Data were drawn from 138 trials and 98,000 patients.[172] The mortality rate of patients randomized to receive class I agents was significantly higher than that of patients receiving placebo (OR, 1.14; 95% CI, 1.01 to 1.28; $P = .03$).

Given the data presented, it is reasonable to ask whether the reason for the failure of these antiarrhythmic drugs to prevent SCD is the intrinsic ineffectiveness of drug action or the method of guiding selection of the drug. If the problem were the method of guiding selection of potentially effective drugs, it would be expected that although the drugs might not prevent an arrhythmia, at least they would not be proarrhythmic. However, most antiarrhythmic drugs other than amiodarone were shown to provoke SCD in clinical trials. This suggests that the failure to prevent SCD is based on the molecule rather than the selection paradigm. The results of the Electrophysiologic Study Versus Electrocardiographic Monitoring (ESVEM) study provide support for this view.[122] In this study, 486 patients with sustained monomorphic VT, inducible with programmed electrical stimulation (PES) and 10 PVCs or more per hour on Holter monitoring, were randomly assigned to guidance by demonstrating suppression of PES-stimulated VT or Holter recording suppression of ventricular ectopy. Although the PES protocol used in ESVEM was limited, the results in ESVEM were no different in either arm, indicating that PES guidance was not better than Holter guidance. In contrast, the Calgary study, using a standard PES protocol, showed superior results with PES-guided therapy for the prevention of recurrent VT or VF in less drug-refractory patients.[123,124]

It can be concluded from the studies presented that the antiarrhythmic drugs, excluding amiodarone, that have been tested may not prevent death from ventricular arrhythmias and, depending on the drug, may even increase it. As a result, antiarrhythmics other than amiodarone that have been studied have a limited role in the prevention of SCD and should be considered after other, better treatments have been rejected.

Amiodarone

A number of early studies suggested that amiodarone, unlike other antiarrhythmics, may have a role in suppressing VTs in the post-MI population. The Basel Antiarrhythmic Study of Infarct Survival (BASIS) randomized 312 patients with previous MI and complex ventricular ectopy to amiodarone, individualized drug therapy starting with procainamide, or no antiarrhythmic drug therapy.[173] After 1 year of follow-up, amiodarone-treated patients had a significantly greater survival compared with patients treated with no antiarrhythmic therapy (95% vs. 87%; $P = .048$). Amiodarone-treated patients also had better survival compared with patients who received individualized therapy, but this did not reach statistical significance. Ceremuzynski et al randomized 613 patients with previous MI who were ineligible to receive β-blockers to amiodarone or placebo.[174] A statistically significant ($P = .048$) reduction in cardiac mortality was seen in amiodarone-treated patients, although the reduction in total mortality did not achieve statistical significance. The meta-analysis by Teo et al, discussed earlier, showed a significant mortality reduction in amiodarone-treated patients with previous MI.[172] Taken together, these studies suggested that amiodarone may reduce arrhythmic death.

This picture was further clarified by the European Myocardial Infarction Amiodarone Trial (EMIAT) and the Canadian Amiodarone Myocardial Infarction Trial (CAMIAT).[175,176] EMIAT randomized 1486 patients who had an LVEF of 40% or less, 5 to 21 days after an MI, to treatment with amiodarone or placebo. No difference was observed in the primary endpoint of total mortality or in cardiac mortality. Arrhythmic death was reduced from 7% in the placebo group to 4% in the amiodarone group ($P = .05$). All the mortality benefit occurred in amiodarone-treated patients, who were also treated with a β-blocker. In CAMIAT, 1202 patients with a history of MI and frequent ventricular ectopy (>10 PVCs per hour or at least one episode of VT) were randomized to receive amiodarone or placebo. A reduction was seen in the endpoint of resuscitated VF or arrhythmic death from 6% in the placebo group to 3.3% in the amiodarone group ($P = .03$). No difference in total mortality was observed. As in EMIAT, only amiodarone-treated patients who were also on a β-blocker appeared to derive any benefit. Two recent meta-analyses that provide a quantitative overview of the available randomized trials have been published. The Amiodarone Trials Meta-Analysis Investigators examined 13 randomized trials involving 6553 patients.[177] Five trials of patients with CHF and eight trials involving patients with previous MI were included. The mean LVEF in this population was 0.31. They found a 29% reduction in SCD (OR, 0.71; 95% CI, 0.59 to 0.85). No difference was seen between the post-MI and CHF populations. Sim et al studied 15 randomized trials of amiodarone to prevent SCD using the random effects model.[178] Amiodarone was found to significantly reduce the risk of total mortality (OR, 0.77; 95% CI, 0.66 to 0.89; $P < .001$) and SCD (OR, 0.70; 95% CI, 0.58 to 0.85; $P < .001$).

These data suggest that, unlike other antiarrhythmic drugs, amiodarone may reduce arrhythmic death in the post-MI population and that its effect appears to be greater if there is concomitant β-blocker therapy.

In the Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients (OPTIC) trial, amiodarone was more effective that β-blockers alone or sotalol in preventing ICD discharges for ventricular arrhyhthmias.[179] However, amiodarone is rarely recommended as the sole therapy for the secondary prevention of SCD in patients with a history of VF not caused by a reversible cause, the ICD being the therapy of choice. The fact that the reduction in arrhythmic death is not easily translated into an improvement in total mortality is likely attributable to the limited protective effect of amiodarone. SCD-HeFT did not show any mortality benefit from amiodarone versus placebo; the HR for mortality in 845 amiodarone-treated patients followed up to 5 years versus the 847 patients treated with placebo was 1.06 (97.5% CI, 0.86 to 1.30).

Nonpharmacologic Therapy

Revascularization

As previously discussed, ischemia appears to be a precipitating event in SCD and is frequently caused by plaque disruption and coronary thrombus formation. Data supporting the usefulness of anti-thrombotic agents suggest a potential antiarrhythmic role for revascularization. Interestingly, trial-derived data bearing directly on the issue of revascularization are rare. In the Coronary Artery Surgery Study (CASS) registry, revascularization was independently associated with improved survival free of SCD (SCD occurred in 4.9% of patients assigned to medical therapy and 1.6% of patients assigned to surgical therapy).[180] Garan et al showed that myocardial revascularization can result in elimination of PES-inducible ventricular tachyarrhythmias.[181] Hii et al found that a patent infarct-related artery was associated with the effective drug suppression of inducible VT at PES.[182] In sum, data supporting a role for ischemia in the production of ventricular arrhythmias and studies suggesting a positive treatment effect of

eliminating the ischemia lead to the conclusion that elimination of inducible ischemia should be a component of treatment to prevent SCD.

Implantable Cardioverter-Defibrillator

Since the first implantation of an ICD by Mirowski in 1980, these systems have continued to evolve.[183] Today, they are generally placed transvenously, with an implantation-related mortality rate of less than 1%.[184] Current systems are capable of defibrillation of VF, tiered therapy of VT (competitive pacing, synchronized cardioversion, defibrillation), and antibradycardia pacing. Increasingly sophisticated electrogram storage and telemetry are useful for rhythm diagnosis.

A number of randomized, controlled clinical trials in patients with malignant ventricular arrhythmias, including SCD, have been performed and have provided an increasingly clear picture of the appropriate role of and considerations for the ICD (Box 46-1). The AVID trial was a secondary prevention study that randomized patients with a history of symptomatic VT or VF to ICD implantation or to antiarrhythmic therapy.[131] Randomized patients must have been resuscitated from VF or have had an episode of VT that was hemodynamically compromising or that was associated with an LVEF less than 40%. A total of 1016 patients were randomized to immediate ICD implantation or antiarrhythmic drug therapy. Although sotalol or amiodarone was permitted in the antiarrhythmic drug arm, only 2.6% of patients randomized to antiarrhythmic drug were discharged on sotalol. Thus, for all practical purposes, this was an amiodarone versus ICD trial. The trial was stopped early because of significantly better survival in ICD-treated patients (75.4% vs. 64.1% at 3 years; $P < .02$). Similar patient populations were studied in CIDS and CASH, with results similar to AVID.[134,135]

MADIT was a primary prevention trial that studied 196 patients with previous MI, nonsustained VT, and an LVEF of 35% or less who were inducible to a sustained monomorphic VT at PES not suppressible by procainamide.[185] This population was different from the AVID patients in that they did not have a spontaneous sustained ventricular arrhythmia but had shown that VT could be induced by PES. These patients were randomly assigned to immediate ICD implantation or antiarrhythmic drug therapy. At 1-month follow-up, 74% of the patients in the antiarrhythmic drug therapy group were on amiodarone. Survival was significantly better in the ICD group than in patients treated with an antiarrhythmic drug (mostly amiodarone) (HR for overall mortality, 0.46; 95% CI, 0.26 to 0.82; $P = .009$).

All the ICD trials (AVID, MADIT, CIDS, CASH) presented thus far entered patients known to be at high risk for a fatal arrhythmia because they had a history of prior VT, either as a presenting problem or at PES. The Coronary Artery Bypass Graft PATCH (CABG-PATCH) trial examined patients at risk of SCD because of the presence of coronary disease for which they were to undergo coronary artery bypass grafting (CABG), who had an LVEF of 35% or less, and who had an abnormal signal-averaged ECG.[186] In contrast to the patients presented in the other studies, these patients had no history of a sustained VT that occurred spontaneously or at PES. This study randomly assigned 900 patients to ICD implantation or no implantation at the time of CABG. During an average follow-up of 32 ± 16 months, no significant difference was seen in mortality between patients assigned to ICD and those assigned to no ICD. The HR for total mortality with ICD placement was 1.07 (95% CI, 0.81 to 1.42). In CABG-PATCH, 71% of the deaths were nonarrhythmic, which accounts for the absence of benefit from the ICD.[187] It is possible that the revascularization reduced the frequency of VTs by removing the contributing role of inducible ischemia. The results of this trial do not provide support for the use of the signal-averaged ECG in risk stratification.

The Multicenter Unsustained Tachycardia Trial (MUSTT) studied patients with CAD, an LVEF of 40% or less, and nonsustained VT on Holter recording and who had inducible, sustained monomorphic VT or VF.[188] Patients were randomized to standard therapy for coronary disease or standard therapy with a PES-guided attempt to suppress inducible VT or VF. Patients in whom inducible VT or VF was suppressed or whose VT was hemodynamically tolerated were treated with the drug that suppressed the VT (or rendered it tolerable). Patients who continued to be inducible to a sustained VT at PES that was hemodynamically intolerable had an ICD placed. The primary endpoint of the study was cardiac arrest or death. A total of 704 patients were randomized. The patients who received the ICD because of nonsuppressibility would be expected to be the highest risk group, but they had a better survival compared with patients not receiving antiarrhythmic therapy and those who were suppressible with PES-guided antiarrhythmic therapy (RR, 0.24; 95% CI, 0.13 to 0.45; $P < .001$). No difference was seen in mortality rate or cardiac arrest between patients who received no antiarrhythmic therapy and those with antiarrhythmic drug suppression of inducibility. Interestingly, unlike the other ICD trials, it is possible to compare ICDs with standard treatment without an antiarrhythmic drug in patients who have had a demonstrated VT (in this case, at PES). These data suggest that the ICD is the most effective approach to preventing SCD in these patients. Also, they proved an important additional demonstration of the ineffectiveness of PES-guided antiarrhythmic drug selection. The conclusions drawn from MUSTT suggest that the potentially large group of coronary patients with depressed ejection fraction and nonsustained VT who are inducible into a sustained monomorphic VT or VF by PES should have an ICD inserted. MADIT-II randomized patients with previous MI and an LVEF of 30% or less to ICD or standard therapy.[189] The primary endpoint was total mortality. Most patients were in NYHA class I or II. The ICD arm had a 31% relapse risk reduction in total mortality, suggesting that an important role for SCD prevention exists in this population.[189] However, most of the benefit was seen in patients with a prolonged QRS complex on the resting ECG. In summary, the accumulated data suggest that the ICD reduces mortality in patients at high risk for a fatal VT and that it is more effective than amiodarone in doing so.

A consideration of these facts leads to the current management approach to patients at risk for SCD:

1. Patients resuscitated from VF or with VT associated with hemodynamic compromise or reduced LVEF (≤0.40) should have an ICD inserted. They should also be treated with aspirin, β-blockers, and ACE inhibitors, as tolerated, as well as revascularization if inducible ischemia is present.

2. Patients with coronary disease, reduced LVEF (31% to 40%), and nonsustained VT who have a sustained monomorphic VT induced by PES should also have an ICD placed. They should be treated with aspirin, β-blockers, and ACE inhibitors, as tolerated, as well as revascularization if inducible ischemia is present. The presence of nonsustained VT may be useful as a

Box 46-1 Indications for Implantable Cardioverter-Defibrillator Therapy for Patients at Risk of Ventricular Fibrillation

CLASS I

1. ICD therapy is indicated in patients who are survivors of cardiac arrest due to VF or hemodynamically unstable sustained VT after evaluation to define the cause of the event and to exclude any completely reversible causes. *(Level of Evidence: A)*
2. ICD therapy is indicated in patients with syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced at electrophysiological study. *(Level of Evidence: B)*
3. ICD therapy is indicated in patients with LVEF less than 35% due to prior MI, at least 40 days after MI, and who are in NYHA functional class II or III. *(Level of Evidence: A)*
4. ICD therapy is indicated in patients with nonischemic DCM who have an LVEF 35% or less and who are in NYHA functional class II or III. *(Level of Evidence: B)*
5. ICD therapy is indicated in patients with left ventricular dysfunction caused by prior MI, at least 40 days after MI, and who have an LVEF less than 30%, and are in NYHA functional class I. *(Level of Evidence: A)*
6. ICD therapy is indicated in patients with nonsustained VT from prior MI, LVEF less than 40%, and inducible VF or sustained VT at electrophysiological study. *(Level of Evidence: B)*

CLASS IIA

1. ICD implantation is reasonable for patients with unexplained syncope, significant left ventricular dysfunction, and nonischemic DCM. *(Level of Evidence: C)*
2. ICD implantation is reasonable for patients with HCM who have 1 or more major† risk factors for SCD. *(Level of Evidence: C)*
4. ICD implantation is reasonable for the prevention of SCD in patients with ARVD/C who have 1 or more risk factors for SCD. *(Level of Evidence: C)*
5. ICD implantation is reasonable to reduce SCD in patients with long QT syndrome who are experiencing syncope, VT, or both while receiving β-blockers. *(Level of Evidence: B)*
6. ICD implantation is reasonable for nonhospitalized patients awaiting transplantation. *(Level of Evidence: C)*
7. ICD implantation is reasonable for patients with Brugada syndrome, who have had syncope. *(Level of Evidence: C)*
8. ICD implantation is reasonable for patients with cardiac sarcoidosis, giant cell myocarditis, or Chagas disease. *(Level of Evidence: C)*

CLASS IIB

1. ICD therapy may be considered in patients with nonischemic heart disease, who have an LVEF of 35% or less and who are in NYHA functional class I. *(Level of Evidence: C)*
2. ICD therapy may be considered for patients with long QT syndrome and risk factors for SCD. *(Level of Evidence: B)*
3. ICD therapy may be considered in patients with syncope and advanced structural heart disease, in whom thorough invasive and noninvasive investigations have failed to define a cause. *(Level of Evidence: C)*
4. ICD therapy may be considered in patients with a familial cardiomyopathy associated with SCD. *(Level of Evidence: C)*
5. ICD therapy may be considered in patients with left ventricular noncompaction. *(Level of Evidence: C)*

CLASS III

1. ICD therapy is not indicated for patients who do not have a reasonable expectation of survival with an acceptable functional status for at least 1 year, even if they meet ICD implantatio criteria specified in the class I, IIa, and IIb recommendations above. *(Level of Evidence: C)*
2. ICD therapy is not indicated for patients with incessant VT or VF. *(Level of Evidence: C)*
3. ICD therapy is not indicated in patients with significant psychiatric illnesses that may be aggravated by device implantation or that may preclude systematic follow-up. *(Level of Evidence: C)*
4. ICD therapy is not indicated for NYHA class IV patients with drug-refractory congestive heart failure who are not candidates for cardiac transplantation or CRT-D. *(Level of Evidence: C)*
5. ICD therapy is not indicated for syncope of undetermined cause in a patient without inducible ventricular tachyarrhythmias and without structural heart disease. *(Level of Evidence: C)*
6. ICD therapy is not indicated when VF or VT is amenable to surgical or catheter ablation (e.g., atrial arrhythmias associated with the Wolff-Parkinson-White syndrome, righty or left ventricular outflow tract VT, idiopathic VT, or fascicular VT in the absence of structural heart disease). *(Level of Evidence: C)*
7. ICD therapy is not indicated for patients with ventricular tachyarrhythmias from a completely reversible disorder in the absence of structural heart disease (e.g., electrolyte imbalance, drugs, or trauma). *(Level of Evidence: B)*

ARVD/C, *Arrhythmogenic right ventricular dysplasia or cardiomyopathy;* CRT-D, *cardiac resynchronization therapy–defibrillator;* DCM, *dilated cardiomyopathy;* HCM, *hypertrophic cardiomyopathy;* ICD, *implantable cardioverter-defibrillator;* LVEF, *left ventricular ejection fraction;* MI, *myocardial infarction;* NYHA, *New York Heart Association;* SCD, *sudden cardiac death;* VF, *ventricular fibrillation;* VT, *ventricular tachycardia.*
Adapted from Epstein, AE, DiMarco, JP, Ellenbogen, KA, et al: ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: American College of Cardiology/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the American Association for Thoracic Surgery and Society of Thoracic Surgeons, J Am Coll Cardiol *51:1–62, 2008.*

screening tool for detecting higher risk for sustained ventricular arrhythmias but is likely superfluous in a patient with a history of sustained arrhythmia, including at PES.

3. Patients with CAD, prior MI, and severe left ventricular dysfunction (LVEF <30%) should be risk stratified (e.g., by QRS width and ≥120 ms) or otherwise considered for ICD therapy.

Primary Prevention of Sudden Cardiac Death

At this point, no doubt exists about the capacity of the ICD to prevent arrhythmic death. This means that any patient destined to have a potentially fatal ventricular arrhythmia (in spite of otherwise appropriate medical therapy) could potentially benefit from having an ICD in place. A central issue for future investigation is the identification of patients at sufficiently high risk of SCD

to justify the morbidity and cost of placing a device. Some subpopulations of patients described earlier may be effectively treated with amiodarone. For instance, a post hoc analysis of the AVID database suggests that ICDs have no benefit over amiodarone for patients with LVEF greater than 35%.[190] A randomized trial in such patients would be needed to make definitive treatment recommendations.

Certain populations of patients are known to be at risk for SCD, but because of competing risks of death, it is not clear whether the ICD will confer a benefit to the population as a whole. The Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) study used a risk factor representing autonomic dysfunction as a risk stratifier to allow defibrillation therapy to more effectively focus on the highest-risk patients. A reduction in heart rate variability (HRV) has been shown to portend a worse prognosis in patients with CAD.[191-193] Patients in DINAMIT had low HRV and an ejection fraction of 35% or less. They were within 40 days of an acute MI. No mortality benefit was seen in patients randomized to the ICD (n = 332) compared with control patients (n = 342), with an HR for all-cause death of 1.08 (95% CI, 0.76 to 1.55) in the ICD versus control groups, over 30 ± 13 months of follow-up.[194]

In the Defibrillators In Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) study, 458 patients with nonischemic cardiomyopathy, an LVEF of 35% or less, and more than 10 PVCs per hour or any episode of unsustained VT were randomized to standard medical therapy versus standard therapy plus ICD. The HR for all-cause mortality after 29 ± 14.4 months of follow-up in the ICD versus control groups was 0.65 (95% CI, 0.4 to 1.06; $P = .08$).[195]

The entire discussion to this point has focused on populations known to be at high risk for SCD. Myerberg and others have emphasized the fact that the majority of cardiac arrests occur in the low-risk, but very large, population of patients whose increased risk has not come to clinical recognition.[196] To make major inroads into the prevention of SCD, learning how to screen the asymptomatic population inexpensively, but safely and effectively, will be necessary. Identifying high-risk patients in the low-risk, asymptomatic population and identifying members of known high-risk populations who are not at high enough risk to justify ICD placement is the next frontier in SCD prevention.

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CHAPTER 47

Sudden Cardiac Death

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Despite the significant decline in coronary artery disease (CAD)–related death over the last few decades in North America and Europe, sudden cardiac death (SCD) remains a major cause of mortality and therefore an important public health issue. In developing nations, in contrast, the true burden of SCD is difficult to assess because of lack of data, but it would be reasonable to assume that it significantly contributes to overall mortality rates. Significant advances have been made in the prediction and prevention of SCD, but considerable challenges that limit the efficacy and cost-effectiveness of available methods remain. A move toward a multi-disciplinary approach targeting abnormalities at the cellular level, combined with accurate and early risk stratification and effective intervention, will undoubtedly help rein in the epidemic of SCD in the twenty-first century.

Definition

The term *sudden cardiac death* refers to unexpected natural death from a cardiovascular cause within a short period, generally less than 1 hour from the onset of symptoms.[1] The time and mode of death are therefore unexpected.[2] By definition, this occurs in individuals who do not have prior conditions that could be fatal in the short term. The use of 1 hour in this definition is arbitrary and therefore subject to different interpretations. It is also important to distinguish a primary arrhythmic cause of death from, for example, an episode of worsening heart failure that culminates in a life-terminating arrhythmia and from other causes of sudden death such as pulmonary embolism, cerebral infarction, and ruptured aneurysms. This distinction is important both for the proper identification of SCD and the study of this phenomenon. More recently, the use of the term *sudden cardiac arrest* (SCA, synonymous with SCD) has been advocated.

Epidemiology

SCD is a major cause of death in North America and other Western societies, accounting for 10% of all deaths and up to 50% of heart disease–related deaths.[3] The incidence of SCD (emergency medical services [EMS]–assessed, out-of-hospital cardiac arrests) in the United States is generally estimated to be 95.7 per 100,000 person years.[4] Approximately 60% of out-of-hospital cardiac deaths are treated by EMS personnel.[5] Among these EMS-treated, out-of-hospital arrests, 23% have an initial shockable rhythm, and 31% of these receive bystander cardiopulmonary resuscitation (CPR).[6] Median survival rate to hospital discharge after EMS-treated, out-of-hospital cardiac arrest with any first recorded rhythm is 7.9% and for ventricular fibrillation (VF) is 21%. However, such median statistics of survival do not reflect regional variations of community-specific survival rates. Of note, the quantification of SCD is so fraught with difficulties that no comprehensive record of all SCDs exists. Surrogate data often are used to estimate its incidence, especially in the out-of-hospital setting. This includes deaths from "coronary heart disease" and "cardiac arrest," defined as coronary death that occurred within 1 hour of symptom onset in the out-of-hospital setting and without other probable causes of death.[7]

As medical interventions continue to evolve and improve, the incidence and distribution of risk factors that contribute to SCD continue to change. Although the morbidity and mortality rates of cardiovascular disease have declined in the past 30 years, much less improvement has been observed in the incidence of out-of-hospital cardiac arrests. However, the incidence of cardiac arrest with an initial recorded rhythm of VF specifically has decreased over time, which is a recent trend that reflects the overall decline in cardiac mortality.[8,9] The reduction in the incidence of VF is likely multi-factorial in origin and is attributable to improvements in primary and secondary prevention of heart disease. Current epidemiologic data indicate that in developed countries, structural coronary arterial abnormalities and their consequences account for 80% of fatal arrhythmias.[10,11] Dilated and hypertrophic cardiomyopathies account for the next largest group of SCD. The remainder are caused by a variety of other cardiac disorders such as congenital heart disease (CHD) and primary electrophysiological disorders.

The epidemiology of SCD in adolescents and young adults (aged 10 to 30 years) is distinctly different from that in the adult population. The incidence of SCD in this population is two orders of magnitude less than in the adult group (1 per 100,000 vs. 1 per 1000 individuals annually).[12] Although coronary atherosclerosis accounts for the majority of cases of SCD in individuals older than 40 years, it is an uncommon cause in the younger age group.[13] Instead, causes such as hypertrophic cardiomyopathy, myocarditis, right ventricular dysplasia, anomalous coronary arteries, Brugada syndrome, long QT syndrome (LQTS), idiopathic VF, and commotio cordis are the underlying etiologies in this group. Because some of these conditions are genetically determined, a modest age inverse relationship seems to exist in this group, with adolescents having a somewhat higher mortality risk compared with young adults.[11] A unique subgroup in this younger population is composed of competitive athletes, among whom the

rate of SCD currently is approximately 0.4 to 0.6 per 100,000 person-years.[14,15] The large numbers of SCD and the wide range of survival rates have significant potential implications for public health; for example, in the United States and Canada, an additional 7500 lives would be saved if survival from SCD could be increased to 12%.

Mechanisms

From a clinical perspective, the causes of SCD can be divided into two broad categories: (1) ventricular tachyarrhythmias (VA) and (2) pulseless electrical activity (PEA) and asystole. The National Registry of CPR is a prospective, multi-site, in-hospital resuscitation registry sponsored by the American Heart Association. In a study using this database, of the 51,919 index arrests evaluated in 411 centers, pulseless VT was diagnosed in 7%, VF in 17%, PEA in 37%, and asystole in 39%.[16] Subsequent ventricular tachycardia (VT) or VF occurred in 26% of patients with an initial documented rhythm of PEA and in 25% of patients with asystole. Thus VT or VF was seen in 44% of all adult in-hospital cardiac arrests. This must be compared with out-of-hospital cardiac arrests, where among cases of EMS-assessed cardiac arrest, the incidence of VT or VF was 13% and PEA and asystole were 33% and 47%, respectively, for cases in which the initial rhythm was unknown, not determined, or not analyzed by EMS.[8] A factor that has important implications in out-of-hospital cardiac arrests (as opposed to in-hospital cardiac arrests) is the median time of 7.24 minutes from call to arrival of first advanced life support.[8]

Pathophysiology

SCD caused by VA can be viewed as an electrical event that occurs when two distinct conditions are present: (1) a vulnerable substrate and (2) a trigger. This substrate, usually a structural abnormality, is modulated by various transient events that may disturb the homeostatic balance and initiate an arrhythmia. The substrate itself can be a result of acute reversible causes such as ischemia or the result of chronic changes such as ventricular myocardial scar. Other pathologic states that may result in an anatomic substrate for VT or VF include cardiomyopathy—nonischemic, hypertrophic, and valvular.

In recent years, significant advances in the understanding of the mechanism of VF have taken place. Controversy exists regarding whether VF is maintained by wandering wavelets with constantly changing re-entrant circuits or by a mother rotor that consists of a sustained and stationary re-entrant circuit that, in turn, gives rise to variable, less-organized daughter wavelets spreading through the rest of the ventricle.[17,18] Certain anatomic structures can serve as anchors for rotors, allowing stability within the re-entrant circuit.[19] Weiss et al have reported from their studies on porcine hearts that these anatomic sites can be papillary muscles, blood vessels, Purkinje fibers, or locations near the interventricular septum.[20] Studies have suggested that Purkinje fibers play an important role in the initiation of VF, whereas others have suggested that they play a role in the maintenance of VF.[21,22] Predispositions to SCD may also occur at a cellular level. Ion channelopathies can initiate various electrical disturbances, ranging from torsades de pointes in LQTS to that of idiopathic VF in Brugada syndrome.[1,23] Certain mutations are significant enough that their mere presence is associated with a very high risk of SCD. However, other mutations (e.g., the recessive long QT mutation in the *HERG* gene) may, by themselves, be insufficient to cause SCD but may predispose patients to torsades de pointes in the presence of other factors such as drugs that prolong the Q-T interval.

The role of ischemia as an initiating factor for ventricular arrhythmias has been extensively investigated and is particularly relevant because it is a frequent etiology implicated in SCD. Ischemia causes acute changes at the cellular level that alter local conduction velocity and refractoriness. The resulting dispersion of conduction and repolarization establishes an environment that is ripe for re-entry. In animal experiments, within the first few minutes after coronary occlusion, an arrhythmogenic period that slowly abates after 30 minutes has been observed. These first 30 minutes can be divided broadly into the first 10 minutes, during which the changes are caused by direct ischemic injury, and the second 20 minutes, during which either arrhythmogenicity occurs because of either reperfusion or the evolution of injury in the various layers of the myocardium.[24,25] Local changes occur in the ischemic myocardium; these include decrease in local tissue pH to less than 6, increase in interstitial potassium (K^+) levels to greater than 15 mmol/L, increases in intracellular calcium (Ca^{2+}), and other neurohormonal changes. All these factors contribute to the altered electrophysiological properties of tissue, including slowed conduction velocity, reduced excitability and prolonged refractoriness, reduced cell-to-cell coupling, and even spontaneous electrical activity.[26] In addition to the local micro–re-entrant and macro–re-entrant circuits that may be generated, regional increases in automaticity and triggered activity also occur because of afterdepolarizations.

Disease States Leading to Sudden Cardiac Death

Because the majority of cases of SCD result from CAD, it is not surprising that the risk factors for SCD mirrors those of CAD. The incidence of SCD increases with age and is more common in men than women.[27] The incidence of SCD tends to be higher in whites than in other racial groups. Classic coronary risk factors have been noted to be associated with SCD in various studies such as the Framingham Study and the Paris Prospective Study. These risk factors include hypertension, diabetes, high cholesterol levels, smoking, lack of regular exercise, and structural changes such as left ventricular hypertrophy.[28-31] These factors are prevalent but are limited by their moderate individual positive predictive value. Left ventricular dysfunction has been shown to be a strong independent predictor of SCD in both ischemic and nonischemic cardiomyopathies. Of note, in patients with severely decreased left ventricular function and advanced heart failure, competing causes of SCD such as electromechanical dissociation and asystole exist.

Observations from population-based studies demonstrate a marked increase in the risk of SCD in first-degree relatives of SCD victims. In a study from Seattle, first-degree relatives of patients with SCD (before age 65 years) had 2.7-fold higher risk of SCD compared with age-matched and gender-matched controls after adjustment for risk factors.[32] A Dutch case-control study demonstrated that patients with VF during myocardial infarction (MI) are more likely to have a family history of SCD than those with MI but no VF.[33] Polygenic traits leading to SCD and monogenetic

SCD syndromes such as LQTS, Brugada syndrome, hypertrophic cardiomyopathy, and arrhythmogenic right ventricular dysplasia contribute to the genetic component of SCD.[34] More recently, research has begun to elucidate the role of newly identified genetic variations at the population level.

Coronary Artery Disease

Approximately 80% of patients who experience SCD have coronary atherosclerotic arterial disease as an underlying substrate. In survivors of SCD, critical flow-limiting coronary stenoses are found in approximately 40% to 86% of patients, depending on the age and gender of the population.[29,30,35] Although less than 50% of the resuscitated patients have evidence of an acute MI, autopsy studies have revealed that a recent occlusive coronary thrombus can be found in 20% to 95% of victims of SCD.[31,36,37] The temporal pattern of SCD closely parallels the patterns of MI and acute ischemic events. In addition, healed infarctions are found in 40% to 75% of hearts of SCD victims at autopsy.[36,38-40] The extent to which superimposed acute ischemia plays a role in the pathogenesis of SCD is unclear in patients who do not develop enzymatic or electrocardiographic evidence of an acute MI. However, rapid fibrinolysis of a ruptured plaque could occur such that no visible evidence remains at autopsy. Similarly, cholesterol-laden plaque could conceivably rupture and embolize microscopic debris into distal coronary vessels that could lead to microscopic necrosis and ventricular arrhythmias and yet not be visible at autopsy.[41] Because the vast majority of patients die within minutes of onset of symptoms, histologic or enzymatic evidence of ischemia or infarction may be difficult to ascertain. In addition to the most common forms of CAD, nonatherosclerotic CAD includes congenital malformations such as anomalous origin of coronary arteries; inflammatory arteritis also can lead to SCD. These disorders typically manifest early in life but are relatively uncommon.

Dilated Cardiomyopathy

Idiopathic dilated cardiomyopathy accounts for approximately 10% of cases of SCD in the adult population (Figure 47-1). Depending on the severity of the myopathy, the annual incidence can range from 10% to 50%.[36] Bundle branch reentrant VT appears to represent an important cause of VAs in this population.[37] However, as the myopathy progresses and congestive heart failure worsens, the incidence of VT or VF decreases, and the primary terminal event more frequently becomes electromechanical dissociation or asystole.[42] As with ischemic heart disease, the overall left ventricular ejection fraction (LVEF) is an important prognostic factor. Worsening New York Heart Association (NYHA) functional class and the occurrence of syncope are both important clinical prognostic factors for SCD in patients with dilated cardiomyopathy.[40]

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is now regarded as the most common cause of SCD in young people, including competitive athletes (Figure 47-2).[43-45] The annual mortality rate in patients with HCM in select regional and community-based cohorts is thought to be approximately 1%. The architectural myocardial fiber disorganization, scarring, and the presence of microvascular disease likely account for the proarrhythmic substrate. The conventional risk factors for HCM assume greater weight in patients younger than 50 years and include family history of one or more HCM-related form of SCD, more than one episode of unexplained recent syncope, massive LVH (thickness ≥30 mm), nonsustained VT on 24-hour Holter monitoring, and hypotensive or attenuated blood pressure response to exercise. Although implantable cardioverter defibrillators (ICDs) for primary prevention in this population usually require meeting at least two of these criteria, the need for ICD interventions for VT or VF in patients with

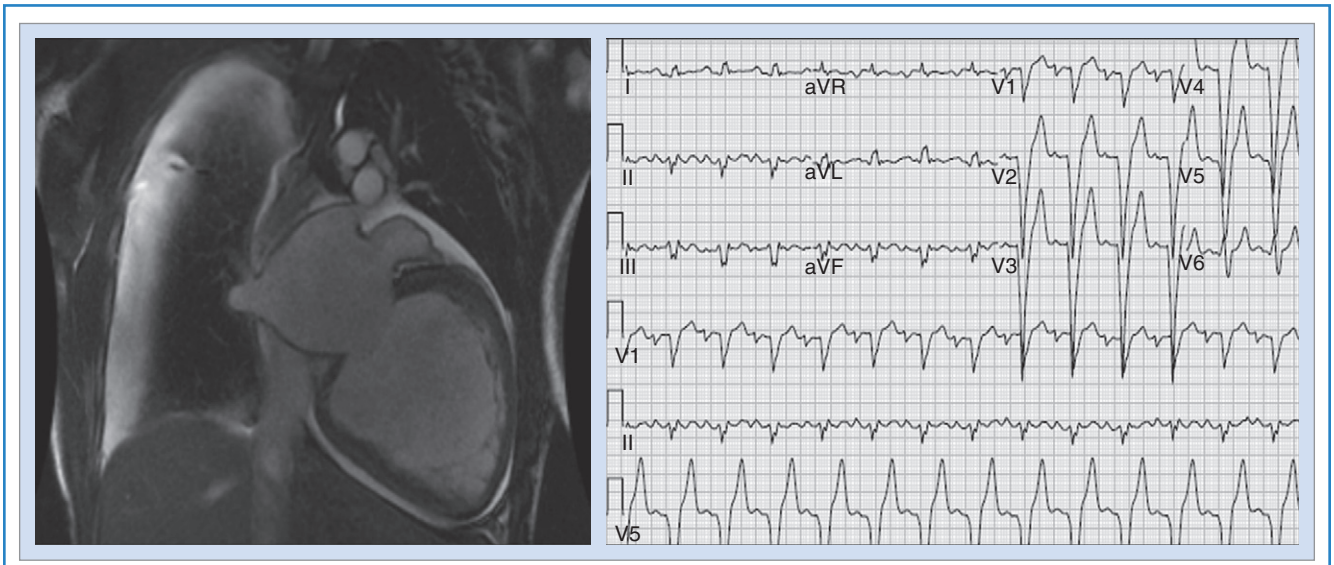

FIGURE 47-1 A 32-year-old man who presented with syncope was noted to have a decreased ejection fraction with no evidence of coronary artery disease. Cardiac magnetic resonance imaging revealed a dilated left ventricle and left atrium. An accompanying electrocardiogram revealed left bundle branch block, a common conduction defect seen in this population.

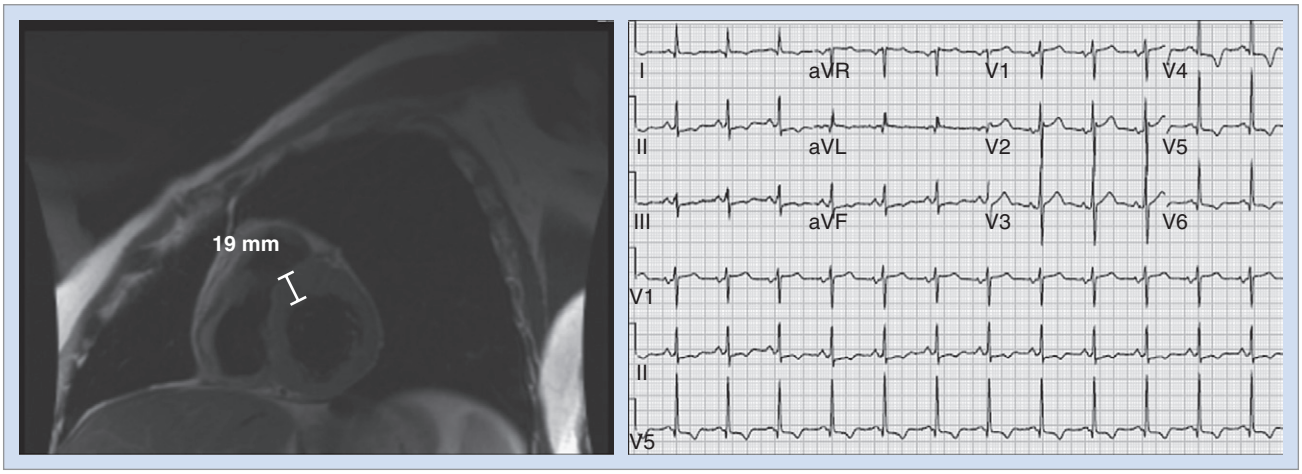

FIGURE 47-2 A middle-aged man with a known diagnosis of hypertrophic cardiomyopathy. Cardiac magnetic resonance imaging revealed asymmetric septal hypertrophy.

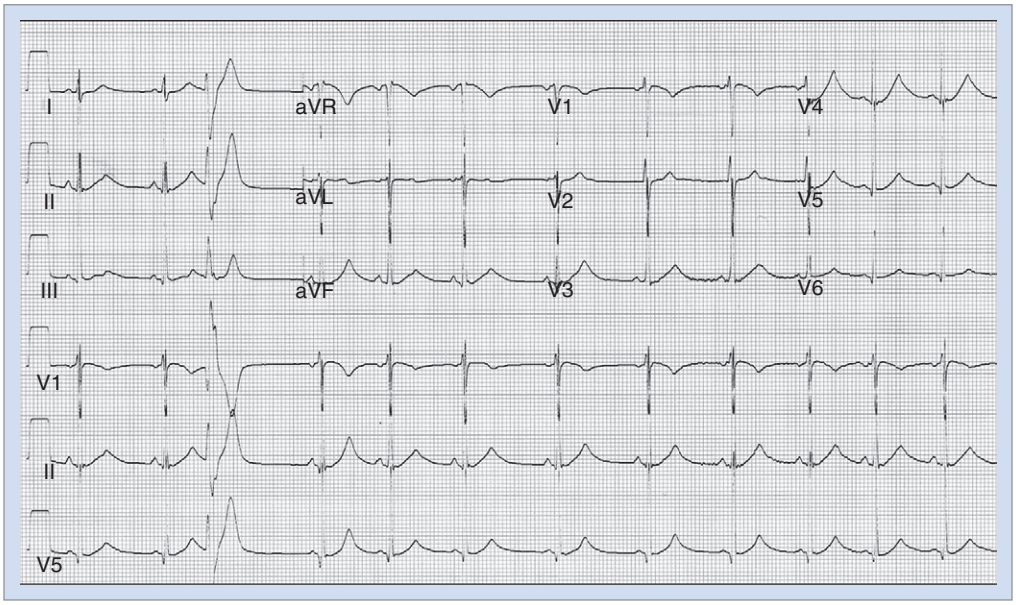

FIGURE 47-3 A 17-year-old man presented with two episodes of syncope. The 12-lead electrocardiogram revealed features of long QT syndrome.

single risk factors must be kept in mind when deciding about ICD implantation in this population.[46] Of the above criteria, nonsustained VT and blood pressure response have poor positive predictive value.[47] It has recently been demonstrated that certain mutations such as nonsarcomeric *LAMP2* cardiomyopathy, double sarcomere mutations, and delayed enhancement on cardiac magnetic resonance imaging (MRI) are associated with SCD.[48-51] Conversely, the apical variant of hypertrophic cardiomyopathy has been demonstrated to carry a relatively lower risk for SCD.[52]

Long QT Syndrome

LQTS (Figure 47-3) is a primary cardiac arrhythmogenic disorder typically characterized by prolongation of the Q-T interval corrected for heart rate (QTc) and abnormal T waves. Subjects with LQTS may present with a nearly normal electrocardiogram (ECG) or with a prolonged Q-T interval. The syndrome is associated with a specific ventricular arrhythmia called *torsades de pointes* and often presents as recurrent syncope. Hundreds of mutations have been identified, and these have been described in up to 12 genes.[47] This is most often caused by decreased outward K^+ current, I_{Ks} (LQT1, LQT5) or I_{Kr} (LQT2, LQT6), or by enhanced activity of mutant inward sodium (Na^+) current (LQT3). Polymorphic VT associated with a prolonged Q-T interval is believed to be initiated by early afterdepolarizations (EADs) in the Purkinje system and maintained by transmural re-entry in the myocardium. Clinical presentations vary with the specific gene affected and the specific mutation. Some patients with LQTS mutations may not manifest any phenotypic abnormality. In high-risk LQT1

and LQT2, patients should be routinely managed with β-blockers as a first line-therapy and should be referred for primary ICD implantation if they become symptomatic during therapy or when compliance or intolerance to medical therapy is a concern.[53] Patients with LQT3, those with frequent and recent syncope, those with excessive Q-T prolongation (>550 ms), and women with LQT2 and a QT interval greater than 500 ms may be at increased risk and may require ICD implantation.

Congenital Short QT Syndrome

Congenital short QT syndrome (SQTS) is a relatively recently described disorder characterized by a very short Q-T interval (<320 ms) and a susceptibility to atrial fibrillation (AF) and VF. At electrophysiology study, short atrial and ventricular refractory periods with easily inducible AF and polymorphic VT have been identified. Gain-of-function mutations in genes encoding K^+ channels have been identified, which explains the abbreviated repolarization seen in this condition. The suggested treatment is ICD implantation. The ability of quinidine to prolong the Q-T interval has the potential to be effective pharmacological therapy.[54]

Arrhythmogenic Right Ventricular Cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a progressive, heritable myocardial disorder with a broad phenotypic spectrum that can present with VT, SCD, or both (Figure 47-4). The classic form of the disease has an early predilection for the right ventricle, but left-dominant and biventricular subtypes have been also recognized.[55] Desmoplakin and plakophilin-2 are two desmosomal genes that have been implicated in ARVC. A familial form, originally described in people living on the Greek island of Naxos, can present with cardiomyopathy in association with palmo-plantar keratoderma (Naxos disease) and is caused by a defect in the gene for a cellular structural element, plakoglobin.[56] ARVC causes progressive fatty replacement of the ventricular wall. Cardiac MRI is a highly sensitive imaging tool to identify the presence and degree of fatty infiltration in the myocardium; however, because this is not specific, formal criteria have been proposed for the diagnosis of ARVD. Phenotypic heterogeneity and the nonspecific nature of its associated features complicate clinical diagnosis, which often requires multiple tests rather than a single test.[57] The Revised Task Force criteria for the diagnosis are specific and have helped reduce diagnostic ambiguity, but the sensitivity is low, especially in the "concealed" phase of ARVC.[57]

Brugada Syndrome

Brugada syndrome is associated with right ventricular conduction delay and ST elevation in the right precordial leads, characterized by syncope and premature SCD caused by VF (Figure 47-5). This syndrome appears to be responsible for a sudden death syndrome seen among Southeast Asian men.[58,59] ECG manifestations of the syndrome can often be dynamic. Typical ST-segment changes, if absent at baseline, can be revealed by administration of sodium channel–blocking agents such as ajmaline or procainamide. Mutations in the *SCN5A* gene cause loss of function in the Na^+ current I_{na} that can lead to accentuation of unopposed I_{to} currents in the right ventricular epicardium. This leads to loss of the action potential "dome," resulting in heterogeneity of repolarization, and phase 2 re-entry that precipitates VT or VF. The strategy for risk stratification in Brugada syndrome is controversial with respect to the role of electrophysiology testing in patients who do not present with SCD. ICD is the only treatment with demonstrated efficacy in Brugada syndrome. In general, ICD implantation is recommended for patients with symptoms and for asymptomatic

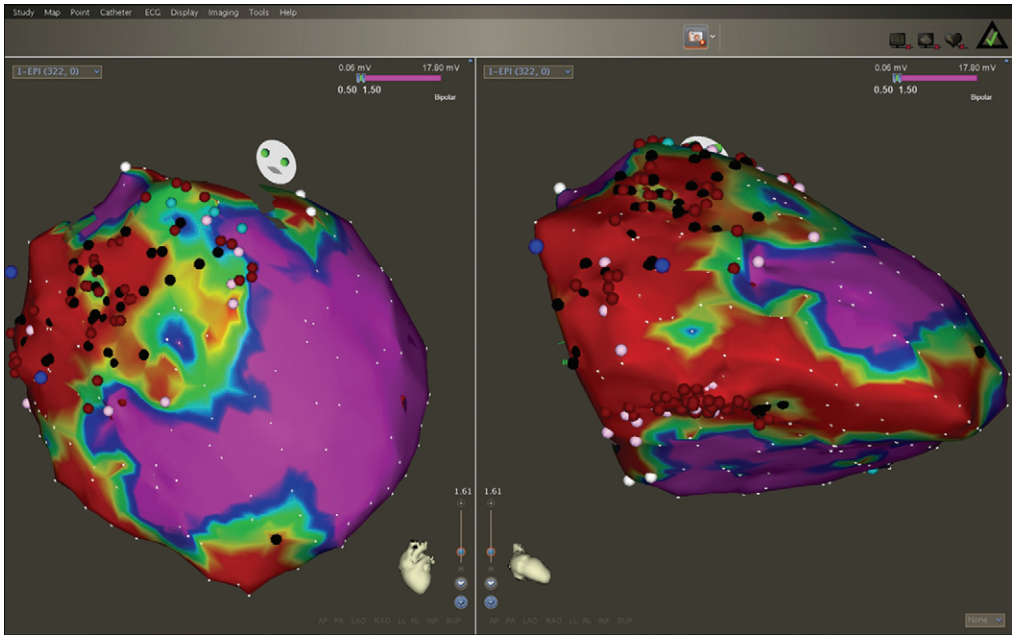

FIGURE 47-4 A 34-year-old man with a diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC) with implantable cardioverter defibrillator shocks for sustained ventricular tachycardia. An electroanatomic map created reveals extensive scar on the epicardial surface of the right ventricle consistent with ARVC.

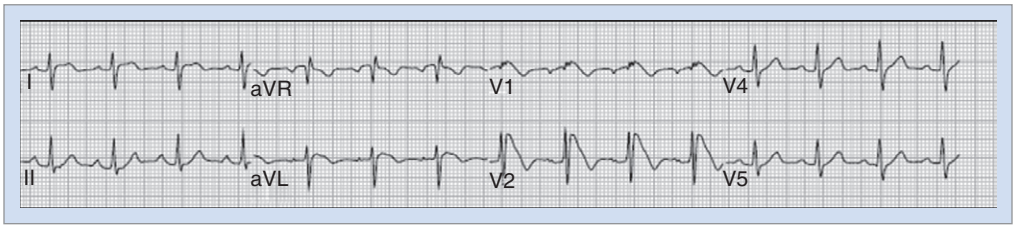

FIGURE 47-5 A 49-year-old Asian man with a history of ventricular fibrillation arrest. The 12-lead electrocardiogram with ST-segment elevation in the right precordial leads was suggestive of Brugada syndrome.

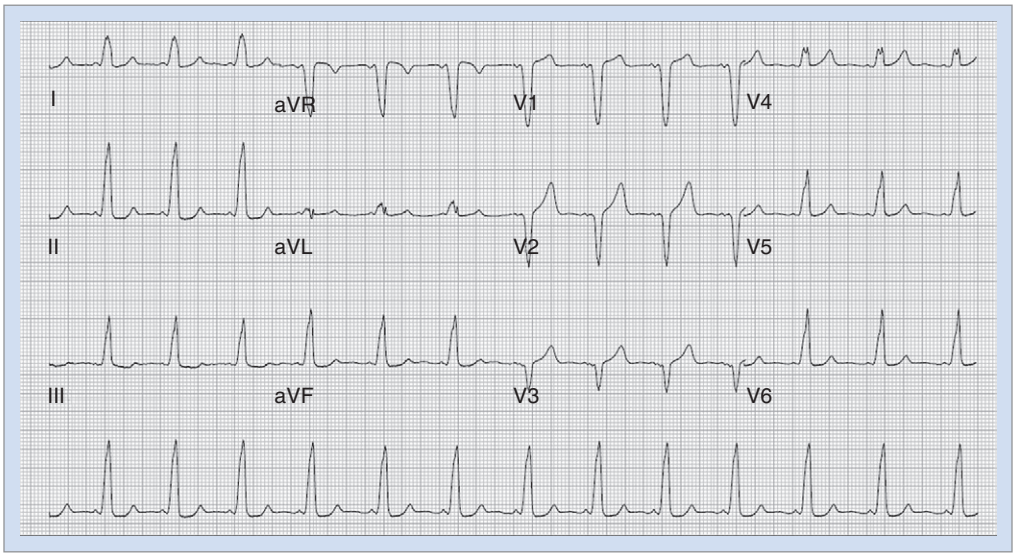

FIGURE 47-6 A young man presented with palpitations and pre-excitation at baseline on the 12-lead electrocardiogram. The pathway was successfully ablated in the anteroseptal region.

patients with inducible ventricular arrhythmias, especially if they have a spontaneous type I ECG pattern. In asymptomatic patients without a family history of SCD and whose type I ECG pattern is documented only after the administration of sodium channel blockers, periodic follow-up is recommended, but an EPS for risk stratification is not required.[60,61] The role of EPS, however, still remains controversial, with some studies not supporting its role in risk stratification.[57]

Wolff-Parkinson-White Syndrome

Wolff-Parkinson-White (WPW) syndrome can lead to SCD if the accessory pathway is able to conduct rapidly in the antegrade direction in the presence of rapid atrial arrhythmias such as AF (Figure 47-6). More recently, a long-term follow-up of patients with WPW syndrome reported a mortality rate of 0.02% per year.[62] Two additional studies with more than 4000 patient-years of follow-up, estimated mortality rates at approximately 0.05% per year.[63,64] However, a study from Italy that prospectively followed up patients with WPW syndrome for 3 years, recorded a much higher event rate (defined as death or potentially lethal arrhythmia recorded on monitoring) at 0.5% per year.[65] Predictors for the development of VF include rapid ventricular response during induced AF, with the shortest R-R interval of less than 240 ms and short antegrade pathway refractory periods. High-risk and symptomatic patients are treated with catheter ablation with very high success rates overall.[66]

Catecholaminergic Polymorphic Ventricular Tachycardia

Patients with catecholaminergic polymorphic ventricular tachycardia (CPVT) can present with exercise-induced syncope, SCD, or both in the absence of any structural heart disease or prolonged Q-T interval. Inheritance can be autosomal dominant or recessive. These patients often have normal resting ECGs, which makes the diagnosis difficult. Stress-related bi-directional VT has been described classically, but patients can present with polymorphic VT or even frequent ventricular ectopy. Responsible mutations have been shown to reside in the cardiac ryanodine receptor and calsequestrin genes.[67-70] Treatment modalities include ICD placement along with β-blocker therapy for symptomatic patients.

Early Repolarization

A multi-center study recently documented an association between idiopathic VF and the presence of early repolarization (ER) abnormalities in inferolateral leads (Figure 47-7).[71] Repolarization changes have also frequently been observed in inferolateral

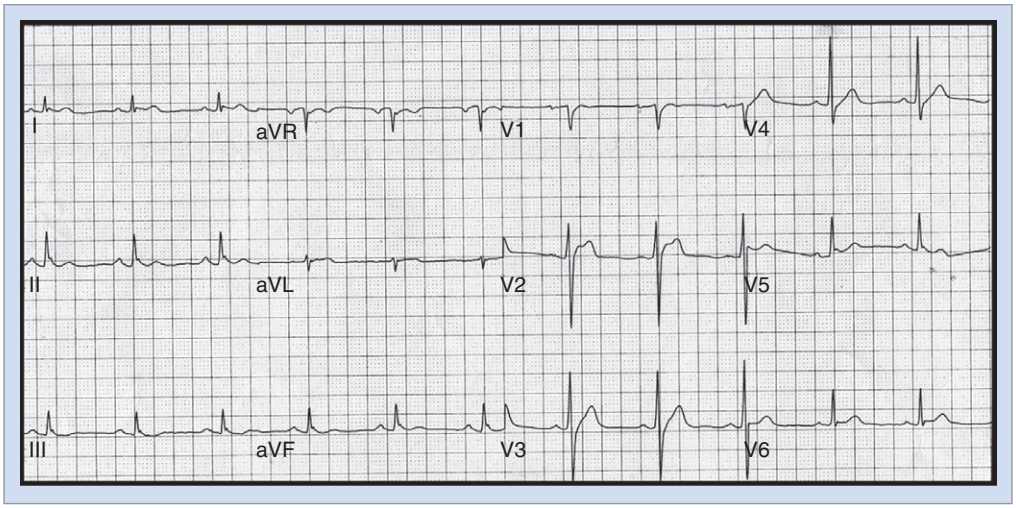

FIGURE 47-7 A 28-year-old man presented with sudden cardiac death. After resuscitation, the 12-lead electrocardiogram demonstrated features consistent with early repolarization, especially in the inferior leads. Cardiac magnetic resonance imaging and coronary evaluation were unremarkable.

precordial leads in patients with Brugada syndrome, mimicking the abnormalities typical of the population presented in the study of Haïssaguerre et al, suggesting a possible overlap of these conditions.[72] This subset of idiopathic VF continues to be further studied and, in addition to ICDs, newer therapies such as quinidine and isoproterenol have been noted to play a role in controlling VF storms that can occur in these patients.

Congenital Heart Disease

Patients with CHD represent an anatomically heterogeneous patient group in which risk stratification can be difficult. Current guidelines indicate ICD implantation for survivors of SCD; ICD is considered a reasonable therapy for patients with sustained VT that is not amenable to either ablation or surgery and for those with unexplained syncope and impaired ventricular function. Tetralogy of Fallot (ToF) represents one of the commonly encountered conditions in adult CHD patient populations. Older age at surgery, residual hemodynamic lesions with right heart failure, impaired LVEF, complex ventricular ectopy, inducible ventricular arrhythmias at EPS, and prolongation of the QRS complex represent some of the associations noted in SCD in patients with ToF.[73-75]

Noncompaction of the left ventricle is a rare congenital cardiomyopathy characterized anatomically by excessive prominent trabeculae and deep intertrabecular recesses in the left ventricle without other major congenital cardiac malfunction. Ventricular arrhythmias and SCD are known to occur, and ICD therapy often is indicated.[76-78]

Commotio Cordis

The term *commotio cordis* refers to a blunt, nonpenetrating, and usually innocent-appearing chest blow that can cause VF. The location of the blow to the chest (directly over the heart) and its timing relative to the cardiac cycle (on the upstroke of the T wave, 10 to 20 msec before its peak) are the primary determinants of commotio cordis.[79,80]

Other Genetic Associations in Patients with Structurally Normal Hearts

SCD likely has a strong genetic component, but only a fraction of the genetic variants that underlie the risk are known; the allelic architecture of SCD thus remains poorly defined.[81] Genome-wide association studies have indicated that common variants in *NOS1AP* are associated with Q-T interval duration and SCD risk in general populations.[82] The common polymorphism *S1103Y-SCN5A* is disproportionately represented in patients with arrhythmia and black patients who have experienced SCD.[83] These variants by themselves are unlikely to be sufficient causes of SCD.

Risk Stratification for Sudden Cardiac Death

Given that the phenomenon of SCD is distributed through the entire population, risk stratification is necessary to delineate the at-risk population. However, criteria used for this attempt to separate artificially the studied population into different levels of risk. Unfortunately, in reality, a continuum of risk exists. Although the focus to prevent and treat SCD targets the high-risk population, the low-risk and intermediate-risk populations comprise the largest proportion of the entire SCD population.

The entire gamut of noninvasive techniques reviewed in the following sections were developed to detect the substrates that leads to VT or VF. These techniques include detection of (1) conduction slowing (signal-averaged electrocardiogram [SAECG]), (2) ventricular repolarization abnormalities (Q-T interval and dispersion, T-wave alternans [TWA]), (3) autonomic variability (heart rate variability, heart rate recovery, baroreceptor sensitivity), (4) extent of myocardial damage and scar formation (LVEF, NYHA class, imaging modalities that delineate scar), and (5) nonsustained VT and ventricular ectopy.

In SAECG, the terminal part of the QRS complex is evaluated for microvolt potentials that reflect delayed activation in the scarred myocardial substrate, thereby detecting areas of slow conduction.[84] In patients with prior MI, the negative predictive value

of this test has been demonstrated to be excellent. However, the usefulness of this test has been limited by its low positive predictive value, and its routine use is not common.[85-87] However, the presence of an abnormal SAECG continues to have a clinical role in ARVC as a minor criterion for its diagnosis.

Q-T interval dispersion examines the difference between the maximal and minimal Q-T intervals from various standard ECG leads, whereas TWA is defined as microvolt changes in the T-wave amplitude from beat to beat.[88,89] Studies evaluating the Q-T interval for prediction of SCD risk in individuals who do not have LQTS have demonstrated mixed results but have generally linked prolonged Q-T interval with increased risk. In recent studies, Q-T interval dispersion has not been shown to be a consistent predictor of SCD.[87,90]

TWA describes alterations in the amplitude of the T wave at modestly increased heart rates (105 to 110 beats/min) elicited by either exercise or atrial pacing. A number of observational cohort studies have suggested that microvolt TWA may work at least as well as electrophysiological testing to predict SCD or major arrhythmic events in ischemic and nonischemic cardiomyopathy.[91-94] The Microvolt T-Wave Alternans Testing for Risk Stratification of Post-Myocardial Infarction Patients (MASTER) study, a prospective study of patients with prior MI and LVEF less than 30%, found that the TWA test results did not influence the frequency of the composite endpoint of arrhythmic death or "appropriate" shock over a 3-year follow-up.[93] The recent Alternans Before Cardioverter Defibrillator (ABCD) trial compared the usefulness of EPS versus TWA testing in patients with ischemic cardiomyopathy and LVEF less than 40%.[96,97] The results led the authors to conclude that EPS and TWA testing were comparable in terms of predicting risk and were complementary to each other. In contrast, a prospective substudy of the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) showed that TWA was not predictive of arrhythmia or death and therefore was not a useful marker in identifying patients who would benefit from an ICD.[98,99] These contrasting results have limited the generalized applicability of TWA in the risk stratification for SCD.

Evidence from both clinical and experimental studies supports a role for the autonomic nervous system in the genesis of VT or VF. An association exists between increased sympathetic activity, reduced vagal activity, or both, with a propensity for VF during myocardial ischemia.[99] The two major measures of autonomic function that have been tested in clinical studies include heart rate variability (HRV) and baroreflex sensitivity (BRS).[40] HRV reflects both the sympathetic and parasympathetic effects on the heart and is measured as the standard deviation of R-R intervals in the heart rate over a 24-hour period. BRS, in contrast, is an indicator of the reflex capacity of the autonomic nervous system and usually is measured by the phenylephrine method.[100] Studies suggest that BRS has potential for SCD risk stratification in patients with CAD and that HRV is a predictor of total mortality but may, in fact, be a better marker of nonarrhythmic death.[101,102] Further studies are needed to establish the clinical usefulness of these parameters for risk stratification and at this time are of limited utility.

LVEF is a well-established and consistent reported risk factor for overall mortality and SCD. It has been used in the risk stratification schema on many primary prevention clinical trials of SCD. In addition, the more recent Multicenter Autonomic Defibrillator Implantation Trial II (MADIT II) used only LVEF (<30%) for risk stratification for inclusion into the protocol. The results of MADIT II indicate that the use of LVEF alone for risk stratification is associated with significant mortality benefit from prophylactic ICD therapy.[103] Impaired EF in certain patient populations, such as in those with early previous MI, have been shown to not be predictive of SCD from trial data.[104] Of note, although low LVEF identifies a group with relatively increased risk, most instances of SCD occur in patients with a more preserved LVEF, which highlights the limited sensitivity of this technique.[105,106] Heart failure itself also can contribute to arrhythmogenesis in patients with ventricular dysfunction and can increase the mortality rate in patients with dilated cardiomyopathy independent of EF. Qualitative descriptions of functional capacity such as NYHA class, although limited by subjectivity, have been well studied. NYHA classes II and III continue to be accepted as criteria to identify at-risk individuals with impaired left ventricular function for whom ICD is indicated.[107-109] The presence of ventricular arrhythmias (premature ventricular contractions [PVCs] and nonsustained ventricular tachycardia [NSVT]) has also been examined in various studies to assess their role in predicting SCD. In one major trial, the positive predictive value of ventricular ectopy after MI for predicting cardiac arrhythmic events or death was limited to 5% to 15%.[103] Frequent ectopy or NSVT is insensitive, failing to identify 47% to 94% of those who experience sudden cardiac arrhythmia.[110] However, if combined with low LVEF, ventricular ectopy becomes a stronger risk factor for death.

Patients with nonischemic cardiomyopathy frequently have high-grade ventricular ectopy and NSVT. However, the relationship with cardiac arrest is much less clear than is the case of ischemic cardiomyopathy. In general, the incremental use of ambient ventricular arrhythmias is limited and may actually reflect the degree of heart failure rather than providing a specific marker of SCD. NSVT, in particular, has been identified as a risk factor for SCD in patients with HCM. In summary, the role of ambient nonsustained ventricular arrhythmias in predicting SCD appears to be limited. In patients with a history of previous MI, the induction of VT during an EPS has been shown to predict a high risk for recurrent arrhythmias and SCD.[111,112] EPS has also been established in a number of other clinical situations, such as in patients with a history of cardiac arrest.[113-115] The predictive value of EPS is highest in patients with a history of MI as opposed to those with nonischemic cardiomyopathy.[1] Although a positive test result predicts increased risk for SCD, a negative result does not exclude risk, particularly in patients with severe left ventricular dysfunction. In MADIT II, ICD use was associated with a significant survival benefit even in the absence of EPS.[103] In the previously reported MADIT I, inducibility in study patients was associated with an increased likelihood of VT; however, the noninducible study subjects had a considerable VT or VF event rate.[116] EPS in patients with normal LVEF is of limited clinical benefit. In patients with conditions such as hypertrophic cardiomyopathy, the role of EPS is uncertain, and negative EPS findings do not exclude high risk for SCD. VF is commonly induced in these patient populations and is of uncertain clinical significance.[117,118] EPS can discriminate between patients with high risk versus low risk for SCD, but if used in isolation, the sensitivity is inadequate, especially in patients with EF less than 30%. EPS is of more value when used in patients with equivocal results after noninvasive testing than as an initial screening test.[119]

SCD in competitive athletics generates considerable attention and concern. Although the American Heart Association consensus panel does not endorse mandatory ECG screening for all competitive athletes, it does not discourage screening initiatives by individual organizations.[120] In contrast, the European Society

of Cardiology recommends that evaluation include electrocardiography, chest radiography, and echocardiography.[121]

Another risk stratification technique that continues to evolve is that of contrast-enhanced MRI, which, if supported by clinical data, could possibly provide information on susceptibility to VAs and therefore SCD. When assessing risk with algorithms, one should be aware that no single risk factor possesses adequate sensitivity but that the presence of multiple risk factors will inappropriately reduce the number of patients who qualify for ICD therapy. Overcoming such limitations requires balancing the sensitivity and specificity of various risk stratification approaches.[103]

Interventions Targeting Sudden Cardiac Death

Strategies that target risk factors include those that attempt to reduce the incidence of CAD, screening for CAD, and so on. Instituting percutaneous or surgical therapies, early access to medical care after the onset of warning symptoms, expanding the pool of people trained in advanced and basic cardiac life support and providing external automated defibrillators (AEDs), and, implanting ICDs allow reduction in the incidence of SCD. The effects of approaches such as catheter ablation have been shown to reduce the need for ICD therapies for VT but have not been evaluated for prevention of SCD. However, a growing body of literature describes, in certain patients, the role of ablation of PVCs that induce polymorphic VT or VF, thereby having a potential impact on the risk for SCD.

The first experience with pharmacologic prevention of SCD was with β-blocker therapy in the post-infarction population. Although the initial trial designs were not specifically constructed to evaluate SCD, these trials have uniformly demonstrated a clinically important reduction in the incidence of SCD with β-blocker therapy.[122,123] The effect is particularly striking in patients with the lowest EFs. The total mortality reduction with these agents is approximately 25% to 40%, with an approximately 32% to 50% reduction in the incidence of SCD.[119,125-127] Angiotensin-converting enzyme (ACE) inhibitors have also been established to decrease the overall mortality rate in heart failure. Ramipril has been shown to decrease the incidence of SCD by 30% in patients with previous MI who had heart failure.[128] According to a meta-analysis on the use of ACE inhibitors in patients after myocardial infarction, the estimated risk reduction of SCD was approximately 20%.[129]

A substudy of Multicenter MADIT-II suggested a time-dependent beneficial effect of statin therapy on the incidence of ICD intervention for a first VA or cardiac death in 654 patients with CAD treated with an ICD.[130] The cumulative rate of ICD therapy for VT or VF or cardiac death, whichever occurred first, was significantly reduced in those with at least a 90% statin use compared with those with lower statin use ($P = .01$). With time-dependent statin versus no statin therapy, the hazard ratio (HR) was 0.65 ($P < .01$) for the endpoint of VT or VF or cardiac death and 0.72 ($P = .046$) for VT or VF after adjusting for covariates. The Cholesterol Lowering and Arrhythmias Recurrences after Internal Defibrillator Implantation (CLARIDI) study concluded that aggressive treatment with atorvastatin (80 mg daily) in patients with CAD and an ICD resulted in fewer VAs requiring ICD treatment compared with placebo over 1-year follow-up.[131] Goldberger et al demonstrated that statin therapy was associated with decreased risk for death from life-threatening arrhythmias (HR, 0.22; 95% confidence interval [CI], 0.09 to 0.55; $P = .001$) compared with nonstatin therapy in 458 patients with nonischemic dilated cardiomyopathy treated with an ICD in the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) study.[132]

The role of aldosterone antagonists in preventing SCD was delineated by two landmark trials, the Randomized Aldactone Evaluation Study (RALES) and Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival (EPHESUS) trials. RALES was a double-blind, randomized study of heart failure with impaired LVEF of aldactone versus placebo. SCD occurred in 82 of 822 spironolactone-treated patients versus 110 of 841 placebo-treated patients (relative risk [RR], 0.71; 95% CI, 0.54 to 0.95; $P = .02$).[133] EPHESUS was a double-blind, placebo-controlled study of the eplerenone in patients with previous MI and left ventricular dysfunction.[134] SCD occurred in 162 of 3313 in the eplerenone group versus 201 of 3313 in the placebo group (RR, 0.79; 95% CI, 0.64 to 0.97; $P = .03$).

However, when membrane-active antiarrhythmic drugs were used to treat patients with frequent ventricular ectopy, the incidence of SCD increased.[135,136] This was true for both class Ic class III agents such as D-sotalol, as shown in the Cardiac Arrhythmia Suppression Trial (CAST) and the SWORD trials.[137-140] The only membrane-active antiarrhythmic medications approved for the treatment of ventricular arrhythmias that do not carry increased mortality risk in appropriately selected patients with ischemic heart disease are D,L-sotalol and amiodarone. However, in two major trials examining the routine use of amiodarone in patients with previous MI (European Myocardial Infarct Amiodarone Trial [EMIAT] and Canadian Amiodarone Myocardial Infarction Arrhythmia Trial [CAMIAT]), amiodarone did not demonstrate a survival benefit.[141,142] In a higher risk population of patients (Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina) [GESICA]: LVEF <35% and either ischemic or nonischemic cardiomyopathy), empiric amiodarone treatment was shown to affect mortality rate favorably.[143] These data were not corroborated by another trial examining a population composed primarily of patients with ischemic cardiomyopathy (Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy [CHF-STAT]).[144] This trial found no survival benefit with prophylactic amiodarone in patients with congestive heart failure. In the SCD-HeFT study, amiodarone was significantly worse than placebo (HR, 1.44; CI, 1.05 to 1.97; $P < .01$) in the prespecified NYHA class III patients. However, this trend was not seen in the overall study. A recent large meta-analysis, however, indicated that amiodarone decreases the incidence of SCD but not that of overall mortality.[145]

Other primary prevention trials have focused on the efficacy of ICD therapy in the prevention of SCD. Two randomized clinical trials have examined the use of ICDs in patients with prior MI, low LVEF, NSVT, and inducible VT at EPS: MADIT I and the Multicenter UnSustained Tachycardia Trial (MUSTT).[146,147] Both trials demonstrated a significant mortality benefit in patients who received ICDs compared with those patients treated with or without antiarrhythmic medications. The results of these two trials have been extended by the larger and more reflective of contemporary practice MADIT II, a randomized controlled trial in patients with previous MI and LVEF less than 30%. In this prophylactic ICD trial, NSVT was not a required entry criterion, and all-cause mortality was 20% in the control group and 14.2% in the ICD group (RR, 31%; $P = .016$).[148]

The only prospective trial of exclusively nonischemic patients was the Defibrillators in Non-Ischemic Cardiomyopathy Treatment evaluation (DEFINITE) trial, a randomized trial in patients with EF less than 35% and PVCs or nonsustained VT to standard medical therapy or single-chamber ICD. With a primary endpoint of all-cause mortality, statistical significance was not reached, but a strong trend toward reduction of mortality was observed with ICD therapy ($P = .08$). After 2 years, mortality rate was 14.1% in the standard therapy group versus 7.9% among those with ICD, which resulted in a 6.2% absolute reduction and a 35% RR reduction with ICD implantation. The SCD-HeFT study was the largest primary prevention defibrillator trial. Patients with a combination of ischemic (52%) and nonischemic (48%) etiologies in patients with an EF less than 35% with class II to III heart failure were randomized to conventional medical therapy, amiodarone, or ICD therapy. The absolute mortality decrease in the medical group was 7.2% after 5 years in the overall population. The ICD group had a decreased risk of death of 23% compared with the placebo group (HR, 0.77; 95% CI, 0.62 to 0.96) and the total mortality in the medical group was 7.2% per year, with a risk reduction of 23% in the ICD group versus placebo (95% CI, 0.62 to 0.96, $P = .007$). No mortality difference was observed between the amiodarone and placebo groups.

Two other ICD trials that deserve special mention include the Coronary Artery Bypass Graft Surgery with/without Simultaneous Epicardial Patch for Automatic Implantable Cardioverter Defibrillator (CABG-PATCH) and Defibrillator IN Acute Myocardial Infarction Trial (DINAMIT) trials. In the CABG-PATCH trial, routine ICD insertion did not improve survival in patients with CAD undergoing CABG who were believed to be at high risk of SCD on the basis of SA ECG and severe left ventricular dysfunction.[149] DINAMIT examined the role of ICDs in patients 6 to 40 days after MI with an EF less than 35% and impaired autonomic tone. Prophylactic ICD did not reduce overall mortality in high-risk patients who recently had MI. Although ICD therapy was associated with a reduction in the rate of death from arrhythmia, this was offset by an increase in the rate of death from nonarrhythmic causes.[150]

Similar to primary prevention trials using ICDs, three secondary prevention trials (Antiarrhythmic Versus Implantable Defibrillators [AVID], Canadian Implantable Defibrillator Study [CIDS], and Cardiac Arrest Study Hamburg [CASH]) have been conducted in survivors of VT, VF, or both. The AVID trial is the only trial that demonstrated statistically significant mortality reduction from ICD therapy in secondary prevention. The CIDS and CASH trials, however, failed to demonstrate statistically significant reductions in mortality with ICD therapy for secondary prevention. However, current guidelines allow implantation of ICD in all patients with aborted or resuscitated SCD unless the SCD was caused by an obviously reversible cause.

Despite the efficacy of ICD therapy in very-high-risk patient subsets, it is important to realize that this subset represents a select minority of the total number at risk for SCD. Protection against SCD by ICD implantation is expensive in high-risk populations and would be significantly more expensive in the larger but lower-risk populations. Substudy analyses of these large trials suggest that much of the benefit of ICD is realized in the sickest patients (i.e., those with the lower LVEFs).[151,152] Therefore identifying and improving risk stratification methods to better characterize patients at highest risk for SCD continues to be an area of active research. Other newer implantable therapies such as subcutaneous implantable defibrillators have recently been studied and appear to be a promising alternative in select patients.[153] On the invasive front, ablating monomorphic PVCs that repeatedly induce polymorphic VT or VF are increasingly reported. These PVCs are often noted to arise from the Purkinje system. Although the initial case reports were described in patients with idiopathic VF with structurally normal hearts, they have now been described in a wider patient population that has come to include patients with recurrent VF caused by various etiologies such as post-MI syndrome, LQTS, Brugada syndrome, and early repolarization syndrome. Although this is an exciting advance in the treatment of SCD, long-term outcomes in these patients are lacking.[154-157]

Community-Based Resuscitation

A very important prognostic variable in determining the effectiveness of resuscitation is the time from cardiac arrest to initial defibrillation. "Links in the chain of survival" is a term used to describe such time-sensitive services that influence the likelihood of successful resuscitation. These links include early activation, CPR, defibrillation, and advanced post-resuscitation care.[158] One of the most effective EMS in the world is located in Seattle. However, only 40% of cardiac arrest patients in the Seattle experience have VF at initial contact, and 26% of those VF individuals get discharged from the hospital with intact neurologic functions.[159] Thus even in an ideal scenario despite prompt CPR, a good EMS response time, and the use of AEDs, only 10% of all cardiac arrest patients will be satisfactorily discharged from the hospital.[160,161] Other communities, however, have been less successful. The reasons for the disappointing success rates are multifactorial and include various population and community characteristics. Early CPR, usually provided by a layperson before EMS arrival, can improve the likelihood of resuscitation. Efforts by professional organizations to train laypeople in CPR and initiatives such as dispatcher-initiated CPR skills have undoubtedly saved thousands of lives.

The interval from collapse to defibrillation is an exceptionally strong predictor of sudden cardiac arrhythmia survival.[162] In a departure from the conventional compression-plus-ventilation approach for bystander CPR, the American Heart Association recommended "hands-only" CPR to be provided by rescuers who are either untrained or not confident in their ability to provide rescue breaths.[163] Early defibrillation has been facilitated by the use of the AED, which assesses the rhythm and, when indicated, delivers a potentially lifesaving shock.[164] A strategy of broad AED deployment in public places has been implemented to reach out to less-experienced operators. Its success in this setting has prompted the U.S. government to mandate AED placement on all airlines and in airports. In the Home Use of Automated External Defibrillators for Sudden Cardiac Arrest (HAT) trial, placing AEDs in homes, however, did not reduce the mortality rate in patients with prior anterior wall infarctions who did not meet standard indications for ICD compared with a standard response training for cardiac arrest.[165] A very low event rate, a high proportion of unwitnessed events, and underuse of AEDs in emergencies, rather than a lack of device efficacy, have been suggested as explanations for these results. Public access defibrillation programs will hopefully improve the outcome from SCD significantly in the future.

Post-Resuscitation Care

Post-resuscitation care involves the care of post-arrest brain and cardiac dysfunctions and the ensuing systemic ischemia or reperfusion response. This is an essential component in the management of SCD because anoxic brain injury is a significant cause of morbidity and mortality in these patients. Evidence from randomized trials support the induction of hypothermia between 32° C and 34° C for 12 to 24 hours in an effort to improve neurologic survival in comatose patients admitted after resuscitation from witnessed VF arrest.[166] Such interventions have helped improve outcomes in patients resuscitated after SCD.

Summary

SCD continues to be a public health problem of major significance. The understanding of the burden of this problem, its mechanisms, and its pathophysiology all continue to expand and evolve. Although we have witnessed significant progress in the field, such as the discovery of newer etiologies, the role of genetics in SCD, community interventions for SCD, and the improving outcomes of SCD survivors, areas that need further advancement through research persist. It is possible that an improved understanding of the pathophysiology of SCD will contribute to the development of safer and more effective pharmacologic, catheter-based, and gene-based therapies for the prevention of SCD.

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CHAPTER 48

Syncope

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Introduction

Syncope is a transient loss of consciousness (TLOC) with subsequent complete resolution and no focal neurologic deficits; it results from cerebral hypoperfusion and does not require specific resuscitative measures. Recent expert consensus conferences, position papers, and narrative reviews have covered the various aspects of syncopal syndromes.[1-9]

Epidemiology

Approximately 40% of people faint at least once in their lives, and at least 20% of adults faint more than once.[10] (Many terms are used by patients to report syncope, such as *faint*, *blackout*, and *funny spell*. To avoid contributing to this plethora of miscommunication, this chapter uses *faint* and *syncope* interchangeably.) Syncope comprises 1% to 6% of emergency department (ED) visits, and most patients are admitted to the hospital largely because of diagnostic uncertainty and concern that an underlying cause might result in morbidity or death.[11-32] People who faint often present first in their teens and twenties and may faint sporadically for decades.[10] This long, usually benign, sporadic history can make for difficult decisions about therapy. An early peak incidence occurs at approximately 15 years for young women; a later important rise in incidence occurs in both sexes after age 65 years.[4] Although many patients of all ages experience simple vasovagal syncope, clinicians need to remain vigilant and look for other causes, including sick sinus syndrome, a variety of tachyarrhythmias, carotid sinus syncope, valvular and structural heart disease, and orthostatic hypotension.[1-4,6]

Impact on the Health Care System

Although syncope accounts for approximately 1% of ED visits, most patients with syncope with otherwise unknown causes in the community and approximately 45% of syncope patients who present to EDs in North America and Europe experience simple vasovagal syncope. In the United States, approximately $2.4 billion is spent yearly in hospitals to treat syncope.[6] In The Netherlands, among those younger than 65 years, 3.8 and 8.5 visits per 1000 person-years are made to family doctors for males and females, respectively.[12] Canadian and Italian estimates for ED presentations are 2.5-fold and 3.5-fold higher, respectively, than the estimates from The Netherlands.[6] The estimated direct impact on U.S. health care is $2.5 to $10 billion annually.[4-6,33,34]

Differential Diagnosis of Syncope

Transient Loss of Consciousness

Patients usually present with a history of TLOC, and although most of these patients experience syncope, the differential diagnosis of TLOC should be considered early in assessment. Other causes of apparent TLOC include epileptic and nonepileptic seizures, cataplexy, narcolepsy, pseudo-syncope, and rarer causes such as drop attacks and nonconvulsive epilepsy. The problem faced by assessing physicians is that patients may present simply with a history of unexplained losses of consciousness. The first step is to determine whether the loss of consciousness occurred because of syncope. The most common confusing presentations are addressed in this section. Not all these cause true loss of consciousness, but they can mimic it and therefore must be considered, albeit briefly.[1,4]

Convulsions and Syncope

Although patients experiencing syncope usually lose motor control and are flaccid while unconscious, they frequently present with a history of convulsions and syncope (Table 48-1).[7,9] This raises the question of whether the patients have true epileptic convulsions or convulsions secondary to cerebral hypoperfusion. Stiffness and myoclonic jerking are not uncommon in the latter case and cause confusion in the minds of those who witness the episode. Convulsive syncope can usually be distinguished from epileptic seizures through careful history taking. Stiffness and myoclonus last only a few seconds; only rarely will these patients have a true generalized convulsion. Patients with convulsive syncope usually have a history of recurrent syncope and presyncope. It is often helpful to elicit a similar history of the characteristic presyncopal prodrome of the patient and the symptoms preceding the apparent convulsion. Convulsive syncope rarely occurs when the patient is in the supine position and is usually brief, lasting only a few seconds. Pallor usually accompanies vasovagal syncope, whereas cardiac syncope and epileptic seizures are often accompanied by cyanosis. Myoclonic tremors usually have a fine amplitude, and epileptic seizures usually have dramatically coarse movements. Tongue biting rarely occurs in convulsive syncope and usually involves the tip of the tongue rather than the lateral tongue, as seen in true epileptic seizures. After a syncopal episode, the patient is briefly dazed, but the condition clears within a minute, whereas epileptic seizures can be followed by

Table 48-1 Diagnostic Questions to Determine Whether Loss of Consciousness Is Due to Seizures or Syncope

QUESTION	POINTS (IF YES)
At times, do you wake with a bitten tongue after your spells?	2
At times, do you have a sense of déjà vu or jamais vu before your spells?	1
At times, is emotional stress associated with losing consciousness?	1
Has anyone ever noted your head turning during a spell?	1
Has anyone ever noted that you are unresponsive, have unusual posturing or jerking limbs during your spells, or have no memory of your spells afterwards? (Score as yes for any positive response.)	1
Has anyone ever noted that you are confused after a spell?	1
Have you ever had spells of lightheadedness?	−2
At times, do you sweat before your spells?	−2
Is prolonged sitting or standing associated with your spells?	−2

The patient has seizures if the point score is ≥1 and syncope if the point score is <1. From Sheldon R, Rose S, Ritchie D, et al: Historical criteria that distinguish syncope from seizures, J Am Coll Cardiol *40:142–148, 2002.*

confusion that can last hours. If a history does not provide a clear conclusion, further testing is warranted.

Pseudo-syncope

Functional or psychogenic syncope is often mistaken initially for true syncope.[7,9] These patients often have an antecedent history of true vasovagal syncope, which usually becomes more frequent before presentation. The patients are usually young women who faint extremely frequently. Only the rare patient faints several times weekly to several times daily, but this is not unusual in pseudo-syncope. The spells can last many minutes, giving an appearance of syncope lasting up to an hour. The history usually does not include the transient autonomic symptoms that often accompany vasovagal syncope, and patients rarely volunteer a history of visual disturbances that often precede true syncope. These visual changes—blurring, tunneling down, spots, stars, and visual blackening—are caused by retinal hypoperfusion and are a reliable marker of a true hemodynamic disturbance.[9] An antecedent history of physical or sexual abuse often exists. The diagnosis can occasionally be confirmed if the patient has a fainting spell in monitored situations such as during a tilt-table test (TTT) or while undergoing electroencephalography (EEG).

Orthostatic Hypotension

Orthostatic hypotension is defined conventionally as a drop in systolic blood pressure of at least 20 mm Hg or a drop in diastolic blood pressure of at least 10 mm Hg. New and more restrictive definitions are under consideration. The drop in blood pressure is a measurement, not a diagnosis. Several syndromes are characterized by presyncope or syncope caused by orthostatic hypotension. Not infrequently, symptomatic orthostatic hypotension occurs because of volume depletion of blood after a heavy meal. Initial orthostatic hypotension occurs within 5 to 20 seconds of arising quickly, often in association with standing and walking. Presyncope is much more common than syncope.[9,35] The hypotension is caused by a transient draw-down of central arterial volume to the exercising bed, accompanied by a delay in baroreceptor-mediated compensation. No specific treatment is necessary. Drug-induced orthostatic hypotension is often caused by polypharmacy, including diuretics, vasodilators, and adrenergic receptor antagonists. Syndromes of orthostatic hypotension, in which symptoms develop over longer periods, usually occur in older patients. Here, the primary symptom is presyncope, and the longer the patient is upright, the worse is the lightheadedness. Syncope occurs less commonly and usually after prolonged upright posture. Primary autonomic failure occurs in the setting of one of several relatively uncommon neurodegenerative diseases such as pure autonomic failure, multiple system atrophy, and Parkinson disease. Finally, secondary autonomic failure can occur with damage to the autonomic nervous system caused by systemic diseases such as diabetes, Parkinson disease, or multiple-system atrophy.[3,4,9,35]

Cardiac Syncope

Syncope caused by arrhythmias or structural heart disease is much less common than vasovagal syncope but carries a risk of significant morbidity and death.[4,5] It is usually caused by an abrupt drop in cardiac output and typically occurs within the first few seconds of onset of the arrhythmia. The most likely reason is that baroreceptor-mediated compensatory vasoconstriction takes 10 to 20 seconds to have an effect, leaving the patient unprotected for that time. However, reports also document the association of vasovagal syncope with supraventricular tachycardia (SVT), atrial fibrillation (AF), and inappropriate sinus bradycardia.[36-38] Factors such as arterial baroreceptor sensitivity, posture of the patient, volume status, associated cardiopulmonary disease, and reflex peripheral vascular compensation all play a role in determining whether tachycardia could be the reason for the syncope. The diagnosis and management of these arrhythmias are covered in detail in other chapters of this book.

Patients often present with undocumented syncope and a documented substrate that might be related to the cause, such as syncope with bifascicular block.[39-43] No clear consensus or firm evidence exists to guide treatment for these patients. In this setting, reasonable equipoise exists, for example, between implanting a loop recorder or performing an invasive electrophysiological study (EPS) and simply performing a therapeutic procedure such as pacemaker insertion. Importantly, the patients should be assessed for other cardiovascular risk factors that may take precedence in investigation and therapy. Patients with severe left ventricular systolic dysfunction and syncope usually require an implantable cardioverter-defibrillator, even though this might not treat neurally mediated syncope.[4]

Reflex-Mediated Syncope

These syndromes, which are common and at times perplexing, are covered in detail in later sections. The two main syndromes are vasovagal syncope and its synonyms and carotid sinus syncope.

Diagnosing the Cause of Syncope

Diagnostic Approach

General principles with good evidence to support them have been reviewed in detail in the recent European Society of Cardiology (ESC) guidelines.[4] History and physical examination are fundamental to the diagnosis of syncope. A detailed and accurate history provides a diagnosis in most cases, a prognosis for vasovagal syncope, an understanding of patient needs and preferences, and an economic basis for further investigation. The efficient use of investigations, as appropriate, should be based on the flow charts presented in the ESC document (Figure 48-1).

The first step in the differential diagnosis is to identify whether the TLOC episode was truly syncope, that is, a self-limited loss of consciousness caused by transient global hypoperfusion. Other causes of TLOC, such as epileptic seizures, narcolepsy, cataplexy, true drop attack, and hypoglycemic coma, should be briefly considered; however, in day-to-day clinical practice, they are rarely mistaken for syncope. Important and life-threatening potential causes such as cardiac syncope from arrhythmias or structural heart disease should be carefully considered in every case.

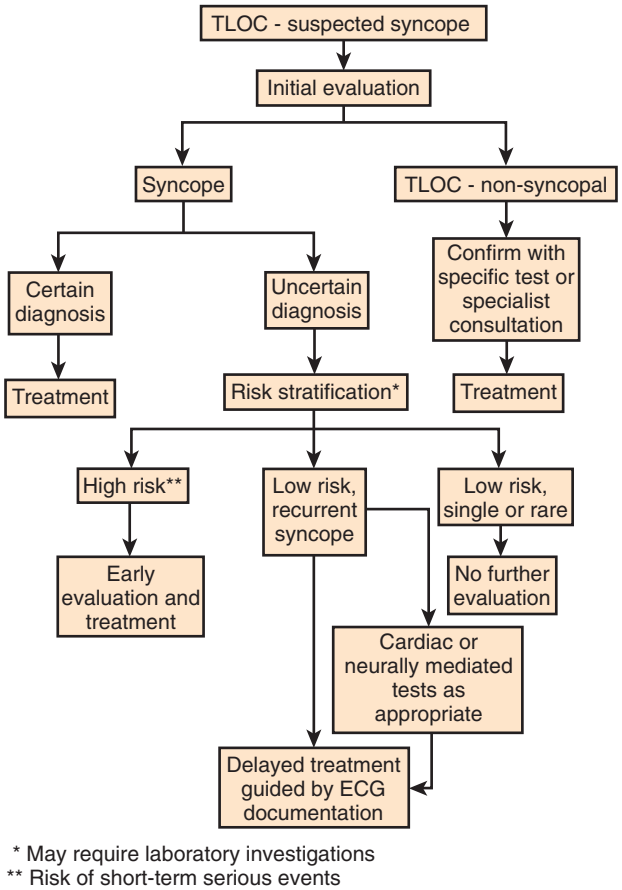

FIGURE 48-1 Flow chart for assessment of transient loss of consciousness *(TLOC)* according to the European Society of Cardiology guidelines. *ECG,* Electrocardiogram. *(From Moya A, Sutton R, Ammirati F, et al: Guidelines for the diagnosis and management of syncope (version 2009): The Task Force for the Diagnosis and Management of Syncope of the European Society of Cardiology (ESC),* Eur Heart J *30:2631–2671, 2009.)*

Specific investigations can be selected on the basis of the initial assessment.[1,4,6]

History and Physical Examination

The initial evaluation of history, physical examination, and the electrocardiogram (ECG) often leads to a certain diagnosis. A Dutch study with more than 500 patients with TLOC found that, based on a 2-year follow-up, physicians who used only history, physical examination, and ECG made a diagnosis in 63% of the patients, with a diagnostic accuracy of 88%.[44] If the diagnosis is certain, usually no further (or minimal) investigations are needed, and the focus then shifts to management. With an uncertain diagnosis, further careful, directed testing is usually necessary. The rare patient with frequent, recurrent episodes, especially in the context of other somatic concerns, may have a psychiatric illness.

Patients with syncope may describe their episodes in a variety of ways, including "dizziness," "fainting," "lightheadedness," and "blackouts." A prodrome may last from less than a second to several minutes. Most episodes occur when the patient is in the upright posture, occasionally in the sitting posture, and very rarely in the supine position. Patients often report additional presyncopal episodes and being able to avert syncope by sitting or lying down quickly. Patients are usually unresponsive for less than a minute and often fatigued for hours or even days after an episode but are oriented and responsive within minutes. Pallor is often observed.[4-7,9]

Recent work has suggested the importance of quantitative diagnostic scores.[45-47] Quantitative histories and diagnostic scores are well known in other fields, and they improve diagnostic accuracy. A comprehensive set of questions that provides a single diagnosis out of all possible diagnoses does not exist; rather, the questions need to be asked in sequences of groups. First, determine if this is syncope or another diagnosis such as epilepsy. A point score that distinguished seizures from syncope with an accuracy of 94% was recently published (see Table 48-1).[47] Second, determine whether the patient has structural heart disease by inquiring about his or her cardiovascular history. If the patient does not have structural heart disease, the diagnostic difference between reflex neurally mediated syncope and arrhythmic syncope depends on specific provocative situations, associated symptoms and signs, age of onset, and underlying arrhythmias. A quantitative score (Table 48-2) that works with more than 90% accuracy in patients younger than 60 years is widely available.[46] Older patients often require further investigation.[48] Another quantitative score has 99% sensitivity and 68% specificity for ventricular tachycardia (VT) in patients with structural heart disease (Table 48-3), and it is accurate with regard to diagnosis as well as arrhythmic and fatal outcomes.[45]

These scores have several uses. They provide validated, quantitative, objective, diagnostic inclusion criteria that, by reducing the need for TTT, provide rapid translation of clinical trial results into community practice. In this setting, they provide reproducible criteria for clinical studies.[49] Although these scores should not be the sole basis for diagnosis, they are useful aids in clinical practice. Finally, they may eventually provide a framework for evidence-based definitions of syndromes.

Finally, current understanding about predicting vasovagal syncope recurrence is much clearer.[50-54] Almost all the predictive power is in the year immediately before presentation. A patient who has not fainted in the previous year has only a 7% risk of

Table 48-2 Calgary Syncope Symptom Score for Structurally Normal Hearts

QUESTION	POINTS (IF YES)
Is there a history of at least one of the following: bifascicular block, asystole, supraventricular tachycardia, diabetes?	–5
At times, have bystanders noted you to turn blue during your faint?	–4
Did your syncope start at age 35 years or older?	–3
Do you remember anything about being unconscious?	–2
Do you have spells of lightheadedness or faint with prolonged sitting or standing?	1
Do you sweat or feel warm before a faint?	2
Do you have spells of lightheadedness or faint with pain or in medical settings?	3

The patient has vasovagal syncope if the point score is ≥–2.
From Sheldon R, Rose S, Connolly S, et al: Diagnostic criteria for vasovagal syncope based on a quantitative history, Eur Heart J *27:344–350, 2006.*

Table 48-3 Calgary Syncope Symptom Score for Structural Heart Disease*

QUESTION	POINTS (IF YES)
Was your age at first faint at age 34 years or later?	3
Are you a male?	1
Have you become lightheaded or fainted with prolonged sitting or standing?	–1
Have you become lightheaded with stress?†	–2
At times, are you tired for more than 1 minute after a fainting episode?	–2
Do you have recurrent headaches?	–2

**Diagnostic questions to determine whether syncope is caused by ventricular tachycardia or vasovagal syncope.*
†The term "stress" was used in its colloquial sense and meant to capture psychosocial stress.
The patient has ventricular tachycardia if the score is ≥1 and vasovagal syncope if the score is <1.
From Sheldon R, Hersi A, Ritchie D, et al: Syncope and structural heart disease: Historical criteria for vasovagal syncope and ventricular tachycardia, J Cardiovasc Electrophysiol *21:1358–1364, 2010.*

syncope in the next year, but a patient with at least one faint in the previous year has a 42% risk of syncope in the next year.[50]

Selection of Tests

The first stage of testing screens for a substrate for syncope, including careful clinical assessment, a resting ECG, and, when appropriate, short-term ECG monitoring, echocardiography, and blood work.[6] This provides a presumptive diagnosis in most patients as well as a prognosis, which is particularly important because syncope with underlying heart disease is a risk for sudden cardiac death (SCD). The yield of blood tests in detecting the cause of syncope is only 2% to 3%, detecting mostly electrolyte or metabolic abnormalities causing seizure. A hematocrit level less than 0.3 is useful for the detection of gastrointestinal bleeding.[27,55,56] Blood tests (hemoglobin, electrolytes, cardiac biomarkers) should be performed only in the presence of a clinical suspicion of occult hemorrhage, arrhythmias/seizures caused by electrolyte or metabolic abnormalities, or myocardial infarction (MI).

Tests such as echocardiography, coronary angiography, and radionuclide scintigraphy are of little value in unselected populations and should only be used when indicated by clinical assessment.[57] The primary role of this form of testing is to establish or exclude the presence of potentially contributory structural heart disease. An echocardiogram should be obtained in the presence of known heart disease, data suggestive of structural heart disease, syncope secondary to cardiovascular cause, syncope with exertion, or a murmur.

Computed tomography (CT) of the head is performed in nearly half of all syncope patients but has a less than 1% likelihood of detecting a cause.[58] Similarly, conventional EEG is rarely useful in the investigation of unselected patients with syncope. In contrast, although the yield of an ECG is less than 5% in unselected patients, it is noninvasive and inexpensive and can detect life-threatening abnormalities. Accordingly, it is recommended in all patients.

The second stage of testing is aimed at the specific cause of syncope. Here, provocative testing is used to induce a syncopal episode or to detect an abnormal physiological response that might explain the history of syncope. This includes tests such as TTT and EPS. Interpretation of these tests requires considerable judgment because these tests induce a physiological response (not the event itself) and are plagued by lack of sensitivity, lack of specificity, or both. An alternative approach is the use of long-term ECG monitoring with a Holter monitor and external and implantable loop recorders to document the cardiac rhythm associated with a spontaneous episode of syncope. Current devices do not detect hypotension.[1,4,6]

Tilt-Table Testing

TTT creates orthostatic stress that results in venous pooling and may simulate the hemodynamic changes seen in vasovagal syncope.[59-67] The test is performed with continuous ECG and blood pressure monitoring; patients are initially placed in the supine position, and the table is tilted to an angle of 60 to 80 degrees. The patient is kept at this angle for 20 to 45 minutes; further drug provocation with isoproterenol, clomipramine, or nitroglycerin can be used for another 15 to 20 minutes. If symptomatic hypotension and bradycardia occur, the patient is promptly returned to the supine position to prevent injury and the test is concluded. Syncope or presyncope with a cardioinhibitory response, vasodepressor response, or both reproducing the patient's symptoms is considered a positive outcome.

As simple as TTT seems, these tests, in fact, contain numerous variables that affect the test outcome.[65] Controlled studies have shown that the likelihood of positive tests depends on the angle and duration of the head-up tilt, whether and how a drug challenge is used, the number of head-up iterations during the test, the volume status of the subject, and the subject's age. A variable correlation exists between the symptoms provoked by TTT and by the subject's clinical symptoms and widely variable and usually

unvalidated hemodynamic criteria to indicate a positive test. The test has not been validated against a gold standard population, and different TTT protocols identify patient populations that do not completely overlap. Patients with otherwise idiopathic syncope have the same baseline symptoms and symptom burden, the same clinical outcome, and the same statistical relationships between baseline symptoms and clinical outcome, regardless of a positive or negative TTT result.[52] Finally, an intractable trade-off between diagnostic accuracy and specificity seems to be present. The mechanism observed with syncope at the time of TTT may not correlate with clinical episodes. Hence TTT should be used only in individuals in whom the history, physical examination, and ECG have not established the diagnosis.

Electrocardiographic Monitoring

The most common initial investigation is an ECG. The correlation between observed abnormalities on the ECG and the clinical presentation is often difficult to establish. Accordingly, ambulatory monitoring is often performed in patients with syncope. However, syncope occurs, on average, in only 4% of patients during monitoring (range, 1% to 26%), demonstrating its limited impact on the workup of patients with syncope. Short-term monitoring may be useful in the primary care setting when symptoms are frequent, often fulfilling the role of a rule-out test that lays to rest any concerns about a more sinister cause, typically recording sinus rhythm or sinus oscillation consistent with vasovagal syncope.

Recent advances in cardiac arrhythmia monitoring permit a much longer sampling period, which improves diagnostic yield. The external cardiac loop recorder continuously records and stores an external single-lead electrogram with a 4- to 18-minute memory buffer. After spontaneous symptoms occur, the patient activates an event button that stores the previous 1 to 10 minutes of recorded information, which can subsequently be downloaded and analyzed. This system can be used for weeks at a time.

The implantable loop recorder (ILR) is an ideal device for obtaining rhythms on a continuous basis.[4,6,68] Its use is driven by the importance of symptom-rhythm correlation, particularly in settings in which syncope could have one or more causes. For example, AF may cause syncope because of tachycardia onset or pauses after arrhythmia termination. In addition, the high population prevalence of vasovagal syncope often raises vasodepression as a competing diagnosis when arrhythmias are considered.

The ILR is implanted under the skin and does not require any leads or external sensors; it has a pair of sensing electrodes on the shell. It can be automatically activated by an arrhythmia (high and low rate events) or by the patient using an external programmer. Current models have a battery life of 3 years and record the ECG signatures of infrequent syncopal episodes. Several studies have confirmed the usefulness of the ILR in establishing a symptom-rhythm correlation for syncope.[68-78] On the whole, syncope recurs in 30% to 50% of patients. A few patients have tachyarrhythmia during syncope, but most of the heart rhythm disturbances are bradycardic. Many of these appear to be caused by reflex-mediated suppression of the sinoatrial and atrioventricular nodal functions during vasovagal syncope. However, the most common rhythm detected is sinus rhythm; presumably the cause of syncope is vasodepression without bradycardia. In the largest study, bradycardia was seen to accompany syncope in less than 30% of cases. The International Study on Syncope of Uncertain Etiology (ISSUE) investigators implanted ILRs in 111 patients with probable vasovagal syncope, regardless of their TTT results. Syncope recurred in 34% of patients, with marked bradycardia or asystole being the most common recorded arrhythmia during syncope (46% and 62%, respectively). The ISSUE investigators reported a classification of rhythm findings that helps distinguish among the causes of bradycardia (Box 48-1).[69]

Box 48-1 Classification of Rhythm Findings During Syncope as Documented by an Implantable Loop Recorder

Type 1: Asystole (RR pause ≥3 seconds)
Type 1A, sinus arrest
- Progressive sinus bradycardia or initial sinus tachycardia followed by progressive sinus bradycardia until sinus arrest

Type 1B, sinus bradycardia plus AV block
- Progressive sinus bradycardia followed by AV block and ventricular pause(s) with concomitant decrease in sinus rate
- Sudden-onset AV block and ventricular pause(s) with concomitant decrease in sinus rate

Type 1C, AV block
- Sudden-onset AV block and ventricular pause(s) with concomitant increase in sinus rate

Type 2: Bradycardia (decrease in heart rate >30% or <40 beats/min for >10 seconds)
Type 2A: Decrease in heart rate >30%
Type 2B: Heart rate <40 beats/min for >10 seconds

Type 3: No or Slight Rhythm Variations (variations of heart rate <30% and >40 beats/min)

Type 4: Tachycardia (increase in heart rate >30% and >120 beats/min)
Type 4A: Progressive sinus tachycardia
Type 4B: Atrial fibrillation
Type 4C: Supraventricular tachycardia (except sinus)
Type 4D: Ventricular tachycardia

AV, Atrioventricular.
From Brignole M, Moya A, Menozzi C, et al: Proposed electrocardiographic classification of spontaneous syncope documented by an implantable loop recorder, Europace *7:14–18, 2005.*

Two prospective randomized trials, one in Canada and one in the United Kingdom, compared early use of the ILR to conventional testing in patients undergoing a cardiac workup for unexplained syncope.[6,73,79] Taken together, they demonstrated that ILR resulted in a higher diagnostic yield, at an earlier time, and at a generally lower cost compared with a conventional strategy. The ILR is not for everyone, and the recent European Heart Rhythm Association guidelines suggest a reasonable approach to its use (Figure 48-2).[68] Clearly, the ILR is a useful tool for investigating patients with recurrent unexplained syncope when noninvasive test results are negative.[4-6,68]

Reflex Neurally Mediated Vasovagal Syncope

Vasovagal syncope is characterized by paroxysmal, reflex-mediated hypotension and bradycardia. It is the most common of the neurally mediated syncopal syndromes. Prolonged standing, sight of blood, pain, and fear are common precipitating stimuli for this common faint. Serotonin, opiate, and β-adrenergic receptors may mediate the integration of this reflex response. Bradycardia is caused by increased vagal tone, and hypotension is caused by withdrawal of α-adrenergic tone to venous and resistance vessels.

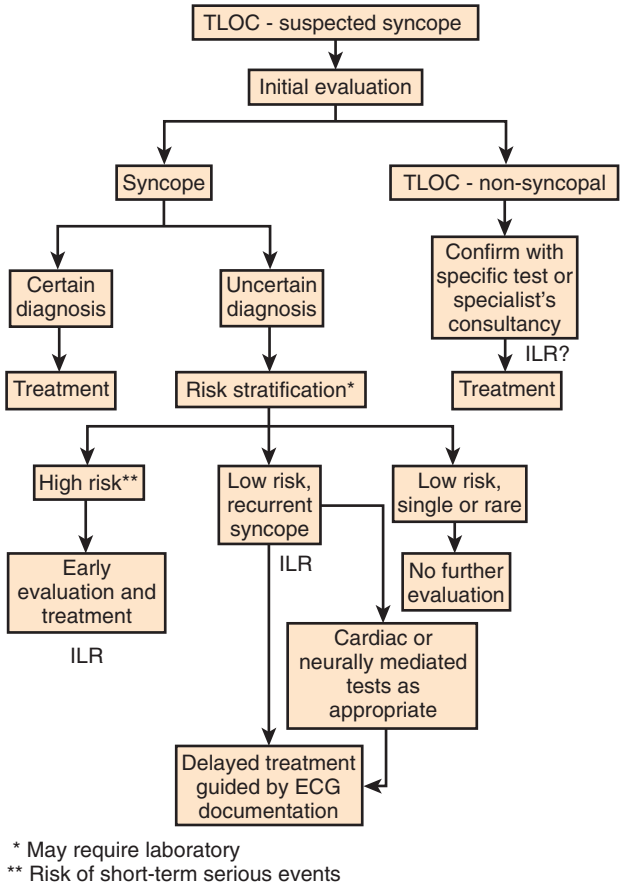

FIGURE 48-2 Implantable loop recorder *(ILR)* in the workup of transient loss of consciousness *(TLOC). ECG,* Electrocardiogram. *(From Brignole M, Vardas P, Hoffman E, et al: Indications for the use of diagnostic implantable and external ECG loop recorders,* Europace *11:671–687, 2009.)*

Symptoms

Patients develop nausea, diaphoresis, pallor, and loss of consciousness because of hypotension with or without significant bradycardia. Return to consciousness after seconds to 1 to 2 minutes is the norm. Those with adequate warning may be able to simply sit or lie down to prevent a full faint. However, some patients have little or no prodrome, no recognized precipitating stimulus, or marked bradycardia accompanying the faint. Older patients usually have an atypical presentation and may have a prodrome but may not recall it because of retrograde amnesia.[9]

Syncope Severity and Quality of Life

The vasovagal syncope syndrome has an extremely wide range of symptom burden. The symptom burden varies from a single syncopal spell in a lifetime to daily faints. Patients with frequent syncope have a markedly reduced quality of life, similar to that of patients with severe rheumatoid arthritis or chronic low back pain.[80] The reduction in quality of life correlates with the frequency of syncope.[81] Quality of life is substantially impaired in all dimensions of health, particularly in terms of mobility, usual activities, and self-care.[82-85]

Natural History

Vasovagal syncope affects all ages and both sexes. It usually first presents in adolescence and early adulthood, and the predilection to fainting is lifelong. Most patients seen in referral clinics have fainted repeatedly; in the authors' specialty referral clinic, the median number of faints is 10 to 15, and the median duration of syncopal history is 15 to 20 years. In many patients, syncope appears to occur in clusters that last months to years. Many patients have more frequent presyncopal spells that limit daily activities. Therefore, most patients with syncope do not require lifetime therapy, but they frequently merit treatment that lasts from months to years.[86] When assessing patients with syncope, clinicians need to be alert to the surprisingly marked impairment of quality of life that many patients endure, provide a perspective that lasts decades, and remember that the clinical state will probably fluctuate.[4,50,51]

Diet and Physical Maneuvers

Patients with syncope are encouraged to increase their salt and fluid intake, although the evidence in favor of this therapy is weak (Table 48-4). Patients with positive TTT result convert to a negative response on a subsequent test after receiving an intravenous volume load, and orthostatic tolerance improves with increased dietary salt. The usual reported dose of salt tablets is 6 to 9 g (100 to 150 mmol/L) per day. No substantial evidence exists supporting the use of exercise training to prevent syncope.

Considerable evidence supports the use of physical counterpressure maneuvers (PCM). During PCM, the presyncopal patient does isometric contractions of either the legs (by leg crossing) or the arms and hands (by pulling apart gripped hands), or squats. The Physical Counterpressure Manoeuvres Trial (PC Trial) was a randomized, controlled trial comparing conventional therapy (fluid and salt intake, counseling, avoidance) against conventional therapy augmented by one of three maneuvers in 208 patients with vasovagal syncope.[87] After 18 months of follow-up, PCM provided a significant 36% relative risk reduction. However, 35% of patients had insufficient prodromes to perform the techniques. These techniques should form the evidence-based core of the early, conservative care of vasovagal syncope.[1,2,8]

β-Blockers

At least five randomized clinical trials of β-adrenergic blockers for the prevention of syncope have been published (see Table 48-4).[1,2] On the whole, the results were negative. One small, early study of atenolol showed positive results.[88] The Prevention of Syncope Trial (POST) was a pivotal randomized, placebo-controlled, double-blind trial assessing the effects of metoprolol in vasovagal syncope over a 1-year treatment period.[89] Metoprolol provided no benefit, with nearly identical outcome rates in both study arms.

Fludrocortisone

Fludrocortisone is a corticosteroid with mainly mineralocorticoid activity that results in sodium and water retention and potassium excretion, which would increase blood volume.[1,2] A randomized, double-blind, placebo-controlled study found more symptoms in children treated with fludrocortisone compared with the group treated with placebo (see Table 48-4).[90] The second Prevention of

Table 48-4 Evidence-Based Therapy for Vasovagal Syncope

TREATMENT	TREATMENT EFFECT	EVIDENCE
LIFESTYLE CHANGES		
Increased intake of salt and fluid	Probably helpful	Moderate evidence
Physical exercise	Debatable effect	Weak evidence
Physical counterpressure	Probably helpful	Good evidence
ORTHOSTATIC TRAINING		
Tilt training	Debatable effect	Moderate evidence
Home orthostatic training	Probably unhelpful	Good evidence
PHARMACOLOGIC THERAPY		
β-Blockers	Probably unhelpful	Good evidence
Selected serotonin reuptake inhibitor antidepressants	Debatable effect	Moderate evidence
Midodrine	Probably helpful	Good evidence
Fludrocortisone	Debatable effect	Weak evidence
CARDIAC PACEMAKERS		
Cardiac pacemakers: routine use	Probably unhelpful	Good evidence
Cardiac pacemakers: selected use in refractory cases with asystole	Debatable effect	Weak evidence

From Kuriachan V, Sheldon RS, Platonov M: Evidence-based treatment for vasovagal syncope, Heart Rhythm *5:1609–1614, 2008.*

Syncope Trial (POST II), a multi-national, randomized, double-blind, controlled clinical trial assessing the effectiveness of fludrocortisone in adults with recurrent vasovagal syncope ended in July 2011. Results are pending.

α-Agonists

Midodrine is the sole α-adrenergic agonist with evidence of effectiveness. It is peripherally active, as is its metabolite. It alleviates the reduction in peripheral sympathetic neural outflow, which is responsible for venous pooling and vasodepression central to vasovagal syncope.[91,92] A randomized, placebo-controlled, single-pill trial of midodrine to prevent syncope on TTT was positive (see Table 48-4).[93] Two randomized, open-label trials showed positive results and prevention of syncope for up to 22 months.[94] A randomized, placebo-controlled, double-blind, crossover study reported that midodrine significantly increased the number of symptom-free days in 16 highly symptomatic patients.[95] However, the study period was only 28 days. The drug is well tolerated, albeit requiring frequent dosing. Side effects included supine hypertension, nausea, scalp paresthesias, piloerection, and rash but were dose related and easily reversible. Midodrine should not be used in patients with hypertension or heart failure.[1,2]

Serotonin Reuptake Inhibitors

The important role of serotonin in the regulation of heart rate and blood pressure led to speculation that fluctuation in central serotonin levels may contribute to vasovagal syncope. Indeed, a randomized, double-blind, placebo-controlled study of 68 consecutive patients who had not responded to other treatments reported positive outcomes.[96] Disappointingly, a recent second randomized, placebo-controlled study of 96 patients found fluoxetine, propranolol, and placebo to be equal.[97] Therefore evidence for the use of these drugs with vasovagal syncope is conflicting, and the drugs are not currently recommended.[1,2]

Permanent Pacemakers

Three open-label, historically controlled trials and three open-label, randomized clinical trials of permanent pacemakers in patients with frequent vasovagal syncope reported an approximate 90% reduction in the likelihood of a recurrence of syncope in paced patients (see Table 48-4). However, a placebo effect from the pacemaker could not be excluded. The Second Vasovagal Pacemaker Study (VPS II) was an international, placebo-controlled, double-blind, multi-center trial.[98] Patients with active pacemakers had no significant benefit from pacing; this was confirmed by a smaller second study, the Vasovagal Syncope and Pacing Trial (SYNPACE).[99]

One unresolved question is whether the subset of patients with vasovagal syncope who have asystolic pauses during spontaneous syncope might benefit from pacing. Accordingly, the ISSUE investigators are conducting ISSUE 3, a multi-center, placebo-controlled, prospective, double-blind, randomized study.[100] Patients with asystolic pauses detected by an ILR will have a pacemaker implanted with double-blind randomization to active pacing or sensing only; the design is similar to that of the VPS II study.[1,2,101,102]

Carotid Sinus Syncope

Carotid sinus syncope is a syndrome of syncope associated with a consistent clinical history, carotid sinus hypersensitivity, and the absence of other potential causes of syncope.[4,98] Historical features that suggest the diagnosis are syncope or presyncope occurring with carotid sinus stimulation that reproduces clinical symptoms, or fortuitous Holter monitoring or other documentation of asystole during syncope following maneuvers that could stimulate the carotid sinus. The incidence of carotid sinus syncope is low and may be approximately 35 per 1 million per year. Carotid sinus syncope occurs in older patients, mainly in men. It tends to occur abruptly, with little prodrome, and only half the patients may recognize a precipitating event. These most typically include wearing tight collars, shaving, head turning (as in looking back to reverse a car), coughing, heavy lifting, and looking up.

Physical Diagnosis

Carotid sinus hypersensitivity denotes the abnormal physiological responses, which could be cardio-inhibitory, vasodepressor, or both, to 5 to 10 seconds of carotid sinus massage (CSM). A cardio-inhibitory response to carotid sinus massage is defined as 3 seconds or more of ventricular standstill or asystole. A vasodepressor response to carotid sinus massage is defined as a drop in

systolic blood pressure of 50 mm Hg or more during massage and may be difficult to demonstrate in patients who have a significant cardio-inhibitory component. The presence of asymptomatic carotid sinus hypersensitivity is common in older adults.

Older patients with unexplained falls may have positive CSM responses, suggesting that carotid sinus syncope is responsible for many unexplained or recurrent falls. However, physiological carotid sinus hypersensitivity is far more common than carotid sinus syncope, and care should be taken in the interpretation of these results. Little is known about the natural history of carotid sinus syncope. Even though it may have a substantial effect on quality of life, it has not been shown to affect mortality. Even in the absence of pacing, only 25% of patients may have a syncope recurrence in the first year of follow-up.

Randomized Studies of Pacing

Recent prospective, randomized trials have examined outcomes on the basis of presence of pacing and mode.[4,101] One prospective, randomized trial reaffirmed the important role of permanent pacing for carotid sinus syncope.[103] Sixty patients with carotid sinus syncope were randomized to pacing or nonpacing therapy. During a follow-up of approximately 3 years, syncope recurred in 51% patients of the nonpaced group and in 9% of the paced group.

Pacing of patients with carotid sinus syndrome has been associated with a reduction in falls; furthermore, among patients with unexplained and recurrent falls, carotid sinus hypersensitivity is an important risk factor. The Syncope and Falls in the Elderly Pacing and Carotid Sinus Evaluation (SAFE PACE) trial was designed to determine whether cardiac pacing reduces falls in older patients with unexplained falls and a cardio-inhibitory response to CSM.[104] Patients were randomized to receive a dual-chamber pacemaker with rate-drop responsiveness or no intervention. Patients who received a pacemaker had a highly significant 58% reduction in falls and a 40% reduction in syncope. Although these results suggest that many unexplained falls in older adults are caused by carotid sinus syncope and that they can be prevented with pacing, this was an open-label trial. The SAFE PACE II study randomized 141 older patients with unexplained falls and cardio-inhibitory carotid sinus hypersensitivity to receive a rate-drop-responsive, dual-chamber pacemaker or an ILR.[105] No significant differences in falls between the paced and the loop recorder group were observed. These results are at odds with the findings in SAFE PACE, possibly because of differences in patient population or because of limited power.

Only one double-blind, placebo-controlled, crossover study of pacing in patients with recurrent, unexplained falls and carotid sinus hypersensitivity has been published. All 34 participants received a dual-chamber pacemaker with a rate-drop response programmer and were randomized to the DDD/RDR mode (on) versus the ODO mode (off); after 6 months, patients crossed over to the opposite mode. The relative risk of falling with the pacemaker on versus off was not statistically significant between the groups.[106]

Pacemaker Programming

AAI pacing is contraindicated because many patients may eventually demonstrate associated atrioventricular block. If pacemakers must be used, they should be either ventricular or dual-chamber pacemakers.

Standardized Approaches in the Emergency Department

Epidemiologic findings of patients with syncope from EDs in Australia, Europe, the United Kingdom, and the United States report that the average patient age is 61 years and that 45% are men. The final diagnoses include vasovagal syncope in 43% of patients, cardiac in 14%, and other (including undiagnosed syncope) in 43%. Decision making in ED syncope assessment is often driven by risk assessment rather than by a precise diagnosis. Risk assessment decisions are aimed at two timelines for outcomes: (1) poor outcomes in the first 7 to 30 days, which mandate admission, and (2) poor outcomes beyond 30 days, which mandate early specialist assessment.[6]

Events After Presentation

Patients with syncope who present to the ED have a significant risk during follow-up, although this risk varies widely depending on the etiology.[6] The composite estimate of outcomes is that approximately 0.7% of patients die in the next 7 to 30 days, and approximately 10% of patients die within 1 year. Nonfatal severe outcomes are generally defined as a significant new diagnosis, clinical deterioration, serious injury with recurrence, or a significant therapeutic intervention. An average of 7.5% of syncope ED visits have a nonfatal severe outcome while these patients are in the ED, and another 4.5% have a nonfatal severe outcome in the next 7 to 30 days.[6] Only half of the nonfatal severe outcomes have cardiovascular causes. Therefore only a minority of patients will benefit from urgent assessment and treatment outside the ED, and only half of these are for cardiovascular disorders. In the case of some patients, the syncopal event may have little to do with overall outcome because many of the risk factors seem to identify older patients with high morbidity rates.

Risk Factors for Nonfatal Severe Outcomes

The most commonly identified risk factors for severe outcomes include an abnormal ECG, a history of cardiovascular disease, and hypotension; others include age greater than 60 years, syncope without prodrome, syncope occurring while supine and while exercising, hypertension, dyspnea, and anemia.[15-23,27,33,107-111] The Canadian Cardiovascular Society defined major risk factors as those independently identified in more than one report and minor risk factors as those identified in only one report (Table 48-5). Patients with major risk factors should have an urgent cardiac specialist assessment within 2 weeks.[6]

Emergency Department Risk Rules

On the whole, the ED diagnostic procedure for syncope has a sensitivity of 95% for early adverse outcomes and more than 99% for mortality.[13,17,21,27,33,107,108,112-114] This is accompanied by specificities in the range of 30% to 60%. Therefore the key priority of a decision rule would be to maintain sensitivity and increase specificity. A common feature of the ED risk stratification rules is that to achieve 95% sensitivity for an early adverse event, the presence of any single risk factor moves the patient from the low-risk group. Standardized scores have been developed in Europe, the United Kingdom, and the United States. Although the scores predict outcome, they do not necessarily identify a treatable

Table 48-5 Risk Factors for Short-Term Outcomes According to the Canadian Cardiovascular Society

RISK FACTOR	VARIABLE
MAJOR (URGENT NEED FOR CARDIAC ASSESSMENT)	
Abnormal electrocardiogram	Any bradyarrhythmia, tachyarrhythmia, or conduction disease New ischemia or old infarct
History of cardiac disease	Ischemic, arrhythmic, obstructive, valvular
Hypotension	Systolic blood pressure <90 mm Hg
Heart failure	Either past history or current state
MINOR (POSSIBLE NEED FOR URGENT CARDIAC ASSESSMENT)	
Age	>60 years
Dyspnea	
Anemia	Hematocrit <0.30
Hypertension	
Cerebrovascular disease	
Family history of early sudden cardiac death	Age <50 years
Specific situations	Syncope while supine, during exercise, or with no prodromal symptoms

Major risk factors were independently derived in more than one study; minor risk factors were derived in only one study. Patients with syncope should have an urgent cardiac assessment in the presence of a single major risk factor.
From Sheldon RS, Morillo CA, Krahn AD, et al: Standardized approaches to the investigation of syncope: A position paper of the Canadian Cardiovascular Society, Can J Cardiol *27(2):246–253, 2011.*

Table 48-6 The ROSE Rule with BRACES Mnemonic

B	**B**NP level ≥300 pg/mL
	Bradycardia ≤50 in ED or prehospital setting
R	**R**ectal examination showing fecal occult blood (if suspicion of gastrointestinal bleeding)
A	**A**nemia (hemoglobin ≤90 g/L)
C	**C**hest pain associated with syncope
E	**E**CG showing Q wave (not in lead III)
S	**S**aturation ≤94% on room air

A patient should be considered high risk and admitted if any of the seven criteria in the ROSE (Risk Stratification of Syncope in the Emergency Department) rule are present.
BNP, *B-type natriuretic peptide;* ED, *emergency department;* ECG, *electrocardiogram.*
From Reed MJ, Newby DE, Coull AJ, et al: The ROSE (Risk Stratification of Syncope in the Emergency Department) study, J Am Coll Cardiol *55:713–721, 2010.*

cause. The two studies with the best methodology and external validation are the San Francisco Syncope Rule and the Osservatorio Epidemiologico della Sincope nel Lazio (OESIL) score.[27,111] Both were thoroughly developed, starting with epidemiologic risk factors and proceeding through validation studies. Very recently, the Risk Stratification of Syncope in the Emergency Department (ROSE) study reported the development and validation of a score (based on the BRACES mnemonic) for identifying high-risk patients with syncope (Table 48-6).[33]

The OESIL group identified four risk factors for 1-year mortality: (1) age greater than 65 years, (2) cardiovascular disease, (3) syncope without prodrome, and (4) an abnormal ECG.[111] The risk score resulted in 0 to 4 points, with 1-year mortality rates ranging from 0.8% to 57%. This was partly validated in a small study by British investigators, who found 3-month serious outcomes to range from 0% to 37%, with deaths accounting for half the outcomes. Martin et al identified four similarly weighted independent risk factors (age greater than 45 years, history of heart failure, history of ventricular arrhythmias, and an abnormal ECG) that predicted 1-year death rates ranging from 2% to 30%.[115] Therefore the factors that predict 1-year mortality are advanced age, cardiovascular disorders, and an abnormal ECG.

The San Francisco Syncope Rule (SFSR) identified independent predictors of serious morbidity and mortality within 7 days of presentation to the ED.[27] High-risk patients could be identified by the presence of any one of five factors: (1) dyspnea, (2) hypotension, (3) congestive heart failure, (4) abnormal ECG, and (5) anemia. Although the SFSR was reported to have 96% sensitivity and 62% specificity, subsequent validation studies reported reduced accuracy. Admission rates with the SFSR would be increased with no gain in sensitivity when compared with the actual decision made by the ED physician.[6]

Impact of Guidelines

Do the ESC guidelines improve care? In 2001 and 2007, the American College of Emergency Physicians issued guidelines for the ED management of patients with syncope. A study that used high-risk features as a tool for identifying cardiogenic syncope had very high sensitivity and specificity statistics and, if implemented, would have reduced admissions by 29%, whereas the use of medium-risk features decreased specificity and increased admissions. The ESC guidelines recommend admission for significant heart disease, abnormal ECG, syncope during exercise or while supine, severe injury, family history of SCD, preceding palpitations, frequent episodes or high suspicion of cardiac syncope, arrhythmias, cardiopulmonary or neurologic disorders, or pacer implantation. McCarthy et al retrospectively assessed a pathway developed on the basis of these guidelines and found that 9.6% of the admissions could have been avoided if the pathway was used.[14] Del Greco et al reported that the 2001 guidelines had no apparent effect on length of stay, extent of testing, or cost of hospitalization.[116,117] Although ED syncope decision rules may have prognostic value, there is no compelling evidence that they improve diagnostic accuracy or reduce costs, and they may substantially increase costs.[6]

Syncope Management Units

The generally benign short-term outcome of patients with syncope raises the possibility of an entirely outpatient assessment of patients who do not have a declared outcome in the ED.[6] The term *syncope unit* refers to any organized approach to investigation or,

more narrowly in North America, as a geographically contained unit for assessing syncope. The ESC 2009 guidelines recommend the establishment of formal syncope units, either virtual or geographically contained, staffed by syncope experts, with easy access to all referring physicians.[4]

Kenny et al first introduced the concept of a dedicated syncope clinic or unit in a study of 65 consecutive older patients. A causal diagnosis was reached in 92% of patients. Subsequently, three small observational studies showed that with older patients, dedicated units achieved a diagnosis in almost all.[117,118] However, none of these studies was controlled, and many diagnoses simply turned out to be accurate clinical judgments. In one study, a syncope and falls day clinic for older patients achieved a dramatic estimated reduction in bed occupancy (35% vs. 97% of expected) and length of stay (2.7 vs. 10.9 days expected).

Brignole et al compared six Italian hospitals that had an organized syncope unit with six matched hospitals not offering this service.[119] A weak trend to fewer admissions and tests performed in the syncope unit hospitals was observed, but only 11% of eligible syncope patients had been referred to the unit. Ammirati et al reviewed 102 consecutive patients referred to their syncope unit as either outpatients or during hospitalization in a retrospective observational study.[120] The syncope unit appeared to increase the diagnostic yield from 75% to 82% and reduced hospital costs by 85%, largely by eliminating unnecessary tests.

The Syncope Evaluation in the Emergency Department Study (SEEDS) was the only randomized study evaluating the efficiency and accuracy of the investigation of syncope with a dedicated syncope unit.[28] SEEDS randomized 103 patients with intermediate risk for syncope to a syncope unit evaluation compared with a standard care approach. The unit provided 6 hours of ECG monitoring, echocardiography, an early TTT, and an arrhythmia consult. The diagnostic yield was higher in the syncope unit arm (67% vs. 10%), mostly because of vasovagal syncope incidence. Admission rates were lower in the syncope unit group (43% vs. 98% in the control group). No differences in total mortality or syncope recurrence were noted. Formal syncope units may increase the diagnostic yield and prevent unnecessary admissions and testing. This may be explained by advanced access to specialist assessment and related testing.

Syncope Investigation Protocols in the Hospital

Noting the limited impact of published guidelines, Brignole et al used the ESC 2001 guidelines to develop software with specific prompting tools and compared its effectiveness to conventional unstructured approaches.[55] The Evaluation of Guidelines in Syncope Study 2 (EGSYS-2) was a parallel-arm, non-randomized comparison of 745 patients with syncope that showed an improved diagnostic yield (95% vs. 80%), a reduced admission rate (39% vs. 47%), and reduced costs. Later, it was validated in 541 patients in 11 large hospitals. Use of the software led to adherence to a guideline-based approach in 86% of patients and yielded a diagnosis in 98% of cases. Half of the diagnoses were initially obtained after clinical assessment and ECG, with limited and specified testing (1.9 tests per patient) yielding the remainder of the diagnoses. It is important to realize that, by design, the algorithm should have provided 100% diagnostic yield (whether correct or not), and a "syncope expert" was available by telephone to provide advice.

Similarly, Farwell and Sulke used a syncope diagnostic protocol at a single large hospital and compared the outcomes in 421 patients with those in 660 historic controls.[79] The diagnostic yield increased from 71% to 78%, as did appropriate testing such as TTT and monitoring. However, very poor adherence to the protocol led to many more hospital admissions than recommended, and irrelevant testing such as brain imaging persisted. This led to unexpected and dramatic increases in costs and bed occupancy. Finally, Sarasin et al used a systematic investigation strategy that featured baseline assessment with ECG and limited laboratory testing in 611 patients.[112] This simple initial stage led to a diagnosis in 69% of patients, with targeted testing in an additional 7%. Extensive testing was used only in the remaining 155 patients.

What lessons can be drawn from these studies? Algorithmic testing seems to be effective but probably will not work if it is complicated and not supported by expert advice. However, coupled with implementation tools, it improves the diagnostic yield and may reduce costs. The most important features of algorithmic testing may be facilitated access to specialist assessment and an online prompting tool.[6]

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CHAPTER 49

Asymptomatic Electrocardiogram Abnormalities

Raymond W. Sy, Allan C. Skanes, and George J. Klein

Introduction

Electrocardiographic abnormalities frequently appear in patients undergoing Holter monitoring or electrocardiography in the context of "routine screening" or investigation of an unrelated issue. The thoughtful physician will not want to miss an opportunity to prevent a potentially adverse outcome related to this but also considers that needless attention to a nonsignificant abnormality is not productive and possibly harmful. A thoughtful assessment will include such questions as:

1. Is the abnormality a true abnormality, or does it merely mimic a potentially harmful abnormality?
2. Is the abnormality associated with potentially adverse outcomes?
3. What is the positive predictive value of the abnormality in question for a specific adverse outcome?
4. Is the risk of the abnormality sufficiently compelling to warrant the risk and expense of further investigation?
5. Is the condition underlying the abnormality treatable?

Asymptomatic Wolff-Parkinson-White Pattern

Case 1

A 14-year-old boy was seen in the emergency department because of noncardiac chest pain following chest trauma during a basketball game. The electrocardiogram (ECG) seen in Figure 49-1 was recorded. He had never been aware of palpitations or syncope. Electrocardiographic pre-excitation was noted.

The most appropriate next step would be to:

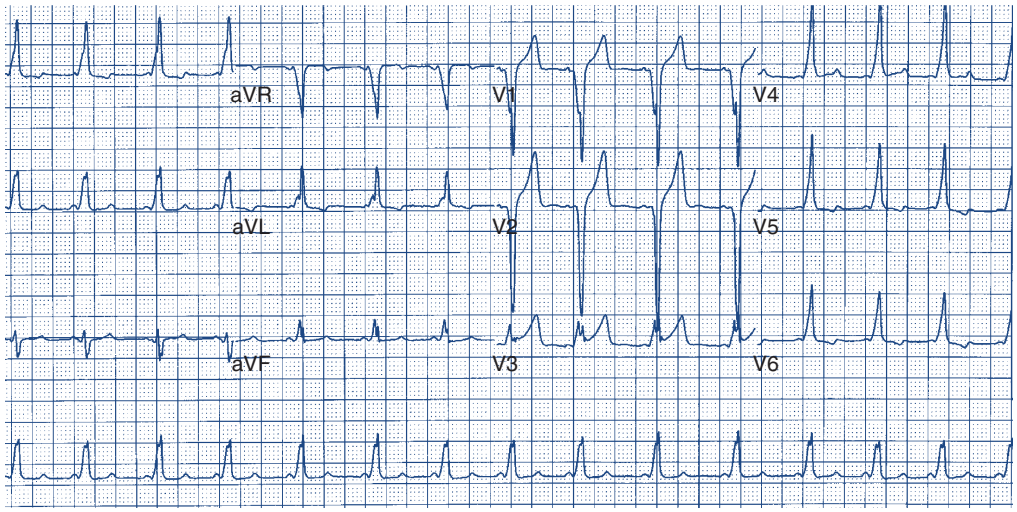
1. Reassure the patient and his family that no further follow-up is necessary.
2. Schedule an electrophysiological study (EPS).
3. Schedule an ECG.
4. Advise a treadmill exercise test.

The ECG findings now known as *ventricular pre-excitation* (δ-wave and short P-R interval) were first described in 1930.[1] Initial interest was in the arrhythmias associated with the ECG pattern, although it was later observed that many individuals with identical ECG patterns remained asymptomatic and had a benign course. Radiofrequency (RF) ablation of accessory pathways has become the preferred treatment option for patients with Wolff-Parkinson-White (WPW) syndrome because it is curative and has a low rate of associated complications. The question that remains is whether this treatment should be extended as a prophylactic measure to asymptomatic individuals with the WPW pattern on ECG to prevent the small risk of sudden cardiac death (SCD).

Several studies have provided an estimate of the prevalence of the WPW pattern. It is estimated that 0.1% to 0.15% of the population will have ECG manifestations of WPW, of which approximately 50% will never have had symptoms.[2] New cases arise at a rate of approximately 0.004% per year.[2] However, the true incidence is likely higher, given that the WPW pattern is frequently intermittent and may be missed on ECG and that many individuals never receive an ECG in their lifetime.

Although estimates vary, the incidence of SCD among patients with WPW appears to be at most 0.1% per year.[2,3] Munger et al did not report any SCDs in their large (113 patients) retrospective review. No deaths occurred among 293 patients studied in a recent prospective study that examined the usefulness of the EPS and ablation in asymptomatic individuals.[4] Autopsy studies delving into the issue are generally limited by the difficulty in finding accessory pathways on routine tissue sections, but most cases of unexpected SCD are related to coronary or other unrecognized structural heart diseases. Nonetheless, SCD in an asymptomatic young individual with WPW pattern is a tragic event that cannot be ignored.

The most common cause of SCD in patients with WPW is ventricular fibrillation (VF) triggered by atrial fibrillation (AF). In these cases, AF is associated with a rapid ventricular response because of the presence of at least one accessory pathway with a short anterograde refractory period. It follows that only those patients who have accessory pathways capable of mediating a rapid ventricular rate are at risk for developing SCD. It has been found that VF rarely occurs when the shortest R-R (SRR) interval during induced AF is greater than 250 ms.[5] AF is usually preceded by AV re-entrant tachycardia in these patients, presumably because of the electrophysiological, hemodynamic, and metabolic consequences of supraventricular tachycardia (SVT). Hence, the failure to induce tachycardia would independently predict a good prognosis.[6] Interestingly, the presence of multiple accessory pathways in a given individual increases the risk of



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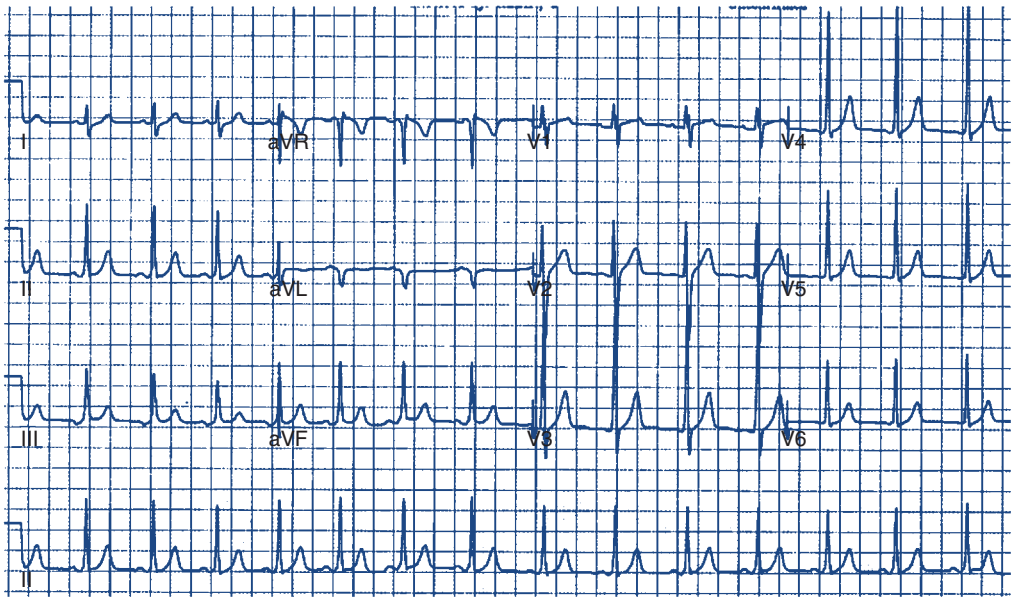


B

FIGURE 49-1 Wolff-Parkinson-White pattern.

SCD by an odds ratio of 3.1, presumably because of increased ventricular desynchronization related to multiple pre-excitation wavefronts.[7]

Because of the rarity of the outcome in question (<1/1000 patients/year) it is evident that predicting outcomes with any test is problematic. As one would expect from such a low incidence of SCD, the negative predictive value of the EPS is excellent. Klein et al have categorized the risk of SCD on the basis of the SRR interval during spontaneous or induced AF as follows[8]:

1. Definite risk: shortest pre-excited R-R interval <220 ms
2. Probable risk: shortest pre-excited R-R interval <250 ms but >220 ms
3. Possible risk: shortest pre-excited R-R interval <300 ms but >250 ms
4. Negligible risk: shortest pre-excited R-R interval >300 ms

It must be emphasized that "definite" risk in this stratification is not equivalent to "high" risk. The use of the SRR less than 250 ms as a marker of risk in clinical practice is not as helpful as may be believed; 17% of asymptomatic individuals with WPW will have SRRs in this range, a far greater proportion than that expected to have an event.[8] Using an SRR of less than 250 ms, sensitivity of 77.8%, specificity of 48.3%, and predictive accuracy of 18.9% can be obtained.[9] Combining the findings of multiple accessory pathways and SRR less than 250 ms lowered the

sensitivity (from 88% to 29%) but increased the specificity (from 36% to 92%) and the positive predictive value (from 9% to 22%).[7] Pappone et al reported that the combination of a short pathway effective refractory period (ERP) (<250 ms) and inducible tachycardia had sensitivity of 93.7%, specificity of 67.6%, and positive and negative predictive values of 46.9% and 97.3%, respectively, for subsequent arrhythmia.[6] Isoproterenol, which is often used in an attempt to induce tachycardia, AF, or both, will cause an even greater percentage of individuals to have an SRR less than 250 ms. Therefore the already poor positive predictive value of an SRR less than 250 ms can be expected to worsen. Despite its limitations, the EPS remains the gold standard for the determination of risk of SCD in asymptomatic patients with WPW.

Noninvasive methods for evaluating the risk for SCD have been described: Holter monitoring to determine whether intermittent pre-excitation is present (therefore making it extremely unlikely for the SRR of the pathway to be <250 ms), *sudden* loss of pre-excitation on an exercise test, with infusion of ajmaline or procainamide (suggesting a long refractory period for the pathway), and trans-esophageal pacing.[10-12] With the exception of trans-esophageal pacing, all of these methods rely on assessments of accessory pathway conduction in sinus rhythm and are imperfect substitutes for a test that, in itself, has limitations. Trans-esophageal pacing has its proponents, but it provides less information than catheter EPS and arguably involves similar risk and discomfort.[13]

What, then, is the best approach for the management of the asymptomatic patient, given that SCD as a first manifestation of the WPW syndrome is a very rare occurrence? Since serious complications from RF ablation in experienced centers occur infrequently (~1%), it becomes difficult to make a categorical recommendation for or against ablation. Clearly, studying all patients with asymptomatic WPW and ablating those with an SRR less than 250 ms will result in increased morbidity and mortality among patients who may never develop any symptoms. However, an approach that involves *not* studying any asymptomatic individuals may result in some preventable deaths. Many physicians may prefer to accept a small procedural risk with a finite risk interval over a longer term risk of potentially lethal arrhythmias.[14,15]

Equally important is the patient's or his or her caregiver's ability to accept a small, but ongoing risk of SCD. If this is not addressed, it may result in anxiety and needless restriction of recreational or occupational activities. On the one hand, some patients may choose ablation. On the other hand, some individuals may be less concerned about the theoretical risk of arrhythmia versus a real procedural risk.

Finally, two other factors may influence the discussion:

1. Ablation of some accessory pathways is associated with higher risk than that of others. For example, attempted ablation of a "mid-septal" accessory pathway that is close to the AV node carries a higher risk of AV block and the need for permanent pacemaker implantation.

2. The incidence of SCD as a first presentation of WPW syndrome decreases with age. For example, a 60-year-old male is much less likely to have this outcome compared with a 10-year-old.

Since both the risks of treating and not treating are low, it is difficult to give an all-encompassing recommendation regarding ablation of asymptomatic WPW. It is reasonable to recommend ablation if the patient is otherwise prevented from pursuing a professional or important recreational activity. In all other cases, the decision to undergo an EPS and to proceed with ablation should be individualized. Given that several emotional, personal, and social issues are involved in the consideration and that the risks associated with either approach are minimal, the ultimate decision must rest with the patient.

Discussion of Case 1

Since asymptomatic patients have a small but statistically measureable risk of SCD, an informed discussion with the patient and his family is required; reassurance alone is not appropriate. The patient and his family also need to be aware of the potential risks associated with further investigations such as an EPS. It may also be reasonable to review the situation in the follow-up to give the patient and his family a chance to carefully consider their choices, since the situation is not a medical emergency.

In this case, the δ-wave was prominent and could be easily monitored during a treadmill test. This is the least-invasive and most appropriate next step. If loss of pre-excitation occurs with exercise, this classifies the accessory pathway as benign and eliminates concerns of SCD. An EPS is probably premature at this point but may be required if the treadmill test is not prognostically helpful. Treadmill testing is particularly problematic when minimal pre-excitation occurs (see Figure 49-1, *B*). In such cases, an EPS may be the only method of risk evaluation. An echocardiogram is not useful under the circumstances because most patients with WPW have structurally normal hearts.

In this case, constant pre-excitation was seen on treadmill testing despite a maximal heart rate of 180 beats/min. The patient and his family wanted further assessment to determine the patient's ability to play competitive sports. Following a discussion about the risks and benefits, the patient underwent an EPS. A mid-septal accessory pathway was documented. No tachycardia was inducible. No AF was inducible. Conduction over the accessory pathway failed at a pacing cycle length of 320 ms (188 beats/min), which suggested that rapid conduction over the accessory pathway during AF would not be possible. As such, the patient was at low risk for SCD. In addition, the accessory pathway was located very close to the AV node, presenting only a small risk of inadvertent AV block, so no ablation was performed.

Repolarization Abnormalities

Many primary repolarization changes on the 12-lead ECG are benign or normal variants such as early repolarization. Others may result from the presence of structural heart disease (e.g., myocardial infarction [MI], dilated cardiomyopathy, and hypertrophic cardiomyopathy) or the consequence of pharmacologic agents (e.g., antiarrhythmic drugs). The congenital long QT syndrome (LQTS), short QT syndrome (SQTS), and Brugada syndrome are relatively uncommon diseases associated with potentially life-threatening ventricular arrhythmias. In general, diagnoses of these conditions are complicated because of the significant overlap in the ECG manifestations of normal and disease conditions. The management of these conditions continues to evolve. The following sections discuss the typical ECG changes and clinical features that accompany the most common

pathologic repolarization abnormalities. Readers are also directed to Chapters 62 to 64 for additional information.

Long QT Syndrome

Case 2

A 36-year-old accountant was referred for assessment after the unexpected death of his 24-year-old brother who was previously well. The postmortem examination revealed no obvious cause of death. A 27-year-old sister is alive and well. His mother, who was known to have epilepsy, had died at age 46 in a motor vehicle accident. The patient's ECG shows a very long Q-T interval (QT = 600 ms, QTc = 545 ms) (Figure 49-2, *A*). He was not taking any medication and jogged regularly. An ECG done 2 years previously for an insurance physical was reported as normal (Figure 49-2, *B*).

The most appropriate course of action at this time would be to:

1. Reassure the patient by not performing further investigation.

2. Schedule a treadmill exercise test.

3. Schedule an EPS.

4. Recommend β-blocker therapy.

The congenital LQTS is a rare disorder (incidence 1:3000 to 1:10 000) characterized by prolongation of the Q-T interval, recurrent syncope, and SCD.[16] Two major clinical variants were originally described: (1) Romano-Ward syndrome (autosomal dominant inheritance) and (2) Jervell Lange-Nielson syndrome (autosomal recessive inheritance), in which patients also have congenital deafness. Over the past 10 years, great advances have been made in understanding the genetic and cellular bases for LQTS. At least 10 distinct genotypic variants of LQTS encompassing hundreds of mutations have now been identified (Table 49-1), and a genetic diagnosis is now obtainable in 50% to 60% of

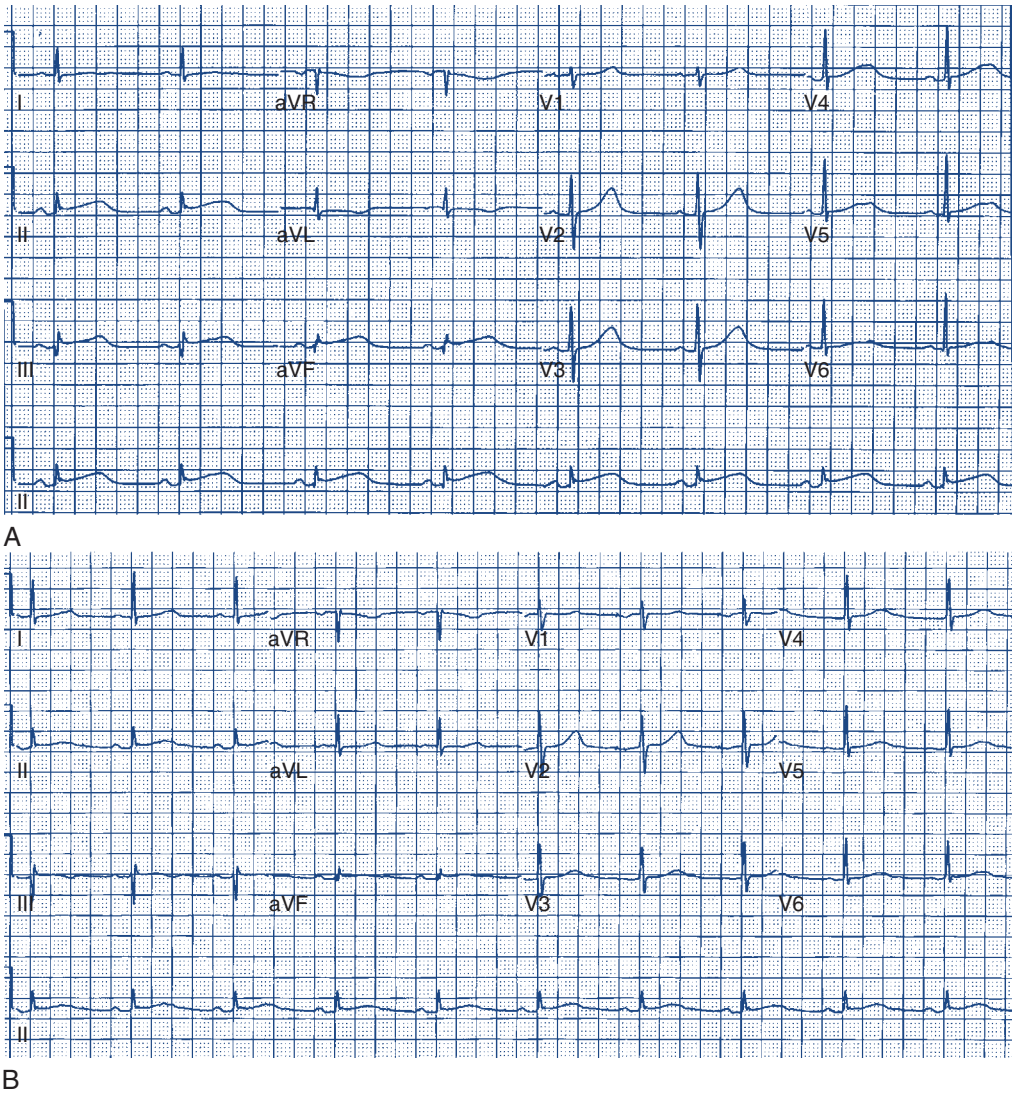


FIGURE 49-2 Long QT syndrome.

Table 49-1 Classification of Long QT Syndrome

TYPE	LOCUS	GENE	PROTEIN	% CASES
LQT1	11p15.5	*KCNQ1 (KVLQT1)*	I_{Ks} (α-subunit)	42 (40–55)
LQT2	7q35-q36	*KCNH2 (HERG)*	I_{Kr} (α-subunit)	45 (35–45)
LQT3	3p21-p24	*SCN5A*	I_{Na} (α-subunit)	8
LQT4	4q25-q27	*Ankyrin-B (ANK2)*	?	<1
LQT5	21q22.1-22.2	*KCNE1 (MinK)*	I_{Ks} (β-subunit)	3
LQT6	21q22.1-22.2	*KCNE2 (MiRP1)*	I_{Kr} (β-subunit)	2
LQT7	17q23.1-q24.2	*KCNJ2*	Kir2.1	<1
LQT8	12p13.3	*CACNA1C*	$I_{Ca\text{-}L}$	<1
LQT9	3p25	*CAV3*	Caveolin-3	<1
LQT10	11q23	*SCN48*	I_{Na} (β-subunit)	<1

Modified from Ruan Y, Liu N, Napolitano C, Priori S: Therapeutic strategies for long QT syndrome: Does the molecular substrate matter? Circ Arrhythmia Electrophysiol *1:290–297, 2008; Roden DM: Clinical practice. Long-QT syndrome,* N Engl J Med *358(2):169–176, 2008; and Splawski I, Shen J, Timothy KW, et al: Spectrum of mutations in long-QT syndrome genes. KVLQT1, HERG, SCN5A, KCNE1, and KCNE2,* Circulation *102(10):1178–1185, 2000.*

patients.[17] Three genotypes (LQT1, LQT2, and LQT3) account for more than 90% of cases.[18-20] The principal abnormality in LQTS is prolongation of the action potential duration caused by a reduction in the outward potassium current (LQT1 and LQT2) or, less commonly, by a persistent inward sodium current during the plateau phase (LQT3). Action potential prolongation provokes the development of early afterdepolarizations, which may produce a triggered action potential resulting in a premature beat.[21] Such impulses can initiate a polymorphic VT, known as *torsades de pointes*, which underlies the clinical symptoms of palpitations, syncope, or SCD caused by VF.

The classic description of events in LQTS involves exercise-induced or emotion-induced syncope or cardiac arrest. Symptoms often begin in adolescence, though they may begin earlier in patients with LQT1.[20] It is common for patients to be investigated and misdiagnosed as having a seizure disorder. Clinical events in LQTS are often seen in the context of heart rate acceleration precipitated by exercise, emotion, or sudden arousal.[20,22,23] Patients with LQT1 are particularly prone to events during hyperadrenergic states, with swimming identified as a specific trigger in such patients.[20,23] The history of arousal to an auditory stimulus such as a sudden loud noise (classically, a telephone call at night or an alarm clock going off) is strongly predictive of LQT2.[20,22] Events that occur during rest or sleep are more suggestive of LQT3.[20] Many of these circumstances represent the setting of sudden or marked changes in adrenergic tone and heart rate that may influence repolarization and subsequent vulnerability to arrhythmia.

The hallmark of LQTS is prolongation of the QTc (>440 ms in men and >460 ms in women), although considerable overlap occurs with QTc in normal populations. The QTc of genotype-positive patients overlaps with normal in up to one third because of variable penetrance.[24-26] Also, 10% to 15% of QTc in normal adults are greater than 440 ms.[27] Since repolarization is affected by factors such as sympathetic outflow, electrolyte balance, and pharmacologic agents, it is not surprising that considerable temporal variation may be present in QTc and that increased sampling improves diagnostic accuracy. In the absence of obvious reversible causes of QTc prolongation (Table 49-2), a diagnosis of LQTS can be made on the basis of ECG features and clinical presentation.[28] The mean QTc does not differ among the LQT1, LQT2, and LQT3 types but is significantly longer in Jervell Lange-Neilson syndrome.[20] In addition to QTc prolongation, qualitative abnormalities may also be found in LQTS, including ST-T wave changes, U waves, T-wave alternans, increased QT dispersion,

Table 49-2 Secondary Causes of QT Prolongation

FACTOR	MECHANISM
Bradycardia	↑ APD ↑ APD prolongation with class III agents
Drugs*	Mainly I_{Kr} blockade
Electrolyte disorders (hypokalemia, hypomagnesemia, hypocalcemia)	Hypokalemia ↓ I_{Kr} and ↑ I_{Kr} sensitivity to pharmacologic blockers
Left ventricular hypertrophy/failure	↓ K^+ currents (I_{to}, I_{Kr}, I_{Ks}) Changes to I_{CaL} and intracellular calcium (Ca^{2+})
Miscellaneous (e.g., anorexia, cerebrovascular disease, HIV infection, hypothyroidism, hypothermia, ionic contrast media)	

**The major classes of drugs are antiarrhythmic drugs, antihistamines, macrolide antibiotics, antipsychotics, and antidepressants. An updated online list of specific drugs that prolong the Q-T interval is available at www.qtdrugs.org or www.torsades.org.*
APD, *Action potential duration.*
Modified from Walker BD, Krahn AD, Klein GJ, et al: Congenital and acquired long QT syndromes, Can J Cardiol *19(1):76–87, 2003.*

and sinus bradycardia.[21] Although not highly specific, characteristic ST-T wave morphologies may allow the prediction of LQT type: broad-based T waves typify LQT1; low amplitude, notched T waves occur in LQT2; and long isoelectric ST segment with late-onset T wave occur in LQT3.[26]

It has been estimated that LQTS causes 3000 to 4000 SCDs per year in children and young adults in the United States.[29] Long-term registry data suggest that annually the risk of syncope is 5% and the risk of LQTS-related death before the age of 50 years is approximately 1% in symptomatic patients, with the risk being significantly lower in asymptomatic patients.[26,30] The most important predictor of risk is QTc duration, although age, gender, and genotype can be confounders. Using data from an international registry, three risk groups relating to the probability of experiencing a first cardiac event before the age of 40 years have been identified[31]:

- High risk (≥50%): LQT1, LQT2, and male LQT3 patients with QTc ≥500 ms
- Intermediate risk (30% to 49%): all female LQT3 patients; male LQT3 patients and female LQT2 patients with QTc <500 ms
- Low risk (<30%): LQT1 and male LQT2 patients with QTc <500 ms

Although a family history of cardiac events would intuitively appear to be prognostically important, this has not been borne out in clinical studies.[32,33]

β-Adrenoreceptor blockade is the mainstay of therapy (aiming for a reduction in peak exercise heart rate of >20%), and it is recommended for most patients with LQTS.[34] Survival can be dramatically improved with aggressive treatment with β-blockers, left cervical sympathectomy, pacemakers, and an implantable cardioverter defibrillator (ICD).[17,34] Lifestyle modifications, family screening, and genetic testing and counseling are also important considerations. In particular, genotyping may occasionally assist with diagnosis, family screening, and management.[35] For example, β-blockers may be less effective in LQT3, and genotype-specific therapies such as potassium replacement for LQT2 and mexiletine for LQT3 are being evaluated.[36,37]

Discussion Case 2

The patient in question clearly has marked QTc prolongation in the absence of medication. The family history is a cause for concern and suggests that his brother and mother (LQTS is frequently misdiagnosed as epilepsy) both had LQTS. This man previously had a normal ECG, and it is not unusual for such patients to have variability of the Q-T interval at different times. In more borderline cases, scoring systems incorporating ECG, clinical features, and family history may be helpful.[28] In this case, the best answer would be to recommend treatment with β-blocker. An argument can be made for an ICD in such a patient, although ICDs are usually reserved for high-risk patients such as those with recurrent symptoms who are on β-blockers or survivors of cardiac arrest (class IIa recommendation). Treadmill testing will not influence the decision to treat, although exercise may be diagnostically useful, especially if arrhythmias are observed. The EPS is generally of no value in LQTS. Where available, genetic counseling and family screening should also be offered.

Brugada Syndrome

Case 3

A 42-year-old man was referred for assessment of symptoms of atypical chest pain and ECG abnormalities (Figure 49-3). The patient was otherwise well. His father died suddenly in his mid-40s but no further details about his death are available.

The most appropriate next step to clarify the diagnosis of the ECG abnormality would be to:

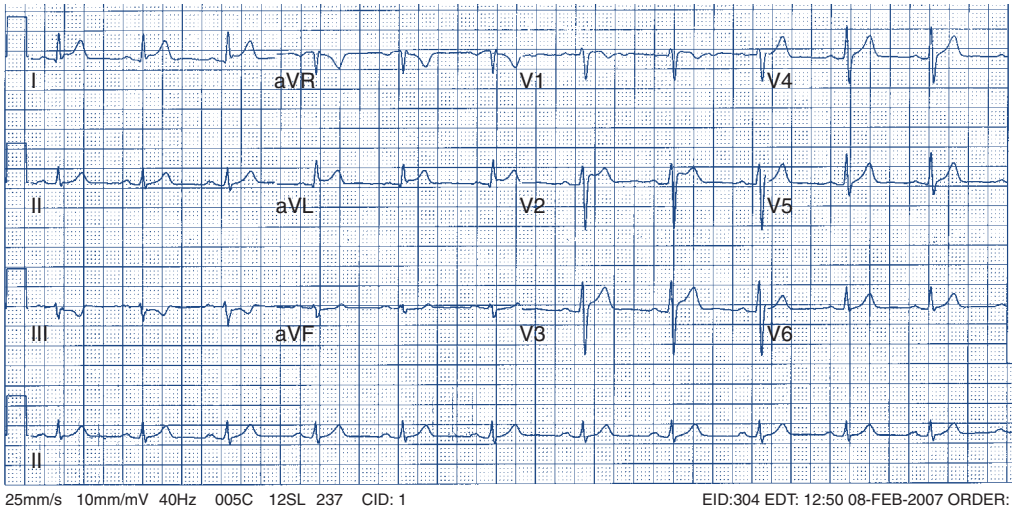
1. Schedule genetic testing.
2. Schedule exercise treadmill testing.
3. Administer procainamide infusion.
4. Schedule an EPS.

Brugada syndrome is an inherited disorder (autosomal dominant with variable expression) characterized by syncope and SCD from polymorphic VT and VF.[38] First described in 1992, it is now a recognized cause of SCD, particularly in southern Europe and in southeast Asia. Brugada syndrome is much more common in men and usually presents in the third and fourth decades of life. The primary abnormality is heterogeneous shortening of the action potential duration, particularly affecting the right ventricle, which results in phase 2 re-entry and polymorphic VT.[39] In up to 20% of affected individuals, mutations may be demonstrated in the *SCN5A* gene that encodes the fast inward sodium (Na^+) current (I_{Na}).[40] In a canine right ventricular wedge preparation, it has been shown that the combination of a weaker I_{Na} in the presence of a large transient outward potassium (K^+) current (I_{to}) results in a dramatic truncation of the epicardial action potential and marked transmural heterogeneity of repolarization.[39]

The Brugada ECG pattern is characterized by "pseudo–right bundle branch block (RBBB)" with ST-segment elevation in precordial leads V1 to V3 (reflecting predominant right ventricular abnormality). Three patterns of ST elevation have been described (see Figure 49-3, *B*):

Type 1: ≥2 mm of ST elevation descending with upward convexity to an inverted T wave ("coved" pattern)
Type 2: ≥1 mm of ST elevation descending toward the baseline and then rising again to an upright or biphasic T wave ("saddleback" pattern)
Type 3: <1 mm ST elevation with saddleback pattern

For diagnostic purposes, these changes should be seen in two or more precordial leads. The pseudo-RBBB is probably secondary to a prominent J wave, and it can be differentiated from typical RBBB by the absence of a prominent S wave in V6. The Q-T interval is usually normal, although patients with both Brugada syndrome and LQTS have been described. Importantly, Brugada syndrome remains a diagnosis of exclusion because similar ECG changes may also be seen in other disease states such as antero-septal MI, acute pericarditis, arrhythmogenic right ventricular dysplasia, electrolyte derangement, and hypothermia. In some patients, the ECG pattern fluctuates and can be unmasked by many conditions, including febrile illness, antiarrhythmic and psychotropic medications, heavy alcohol consumption, and cocaine abuse.



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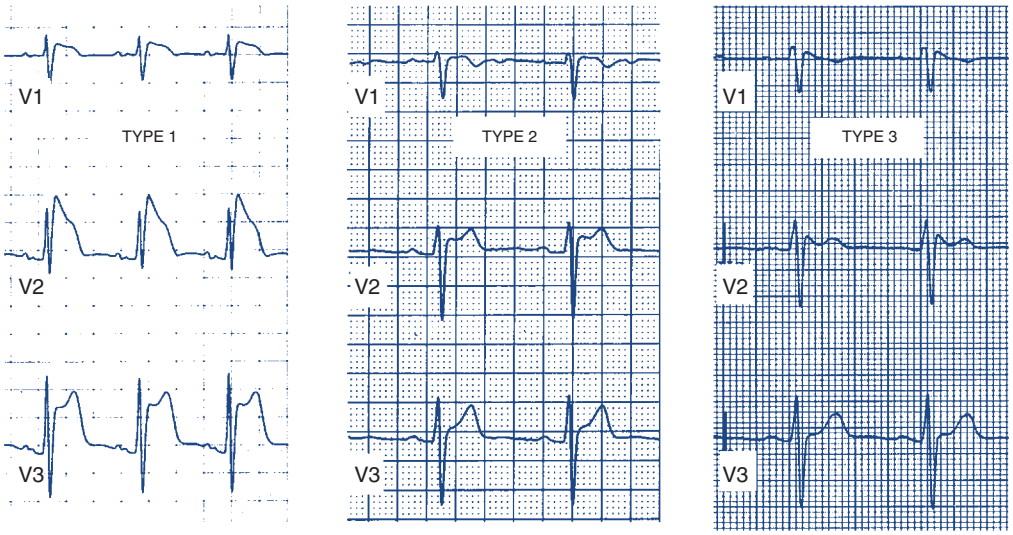

B

FIGURE 49-3 Brugada syndrome.

Differentiation of the Brugada ECG pattern from prominent early repolarization changes in the right precordial leads of otherwise healthy patients may occasionally be difficult, and pharmacologic provocation may be particularly useful in such patients with nondiagnostic ECGs. Administration of the Na^+ channel–blocking agents flecainide, ajmaline, and procainamide may convert a type 2 or 3 ECG pattern to the classic type 1 pattern, but reports of the sensitivity and specificity of this observation have been conflicting.[41,42] Likewise, it has been noted that moving ECG leads V1 and V2 one or two interspaces higher (third and second interspaces, respectively) can increase the sensitivity of the ECG to diagnose a spontaneous type 1 pattern.[43,44] Although none of the normal subjects had a Brugada pattern in the initial report, the specificity of this test requires a larger cohort for confirmation. The signal-averaged ECG will show late potentials in approximately 50% of patients and may be another marker of disease in borderline cases.[45] Exercise stress testing does not usually provoke ventricular arrhythmias because most events occur at night or during episodes of high vagal tone.[45]

The diagnosis of Brugada syndrome is made on the basis of a spontaneous or induced type 1 Brugada pattern on ECG in concert with clinical symptoms (e.g., unexplained syncope or seizure, nocturnal agonal respiration), documented arrhythmia, or a family history of typical type 1 Brugada ECG pattern or SCD before the age of 45 years.[46] A recent consensus conference on Brugada syndrome has recommended ICDs for those with aborted SCD as well as for those with syncope, seizures, and nocturnal agonal respiration without another obvious cause.[45] This holds true whether the type 1 ECG is spontaneous or induced.

The risk of life-threatening events in asymptomatic patients is substantially lower, and the annual risk of sudden cardiac arrest has been variably reported to be 0.35% to 1.7%.[47-49] Although controversial, for asymptomatic individuals with a spontaneous

type 1 ECG, an EPS should be considered (class IIa indication). In asymptomatic patients with an induced type 1 ECG, an EPS is justified in those with a family history of SCD suspected to be caused by Brugada syndrome (class IIb indication). Induced type 1 ECG, in the absence of a family history of SCD, provides diagnostic data only, and close monitoring is recommended. However, it is noteworthy that a recent meta-analysis has raised questions about the usefulness of EPS for risk stratification in Brugada syndrome.[50]

Discussion Case 3

The right precordial leads in the ECG demonstrated ST elevation suggestive of a type 2 Brugada ECG pattern. Genetic testing may prove to be the best diagnostic test in the future, but it is not widely available at present, and mutations are only demonstrated in a minority of patients. Treadmill testing is not useful in this syndrome. Challenge with sodium channel blockade (most commonly intravenous procainamide in North America) can unmask the type 1 pattern, confirming the diagnosis of Brugada syndrome. EPS with pacing maneuvers alone provides little "diagnostic" information, but it may be useful as a prognostic test, although, as noted above, this remains controversial. Thus procainamide infusion is the best option.

An echocardiogram was also performed in this patient to eliminate underlying myocardial disease as a cause for the ECG abnormalities. Some centers would also consider cardiac magnetic resonance imaging (MRI) to exclude arrhythmogenic right ventricular dysplasia (ARVD) (see following section). In this case, the echocardiogram was completely normal, and challenge with intravenous procainamide induced diagnostic type 1 ECG pattern. An EPS was performed and induced nonsustained polymorphic VT but no sustained arrhythmia. Nonetheless, the family history of the father's SCD at or near the age of 40 years was cause for concern, and an ICD was offered to this patient.

Without a family history of SCD, an ICD would not be recommended to this patient without evidence of spontaneous type 1 pattern, even in the setting of an inducible type 1 pattern with procainamide. This group of patients appears to remain at low risk for death caused by arrhythmia.[43,50] In all circumstances, a clear discussion with patients, especially individuals who are highly risk averse, is required to delineate individual tolerances for small risks of arrhythmic events and ICD-related events.

Short QT Syndrome

The finding of a short Q-T interval on routine ECG should raise the possibility of congenital short QT syndrome (SQTS)—a recently described familial disorder characterized by marked shortening of the Q-T interval (QTc generally <340 ms) and narrow, high-amplitude T waves. SQTS is a rare condition, and its true prevalence is unknown. In several small series, the inheritance has been found to be autosomal dominant, and patients are at an increased risk of both atrial and ventricular arrhythmias, predominantly AF and SCD secondary to VF.[51-53] The genetic abnormalities described for SQTS, so far, involve genes similar to those implicated in LQTS and Brugada syndrome, with gain-of-function mutations in K^+ channel genes and loss-of-function mutations in L-type calcium (Ca^{2+}) channels.[54-57]

The difficult clinical question is: Is it possible to distinguish a "pathologically short QTc" from an "abbreviated QTc at the low end of the normal range"? The reported QTc among patients diagnosed with SQTS in the published literature has been less than 340 ms, often less than 300 ms. In comparison, two community surveys have addressed the "normal range" of QTc. In a study of more than 12,000 healthy young individuals undergoing routine ECG, the shortest QTc was 335 ms, and no SCDs occurred in patients with QTc in the lowest 0.5% (335 to 360 ms). This suggests little overlap between SQTS and the normal range.[58,59] However, in a separate community survey of more than 10,000 middle-aged Finnish participants, the shortest QTc was 305 ms, and the prevalence of a QTc less than 340 ms was 0.4% and less than 320 ms was 0.1%, suggesting some degree of overlap. Reassuringly, again, no SCDs occurred in individuals with a QTc less than 340 ms.

At present, few data are available to guide the risk stratification and management of patients with suspected SQTS. ICDs have been suggested as first-line therapy in patients with a personal or family history of SCD associated with SQTS.[53,60]

Early Repolarization Abnormalities

Early repolarization changes are present in 2% to 5% of the population, being more common in young athletic individuals. The ECG shows variable elevation of the J-point with or without associated slurring or notching. These changes are most commonly seen in the anterior precordial leads but may occur in other leads and show circadian variation.[61] Although such changes are generally understood to be benign, a recent study from Haissaguerre et al described an increased incidence of early repolarization changes in the inferolateral leads in survivors of cardiac arrest caused by idiopathic VF compared with controls.[62] Although, the findings of this study are provocative, the sensitivity, specificity, and predictive accuracy of this finding have yet to be established. Many asymptomatic individuals have early repolarization changes and yet are extremely unlikely to have increased risk. Therefore the abnormality may be an important diagnostic sign in high-risk patients with a history of unexplained syncope or a family history of SCD, but the same observation in an otherwise completely healthy patient should not cause alarm or warrant further investigation.[61]

Asymptomatic Arrhythmias

Ventricular Ectopy

Case 4

A 49-year-old man has Holter monitoring performed because of palpitations. No symptoms are noted in the patient's diary, but asymptomatic ectopy similar to that seen on the 12-lead ECG in Figure 49-4 is recorded. He is referred for further assessment.

The most appropriate next step would be to:

1. Reassure the patient by not scheduling a follow-up.
2. Schedule an echocardiogram.
3. Schedule a cardiac MRI scan.
4. Schedule coronary angiography.

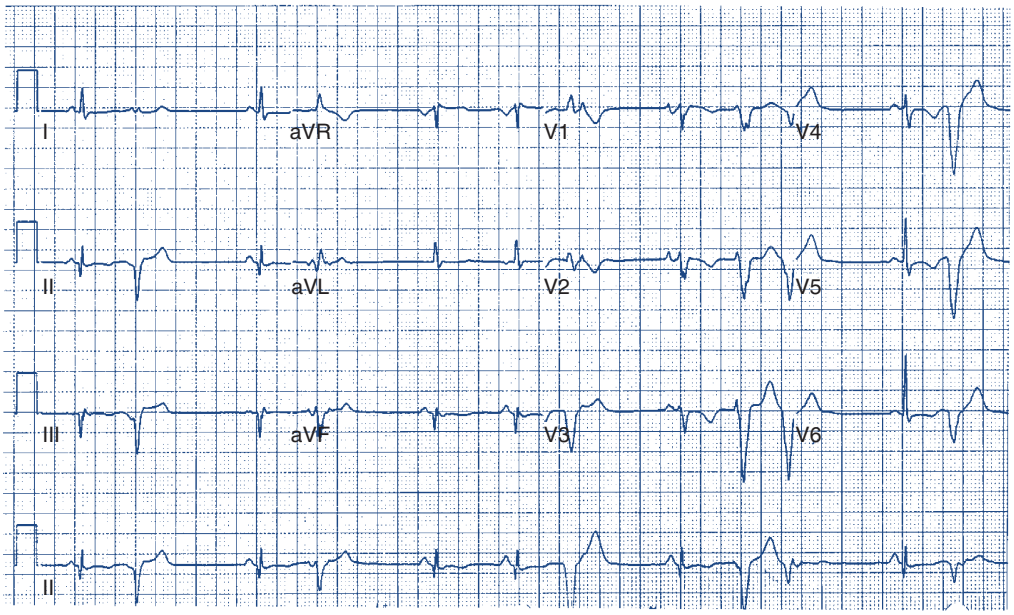

FIGURE 49-4 Ventricular ectopy.

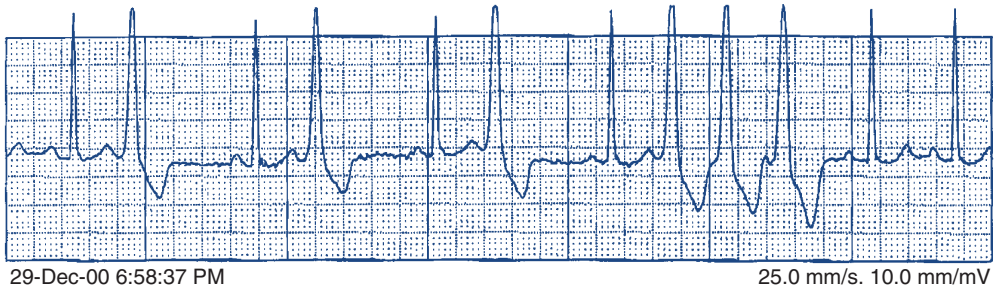

FIGURE 49-5 Ventricular premature beats from the right ventricular outflow tract as recorded in lead II from a Holter monitor.

ECGs and Holter monitoring frequently record unexpected ventricular ectopy as isolated ventricular premature beats (VPBs) or runs of nonsustained VT. It is imperative to know the setting in which this occurs. Frequent ectopy and nonsustained VT are risk factors for SCD in the setting of established ischemic heart disease. However, ectopy in the presence of a structurally normal heart is benign and generally requires no further therapy beyond reassurance. As such, the most relevant question in the patient with such ectopy generally is: "What is the status of ventricular function?"

Ectopy in the Setting of a Structurally Normal Heart

Forms of benign VT found in patients with a structurally normal heart have been described to occur in both the left and right ventricles—called *idiopathic VT*. Some forms of idiopathic VT present with repetitive bursts of nonsustained monomorphic ectopy, especially from the right ventricular outflow tract (RVOT). The ectopy has a characteristic left bundle branch block (LBBB) morphology with large-amplitude R waves in the inferior leads with T-wave inversions. Figure 49-5 shows VPBs from the RVOT as recorded in lead II from the Holter monitor. Idiopathic forms of left ventricular tachycardia have also been recognized and can produce asymptomatic ectopy.[63,64] Patients with asymptomatic idiopathic ectopy need no further investigations or therapy.

Arrhythmogenic Right Ventricular Dysplasia

The right ventricle can occasionally be the source of serious arrhythmia that presents as asymptomatic ectopy, and this needs to be distinguished from idiopathic forms of ectopy, including RVOT tachycardia. ARVD is characterized by palpitations, syncope, and SCD caused by ventricular arrhythmias in the setting of pathologic fibro-fatty infiltration of the right ventricle.[65] It is most commonly diagnosed in young males, although cases at all ages and in both genders have been described. The disease is regarded as a progressive cardiomyopathy that may also affect the left ventricle, although the septum is typically spared. Both familial and sporadic forms of ARVD have been described, with the former usually displaying an autosomal dominant inheritance. ARVD may rarely be a component of the autosomal recessive

Naxos disease, which is associated with hyperkeratosis of the palms and soles and woolly hair. ARVD is understood to be a disorder of cell adhesion and relates to mutations of genes that encode desmosomal proteins.[66]

In spite of considerable controversy regarding the sensitivity and specificity of testing, the diagnosis of ARVD is currently based on family history and the presence of ECG and structural abnormalities.[65] The ECG in sinus rhythm may demonstrate abnormalities related to delayed right ventricular activation such as QRS prolongation, RBBB, a distinct low-frequency, a low-amplitude wave after the QRS (ε-wave), and T-wave inversion in the right precordial leads. Late potentials on the signal-averaged ECG are also seen in ARVD. Structural abnormalities can be found on echocardiography, right ventricular angiography, nuclear imaging, and MRI. Invasive EPS with electroanatomic mapping may identify areas of low-voltage electrograms, and programmed ventricular stimulation may induce one or more types of sustained monomorphic VT and less commonly VF. Finally, myocardial biopsy with immunohistochemical analysis and genetic testing may also be considered.[67]

ICDs are frequently prescribed for patients with ARVD and are generally recommended to patients with documented sustained VT or VF and to those otherwise deemed as "high risk," including those with unexplained syncope, extensive or left ventricular involvement, or a malignant family history.[34] EPS does not appear to be useful for risk stratification.[68] Exercise restriction should also be discussed, and antiarrhythmic drug treatment and RF ablation are adjunctive measures for reducing the frequency of ventricular arrhythmias.[69]

When considering the evaluation of a patient with ventricular ectopy of LBBB morphology, historical features need to be carefully considered, especially when the ectopy does not arise from the RVOT. Major and minor Specific Task Force diagnostic criteria based on the arrhythmia, family history, ECG criteria, imaging, and histopathology of tissue have been created for ARVD.[65] In patients with ARVD and a single risk factor for SCD, it is reasonable to consider ICD therapy (class IIa recommendation).[68,70]

Discussion Case 4

The baseline 12-lead ECG has features of ARVD with terminal low-amplitude voltage seen best in leads V1 to V3 (major criterion). Accompanying T-wave inversions are also seen (minor criterion). The ectopy has an LBBB morphology with left superior axis, which suggests a source from the right ventricular apex (minor criterion). It is clearly not from the RVOT and therefore cannot be immediately dismissed as benign. Imaging of the right ventricle is required. Echocardiography is highly variable for imaging the right ventricle and, in general, is not of sufficient quality to diagnose ARVD. In experienced hands, cardiac MRI is the best imaging modality for ARVD, and diagnostic criteria have been developed.[65] Coronary angiography will not provide useful information. Any coronary lesions would have to be interpreted as incidental.

In this case, an echocardiogram suggested a dilated hypokinetic right ventricle. A rest and exercise multi-gated acquisition (MUGA) scan confirmed these changes, and an MRI scan demonstrated an enlarged right ventricle with evidence of fibro-fatty infiltration consistent with ARVD (major criterion). In the absence of high-risk features, the patient was monitored closely.

Atrial Fibrillation and Other Supraventricular Arrhythmia

Case 5

A 59-year-old asymptomatic man presented for preoperative assessment with the following ECG (Figure 49-6). An echocardiogram demonstrated reduced left ventricular function and an estimated ejection fraction of 35%.

The appropriate first management would be to schedule:

1. Direct current (DC) cardioversion.
2. Pharmacologic cardioversion.
3. Pharmacologic rate control.
4. AV nodal ablation and pacemaker implantation.

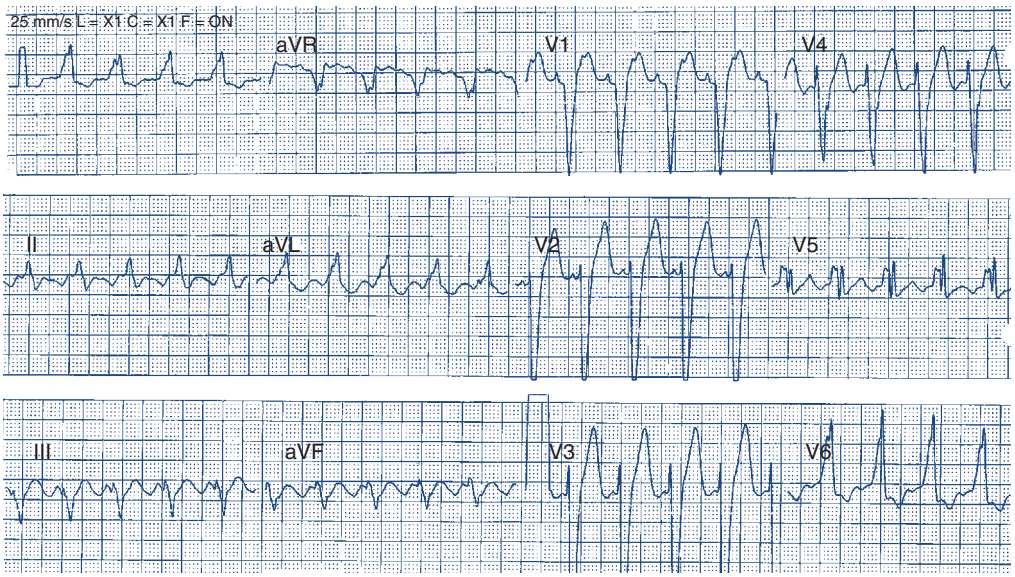

FIGURE 49-6 Atrial flutter.

Not infrequently, patients are found to have paroxysmal or persistent AF of unknown duration and are unaware that any dysrhythmia is present.[71] A similar presentation can occur in atrial flutter (see Figure 49-6). Several issues need to be addressed in such patients. These relate to decisions about occult tachycardia-induced cardiomyopathy, anticoagulation, and possible cardioversion.

Tachycardia-Induced Cardiomyopathy

The syndrome of tachycardia-induced cardiomyopathy has been well described in the setting of poorly controlled AF.[72,73] Importantly, it is usually reversible if rate control can be achieved.[72,73] Assessment of left ventricular function should be made in all such patients and aggressive rate control initiated in patients with impairment of left ventricular function. Repeated Holter monitoring can be performed to ensure adequate rate control, ideally below 100 beats/min except for periods of exercise. For those patients with persistent left ventricular dysfunction and failure of pharmacologic rate control, DC cardioversion, catheter ablation of atrial flutter or AF, or AV nodal ablation and permanent pacemaker insertion could be considered.

Anticoagulation

Decisions regarding the use of warfarin or aspirin for thromboembolic prophylaxis should be based on thromboembolic risk. The $CHADS_2$ score (***c***ongestive heart failure, ***h***ypertension, ***a***ge ≥75 years, and ***d***iabetes mellitus, each given 1 point; and a past history of transient ischemic attack or stroke given 2 points) is widely used for evaluating thromboembolic risk in those with nonvalvular AF.[74] Warfarin is generally recommended to patients with a $CHADS_2$ score of 2 or above. Importantly, the need for thromboembolic prophylaxis in asymptomatic patients with AF as well as in those with atrial flutter should be determined using the same guidelines.

Cardioversion

Irrespective of the pressure from patients or referring physicians to perform DC cardioversion in asymptomatic patients, no evidence supports the claim that DC cardioversion ensures a better prognosis or reduced risk of stroke in sinus rhythm.[75] Some patients with seemingly asymptomatic AF are unaware that they have had a reduction in functional status until sinus rhythm has been returned. For this reason, consideration is frequently given to perform at least a single cardioversion in minimally symptomatic patients. In general, maintenance of sinus rhythm is known to depend on the duration of AF as well as on left atrial dimension. The former is frequently difficult to assess in asymptomatic patients. Nonetheless, an echocardiographic assessment of left atrial dimension may give some insight into the likelihood of long-term maintenance of sinus rhythm. If a patient sees no improvement in functional status during sinus rhythm, repeated cardioversion is truly unwarranted.

Incessant Supraventricular Tachycardias

A small group of arrhythmogenic substrates allow for relatively slow but frequently incessant SVTs and tachycardia-induced cardiomyopathy.[76] Patients may have a permanent form of junctional reciprocating tachycardia because of a slowly conducting accessory pathway or nodal pathway or may have an incessant atrial tachycardia.[72,77] In the current era, RF ablation forms the first-line therapy in such patients. Alternatively, medication can be used, but maintenance of sinus rhythm is paramount for the improvement of left ventricular function. However, the demonstration of normal left ventricular function argues against any intervention in the truly asymptomatic individual with frequent paroxysmal SVT.

Discussion Case 5

The ECG demonstrates typical atrial flutter with 2:1 conduction and LBBB morphology in the context of asymptomatic left ventricular dysfunction. While it is impossible to know, a primary suspect for causation is tachycardia-induced cardiomyopathy. As a first measure, atrioventricular (AV) nodal blocking agents can be initiated as left ventricular function is known to improve with this measure alone. In the case of atrial flutter, adequate rate control is frequently compromised by even moderate activity. Alternatively, DC cardioversion can be performed after confirmation of low thromboembolic risk with trans-esophageal echocardiography or after 3 to 4 weeks of therapeutic anticoagulation. However, typical atrial flutter can be eliminated with standard ablation techniques, and this is considered the first-line therapy.

Digoxin and small doses of atenolol failed to provide adequate ventricular rate control. The patient underwent an EPS that demonstrated counterclockwise isthmus-dependent atrial flutter. Following successful ablation and resumption of sinus rhythm, left ventricular function returned to normal as documented by echocardiography 3 months later.

Asymptomatic Atrioventricular Nodal and His-Purkinje Disease

Bradyarrhythmias and indications for pacing under such circumstances are discussed elsewhere. Nonetheless, some bradyarrhythmias may present with asymptomatic ECG abnormalities and therefore are briefly discussed here.

Case 6

An otherwise healthy 54-year-old woman was referred for evaluation of an asymptomatic Holter monitor recording (Figure 49-7). Before referral, a diagnosis of Mobitz II second-degree AV block was made, and the patient was informed that she may require a permanent pacemaker. Is this correct?

Atrioventricular Block

Although unusual in the adult population, truly asymptomatic complete heart block is occasionally seen. Older patients with progressive His-Purkinje degeneration as the etiology tend to report symptoms of exercise intolerance or exertional dyspnea on directed questioning. The American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) Guidelines for Device Implantation state that awake, asymptomatic patients with third-degree AV block with documented asystole 3 seconds or more, an escape rate less than 40 beats/min, or an escape rhythm that is below the AV node have a class I indication for pacing.[70] Asymptomatic third-degree AV block with faster average ventricular rates is considered a class IIa indication for pacing.

Asymptomatic type II second-degree AV block can occur at the level of the AV node or below the AV node within the His-Purkinje system. Block at the level of the AV node or within the His bundle (intra-His) produces a narrow QRS, whereas block below the His bundle most often produces a wide QRS. This is an

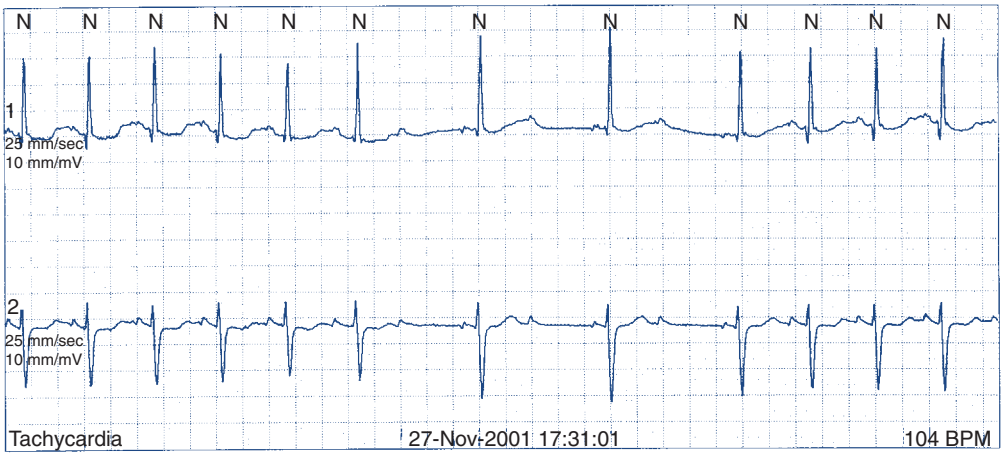

FIGURE 49-7 Atrioventricular block due to atrioventricular nodal disease.

important distinction because block at the level of the AV node does *not* require pacing. Associated bundle branch block or bifascicular block may be helpful to determine the level of block. Occasionally, invasive EPS may be required. The ACC/AHA/HRS Guidelines recognize that asymptomatic type II second-degree AV block with a wide QRS is classified as a class I indication for pacing. Type II second-degree AV block with a narrow QRS has been classified as a class IIa indication for pacing if block at the level of the node cannot be excluded, although the decision to pace should be highly individualized.[70]

Discussion Case 6

On close inspection, a 2:1 block is seen. It is important to determine the level of block in such cases—at the level of the AV node or in the His-Purkinje system. As noted in the earlier discussion, the importance is more than academic. In this case, the QRS complexes are narrow throughout. The P-R interval of the last conducted beat before the block is substantially longer than that of conducted beats following the dropped beats. This suggests that the 2:1 block is Mobitz I and likely at the level of the AV node. This is very common during sleep in healthy individuals. No pacemaker was inserted in this patient. The presence of distal conduction disease (bundle branch block, bifascicular or trifascicular block) suggests that the block is below the level of the AV node (Mobitz II) and that pacing may be indicated despite the asymptomatic nature of the abnormality.[70]

Among patients with asymptomatic bifascicular and trifascicular disease, a small incidence of progression to second- or third-degree AV block is seen.[78] However, no single clinical or laboratory variable is predictive of the progression of AV block. Therefore asymptomatic bundle branch block alone and bifasicular or trifasicular block are not indications for pacing. Asymptomatic bundle branch block may be the first indication of insidious cardiac disease. As such, patients should be evaluated noninvasively with respect to cardiac size and function. In a similar vein, monitoring, especially at night, can record asymptomatic sinus bradycardia or pauses. Unless these are associated with symptoms, pacing is not required.[70]

Conclusion

Abnormalities detected on the ECG in asymptomatic individuals will always remain a challenge. It is important to be certain that the natural history of the asymptomatic condition be considered in the context of possible emotional distress and the potential for morbidity from further investigations and therapy. The risk associated with the abnormality must be seen in this light, as it is "difficult to make an asymptomatic individual feel better."

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CHAPTER 50

Arrhythmias in Women

Anne B. Curtis and Abel Rivero

Introduction

It is well recognized that significant gender-related differences exist in the clinical presentation, course, and prognosis of many cardiovascular disorders, including cardiac arrhythmias. Although the mechanisms responsible for these differences remain largely unknown, it is important for health care providers to consider these differences in the diagnosis and treatment of arrhythmias to provide gender-specific optimal care to their patients. In this chapter, the currently available literature on gender-related differences in electrocardiography, cardiac electrophysiology, and arrhythmias is reviewed.

Gender-Related Differences in Electrocardiography and Cardiac Electrophysiology

Heart Rate and Heart Rate Variability

In 1920, Bazett showed that women have higher resting heart rates than do men.[1] This observation was confirmed in 1989 by the Coronary Artery Risk Development in Young Adults (CARDIA) study, in which the average heart rate in women was 3 to 5 beats/min faster than in men. This gender-related difference in heart rate is present as early as childhood, but the etiology of this disparity is unclear. Potential explanations include differences in exercise tolerance, autonomic modulation, and the intrinsic properties of the sinus node. It has been shown that this difference persists even after sympathetic and parasympathetic blockade with propranolol and atropine, which suggests an intrinsic difference in the sinus node itself as the etiology. Women have also been found to have shorter sinus node recovery times after overdrive pacing.

Gender-related differences are also present in heart rate variability. Several studies of patients who underwent 24-hour Holter monitoring showed that women have a smaller low-frequency component and a smaller low-frequency to high-frequency ratio over the range of heart rate variability, which suggests a greater parasympathetic influence in female hearts.[2] This finding is probably related to hormonal influences on cardiac autonomic modulation. Postmenopausal women who are not on estrogen replacement therapy have lower baroreflex sensitivity and smaller low-frequency and high-frequency spectral components of heart rate variability compared with age-matched men or with women on estrogen replacement therapy. It is possible that these differences are related to the worse outcomes experienced by women after myocardial infarction (MI), since reduced baroreflex sensitivity and a reduced low-frequency component of heart rate variability are associated with an increased risk of life-threatening arrhythmias after MI.

Atrioventricular Conduction Properties

Gender-related differences in atrioventricular (AV) conduction have been reported in several studies. Women have shorter P-R, atrial-His (AH), and His-ventricular (HV) intervals, as well as shorter AV block cycle lengths than do men. The incidence of dual AV nodal pathways is similar in men and women. Among patients with dual AV nodal pathways and symptomatic AV nodal re-entry tachycardia (AVNRT), women have been found to have shorter slow-pathway effective refractory periods (ERP) and tachycardia cycle lengths but similar fast-pathway ERPs compared with men.

Amplitude and Duration of the QRS Complex

QRS complexes of shorter duration and lower amplitude have been reported in women. These differences remain after correcting for cardiac mass, body weight, and disease states such as ventricular hypertrophy. The accuracy of traditional electrocardiographic criteria for the diagnosis of left ventricular hypertrophy (QRS voltage, QRS duration, and the product of QRS voltage and duration) is significantly lower in women than in men.

Differences in Repolarization

Women have nonspecific repolarization changes more frequently than do men, according to an analysis of the electrocardiographic data from 38,000 postmenopausal women who participated in the Women's Health Initiative study. This study revealed that these changes were frequent and could be predictors of cardiovascular events in this population. A wide QRS/T angle, prolonged QRS duration, prolonged QTc interval, and reduced heart rate variability may be predictors of cardiovascular mortality in postmenopausal women.

Q-T Interval and QT Dispersion

Bazett also noted that women have longer Q-T intervals than do men on the surface electrocardiogram (ECG).[1] However, in a normal population, boys and girls have similar corrected Q-T intervals.[3] At the time of puberty, the average male QTc interval shortens, leaving adult women with longer QTc intervals

Table 50-1 Principal Gender-Related Differences in Electrocardiography and Cardiac Electrophysiology

ELECTROPHYSIOLOGICAL PARAMETER	DESCRIPTION
Heart rate	Higher in women
Heart rate variability	Decreased in postmenopausal women
Sinus node recovery time	Shorter in women
AV conduction properties	
P-R, A-H, H-V intervals	Shorter in women
AV block cycle length	Shorter in women
Incidence of dual AVN pathways	Similar in both genders
Slow pathway effective refractory period	Shorter in women
QRS complex	Shorter duration and lower amplitude in women
Nonspecific repolarization changes	More frequent in women
QTc interval	Longer in post-pubertal women
QT dispersion	Lower in women

AV, Atrioventricular; *AH,* atrial-His; *HV,* His-ventricular; *AVN,* AV nodal.

compared with adult men. As men age, their QTc intervals gradually increase, and by age 65 years, their QTc intervals are again comparable with those in women.

Several studies have implicated androgens (specifically testosterone) rather than estrogens in the etiology of this age-dependent gender-related difference in QTc intervals. For example, castrated men have longer repolarization times (JTc interval) compared with noncastrated men; women with virilization syndrome have shorter QTc intervals compared with castrated men and healthy women; and athletes who take large doses of anabolic steroids have shorter QTc intervals. Another study found no effect of hormone replacement therapy on the QTc intervals of postmenopausal women.

QT dispersion—the difference between the longest and the shortest Q-T intervals on a 12-lead ECG—is greater in men than in women. Increased dispersion of repolarization correlates with re-entrant–type ventricular arrhythmias, which may explain, in part, the increased risk of sudden cardiac death (SCD) in men compared with women. In contrast, absolute Q-T interval prolongation may result in arrhythmias related to early afterdepolarizations (EADs), specifically polymorphic ventricular tachycardia (torsades de pointes), the risk of which is higher in women. The principal gender-related differences in electrocardiography and cardiac electrophysiology are summarized in Table 50-1.

Specific Arrhythmias

Supraventricular Tachycardias

Significant gender-related differences exist in the prevalence and clinical course of various supraventricular tachycardias (SVTs). For example, AVNRT has a 2:1 female-to-male predominance, while AV re-entrant tachycardia (AVRT) and the Wolff-Parkinson-White (WPW) syndrome are twice as common in men compared with women. Atrial fibrillation (AF) and ventricular fibrillation (VF) also occur more often in men with WPW syndrome. The gender-related differences in AV conduction properties mentioned above may contribute to the differences in gender distribution observed in patients with AVNRT and those with ventricular pre-excitation. Despite these differences in SVT, radiofrequency (RF) catheter ablation is equally efficacious in men and women.

Evidence of hormonal effects on the triggers and timing of SVTs is also present. In premenopausal women with a history of SVT, the number of SVT episodes and the symptoms vary cyclically, being more pronounced during the luteal phase of the menstrual cycle when progesterone levels are elevated. Another study has reported a perimenstrual clustering of SVT episodes and a cyclical variation in SVT inducibility. Some patients who were not inducible during an electrophysiological study (EPS) performed at mid-cycle have been found to be inducible when the study was repeated during menstruation. On the basis of this study, premenopausal women should be asked about any relationship of their SVT to the menstrual cycle, and EPS should be scheduled accordingly to increase the probability of inducibility.

Inappropriate sinus tachycardia, an uncommon SVT characterized by a high resting heart rate and an exaggerated heart rate response to stress, appears almost exclusively in women. Most patients diagnosed with this disorder are women younger than 40 years. The etiology is not fully understood, but it is thought to involve abnormal autonomic regulation of the sinus node or to be related to an immunologic disorder involving cardiac β-adrenergic receptors.

Atrial Fibrillation

A number of studies have noted differences in the presentations, outcomes, and prognoses between men and women with AF. In the Framingham Heart Study, men were found to have a 1.5-fold higher risk of developing AF compared with women. While the prevalence of AF increases with aging in men, it does not change in women. However, because of the overall greater longevity of women, the absolute number of women with AF is greater than that of men in older age groups. Men are also more prone to developing AF after cardiothoracic surgery and to have lone AF, particularly when it is not familial. A recent study found reduced testosterone levels but similar estrogen levels in men with lone AF compared with controls.

In women, valvular heart disease and heart failure are the predominant cardiac diseases associated with AF, while men more commonly have AF in association with ischemic heart disease.[2] Women with paroxysmal AF tend to present with longer episodes and faster ventricular rates. They are also more likely to have cardioembolic complications. Most importantly, AF has been shown to diminish the survival advantage in women, increasing the risk of death regardless of gender (odds ratio [OR], 1.5 for males, 1.9 for females) (Figure 50-1).[4]

The Euro Heart Survey on Atrial Fibrillation recently reported similar gender-related differences. In a population of 5333 patients, women with AF were older and had a lower quality of life, more significant comorbidities, and more symptoms compared with men. Overall, women were treated less aggressively, with fewer cardioversions and catheter ablations, although both genders were prescribed anticoagulation at similar rates. At 1

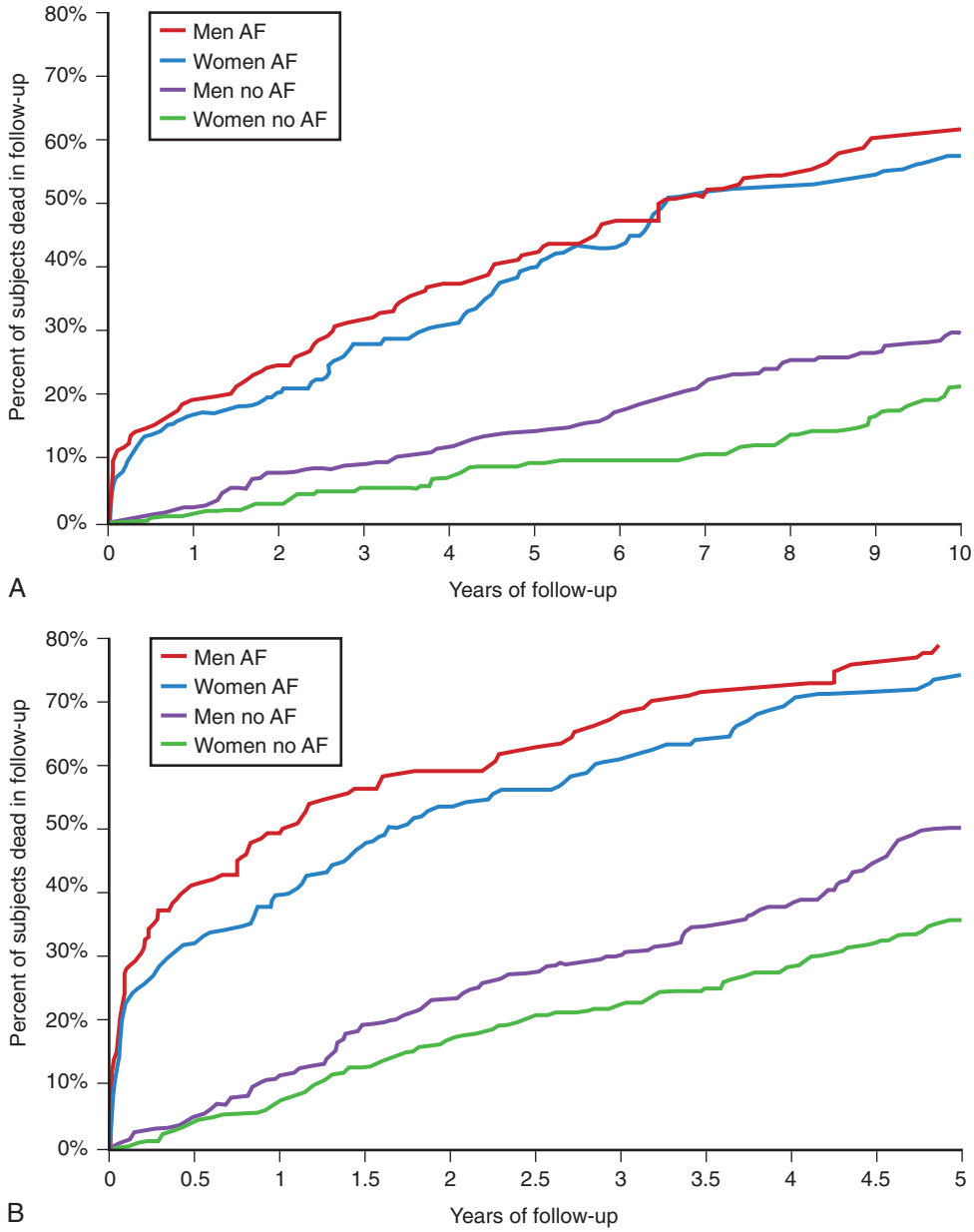

FIGURE 50-1 A, Kaplan-Meier mortality curves for subjects aged 55 to 74 years. A log-rank test gave chi-square values of 42.90 for men ($P < .0001$) and 70.93 for women ($P < .0001$). **B,** Kaplan-Meier mortality curves for subjects aged 75 to 94 years. A log-rank test gave chi-square values of 51.44 for men ($P < .0001$) and 101.51 for women ($P < .0001$). *(From Benjamin EJ, Wolf PA, D'Agonstino RB, et al: Impact of atrial fibrillation on the risk of death: The Framingham Heart Study,* Circulation *98:946–952, 1998.)*

year, women did have a significantly higher rate of stroke (2.2% vs. 1.2%; $P = .011$) and major bleeding events (2.2% vs. 1.3%; $P = .028$). No differences in mortality or heart failure exacerbations were observed.

Although the findings above suggested that a more aggressive treatment approach for women with AF may be warranted, the best way to accomplish this is not readily apparent. Management of thromboembolic risk is difficult in older patients because of the competing risks of stroke and bleeding from anticoagulation.[5] Maintenance of sinus rhythm, an attractive option at first glance, may not be beneficial, as indicated by the results of the AFFIRM trial, in which no difference was shown in survival or quality of life with a rhythm control strategy versus a rate control strategy.[6] In addition, women's greater risk of Q-T interval prolongation and torsades de pointes, as well as the more frequent occurrence of bradyarrhythmias associated with amiodarone use for AF requiring pacemaker insertion, must be recognized when choosing to prescribe antiarrhythmic drugs.

Catheter ablation is an increasingly popular treatment option for patients with AF refractory to medical therapy. Despite the older age, longer history of AF, and greater number of comorbidities in women, AF ablation offers similar acute success rates and complication rates in men and women. At an average of 2 years follow-up, both genders experienced similar percentages of

freedom from arrhythmia (83.1% in women vs. 82.7% in men) in a recent study.

Congenital Long QT Syndrome

Women present with congenital long QT syndrome (LQTS) more often than do men. According to the International LQTS Registry, 70% of patients are female, and female gender itself is an independent risk factor for the development of arrhythmias in congenital forms of LQTS.

Several studies from the International LQTS Registry have shown that this gender-related difference is age dependent (Figure 50-2, *A* to *D*). Locati et al found that before puberty, boys were at higher risk for cardiac events (syncope, cardiac arrest, or SCD). Another study from the same registry found that during childhood, boys who were *LQT1* carriers had a significantly higher risk of cardiac events compared with girls, whereas no gender-related difference existed among those patients who were *LQT2* or *LQT3* carriers. In a more recent analysis from the registry, in which the endpoint of aborted cardiac arrest or SCD was assessed in 3015 children with LQTS, boys were found to have a threefold increase in the risk of these lethal arrhythmias during childhood. Hobbs et al studied 2772 registry patients who were followed up between the ages of 10 and 20 years and found that boys age 10 to 12 years had a fourfold higher risk of SCD compared with girls, but found no significant gender-related difference in the age range of 12 to 20 years (see Figure 50-2, *B*).

Sometime between the end of puberty and the beginning of adulthood, a reversal of gender-related risk occurs. Adult women in the age range of 18 to 40 years have been found to have a 2.7-fold higher risk of aborted cardiac arrest and SCD compared with men (Figure 50-2, *C*). The cumulative probability of aborted cardiac arrest or SCD in this age group is higher among women (11%) than among men (3%).[7] Even after the age of 40 years, when patients with LQTS are expected to have a lower rate of arrhythmias and when the increased prevalence of acquired cardiac diseases should overshadow the effects of LQTS, patients with this entity still experience a high risk for life-threatening cardiac events. This was recently shown by Goldenberg et al, who studied 2759 subjects from the registry and found that the hazard ratio (HR) for affected (QTc >470 ms) individuals versus unaffected (QTc <440 ms) individuals for aborted cardiac arrest or SCD among patients between the ages of 40 and 60 years was 2.65. In this age group, women are affected by a marginally but significantly higher rate of aborted cardiac arrest and SCD compared with men (Figure 50-2, *D*).[7] The difference in the timing of events

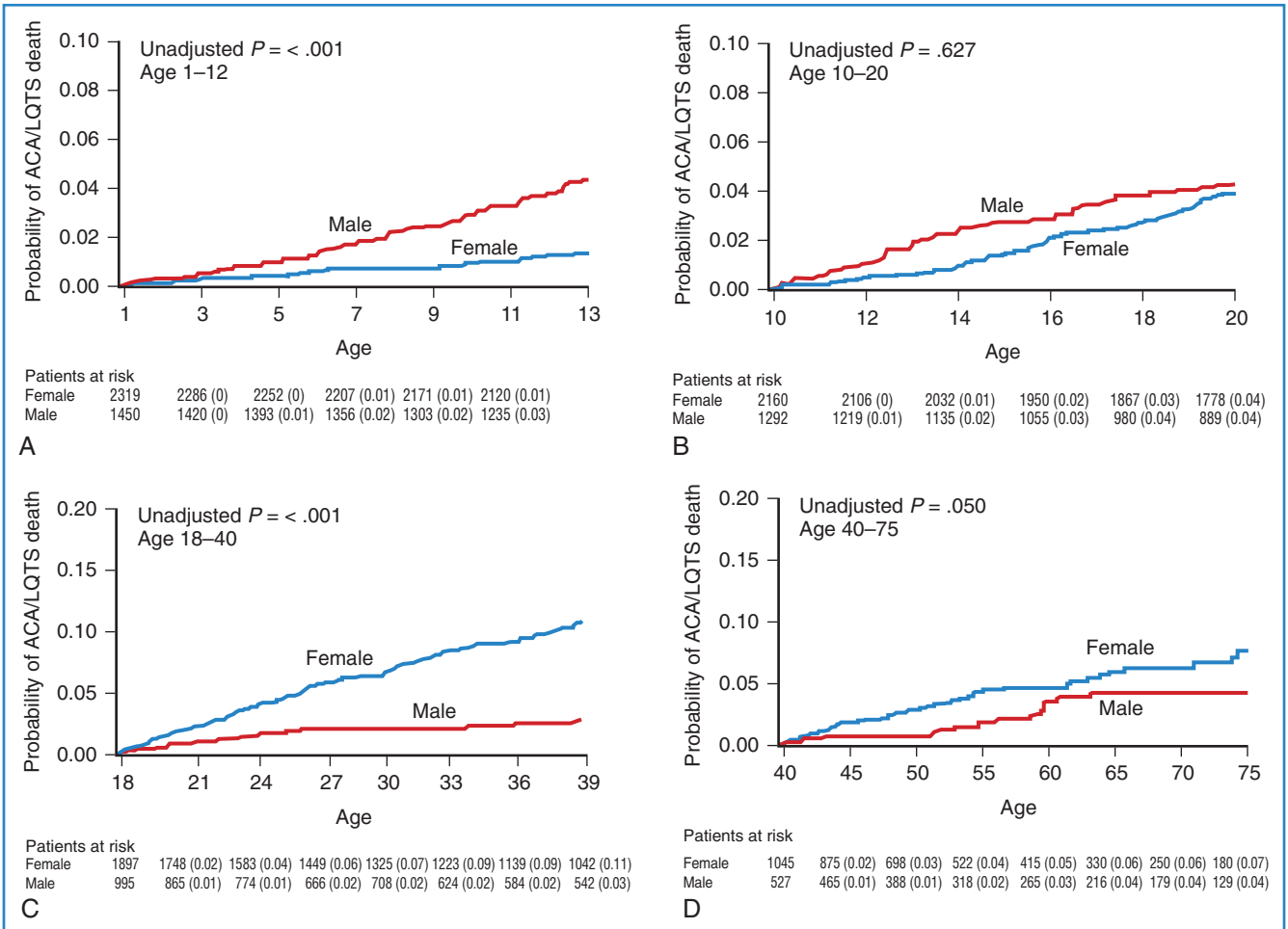

FIGURE 50-2 Risk of aborted cardiac arrest (*ACA*) or sudden cardiac death by gender during childhood (**A**), during adolescence (**B**), during adulthood (**C**), and after age 40 years (**D**). *(From Goldenberg I, Zareba W, Moss AJ: Long QT syndrome,* Curr Probl Cardiol *33[11]:629–694, 2008.)*

is likely related to the shortening of Q-T intervals in boys after puberty, as discussed earlier. In patients carrying the common *LQT1* genotype with mutations that impair the slowly activating delayed rectifier potassium (K^+) current (I_{Ks}), 79% of lethal ventricular tachyarrhythmias are associated with exercise and faster heart rates. Since boys tend to perform more intense physical activities compared with girls, they could be exposed to a greater risk of arrhythmic events during childhood. After puberty, testosterone shortens the QTc interval in boys, whereas estrogens may modify the expression of K^+ channels and have a dose-dependent blocking effect on I_{Ks}. These hormonal influences provide relative protection to postpubertal boys and to men, whereas they predispose female patients to lethal arrhythmias, particularly during menses and pregnancy.[7]

Acquired Long QT Syndrome

Acquired LQTS is more common than congenital LQTS, and women are more frequently affected than are men. Acquired LQTS is usually seen with electrolyte abnormalities or with the use of certain drugs that prolong ventricular repolarization and thus increase the risk for developing torsades de pointes, VF, and SCD. Drugs that are associated with acquired LQTS include many antiarrhythmic drugs such as sotalol, dofetilide, and, rarely, amiodarone, antimicrobials, antihistamines, and psychotropic drugs.

Irrespective of comorbidities such as coronary artery disease (CAD), rheumatic heart disease, left ventricular dysfunction, underlying arrhythmia, or baseline QTc and despite the fact that they account for a much lower percentage of antiarrhythmic drug prescriptions, women comprise the majority of reported cases of antiarrhythmic-induced torsades de pointes (up to 70%). Several studies have shown that women have a higher risk for developing torsades de pointes with administration of prenylamine, quinidine, sotalol, and ibutilide. These findings show that women are more likely to develop torsades de pointes from type IA and type III antiarrhythmic medications.

As noted above, some non-antiarrhythmic medications have also been shown to increase the risk of acquired LQTS and torsades de pointes. The majority of tachyarrhythmic events associated with probucol, terfenadine, and erythromycin have been reported in women.

Mechanisms

As previously discussed, female gender is an independent risk factor for the development of torsades de pointes in both congenital and acquired LQTS. The mechanisms responsible for these gender-related differences are not completely understood, but several recent studies have started to shed light on this topic. For example, it was recently found that LQTS alleles are more frequently transmitted to daughters than to sons.

Sex hormones contribute to these gender-related differences via genomic and nongenomic pathways. They appear to have a direct effect on ion channel densities via intracellular androgen and estrogen receptors in cardiomyocytes. Animal studies have shown that sex hormones have a modulatory role on the level of messenger ribonucleic acid (mRNA) in cardiac calcium (Ca^{2+}) and K^+ channels. However, these hormone-dependent differences in the expression and density of ion channels are small compared with the large differences observed in clinical studies, and they may only partially explain the gender-related differences in ventricular repolarization and arrhythmias.

Several actions of gonadal steroids that are too rapid to be compatible with transcriptional mechanisms have been identified (nongenomic actions). Testosterone rapidly shortens the action potential duration (APD) in guinea pig ventricular myocytes through enhancement of I_{Ks} and suppression of L-type Ca^{2+} currents ($I_{Ca,L}$) without modifying rapidly activating delayed rectifier K^+ currents (I_{Kr}).[8] This phenomenon occurs at physiological concentrations seen in men and is mediated by a testosterone receptor and by sequential activation of several kinases that culminate in the activation of endothelial nitric oxide synthase and nitric oxide production (Figure 50-3). The nongenomic regulation of these two currents by testosterone is a novel regulatory mechanism of cardiac repolarization, which may contribute, at least in part, to gender-related differences in QTc intervals and susceptibility to drug-induced arrhythmias.

The pharmacokinetics of I_{Kr} blockers may also play a significant role in the prevalence of drug-induced QTc prolongation and torsades de pointes in women (Figure 50-4). Since major binding sites to I_{Kr} are intracellular, gender-related differences in the activity of membrane transporters and in recently discovered myocardial cytochrome P450 enzymes may explain the predisposition of women to drug-induced LQTS and torsades de pointes. Studies have shown that many compounds that are cytochrome P (CYP) substrates are also able to bind to I_{Kr}. Sex hormones have a direct effect on hepatic CYP expression. A greater metabolic capacity has been found in men, whereas women have a slower drug clearance and increased drug levels. It is possible that cardiac CYP may also be modulated by sex hormones and that this may lead to gender-related differences in the cardiomyocyte intracellular concentrations of I_{Kr} blockers and to a higher risk for drug-induced LQTS and torsades de pointes in women.[9]

With the greater risk of Q-T interval prolongation and torsades de pointes from a variety of medications, appropriate caution should be exercised when prescribing such medications to women. In fact, it should be one of the considerations in deciding whether to hospitalize a patient for the initiation of antiarrhythmic drugs, particularly if the indication is treatment of ventricular arrhythmias and structural heart disease is present.

Sudden Cardiac Death

Gender-related differences in SCD have also been reported. An analysis of the Framingham study population revealed that, although the risk of SCD increases steadily over time in both genders, women have a significantly lower incidence of SCD in all age groups—less than half that of men. Before age 45 years, the incidence of SCD is low for both genders, but it doubles with each decade of life, starting 20 years later in women. CAD is the most common underlying cardiovascular disease in these patients. However, almost two thirds of women presenting with SCD have no prior diagnosis of CAD, and women with known CAD experience SCD at one fourth the rate of men. Ninety percent of the cases of SCD in women younger than 65 years of age occur without a prior history of CAD. Another study in SCD survivors also found a much higher prevalence of CAD in men compared with women (80% vs. 45%). Ten percent of the women in this cohort had structurally normal hearts, while 3% of the men did. Overall survival rates were similar between groups.

Several studies have evaluated the clinical characteristics and presentation of SCD in women compared with men. Women with out-of-hospital cardiac arrests present more commonly with

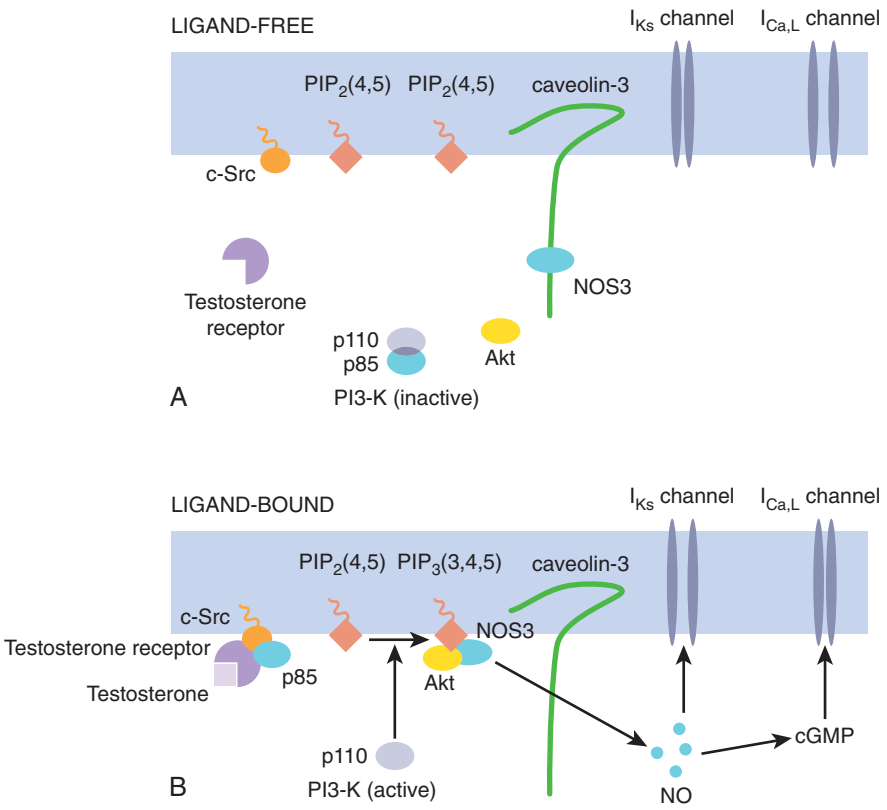

FIGURE 50-3 Proposed schematic model for regulatory mechanism of testosterone on $I_{Ca,L}$ and I_{Ks}. **A,** In the ligand-free condition, NOS_3 interacts with membrane-associated caveolin-3 and is in an inactive state. The rapid effect of testosterone on $I_{Ca,L}$ and I_{Ks} suggests an involvement of the testosterone receptor on the plasma membrane, although molecular identity and the mechanism of plasma membrane localization for the testosterone receptor have not yet been clarified. **B,** When testosterone binds to its receptors, the testosterone receptor, c-Src, and p85 of PI3-kinase form a macromolecular complex, which renders p110 of PI3-kinase free and in an active state, and active PI3-kinase converts PIP2(4,5) to PIP3(3,4,5). Subsequently, PIP3(3,4,5), Akt, and NOS_3 form a complex, which results in NOS_3 activation and NO production. Produced NO then inhibits $I_{Ca,L}$ via a cyclic guanosine monophosphate (cGMP)–dependent manner and enhances I_{Ks} via a cGMP-independent manner. *NO,* Nitric oxide; *cGMP,* cyclic guanosine monophosphate. *(From Bai CX, Kurokawa J, Tamagawa M, et al: Nontranscriptional regulation of cardiac repolarization currents by testosterone,* Circulation *112[12]:1701–1710, 2005.)*

asystole and pulseless electrical activity, whereas men usually present with VT and VF. In a meta-analysis that investigated outcomes among the placebo groups in five pooled multi-center trials of therapy after MI, it was reported that during the first year after MI, women had an equal risk of arrhythmia-related cardiac death versus non–arrhythmia-related cardiac death, whereas men had a greater risk of arrhythmia-related cardiac death in the same time frame. Interestingly, recent animal studies suggested that gonadal hormones influence the susceptibility to ischemia-induced and reperfusion-induced arrhythmias as well as the response to β-adrenergic receptor blockade. Specifically, male sex hormones seem to increase, whereas female sex hormones decrease, the susceptibility to ischemia-induced VT in conscious rats.

A recent analysis from the Second Multi-center Automated Defibrillator Implantation (MADIT II) population found that both women and men with prior MI and decreased ejection fraction manifest increased temporal variability of the Q-T interval. Increased QT variability predicted VT or VF in men but not in women, and decreased coherence between QT variability and HR variability predicted VT or VF in women but not in men.

Brugada Syndrome

Women are less frequently affected by Brugada syndrome. They seem to have a lower risk profile and a better prognosis compared with men. Among these patients, SCD affects men more commonly compared with women, and this gender-related difference is very marked in certain regions such as Southeast Asia, where the ratio of men to women with this syndrome is 8:1. According to a recent prospective, two-center study that included 384 patients with Brugada syndrome, men constituted the majority of patients (70.8%). At inclusion, men had experienced syncope (18% vs. 14%, respectively) or aborted SCD (6% vs. 1%, $P = .04$) more frequently compared with women. Men also had greater rates of spontaneous type 1 ECGs, greater ST-segment elevation, and greater inducibility of VF ($P < .001$ for all). Conversely, conduction parameters and QTc intervals increased significantly more in women in response to sodium channel blockers ($P = .003$ and $P = .001$, respectively). During a mean follow-up of 58 ± 48 months, SCD or documented VF occurred more frequently in men than in women (11.6% vs. 2.8%, $P = .003$). Gender, however, was not an independent predictor of a worse outcome. Previous symptoms were the most important predictors of events in the male

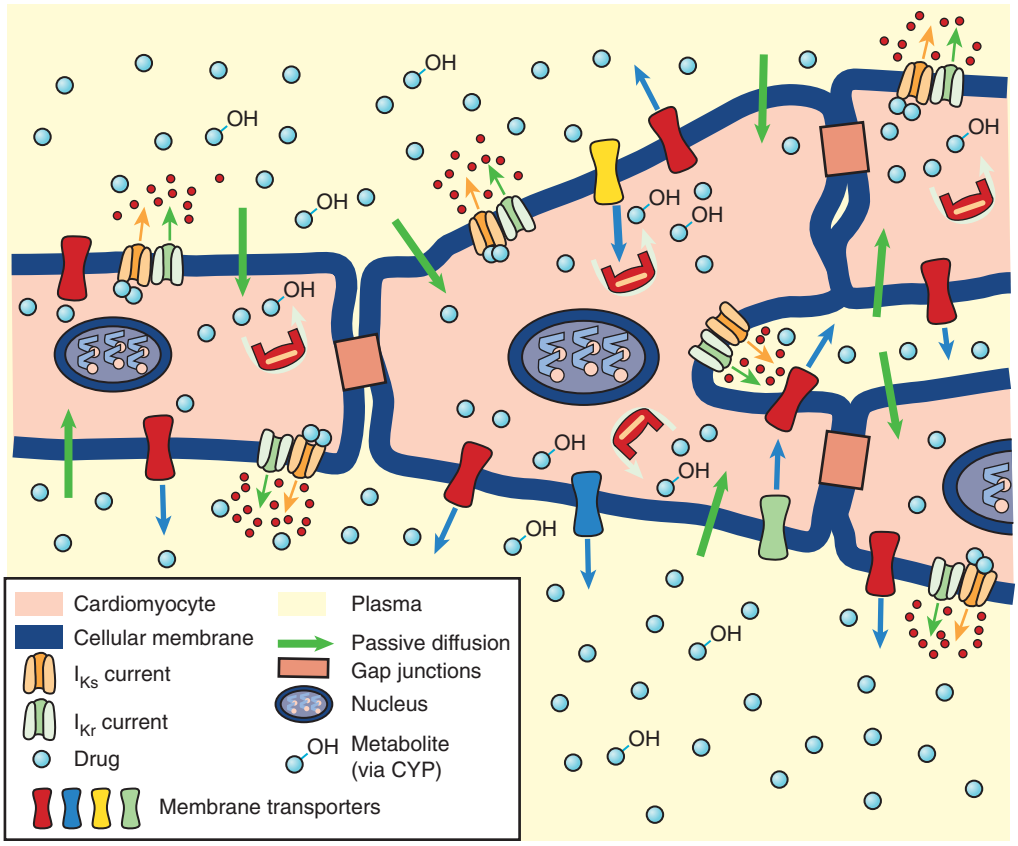

FIGURE 50-4 Pharmacokinetic factors that modulate the occurrence of acquired long QT syndrome. Free concentration of a drug crosses the cellular membrane either by passive diffusion or actively using membrane transporters. A fraction is then either metabolized by cytochrome P (*CYP*) or transported unchanged toward the extracellular milieu by other membrane transporters. The remaining fraction in the intracellular milieu blocks the rapid component of the delayed rectifier potassium current (I_{Kr}). Binding to I_{Kr} is intracellular and induces a decrease in K^+ efflux; this generates a prolongation of the ventricular repolarization and an increase in Q-T interval. I_{Ks}, Slow component of the delayed rectifier potassium current. *(From Hreiche R, Morissette P, Turgeon J: Drug-induced long QT syndrome in women: Review of current evidence and remaining gaps,* Gend Med *5[2]:124–135, 2008.)*

population. In the presence of a very low event rate, a longer P-R interval appeared to be related to a worse outcome in the female population.

Other Ventricular Tachyarrhythmias

Idiopathic right ventricular tachycardia is more prevalent in women. In contrast, idiopathic left ventricular tachycardia (fascicular tachycardia) and arrhythmogenic right ventricular dysplasia are more frequent in men.[2]

Bradyarrhythmias

Women have shorter sinus node recovery times, and yet they are more frequently affected by sick sinus syndrome. Men have longer AV block cycle lengths, and they are twice as likely as women to lack retrograde ventriculoatrial conduction during ventricular pacing. They are more affected by AV block and carotid sinus syndrome compared with women.[2] Even though no gender-related differences in the need for pacemaker therapy exist, some variations in outcome with pacemaker therapy have been reported. In one study, in which 6505 patients were implanted with a cardiac pacing device and followed up for 30 years, women had significantly higher survival rates in all age groups regardless of the indication for pacemaker implantation (sick sinus syndrome, AV block, or AF).

Gender-related differences in cardiac arrhythmias are summarized in Table 50-2.

Gender-Related Differences in Device Therapy

Implantable Cardioverter-Defibrillators: Use and Outcomes

Since women with SCD have CAD less often and present later compared with men, risk stratification and prevention of SCD may be more difficult, and a lower survival benefit from implantable cardioverter-defibrillator (ICD) therapy could be expected in women. On the contrary, accumulating evidence suggests that ICD therapy results in a similar mortality benefit for both genders.

In the Multicenter Unsustained Tachycardia Trial (MUSTT), patients with CAD, nonsustained VT, left ventricular ejection fraction (LVEF) less than 40%, and inducible VT during an EPS were enrolled and randomized to electrophysiology-guided therapy (antiarrhythmic drug therapy, or an ICD if the antiarrhythmic therapy failed) or to a control group. Noninducible patients were not randomized but were followed up prospectively

Table 50-2 Principal Gender-Related Differences in Arrhythmias

ARRHYTHMIA	DESCRIPTION
Inappropriate sinus tachycardia	Occurs almost exclusively in women
AVNRT	More frequent in women (2:1 ratio)
AVRT and WPW	More frequent in men (2:1 ratio)
Atrial fibrillation	
Risk of developing AF	1.5-fold higher in men
Total prevalence	Higher in women
Complications (stroke, bleeding)	Higher in women
Effectiveness of ablation	Similar in both genders
Congenital LQTS	More common in women
SCD in LQTS	More common in boys and adult women
Acquired LQTS	More frequent in women
SCD	More frequent in men; VT and VF are more common in men, whereas asystole and PEA are more common in women
Brugada syndrome	More common in men
Idiopathic right ventricular tachycardia	More common in women
Idiopathic left ventricular tachycardia	More common in men
ARVD	More common in men
Bradycardia	
Sick sinus syndrome	More frequent in women
AV block	More frequent in men
Carotid sinus hypersensitivity	More frequent in men

AF, Atrial fibrillation; *ARVD,* arrhythmogenic right ventricular dysplasia; *AV,* atrioventricular; *AVNRT,* AV nodal re-entrant tachycardia; *AVRT,* AV re-entrant tachycardia; *LQTS,* long QT syndrome; *PEA,* pulseless electrical activity; *SCD,* sudden cardiac death; *VF,* ventricular fibrillation; *VT,* ventricular tachycardia; *WPW,* Wolff-Parkinson-White syndrome.

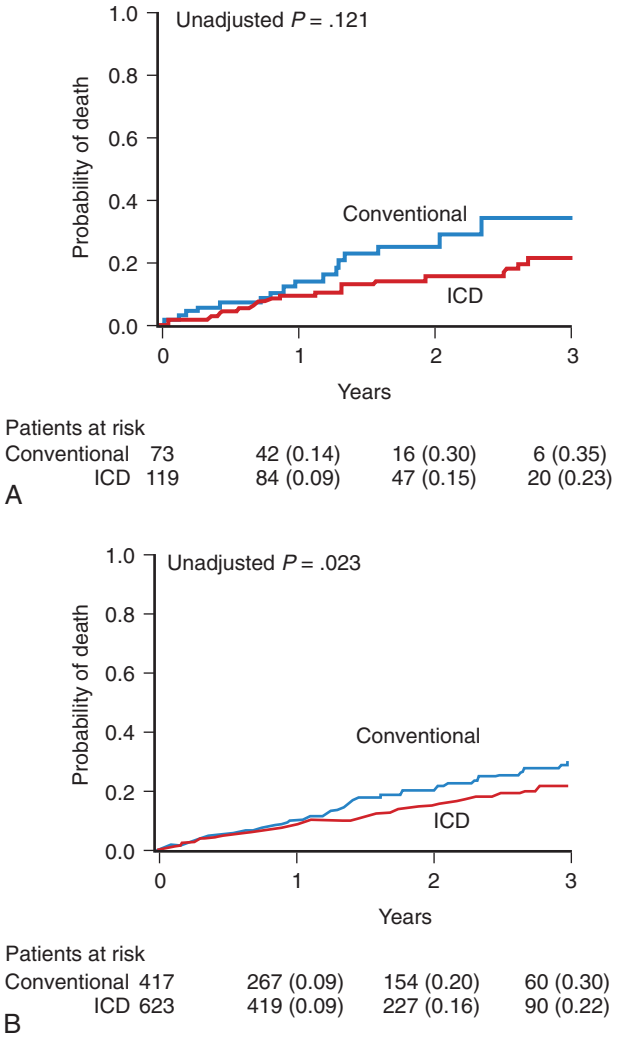

FIGURE 50-5 Cumulative probability of total mortality in implantable cardioverter defibrillator (*ICD*) versus conventionally treated women (**A**) and men (**B**) in the Second Multi-center Automated Defibrillator Implantation (MADIT II) trial. *(From Zareba W, Moss AJ, Hall WJ, et al: Clinical course and implantable cardioverter defibrillator therapy in postinfarction women with severe left ventricular dysfunction,* J Cardiovasc Electrophysiol *16:1265–1270, 2005.)*

in a registry. The female subjects in the trial, who represented only 14% of the total population, were more likely to be older and to have had a recent MI, heart failure, or angina. Despite this, no gender-related differences were observed in event-free survival from SCD. Unfortunately, the small sample size of women limited the power of the trial in detecting any true gender-related difference in outcome. In the MADIT II trial, patients (16% women) with a previous MI and an ejection fraction less than 30% were randomized to conventional medical therapy or to ICD therapy. No significant gender-related differences were seen in the mortality rates in either the control group or the ICD group during an average patient follow-up of 20 months. Both genders demonstrated similar mortality rate reductions from ICD therapy (Figure 50-5). These results confirm that ICDs appear to be safe and effective regardless of gender.[10]

According to recent reports from the American Heart Association, women represent 45% of the total prevalence of CAD and 41% of the incidence of MI and fatal CAD in the United States. However, women appear to be under-represented in ICD clinical trials, averaging only 20% of the study populations (Table 50-3). Furthermore, the reported data on gender-related differences from these trials are limited. The Antiarrhythmics Versus Implantable Defibrillators (AVID) trial reported similar mortality rates in women and men (14.4% vs. 15.5%). The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) demonstrated a significant reduction in mortality with ICD therapy in men but not in women. However, SCD-HeFT did not prospectively identify gender for subgroup analysis.

A retrospective analysis that compiled data from patients with CAD and ICDs over a 10-year period, with an average follow-up of 30 months, showed that women had less sustained VT or VF, fewer days with VT or VF episodes, fewer ICD shocks, and fewer

Table 50-3 Gender Outcomes in Implantable Cardioverter-Defibrillator Clinical Trials

	Enrollment			
TRIAL	**TOTAL**	**% FEMALE**	**ENDPOINT**	**OUTCOME**
AVID	1016	21	Death	Men: 14.4% Women: 15.5%
MADIT I	196	8	Death	Not stratified by gender
MADIT II[10]	1232	16	Death	No significant difference HR in men, 0.66 (P = .011) HR in women, 0.57 (P = .132)
MUSTT	704	10	Arrhythmic death or cardiac arrest	EP-guided therapy: men vs. women: HR, 0.88 (95% CI, 0.35-2.23; P = .35)
SCD-HeFT	2521	23	Death	HR in men, 0.73 (95% CI, 0.57-0.93) HR in women, 0.96 (95% CI, 0.58-1.61)
DEFINITE	458	29	Death	HR in men, 0.49 (95% CI, 0.27-0.90) HR in women, >1.0

CI, Confidence interval; *EP,* electrophysiology; *HR,* hazard ratio.
From Yarnoz MJ, Curtis AB: Sex-based differences in cardiac resynchronization therapy and implantable cardioverter-defibrillator therapies: Effectiveness and use, Cardiol Rev *14(6):292–298, 2006.*

electrical storms independent of clinical and electrophysiological factors. Despite these differences, the overall survival rates following ICD implantation did not differ between genders (Figure 50-6).[11]

Several potential reasons exist for the lower percentage of female enrollees in ICD clinical trials. First, the older age of women at presentation with CAD and SCD might make ICD implantation in them less attractive than in younger men. Second, since fewer women have systolic heart failure or CAD before SCD, fewer women meet eligibility requirements for ICD implantation for primary prevention. Third, women have a lower risk of SCD and lower incidence of spontaneous SVTs compared with men, which reduces the number of women who require ICD placement for secondary prevention.

In clinical practice, as in clinical trials, the use of ICDs seems to be disproportionately low in women. An observational study that included more than 13,000 patients admitted with systolic heart failure (LVEF <30%) to hospitals participating in the American Heart Association's Get with the Guidelines-Heart Failure program reported that among patients eligible for ICD therapy, only 35.4% had an ICD or a planned ICD implantation on discharge. Important gender-related and race-related differences exist in the use of ICDs. After adjusting for patient characteristics and hospital factors, the adjusted odds of ICD use were 0.73 for black men, 0.62 for white women, and 0.56 for black women, compared with ICD use in white men. These differences were not attributable to the proportions of women and black patients at participating hospitals or to differences in the reporting of LVEF.[12] A separate study in a nationally representative sample of Medicare beneficiaries found that men were 3.2 times more likely to receive an ICD for primary prevention and 2.4 times more likely to receive an ICD for secondary prevention of SCD compared with women.

A recent study from the National Cardiovascular Data Registry ICD Registry evaluated the gender-related differences in in-hospital adverse events after first-time ICD implantation.

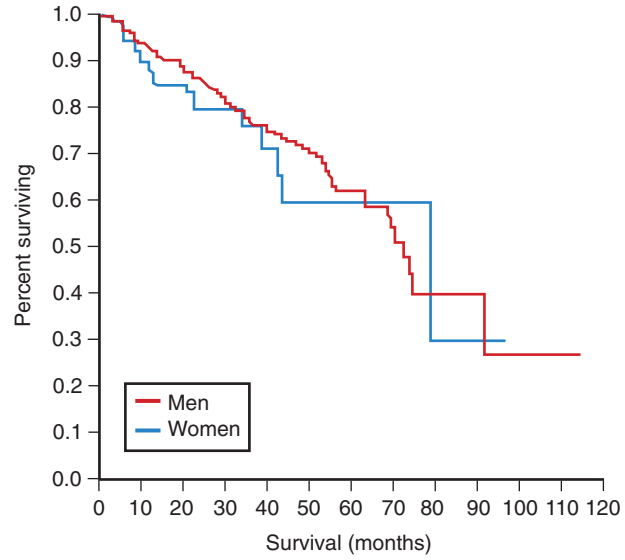

FIGURE 50-6 Kaplan-Meier survival curve comparing total mortality after cardioverter-defibrillator implantation between men and women. *(From Lampert R, McPherson CA, Clancy JF, et al: Gender differences in ventricular arrhythmia recurrence in patients with coronary artery disease and implantable cardioverter-defibrillators,* J Am Coll Cardiol *43[12]: 2293–2299, 2004.)*

Unadjusted analysis showed that women had higher rates of any adverse event (4.4% vs. 3.3%, $P < .001$) and almost twice the rate of major adverse events compared with men (2.0% vs. 1.1%, $P < .001$). After accounting for demographic, clinical, and procedural differences between men and women, women had 32% higher odds of experiencing an adverse event and 71% higher odds of experiencing a major adverse event compared with men. Women

were disproportionately affected by mechanical adverse events (cardiac perforation, coronary venous dissection, lead dislodgment, hemothorax, pneumothorax, and pericardial tamponade). The authors suggested that possible anatomic differences, such as a thinner right ventricular wall and smaller blood vessel diameter, could predispose women to higher rates of adverse events. Despite this gender-related difference in adverse events, in-hospital mortality was similar for both sexes.

Thus, despite significant gender-related differences in the presentation of sustained ventricular arrhythmias and SCD in patients with severe cardiomyopathies, results of the various ICD clinical trials demonstrated that women derive similar benefits from ICD therapy, albeit with more adverse effects, compared with men. However, the sample sizes of women in these trials have been relatively small, and no prospective study has been performed specifically to evaluate the survival benefit of ICD therapy in women.

Cardiac Resynchronization Therapy: Use and Outcomes

Cardiac resynchronization therapy (CRT) has been established as an important therapeutic tool in patients with advanced systolic heart failure and cardiac dyssynchrony. It has been shown to decrease mortality and hospitalizations and to improve quality of life and exercise tolerance. In CRT trials, female patients have represented approximately 31% of the total population, a higher proportion compared with ICD trials. However, relatively few analyses of outcomes in women exist compared with those in men from these trials (Table 50-4). This fact, combined with relatively few CRT trials, limits the amount of data available on differences in outcomes between the genders.

In an analysis of the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial data, with CRT, women were significantly less likely to reach the combined endpoint of first hospitalization for heart failure or death when compared with female controls.[13] Women who underwent CRT also had significantly fewer hospitalizations for heart failure. These differences persisted after controlling for age, heart failure etiology, and other baseline variables. Men did not have any differences in either endpoint (Figure 50-7). In a study from The Netherlands that investigated gender-related differences in response to CRT, both genders demonstrated statistically significant improvements in New York Heart Association functional class, quality of life, and exercise tolerance.[14] No gender-related, statistically significant differences in the number of clinical responders or in survival were noted at 1 year and at 2 years (Figure 50-8). Finally, a recent retrospective analysis that investigated the relationship between anatomic reverse remodeling and ventricular arrhythmias in CRT patients from the InSync III Marquis study found that gender was the most important predictor of treated VT or VF, with female patients having no episodes over a 6-month follow-up.

Both the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) and Cardiac Resynchronization-Heart Failure (CARE-HF) trials showed improved survival with CRT therapy, with very similar HRs for the primary endpoints (composite of death or hospitalization for heart failure) for men and women. The small numbers of patients in the Pacing Therapies for Congestive Heart Failure (Path-CHF) and Multi-Site Stimulation in Cardiomyopathies (MUSTIC) trials (42 and 67, respectively) precluded any comparison between genders.

Reviews of the CRT trials showed that both sexes benefit from CRT, with no statistical difference in survival. Since the number of men and women with heart failure in the United States is approximately the same (2.4 million and 2.5 million, respectively), women, comprising less than one third of the total CRT trial population, seem to be under-represented again. CRT has only been proven to be beneficial in patients with significant systolic heart failure and ventricular dyssynchrony, who continue to have symptoms despite optimal medical therapy. Men younger than 75 years have a higher prevalence of heart failure compared with women (6.2% vs. 4.1%). Also, the prevalence rate of moderate or severe systolic dysfunction in women is one third of that in men. These reasons could account for the lower use of CRT devices in women compared with their use men in these trials. In current clinical practice, CRT devices follow the trend of ICD implantations, mainly because of the use of combination CRT-ICD devices. Women currently comprise 22% to 26% of total ICD recipients, and gender-related differences in implantation rates have been steady over the past few years.[15]

In prior clinical trials and in current clinical practice, women are a clear minority among patients who receive ICD and CRT devices. This is probably a result of the higher proportion of men with CAD and advanced systolic heart failure, but these

Table 50-4 Gender-Related Outcomes in Cardiac Resynchronization Therapy Clinical Trials

	Enrollment			
TRIAL	**TOTAL**	**% FEMALE**	**ENDPOINT**	**OUTCOME HAZARD RATIO (95% CI)**
MIRACLE[13]	453	32%	Clinical (NYHA, 6MHWD, QOL)	Not stratified by gender (women: lower risk of death or hospitalization for heart failure)
Path-CHF	42	48%	Peak oxygen consumption, 6MHWD	Not stratified by gender
MUSTIC	67	25%	6MHWD	Not stratified by gender
CARE-HF	812	26%	Death or unplanned hospitalization for major CV event	Men: 0.62 (0.49-0.79) Women: 0.64 (0.42-0.97)
COMPANION	1520	33%	Death or hospitalization for any cause	No significant difference in hazard ratio

CV, Cardiovascular; *6MHWD,* 6-minute hall walk distance; *NYHA,* New York Heart Association; *QOL,* quality of life.
From Yarnoz MJ, Curtis AB: Sex-based differences in cardiac resynchronization therapy and implantable cardioverter-defibrillator therapies: Effectiveness and use, Cardiol Rev *14(6):292–298, 2006.*

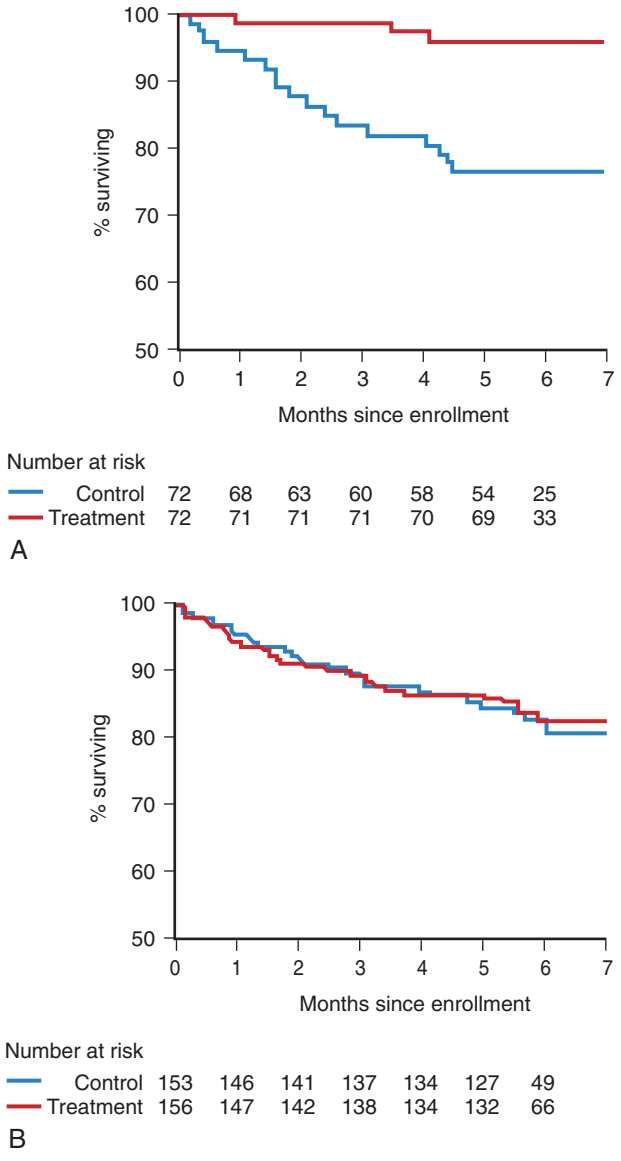

FIGURE 50-7 Kaplan-Meier survival curves for time to first hospitalization for heart failure or death in women (**A**) and men (**B**). *(From Woo GW, Petersen-Stejskal S, Johnson JW, et al: Ventricular reverse remodeling and 6-month outcomes in patients receiving cardiac resynchronization therapy: Analysis of the MIRACLE study,* J Interventional Cardiac Electrophysiol *12:107–113, 2005.)*

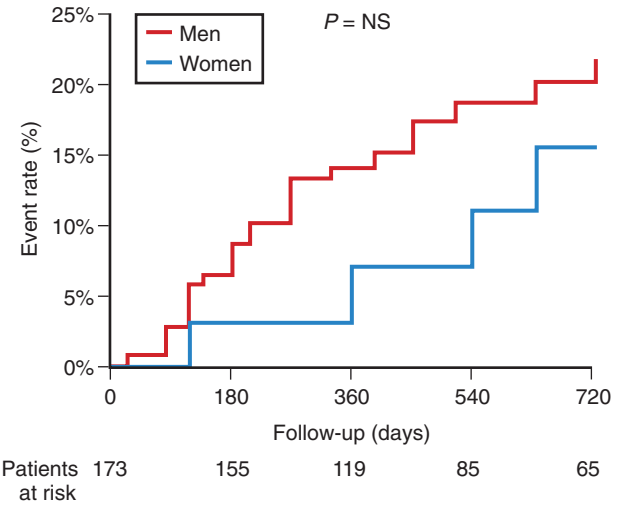

FIGURE 50-8 Kaplan-Meier curves of death or hospitalization for heart failure in men and women after cardiac resynchronization therapy. *(From Bleeker GB, Schalij MJ, Boersma E, et al: Does a gender difference in response to cardiac resynchronization therapy exist?* PACE *28:1271–1275, 2005.)*

gender-related differences in the use of devices do not relate to outcomes, since results of clinical trials show equal benefits in survival and symptoms.

Conclusion

Gender-related differences in the incidence and prevalence of cardiac arrhythmias are apparent. With regard to SVT, women have an increased incidence of AVNRT, whereas men more frequently have accessory pathway–mediated arrhythmias. AF is more prevalent in men in all age groups, but the absolute number of women with AF is higher. Men have a higher incidence of SCD, whereas women with SCD are less likely to have a history of CAD. Women are more likely to have LQTS, either acquired or congenital, and are more likely to develop torsades de pointes compared with men. What is not clear are the mechanisms behind these gender-related differences, with the two most commonly proposed mechanisms being hormonal effects on ion channels and the modulation of autonomic tone. From a clinician's standpoint, knowledge of these gender-related differences in arrhythmias is important both for timely diagnosis and optimal management.

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CHAPTER 51

Electrocardiographic Manifestations of the Athlete's Heart and Management of Arrhythmias in the Athlete

Sanjay Sharma, John Rawlins, and William J. McKenna

Introduction

Participation in regular physical exercise confers well-established benefits with respect to cardiovascular health.[1-3] Paradoxically, young athletes represent a group of individuals who may be particularly vulnerable to the risk of sudden cardiac death (SCD) from unrecognized inherited or acquired disorders of the heart (Table 53-1).[4] SCD in young trained individuals is rare, with an estimated incidence ranging from 1 in 50,000 to 1 in 200,000 patient-years. However, SCDs often receive considerable media attention and have a profound impact on the local, lay, and sporting communities, which perceive young asymptomatic athletes to represent the healthiest segment of society.[5] The youth of the individual, the potential life years lost, and the ability to diagnose most disorders capable of causing sudden death often galvanize emotionally charged and controversial debates among the lay community, medical bodies, and sporting organizations relating to the practical use of pre-participation screening to identify disorders capable of causing SCD. The role of the 12-lead electrocardiogram (ECG) as a screening tool for the diagnosis or identification of athletes requiring further investigation is established in many European countries and is practiced among elite and financially endowed sporting organizations in the United States, although the U.S. guidelines do not currently advocate a mandatory ECG as part of pre-participation screening in athletes in general. Indeed, electrocardiographic screening of athletes is endorsed by the European Society of Sport Cardiology, the International Olympic Committee, and the Fédération Internationale de Football Association (FIFA).[6,7] However, athletes often exhibit anomalous ECG patterns relating to increased vagal tone and chamber size as a consequence of physiological adaptations that overlap with certain disease phenotypes implicated in SCD.[8-11] The differentiation between physiology and pathology is crucial, and an erroneous diagnosis has the potential for serious consequences. This chapter provides a comprehensive overview of the resting ECG in athletes to facilitate the differentiation between physiological changes and pathologic disorders and identifies the prevalence, significance, and management of cardiac arrhythmias in athletes, based on guidelines developed by expert consensus panels in Europe (ESC consensus statement) and the United States (the 36th Bethesda Conference guidelines).[12-14]

The Athlete's Heart

Common Findings on the Resting 12-Lead Electrocardiogram

Regular participation in intensive physical exercise is associated with central and peripheral cardiovascular adaptations to facilitate the generation of a large and sustained cardiac output and to enhance the extraction of oxygen from exercising muscle for aerobic glycolysis, respectively. Collectively, these physiological adaptations have been termed the *athlete's heart.*[15] Specific structural and electrical cardiac remodeling is fundamental to the physiological adaptive process, and most athletes exhibit modest increases in chamber wall thickness and cavity size, as well as changes in parasympathetic and sympathetic tone, as reflected on the surface 12-lead ECG (Table 51-2 and Figure 51-1).[16,17]

Cardiac Rhythm

Common rhythmic ECG findings in athletes include sinus bradycardia, which is present in up to 80% of highly trained athletes, sinus arrhythmia (52%), and first-degree heart block (5%).[18] Occasionally, higher levels of atrioventricular (AV) nodal block may be observed.[19] Such rhythm anomalies are considered secondary to increased vagal tone. In addition, desensitization of β-receptors and changes in the intrinsic properties of the sinoatrial (SA) and AV nodes in response to physical training may also contribute.[20,21] The maximum heart rate is unaffected, and heart block during resting conditions generally resolves immediately on initiation of exercise.[18]

Electrical Voltage Criteria for Cardiac Enlargement

High-magnitude QRS voltages, particularly across the precordial leads, are common manifestations of athlete's heart and may be identified in up to 60% of athletes.[8] Increased QRS voltage criteria can only be partly attributed to a direct consequence of increased cardiac size. In general, poor correlation exists between voltage criteria for cardiac hypertrophy and cardiac dimensions identified at echocardiography. Most correlation studies relate specifically to the assessment of left ventricular hypertrophy either in terms of absolute left ventricular wall thickness or left ventricular mass measurements at echocardiography; these studies demonstrate

poor sensitivity and specificity for the identification of left ventricular hypertrophy at echocardiography for the vast majority of voltage criteria used.[8,11] In our experience, the Sokolow-Lyon voltage criterion for left ventricular hypertrophy, which is the most commonly used in clinical practice, has a sensitivity and specificity of 16% and 60%, respectively, for the identification of left ventricular hypertrophy. Several other factors influence QRS voltage magnitude, including the distance between the heart and the thoracic wall, which is determined by chest wall size, pectoral hypertrophy, and the presence or absence of breast tissue. In contrast, the more stringent electrocardiographic Romihilt-Estes points score of 5 or greater for left ventricular hypertrophy is a less frequent observation in athletes (10% of male athletes) but has a specificity for left ventricular hypertrophy in the range of 90%.[8]

The presence of voltage criteria for right ventricular hypertrophy is less common in athletes; however, incomplete right bundle branch block (RBBB) has been documented in up to 29% of highly trained athletes and is thought to represent mild increases in right ventricular size.[8] Similarly, voltage criteria for left and right atrial enlargement are common findings, present in 14% and 16% of adolescent athletes, respectively.[8] As with voltage criteria for

Table 51-1 Causes of Sudden Cardiac Death in Athletes Younger Than 35 Years in the United States Between 1986 and 2007

DIAGNOSIS AT POSTMORTEM	FREQUENCY (%)
Hypertrophic cardiomyopathy	36
Coronary artery anomalies	17
Myocarditis	5.9
Arrhythmogenic right ventricular cardiomyopathy	4.3
Ion channelopathies (long QT and Brugada syndromes)	3.6
Mitral valve prolapse	3.4
Myocardial bridging	3.3
Premature coronary artery disease	3.3
Aortic stenosis	2.4
Marfan's syndrome	2.7
Idiopathic dilated cardiomyopathy	2.0
Wolff-Parkinson-White syndrome	1.6

From Maron BJ: Sudden death in young athletes, *N Engl J Med* 349:1064–1075, 2003.

Table 51-2 Common Findings in the Resting 12-Lead ECG in the Athlete

ECG FINDING	FREQUENCY (%)
Sinus bradycardia	80
Sinus arrhythmia	52
First-degree AV block	5
Incomplete RBBB	29
LA enlargement	14
RA enlargement	16
Sokolow-Lyon criteria for LVH	45
ST elevation	43
Large-amplitude T waves	22

ECG, Electrocardiogram; *AV,* atrioventricular; *RBBB,* right bundle branch block; *LA,* left atrial; *RA,* right atrial; *LVH,* left ventricular hypertrophy.
From Sharma S, Whyte G, Elliott P, et al: Electrocardiographic changes in 1000 highly trained junior elite athletes, *Br J Sports Med* 33:319–324, 1999.

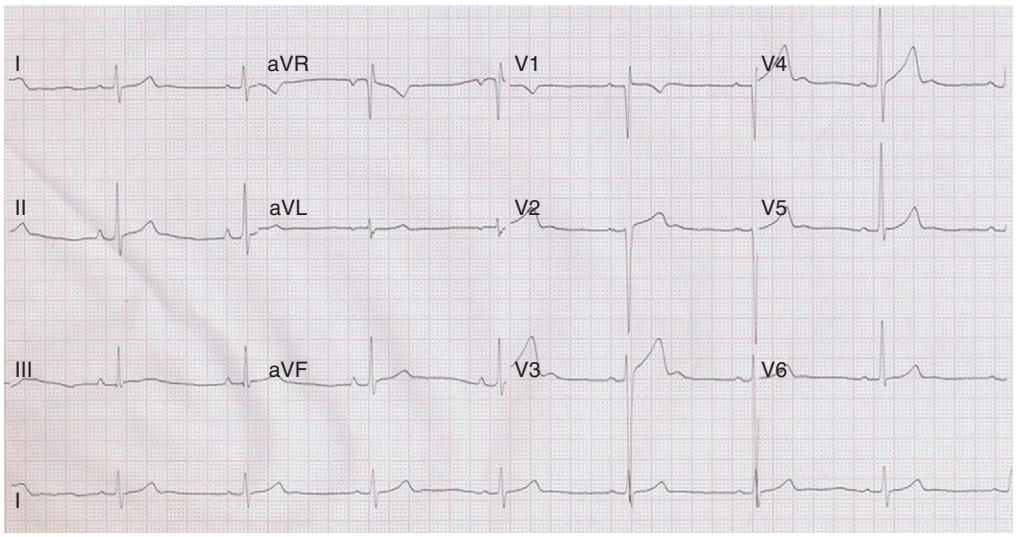

FIGURE 51-1 A normal athlete's electrocardiogram taken from a young professional cyclist during routine pre-participation screening. The electrocardiogram demonstrates sinus bradycardia, voltage criteria for left ventricular hypertrophy, and large-amplitude precordial T waves.

ventricular hypertrophy, the sensitivity and specificity of such voltage scores to predict the presence of left atrial enlargement is poor, with only 0.3% of 347 adult athletes with echocardiographic evidence of left atrial enlargement having positive voltage criteria.[22]

Repolarization Changes

Early repolarization changes are common in athletes and are observed in 40% to 50% of individuals.[8] Specific anomalies include J-point and ST-segment elevations and increased T-wave voltages (>0.2 mV), which reflect modulations in autonomic tone affecting the timing sequence between depolarization and repolarization. The anomalies resolve at increased heart rates during gentle exercise, regress with detraining, and are considered benign.

Impact of Demographic Factors and Sporting Discipline on the Athlete's Electrocardiogram

The majority of data relating to the athlete's ECG are derived from studies in adult white male subjects; however, a variety of demographic factors, including the athlete's age, gender, ethnicity, and body size may influence the normal ECG patterns observed in highly trained individuals.

Age

In general, the qualitative changes that occur in adolescent athletes are similar to those observed in more mature adults. However, voltage criteria for left and right ventricular hypertrophy may be more commonly present in adolescent athletes because of their thin chest walls.[8] T-wave inversions in the right ventricular leads (V1 to V3) may be observed in up to 5% of adolescent athletes and usually regress by the age of 16 years and are representative of the juvenile ECG pattern rather than cardiac pathology (Figure 51-2).[23] In contrast, T-wave inversions in the anterior leads beyond V1 are identified in only 0.1% of adult athletes and warrant further investigations to exclude a cardiac disorder.[23]

Few studies pertain specifically to ECG appearances in elite athletes (those aged ≥40 years); however, some data indicate that among athletes who participate in endurance sporting disciplines such as long-distance running, cycling, and cross-country skiing, a higher prevalence of atrial arrhythmias and heart block is seen compared with the general population.

Gender

The majority of studies assessing cardiac adaptation in athletes have evaluated predominantly white male subjects. In our experience, females exhibit ECG patterns similar to those of males but have a significantly lower prevalence of voltage criteria for cardiac hypertrophy, early repolarization changes, and T-wave inversions.

Ethnicity

The concept that an athlete's ethnic background may alter the appearance of the resting 12-lead ECG has been examined by a number of recent reports comparing ECG patterns between white athletes and those with African or Afro-Caribbean ancestry (referred to as *black athletes*). Racial differences in ECG appearance have been recognized historically, with the observation in the 1950s that J-point and ST-segment elevation may be part of the normal ECG in young black men.[24,25]

Recent studies have demonstrated that black male athletes demonstrate a higher prevalence of voltage criteria for left ventricular hypertrophy as well as bizarre repolarization anomalies that may simulate myocardial infarction (MI), Brugada syndrome, or phenotypic manifestations of both hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy (Figure 51-3). In one study of nearly 2000 American football players (67% black), 5.8% of black players had an ECG appearance that was deemed "markedly abnormal" by the investigators, compared with

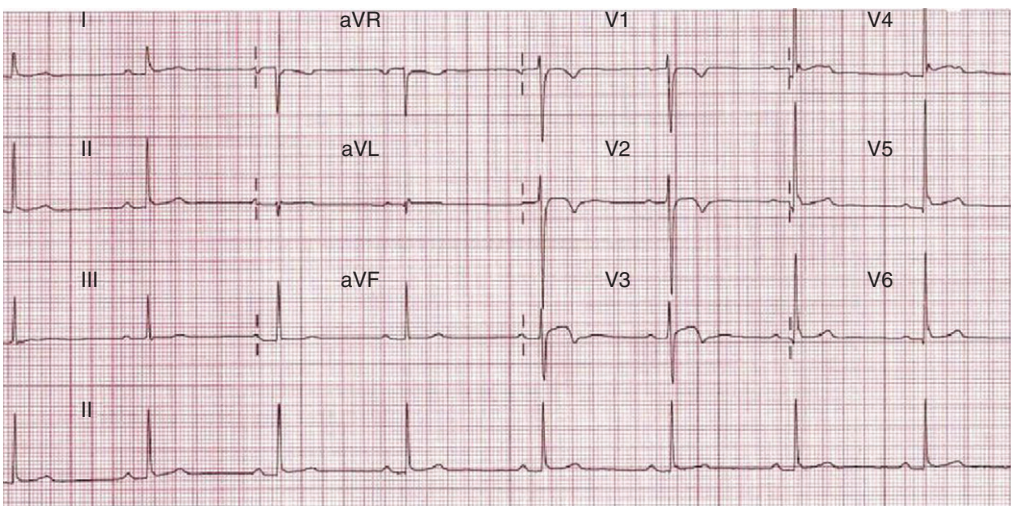

FIGURE 51-2 A 12-lead electrocardiogram taken from a 15-year-old male junior elite tennis player demonstrating T-wave inversions in the anterior leads (V1 to V3), consistent with the juvenile electrocardiogram pattern.

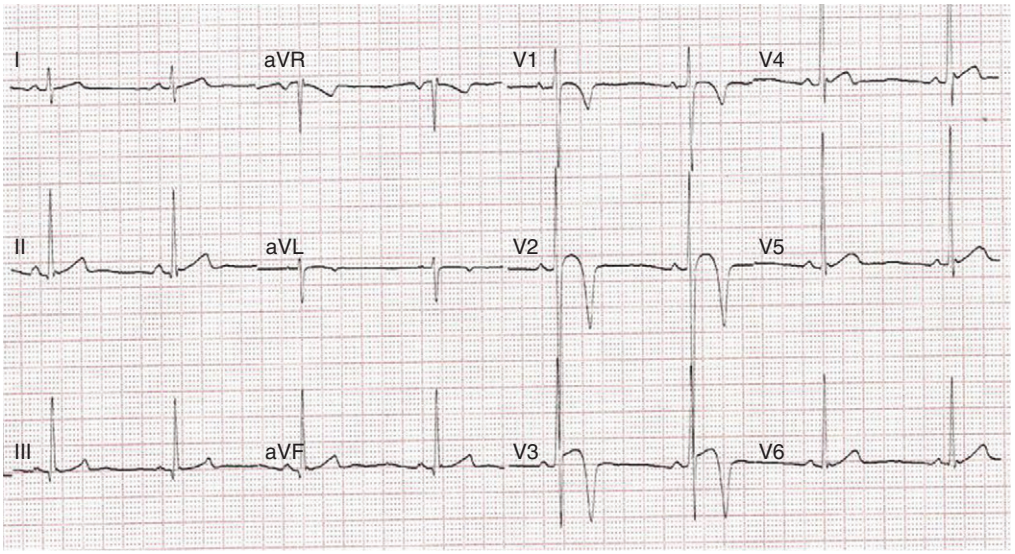

FIGURE 51-3 A 12-lead electrocardiogram taken from a male African endurance athlete, a medalist at the 2008 Beijing Olympics. Note the deep T-wave inversions and convex ST-segment elevation in the anterior precordial leads (V1 to V3). He subsequently underwent further evaluation, which did not reveal any underlying cardiac abnormalities.

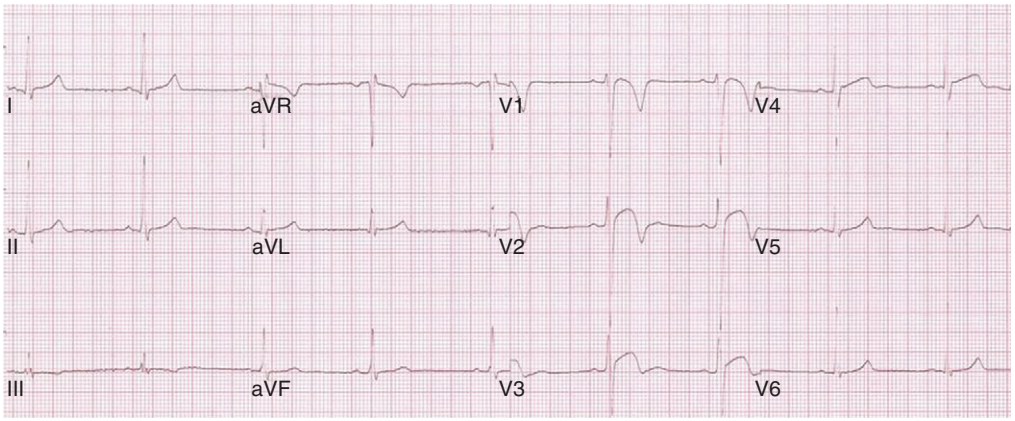

FIGURE 51-4 A 12-lead electrocardiogram taken from a black British premier soccer player exhibiting large QRS complexes, convex ST-segment elevation in leads V1 to V4, and deep T-wave inversions in leads V1 to V3.

only 1.8% of white players.[26] Only a small proportion underwent subsequent echocardiographic evaluation, but the investigators concluded that in the majority of cases, the changes observed represented a normal ethnic variation.

Our experience of evaluating large numbers of adolescent and adult male athletes of Afro-Caribbean origin has revealed that 25% exhibit marked repolarization changes comprising convex ST-segment elevation and deep (≥0.2 mV) T-wave inversions in leads V1 to V4 (Figure 51-4).[27] Such anomalies do not correlate with cardiac hypertrophy, chamber enlargement, or cardiac arrhythmias during exercise testing and on 24-hour ambulatory Holter recordings. Published data pertaining to female black athletes indicate that 14% of adult black female athletes exhibit minor T-wave inversions in the anterior precordial leads compared with less than 1% of white female athletes in the absence of structural heart disease (Figure 51-5).[28] The precise mechanism and significance of such anomalies remains to be elucidated and requires longitudinal assessment.

Sporting Discipline

Sporting discipline affects cardiac adaptation. In general, athletes participating in purely endurance sports such as cycling, rowing, and long-distance running exhibit larger left ventricular cavities and a greater magnitude of left ventricular hypertrophy compared with athletes involved in purely isometric sports, such as wrestling and judo. Athletes participating in long-distance endurance sports are more likely to exhibit sinus bradycardia, voltage criteria

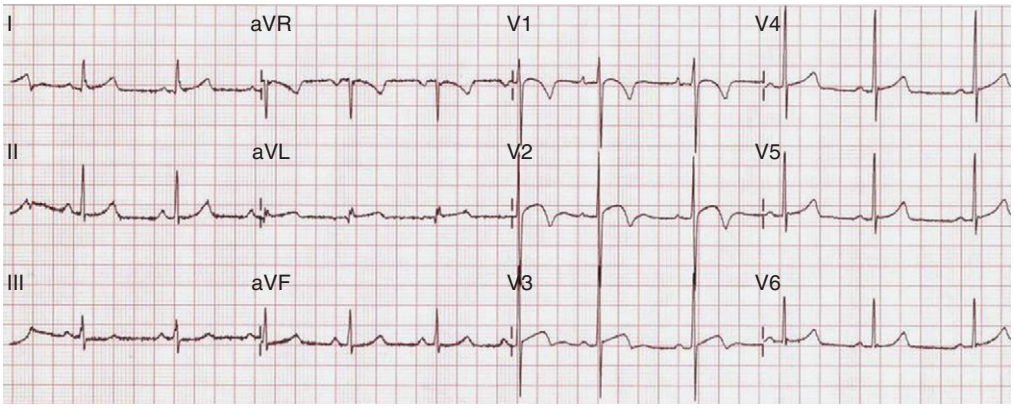

FIGURE 51-5 A 12-lead electrocardiogram taken from a female African endurance runner during routine pre-participation screening demonstrating T-wave inversions in the anterior precordial leads (V1 and V2), accompanied by characteristic convex ST-segment elevation.

for cardiac chamber enlargement, and repolarization changes.[29] We advise caution against such generalizations because the training programs involved in most sports, particularly for athletes participating at the regional or national level, are arduous, physically intensive, and involve a combination of isotonic and isometric exercises. In our experience, an enormous overlap in ECG patterns exists among athletes participating in a large range of ball, racket, endurance, and power sports.

Uncommon Electrocardiogram Findings in White Athletes

T-Wave Inversions

Repolarization changes consisting of ST-segment depression and T-wave inversions are much less frequent than ST-segment elevation and high-voltage T waves, being present in 3% to 4% of white adolescent and adult athletes.[11,23] The prevalence of T-wave inversions is significantly lower in white female athletes and considerably higher in male and female black athletes. These electrical anomalies overlap with the phenotypic manifestations of cardiomyopathy, ion channel disorders, and anabolic steroid abuse (Table 51-3) and warrant thorough evaluation before being attributed to physiological adaptation.[30-33] In a longitudinal study of 123 adult male white athletes with deep T-wave inversions, 39 (32%) had echocardiographic and clinical evidence of cardiac disease and were treated appropriately for their respective conditions.[34] Of the 84 remaining athletes without demonstrable cardiac disease, 81 were followed up for a mean of 9 years (±7; range, 1 to 27 years). Of these, 5 athletes (6%) subsequently developed a cardiomyopathy, with one death and one aborted cardiac arrest as a consequence of ventricular fibrillation (VF) caused by arrhythmogenic right ventricular cardiomyopathy and hypertrophic cardiomyopathy, respectively. The remaining 70 athletes did not develop any pathologic cardiac conditions during the period of follow-up. These data suggest that the presence of deep T-wave inversions in an athlete may be a harbinger of subtle cardiomyopathies and the risk of fatal ventricular arrhythmias and that such athletes should remain under periodic surveillance. T-wave inversion patterns in the anterior precordial leads (V1 to V3/V4) may be acceptable in adolescent athletes and in those of Afro-Caribbean origin; however, T-wave inversions in the lateral leads in adolescent athletes or black athletes warrant further evaluation for cardiac disease.[27]

Table 51-3 ECG Changes in a Number of Cardiac Diseases That May Be Observed During Pre-participation Screening

CARDIAC DISEASE	ECG ABNORMALITIES
Arrhythmogenic right ventricular cardiomyopathy	Anterior T-wave inversions Incomplete or complete RBBB ε-waves
Hypertrophic cardiomyopathy	Left ventricular hypertrophy Pathologic Q waves T-wave inversions—anterior or inferior ST-segment depression Rarely normal
Idiopathic dilated cardiomyopathy	Intraventricular conduction abnormalities
Long QT syndrome	Prolonged Q-T interval
Brugada syndrome	Incomplete or complete RBBB Anterior ST elevation
Anomalous coronary arteries	Normal
Coronary artery disease	Usually normal
Wolff-Parkinson-White syndrome	Short P-R interval δ-waves
Anabolic steroid abuse	Q-T interval prolongation T-wave inversions

ECG, Electrocardiogram; *RBBB*, right bundle branch block.

Prolonged Q-T Interval

A long Q-T interval (>440 ms in males and >450 ms in females) is identified in 0.4% to 0.69% of athletes and is an indication for disqualification from competitive sport to minimize the risk of SCD, according to the European Society of Sports Cardiology

guidelines.[13,35] However, the prevalence of a long Q-T interval in athletes is significantly higher than the actual prevalence of congenital long QT syndrome (LQTS) (0.04%), possibly because the Q-T interval may be overestimated by Bazzet's formula at heart rates below 40 beats/min and measurements may also be influenced by sinus arrhythmia and slightly wider QRS complexes observed in athletes compared with the general population.[36] The positive predictive value (PPV) of an isolated corrected Q-T interval in the 440- to 470-ms range is not precisely known but is likely to be low, probably less than 10%. On the basis of these considerations, the Bethesda guidelines recommend an upper QTc limit of 470 ms in males and 480 ms in females.[14] Our experience of athletes with long Q-T intervals suggests that a QTc 500 ms or greater is highly suggestive of LQTS, even in the absence of symptoms or an overt family history, and is usually associated with the other features of the disorder on exercise stress testing, such as paradoxical prolongation of the Q-T interval with increasing heart rate (up to 120 beats/min) and a long Q-T interval in other first-degree relatives.[35]

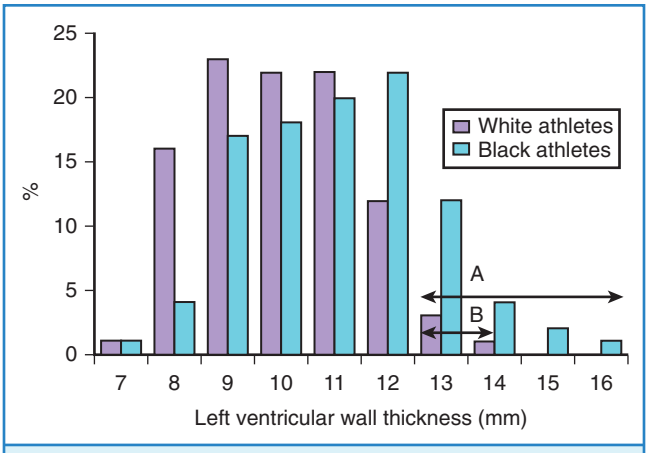

FIGURE 51-6 Distribution of left ventricular wall thickness in 300 highly trained black male athletes and 300 white male athletes of similar age, size, and sporting caliber demonstrating that a significantly higher proportion of black athletes exhibit a wall thickness >12 mm compared with white athletes (18% vs. 3% as indicated by *A* and *B*, respectively). *(From Basavarajaiah S, Boraita A, Whyte G, et al: Ethnic differences in left ventricular remodeling in highly-trained athletes relevance to differentiating physiologic left ventricular hypertrophy from hypertrophic cardiomyopathy,* J Am Coll Cardiol *51[23]:2256–2262, 2008.)*

Overlap with Disease: Athlete's Heart or Cardiomyopathy?

Hypertrophic Cardiomyopathy

Cardiac adaptation to exercise is associated with modest increases in cardiac chamber wall thickness and cavity size. Typically, the left ventricular wall thickness in increased by 15% to 20%, and left ventricular cavity size may be increased by 10%.[16] Occasionally, some male athletes (1.5% to 3% of white and 18% black athletes) (Figure 51-6) exhibit substantial increases in left ventricular wall thickness ranging from 13 mm to 16 mm, which fall within values observed in individuals with morphologically mild hypertrophic cardiomyopathy, which is the commonest cause of death in the young (age <35 years) worldwide (see Table 51-1).[37-40] The distinction between the athlete's heart and hypertrophic cardiomyopathy is vital because an erroneous diagnosis has the potential for serious consequences (see Table 51-3). The differentiation between the two entities is possible with the assessment of cardiac chamber size and indices of systolic and diastolic functions using echocardiography and cardiac magnetic resonance imaging (MRI); abnormalities on the 12-lead ECG may provide crucial information to unravel the clinical dilemma, which may prove challenging.[41-43] The presence of deep T-wave inversions in any lead other than V1 in white athletes and in leads other than V1 to V4 in black athletes, pathologic Q waves, ST-segment depression, and left bundle branch block (LBBB) indicates pathologic left ventricular hypertrophy (Figure 51-7). Conversely, identification of the Sokolow-Lyon voltage criterion for left ventricular hypertrophy in isolation (without other associated features of left ventricular hypertrophy, including ST-segment depression, T-wave inversions, leftward axis, and voltage criterion for left atrial enlargement) is highly suggestive of physiological left ventricular hypertrophy (Figure 51-8).

Arrhythmogenic Right Ventricular Cardiomyopathy

An enlarged right ventricle and ventricular extrasystoles of right ventricular origin may occur in some highly trained endurance athletes, which raises the possibility of arrhythmogenic right ventricular cardiomyopathy, the most common cause of SCD in Italian athletes, accounting for 25% of all sudden deaths in the young during sporting activities.[5] In these circumstances, the identification of T-wave inversions in leads V2 to V4, ε waves (Figure 51-9) and more than 1000 ventricular extrasystoles of right ventricular origin (LBBB morphology) over a 24-hour period would be highly indicative of pathology rather than physiology (Figure 51-10).[44]

Arrhythmias in the Athlete

The identification of a bradyarrhythmia in an asymptomatic athlete is usually an incidental finding during investigation of an irregular pulse or a cardiac murmur or at a pre-participation ECG screening. The majority of bradyarrhythmias observed in athletes are benign and a consequence of increased vagal tone in response to systematic physical conditioning.

Occasionally, arrhythmias in athletes may manifest as intermittent palpitations, dizziness, syncope, angina, or reduction in functional capacity and unmask the presence of a potentially lethal cardiac disorder. (see Table 51-1).[39,40] Syncope during exercise is a particularly ominous symptom and often indicative of a cardiac arrhythmia associated with hemodynamic compromise. Syncope immediately following exercise may be vasovagal in origin or caused by a serious cardiac arrhythmia, and differentiating the two entities retrospectively may be difficult in a clinical setting. A history of prodromal vagal symptoms, absence of chest pain or palpitation during the event, documented pallor, and rapid recovery in the recumbent position are reassuring features. A definitive diagnosis requires symptom/rhythm correlation, which is best obtained by ambulatory ECG monitoring during the training activity associated with the syncope; however, attaching ECG monitoring electrodes is difficult in the presence of excessive perspiration and during highly physical contact sports and is impossible in others such as swimming.

All young symptomatic athletes should be investigated to exclude structural heart disease, accessory pathways, and ion

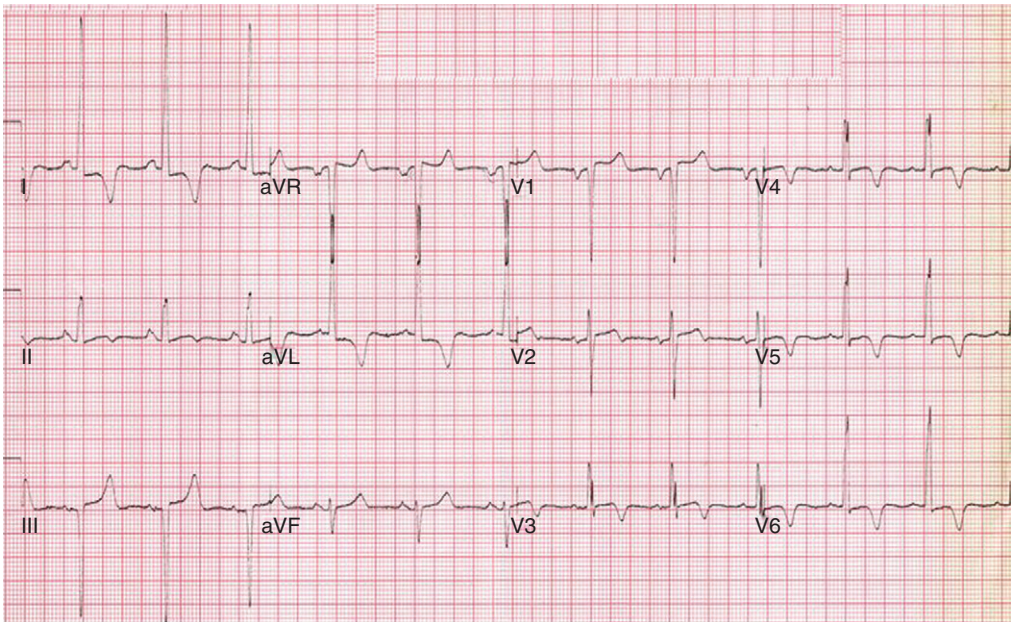

FIGURE 51-7 A 12-lead electrocardiogram of an athlete taken during pre-participation screening; the athlete was subsequently diagnosed with hypertrophic cardiomyopathy. Note the presence of Sokolow voltage criteria for left ventricular hypertrophy associated with deep T-wave inversions in the anterolateral leads (V3 to V6, I, and AvL) and pathologic Q waves in lead III, a combination highly suggestive of pathologic rather than physiological hypertrophy.

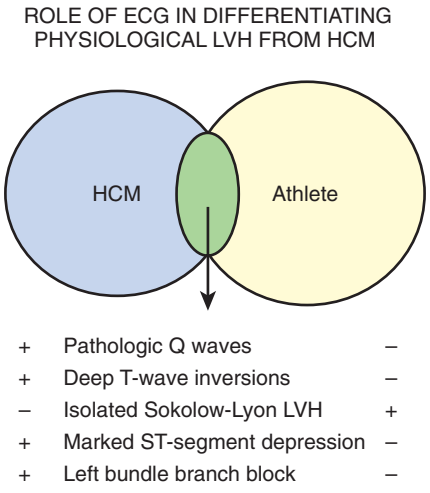

FIGURE 51-8 Venn diagram highlighting the role of the 12-lead electrocardiogram (ECG) in differentiating physiological hypertrophy from hypertrophic cardiomyopathy (*HCM*).

channel disorders by using noninvasive diagnostic tools. In rare circumstances, invasive electrophysiological studies (EPSs) may be necessary to exclude a concealed accessory pathway. Older athletes should undergo exercise stress testing to confirm or rule out underlying coronary atherosclerosis. Consideration should also be given to the fact that most disorders implicated in SCD in young athletes are genetically transmitted; therefore cardiac symptoms, as well as abnormalities on the 12-lead ECG or 24-hour ECG monitoring, should be interpreted in the context of a family history of known hereditary cardiac disorders, premature SCD, and unexplained syncope. A family history of "epilepsy" is also relevant, since cardiac arrhythmias may present with transient convulsion; also, a family history of unexplained drowning may be related to specific LQTS, which may promote ventricular arrhythmias when dividing into cold water.

The American Heart Association's 36th Bethesda guidelines and the European Society of Cardiology (ESC) guidelines relate to the eligibility of an athlete with arrhythmias to continue participation in competitive sports.[13,14] Both documents are the results of expert panels and are based on available scientific data. They do not represent purely evidence-based medicine but reflect the personal experiences of panel members. As such, they should be seen as recommendations and not guidelines. The recommendations for athletic participation for individuals who have cardiovascular disease are broadly similar, but the European recommendations appear to adopt a more conservative and homogeneous approach to athletes with possible hypertrophic cardiomyopathy, LQTS, and Wolff-Parkinson-White (WPW) syndrome.[13]

Bradyarrhythmias

Sinus bradycardia (heart rate <60 beats/min), sinus arrhythmia, wandering atrial pacemaker, first-degree AV block, Mobitz type I second-degree block, and sinus pauses are commonly observed in highly trained athletes (Table 51-4).[17,18] The rhythm disturbances are almost always asymptomatic and are attributed to an enhanced vagotonic state, which is exaggerated during sleep. Once the vagal tone is withdrawn, for example, during exercise, the rhythm reverts to normal and the maximal heart rate is unaffected.[18] Further investigation is not indicated in the absence of symptoms, inappropriately slow rates, or pauses less than 3

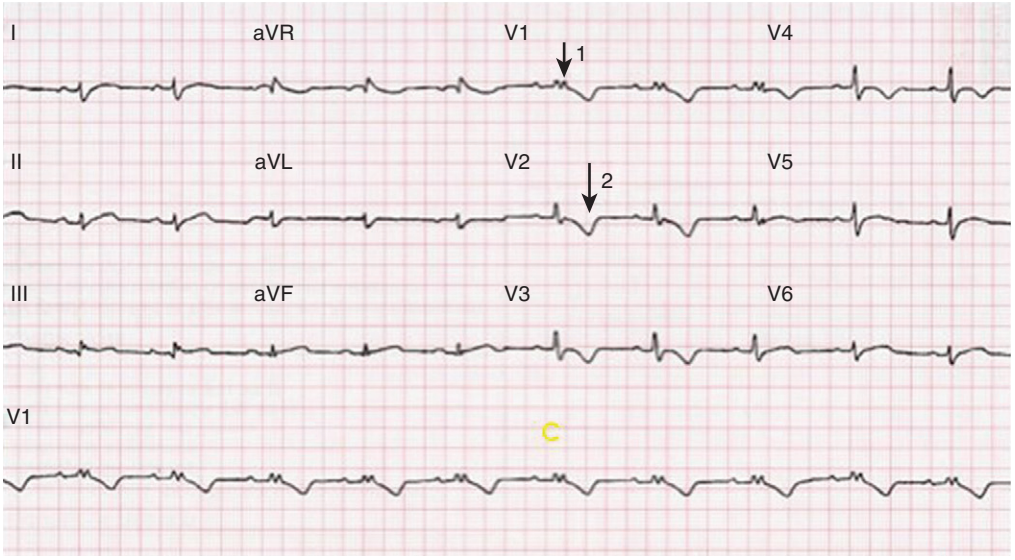

FIGURE 51-9 A 12-lead electrocardiogram of a young athlete demonstrating the presence of ε waves (*1*) and T-wave inversions (*2*) in the anterior precordial leads.

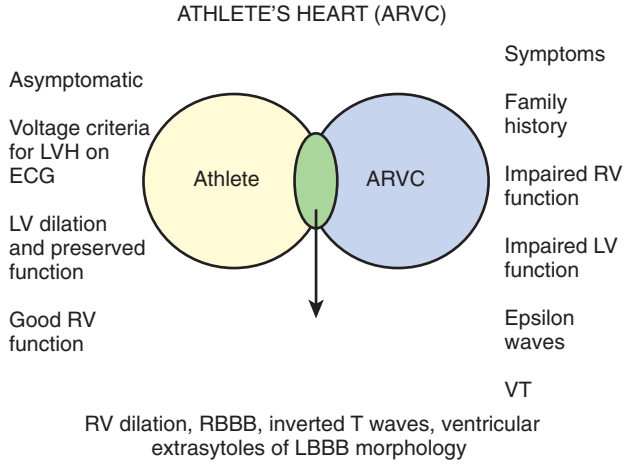

FIGURE 51-10 Venn diagram the role of the 12-lead electrocardiogram (*ECG*) in the identification and diagnosis of arrythmogenic right ventricular cardiomyopathy. *LBBB,* Left bundle branch block; *LV,* left ventricular; *LVH,* left ventricular hypertrophy; RV, right ventricular; *RBBB,* right bundle branch block; *VT,* ventricular tachycardia.

seconds during waking hours. Longer pauses during waking hours, SA exit block, and sick sinus syndrome are uncommon in athletes and should be investigated further with an exercise test. Absence of symptoms, resolution of the bradyarrhythmia, and a satisfactory chronotropic response during the exercise test indicate physiological adaptation. Conversely, the onset of dizziness or syncope during exercise, development of higher degrees of AV block, ST-segment depression, and chronotropic incompetence are indicators of pathology and warrant comprehensive assessment to exclude structural cardiac disease and coronary disease. In the absence of an identifiable cardiac disorder, we recommend such athletes should stop training for 8 to 12 weeks and undergo repeat evaluation with a 24-hour ECG and exercise stress test. Individuals with persistent symptoms, profound bradycardia, or both; sinus pauses exceeding 3 seconds; and evidence of sinus node or AV node dysfunction should undergo more complex investigations for rare genetic disorders of cardiac conduction, including cardiac sodium ion channel abnormalities or mutations in the *lamin A/C* gene.[45,46]

The identification of Mobitz type II second-degree AV block, advanced second-degree AV block, and third-degree AV block on the resting 12-lead ECG is only slightly more common in athletes than in the general population and should be investigated with an exercise stress test to ensure normalization of cardiac conduction at higher heart rates and to exclude inducible myocardial ischemia. A family history of premature (<40 years) cardiac conduction tissue disease should raise suspicion of a familial cardiac conduction tissue disorder and may warrant cardiac pacing.[47]

The prognostic implications of asymptomatic second-degree and third-degree AV block in the absence of underlying cardiac disease are not known, and the benefits of permanent cardiac pacing are uncertain. Indeed, the detrimental effects of unnecessary right ventricular pacing on left ventricular systolic function are now known.[48] The authors' policy is to allow asymptomatic athletes to continue to participate in sporting activity if exercise is associated with reversion to 1:1 AV conduction and a good chronotropic response. The persistence of heart block with exercise is an indication for permanent pacemaker implantation. In symptomatic athletes without an explanatory cause for the heart block, pacemaker implantation before resumption of athletic activity is recommended. Pacemaker implantation is recommended in athletes with heart block caused by an underlying cardiac disorder, irrespective of symptoms, and resumption of athletic activity is guided by the underlying pathologic substrate; for example, individuals with cardiomyopathy can only participate in sporting disciplines involving low physical intensity.[13,14] Athletes with congenital complete heart block who are asymptomatic, have no underlying structural heart disease, exhibit

Table 51-4 Treatments and Restrictions Applied in Athletes with Bradyarrhythmias

DISORDER	SYMPTOMS	TREATMENT	DIAGNOSIS	COMPETITIVE SPORTS
Sinus pause <3 sec	None	ECG, ACM	None	No restrictions
Sinus pause <3 sec	Syncope/LH	ECG, ACM, Echo, ET	? PPM	No bodily collision if PPM implanted
Daytime sinus pause >3 sec	None	ECG, ACM, Echo, ET	? PPM	No bodily collision if PPM implanted
Daytime sinus pause >3 sec	Syncope/LH	ECG, ACM, Echo, ET	PPM	No bodily collision
First-degree HB	None	ECG	None	No restrictions
Wenckebach HB	None	ECG, ACM	None	No restrictions
Wenckebach HB	Syncope/LH	ECG, ACM	PPM	No bodily collision
Mobitz II HB/CHB	None	ECG, ACM	PPM	No bodily collision
Mobitz II HB/CHB	Syncope/LH	ECG, ACM	PPM	No bodily collision

ACM, Ambulatory cardiac monitor; *CHB,* complete heart block; *Echo,* echocardiography; *ET,* exercise test; *HB,* heart block; *LH,* lightheadedness; *PPM,* permanent pacemaker.

narrow QRS complexes, have a resting ventricular rate greater than 40 beats/min, and do not develop ventricular arrhythmias during exercise do not require pacemaker implantation and may participate in all competitive sports.[13,14]

Pacemaker implantation in athletes should be accompanied by an exercise test conducted at the level of activity demanded by the sport to ensure that the paced heart rate increases appropriately.[14] Athletes fitted with a permanent pacemaker are advised to avoid sports involving heavy bodily contact to avoid damage to the pacemaker system.[13,14]

Supraventricular Arrhythmias

See Table 51-5.

Atrial Premature Extrasystoles

Premature atrial complexes are relatively common among athletes and are occasionally experienced as extra beats or identified on routine clinical evaluation.[17,49] In the absence of any other cardiac symptoms or abnormalities on physical cardiac examination or the resting 12-lead ECG, further investigation or treatment is unnecessary, and participation in competitive sport need not be limited.[13,14]

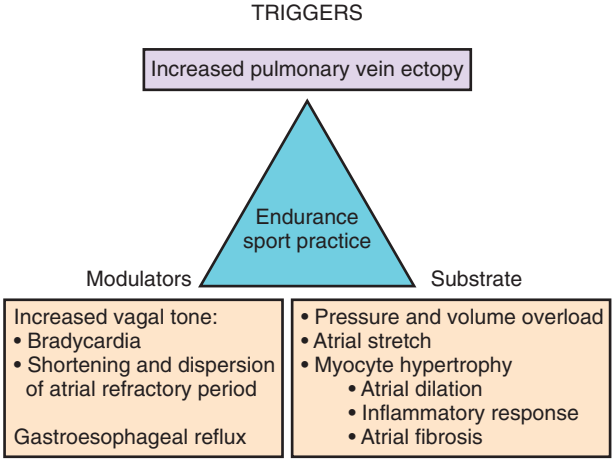

FIGURE 51-11 Classic triangle of Coumel, which suggests possible etiopathogenic factors influencing the development of atrial fibrillation in athletes. *(Modified from Mont L, Elosua R, Brugada J: Endurance sport practice as a risk factor for atrial fibrillation and atrial flutter,* Europace *11:11–17, 2009.)*

Atrial Fibrillation and Atrial Flutter

Both atrial flutter and AF are rare in young trained athletes, and the prevalence of lone AF does not differ between young athletes and nonathletic controls.[22] However, recent longitudinal studies reveal that participation in regular endurance sporting activity predisposes older athletes to the development of AF, atrial flutter, or both.[50-55] An association exists between the number of hours practiced and the risk of developing atrial arrhythmias, with one case-control study showing a relationship between current sports practice with a lifetime of more than 1500 hours of participation and the development of lone AF.[52]

The mechanism seems likely to be related to structural and electrical remodeling of the atria that occur as a consequence of prolonged endurance exercise (Figure 51-11). Dilation of both left and right atria has been observed among young endurance athletes without AF, and veterans with lone AF have larger atria compared with controls.[22,55] Biochemical evidence suggests that chronic atrial volume overload secondary to exercise may lead to a chronic inflammatory response, with subsequent fibrosis and scarring, providing an atrial arrhythmogenic substrate.[56,57] Increased cardiac vagal tone may then trigger AF in athletes. High levels of vagal tone have been shown experimentally to shorten and increase the dispersion of the atrial refractory period, allowing re-entrant atrial arrhythmias to develop within an abnormal atrial substrate.[58-60] In contrast to the nonathletic population, most (70%) athletes exhibit vagally triggered AF.[54]

The evaluation of an athlete who presents with an atrial arrhythmia should include a comprehensive history relating to alcohol and caffeine intake, potential illicit drug use, as well as

Table 51-5 Evaluation and Management of Supraventricular Arrhythmias

CONDITION	SYMPTOMS	ECG	DIAGNOSIS	TREATMENT	COMPETITION
AVNRT	Palpitations Presyncope Syncope	Normal	ECG monitor	RFA EPS BB, CCA, or digoxin	After 3-6 months, if symptom free
WPW (asymptomatic)	None	Short P-R interval δ Waves	ECG	No therapy EPS + RFA	Only after EPS excludes high risk; if high risk, RFA before return to sports
WPW (symptomatic)	Palpitations Presyncope Syncope	δ Waves Short P-R interval	ECG	EPS ± RFA	After 3-6 months, if symptom free
AF	Palpitations	Often normal	ECG monitor	Rate control Anticoagulation Antiarrhythmics	Contact sports should be avoided if anticoagulated
AFL	Palpitations	Often normal	ECG monitor	Rate control Anticoagulation RFA Antiarrhythmics	Contact sport should be avoided if anticoagulated
APE	Palpitations	Often normal	ECG monitor	No therapy; BB if symptoms disabling	Restriction not needed

AF, Atrial fibrillation; *AFL,* atrial flutter; *APE,* atrial premature extrasystole; *AVNRT,* atrioventricular node re-entry tachycardia; *BB,* β-blocker; *CCA,* calcium channel antagonist; *ECG,* electrocardiogram; *EPS,* electrophysiological studies; *RFA,* radiofrequency ablation; *WPW,* Wolff-Parkinson-White syndrome.

laboratory investigations to exclude thyrotoxicosis and echocardiography to confirm or refute the presence of an explanatory congenital or acquired structural cardiac abnormality.

For athletes presenting with isolated atrial flutter, the aim of therapy should be to restore and maintain sinus rhythm. The high success (95%) of curative radiofrequency (RF) ablation procedures for typical atrial flutter makes the procedure the initial choice of therapy for the majority of athletes.[61,62] Resumption to full competitive sport is possible if an EPS demonstrates noninducibility of the atrial flutter 4 to 6 weeks after the initial ablation procedure.[14]

The main treatment strategy for athletes who present with AF is to attempt curative RF ablation in those who are symptomatic during exercise. An alternative strategy is to control the ventricular rate. Concerns regarding the potentially deleterious proarrhythmogenic effects of certain class I agents in the context of strenuous exercise remain; therefore rate control with agents such as digoxin, calcium channel antagonists, or β-blockers maybe preferred.[63] It is of particular note that β-blockers are prohibited specifically in those engaged in a number of sports.[13,14]

Athletes with asymptomatic, established persistent AF, with or without structural heart disease, who maintain an appropriate ventricular response during exercise, comparable with sinus rhythm, while receiving no or appropriate AV nodal-blocking drug therapy, are able to participate in all competitive sports.[14] If structural heart disease is present, the rules for eligibility in competitive sport are governed by the underlying disorder predisposing to the AF. Athletes who have undergone RF ablation procedures to treat AF are able to return to competitive sports, 4 to 6 weeks after the procedure if no evidence of recurrence exists, or an EPS has confirmed noninducibility.[14] If anticoagulation is indicated to reduce the risk of systemic thrombo-embolism associated with AF, the athlete is advised to avoid participation in sporting disciplines associated with heavy body contact.[13,14]

Atrioventricular Nodal Re-entrant Tachycardia

Symptomatic athletes with documented evidence of a supraventricular tachycardia should be investigated with the EPS in the first instance. EPSs enable delineation of the precise mechanism of the arrhythmia and offers highly successful curative rates, exceeding 95% in experienced hands, using RF ablation techniques.[64,65] The complication rate following electrophysiological RF ablation is under 1%.[65] An exercise test should be performed before ablation to induce the tachycardia and identify the rate response during exercise. An athlete without any evidence of structural heart disease can return to full participation in sport 4 to 6 weeks after ablation therapy, in the absence of symptoms or inducible arrhythmia following an exercise test.[14] Alternative therapeutic strategies include pharmacologic therapy with β-blockers or calcium channel antagonists. The response to drug therapy is less clear, and return to competition should be restricted until the athlete has been free from recurrent symptoms for 6 months.[14]

Wolff-Parkinson-White Syndrome

The ECG pattern in WPW syndrome may be identified as an incidental finding in asymptomatic athletes on a resting 12-lead ECG taken as part of pre-participation cardiac screening or may manifest as palpitations or syncope secondary to an AV re-entrant tachycardia or AF. In rare instances, WPW syndrome may present with aborted SCD from VF.

Athletes with symptoms should have RF ablation of the culprit accessory pathway before resuming competition. The procedure is associated with an excellent success rate and a low complication rate.[65,66] Consensus panels vary in their recommendations regarding return to competitive sport after curative ablation; the Bethesda guidelines permit return to competitive sport within 4

Table 51-6 Evaluation and Treatment of Ventricular Arrhythmias in Athletes

ARRHYTHMIA	SYMPTOMS	ECG	TREATMENTS	COMPETITIVE SPORTS
VPE	Palpitation	Normal	Reassurance β-Blockers	No restrictions
NSVT	Palpitations	Usually normal	SHD assessment: if none, reassurance only, if SHD present, further evaluation needed	No restrictions if no SHD If SHD present, restrictions based on type of SHD
VT/VF	Palpitations, presyncope, syncope, SCD	Normal or reflecting SHD	SHD assessment RFA or antiarrhythmics if no SHD If SHD present, ICD	Restricted to low-intensity sports

ICD, Implantable cardioverter defibrillator; *NSVT,* nonsustained ventricular tachycardia; *RFA,* radiofrequency ablation; *SCD,* sudden cardiac death; *SHD,* structural heart disease; *VF,* ventricular fibrillation; *VPE, ventricular premature extrasystole; VT,* ventricular tachycardia.

weeks after therapy, whereas the ESC guidelines suggest postponing sporting activity for a minimum of 3 months.[13,14]

The management of an asymptomatic athlete who demonstrates pre-excitation in a resting ECG is more controversial. The risk of SCD in asymptomatic is low and usually confined to those individuals with accessory pathways with short refractory periods (<250 ms).[67-70] The precise risk of potentially fatal arrhythmias during intensive exercise for prolonged periods is unknown. The Bethesda guidelines recommend electrophysiological investigation of the pathway only in asymptomatic athletes engaged in moderate- to high-intensity competitive sport.[14] In contrast, the ESC advocates mandatory EPS for all asymptomatic athletes to assess the refractory period of the accessory pathway.[13] A very short accessory pathway refractory period and inducible AF with conduction rates exceeding 240 beats/min are both indications for ablation of the accessory pathway to eliminate the risk of future potentially fatal tachyarrhythmias.[70,71]

Ventricular Arrhythmias

See Table 51-6.

Premature Ventricular Extrasystoles and Nonsustained Ventricular Tachycardia

Premature ventricular extrasystoles (PVEs) are common in athletes and are usually benign and asymptomatic. Their presence is rarely a risk factor for SCD or sustained ventricular tachyarrythmias in the absence of structural heart disease.[44] In one study of 355 athletes with PVEs, athletes with frequent PVEs (>2000/24 hours) or nonsustained VT were investigated and followed up. Of these, 1 athlete had evidence of structural heart disease and died suddenly. The remaining 70 athletes stopped training, after which 50 (71%) exhibited complete or partial resolution (<500 PVEs), and none experienced cardiovascular events or sudden death during an 8-year follow-up period.[72]

Based on the findings above, the presence of frequent or polymorphic ventricular extrasystoles and nonsustained VT is an indication for exclusion of structural heart disease and coronary disease with cardiac imaging studies and an exercise stress test, respectively. A structurally abnormal heart or an increase in the frequency of PVEs or associated presyncope or syncope during exercise is an indication for abstinence from exercise of moderate to high physical intensity.[13,14]

The recommendations for brief episodes of asymptomatic nonsustained tachycardia (8 to 10 consecutive beats) in the absence of structural heart disease are the same as those for athletes with PVEs.[13,14]

Sustained Ventricular Tachycardia

The identification of sustained monomorphic or polymorphic VT is an indicator of potentially serious underlying cardiac disease, and further evaluation in all such cases is manadatory.[13,14] All athletes with VT should be subject to comprehensive investigation to exclude cardiomyopathies, ion channel diseases, and coronary disease. In the absence of an obvious structural or electrical substrate during noninvasive testing, an EPS is recommended to identify foci that may be amenable to RF ablation if the patient is symptomatic. The identification of a treatable cardiac disorder such as right ventricular outflow tract VT or idiopathic monomorphic left ventricular tachycardia warrants RF ablation, and return to competition is recommended within 4 weeks (Bethesda)[14] or 3 months (ESC)[13] provided the athlete remains asymptomatic and ventricular tachycardia cannot be induced on maximal exercise or EPSs.[73-75]

The recommendations for sports participation in competitive athletes diagnosed with cardiomyopathy or ion channel disease is determined by the underlying cause, and such athletes cannot participate in sporting disciplines involving moderate-intensity or high-intensity exercise. Coronary revascularization is recommended in patients with significant coronary artery disease (CAD), and eligibility to compete can be confirmed after 6 months, provided no evidence of myocardial ischemia or VT is seen on an exercise stress test and left ventricular function is preserved.[13,14] Similarly, athletes with anomalous coronary artery origins should undergo surgical repair and can return to competitive sports after 6 months if they remain free of a recurrence of VT.[76]

Ventricular Fibrillation and Athletes with Implantable Cardioverter Defibrillators

The management guidelines for athletes who are survivors of SCD are identical to those for sedentary individuals; all individuals in this category warrant implantation of an implantable cardioverter defibrillator (ICD) for secondary prevention purposes.[77-79] Athletes with ICD may only compete is sporting disciplines involving

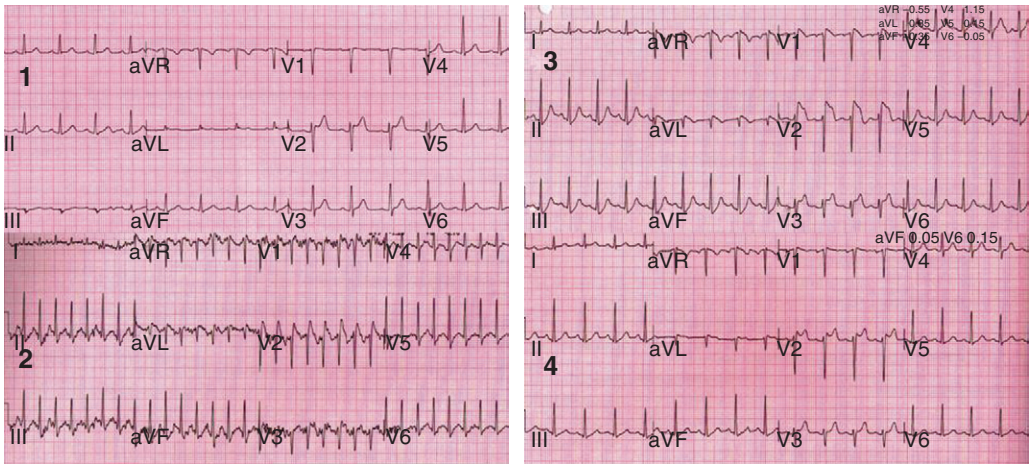

FIGURE 51-12 A 12- lead electrocardiogram (ECG) taken during a standard Bruce protocol exercise test in a young athlete with a history of sudden cardiac death in a first-degree family member. Note the appearance of the characteristic Brugada type 1 ECG—with a dominant S wave, downsloping ST-segment elevation, and T-wave inversions in leads V1 to V3—during maximal exercise (*2*) and in recovery (*3*). The ECG changes resolve and are absent at rest (*1*, before exercise; *4* after exercise).

low physical intensity and should avoid all forms of contact sport. An ICD should not be implanted to allow the athlete to continue at the same level of competition, as the effectiveness of such devices in terminating a potentially lethal ventricular arrhythmia in the context of the metabolic stresses of exercise, including hyperpyrexia, dehydration, electrolyte disturbance or acidosis, is unknown.

Brugada Syndrome

A significant subset of individuals with VF in the absence of structural heart disease have Brugada syndrome, which is explained by genetic mutations within the cardiac sodium channel SCN5A in the majority of cases.[80,81] The classic type 1 ECG pattern includes an RBBB pattern associated with coved ST-segment elevation pattern in leads V1 to V3. Although most deaths from Brugada syndrome occur during resting conditions such as sleep, the identification of Brugada syndrome in a competitive athlete, based on the typical type I Brugada ECG pattern, precludes competition in sporting disciplines of moderate or high physical intensity because of a theoretical risk of fatal arrhythmias associated with high body temperature during exercise and intense vagotonia in predisposed individuals after the exercise (Figure 51-12).[82,83]

Commotio Cordis

Commotio cordis is a term used to denote SCD caused by a fatal ventricular arrhythmia from blunt, nonpenetrating trauma to the precordium usually by a projectile object.[84,85] Most deaths have been reported in young athletes participating in baseball and ice hockey; however, deaths may also occur in hockey, lacrosse, softball, martial arts, and any sport where direct contact with the chest wall is possible. Over 180 deaths have been reported as caused by this condition.[86] SCD is caused by VF, which, in turn, is caused by an impact-induced premature ventricular complex that falls on the preceding T wave. The VF proves resistant to resuscitation in the vast majority of cases with a survival rate of less than 10%. Studies have identified important variables in the pathogenesis of SCD from commotio cordis, including impact timing (impact must occur during a 20-ms window on the upslope of the T wave), speed and location of impact, and hardness of the impacting object. The main therapeutic strategy is to prevent such catastrophes by wearing protective chest shields in sports such as baseball and cricket.[87]

Summary

Athletes are generally regarded as the healthiest individuals in society, but they are not immune from arrhythmias or cardiac disease. The evaluation and management of an athlete with arrhythmia or symptoms suggestive of arrhythmia is an uncommon clinical scenario but often proves to be an important and challenging issue facing the general physician and the sports cardiologist. Correct interpretation of the resting ECG may not only identify potentially fatal cardiac disease in a minority of athletes but also obviate the need for laborious, anxiety-provoking investigations in the majority. Erroneous diagnoses have the potential for serious consequences, including unnecessary disqualification from sport at one extreme and jeopardizing a young life at the other. Although sinus bradycardia and sinus arrhythmia are common in athletes, other bradyarrhythmias and most tachyarrhythmias may be harbingers of cardiac pathology warranting investigation and management as set out by consensus panels in the 36th Bethesda guidelines, the Sports Cardiology nucleus, for in the European Society of Cardiology.[13,14]

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CHAPTER 52

Proarrhythmia Syndromes

Anne M. Gillis

Proarrhythmia usually is defined as provocation of a new arrhythmia or aggravation of an existing arrhythmia during therapy with a drug at concentrations usually not considered toxic.[1-9] However, drug-drug interactions that may lead to unrecognized elevations in drug concentrations, for example, an I_{Kr} (delayed rectifier potassium [K^+] current)–blocking drug and a macrolide antibiotic, that can precipitate proarrhythmia. Other therapies (e.g., devices or ablation procedures) or pathophysiological conditions may also cause proarrhythmia.[2,10,11] The various proarrhythmia syndromes are summarized in Box 52-1, and the drugs and conditions most frequently associated with proarrhythmia are listed in Table 52-1. Most types of proarrhythmia occur in the setting of structural heart disease, but proarrhythmia may also occur in individuals without apparent heart disease. Antiarrhythmic drugs have a higher risk of causing ventricular proarrhythmia, but drugs that are considered generally safe may cause proarrhythmia in susceptible individuals.[2,4-6]

Drug-Induced Long QT Syndrome and Torsades De Pointes Ventricular Tachycardia

The greatest risk of ventricular proarrhythmia has been identified with drugs that prolong the Q-T interval on the electrocardiogram (ECG), which can predispose to a potentially life-threatening form of polymorphic ventricular tachycardia (VT), termed *torsades de pointes VT* (Figure 52-1).[1-9] Other pathophysiological conditions that result in excessive prolongation of the Q-T interval may also cause this proarrhythmia (see Table 52-1).[1-9] Syncope occurring early after the initiation of quinidine therapy was recognized as early as the 1920s, but it was not until the advent of continuous electrocardiographic monitoring that "quinidine syncope" was recognized to be caused by this pause-dependent polymorphic VT.[12] The term *torsades de pointes* was initially coined by Dessertenne in 1966 to describe this polymorphic tachyarrhythmia that is often characterized by beat-to-beat changes in the QRS axis.[13] Torsades de pointes VT often terminates spontaneously and may cause syncope, but it may transition into a sustained polymorphic VT or ventricular fibrillation (VF) and cause sudden cardiac death (SCD) (see Figure 52-1).

The most common drugs and conditions associated with excessive Q-T interval prolongation and torsades de pointes VT are summarized in Table 52-1. An up-to-date list of drugs associated with torsades de pointes VT is maintained at www.longqt.org. Antiarrhythmic drugs that prolong the ventricular action potential duration (APD), including class Ia drugs (quinidine, procainamide, disopyramide) and class III drugs (amiodarone, sotalol, dofetilide, ibutilide, azimilide), have all been reported to cause torsades de pointes VT.[2-9] Rarely, the class Ic drug propafenone has been reported to cause torsades de pointes VT. Associated bradycardia and electrolyte abnormalities (hypokalemia, hypomagnesemia, or both), often caused by diuretic use, increase the probability of torsades de pointes VT in the setting of class Ia or III antiarrhythmic drug use. Although amiodarone significantly prolongs the Q-T interval, the incidence of torsades de pointes VT associated with amiodarone use is relatively low.[2,14] Diuretics, by virtue of causing profound hypokalemia or hypomagnesemia, may be associated with torsades de pointes VT when other drugs are not used. The diuretic indapamide, which blocks the slowly activating component of the slow delayed rectifier K^+ current (I_{ks}), may cause excessive Q-T interval prolongation and torsades de pointes VT.[15]

Noncardiovascular drugs associated with torsades de pointes VT include tricyclic antidepressants (e.g., imipramine), antipsychotic drugs (e.g., haloperidol, risperidone, phenothiazine), antihistamines (e.g., diphenhydramine, terfenadine, astemizole), macrolide antibiotics (e.g., erythromycin, clarithromycin), quinolones (e.g., ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin), pentamadine, anti-fungal agents, and cisapride.[1-9] A number of drugs, including cisapride, terfenadine, and astemizole, have been withdrawn from the market because of an unacceptably high incidence of torsades de points VT. The risk of torsades de pointes VT caused by terfenadine or cisapride is attributed to the accumulation of these drugs in plasma as a consequence of coadministration of another drug (e.g., erythromycin or ketoconazole) that inhibits their cytochrome P450 3A4–mediated biotransformation to noncardioactive metabolites.[5,6,8]

Isolated profound bradycardia (most often in the setting of complete heart block) may be associated with profound Q-T interval prolongation and torsades de pointes VT, particularly in the setting of drugs or other factors that prolong the Q-T interval.[13] Neurologic events such as subarachnoid hemorrhage have been associated with marked repolarization abnormalities, Q-T interval prolongation, and torsades de pointes VT. Adrenergic stimuli in the setting of dobutamine infusion have also been reported to cause torsades de pointes VT. Case reports have also implicated anesthetic agents, including halothane, as a cause for torsades de pointes VT.

Cellular Mechanisms of Torsades De Pointes Ventricular Tachycardia

An increase in inward currents, a reduction of outward currents, or a combination of both during phase 2 and 3 of the ventricular action potential leads to prolongation of the ventricular action potential, which manifests as Q-T interval prolongation on the ECG (Figure 52-2).[1-7] Mutations of genes encoding K^+, sodium (Na^+), and calcium (Ca^{2+}) channels have been linked to the

Box 52-1 Proarrhythmia Syndromes

DRUG INDUCED
Action potential prolonging drugs
Torsades de pointes VT acquired long QT syndrome
Ventricular fibrillation

Sodium Channel–Blocking Drugs
Ventricular fibrillation
Monomorphic VT
Atrial flutter with 1:1 AV conduction

PACEMAKER RELATED OR ICD RELATED
Anti-tachycardia pacing–induced hemodynamically unstable VT or VF
Anti-tachycardia pacing–induced atrial fibrillation
Pause induced VT or VF
Cardiac resynchronization therapy
Antiarrhythmic drug–induced increases in defibrillation threshold

ABLATION RELATED
Left atrial flutter

AV, Atrioventricular; ICD, implantable cardioverter-defibrillator; VF, ventricular fibrillation; VT, ventricular tachycardia.

congenital long QT syndrome (LQTS). Disease states such as left ventricular hypertrophy and heart failure are associated with a reduction in outward currents caused by the downregulation of transient outward K^+ current (I_{to}), I_{Kr}, the inward rectifier K^+ current (I_{K1}), or all, which occurs in a spatially heterogeneous manner.[16,17] A reduction in net outward currents, an increase in inward currents, or a combination of both, facilitates the development of early afterdepolarizations (EADs) that develop in M cells or Purkinje cells because of the activation or reactivation of arrhythmogenic inward currents, including Ca^{2+} channels or the Na^+-Ca^{2+} exchange current.[1-7,18] These EADs may initiate torsades de pointes VT, which is then maintained by re-entry (see Figure 52-2).[1,6] Intracellular calcium overload, as in the setting of heart failure, may facilitate the development of EADs in the setting of acquired LQTS.[17]

In the ventricular myocardium, the APD varies in a spatially heterogeneous manner because of differences in current densities in specific cell types (Purkinje fibers and endocardial, mid-myocardial, or epicardial cells).[1,6,16,18] The ventricular APD is longest in the mid-myocardial layer (M cells) and shorter in the epicardial and endocardial regions. This dispersion of ventricular

Table 52-1 Drugs and Conditions Associated with Torsades de Pointes Ventricular Tachycardia

DRUG CLASS	SPECIFIC DRUGS	DRUG CLASS	SPECIFIC DRUGS
ANTIARRHYTHMIC			Ciprofloxacin
Class Ia	Quinidine		Levofloxacin
	Procainamide		Moxifloxacin
	Disopyramide		Ofloxacin
Class Ic	Propafenone		Trimethoprim-sulfamethoxazole
Class III	Amiodarone		Pentamidine
	d, l-Sotalol	Antifungal	Ketoconazole
	d-Sotalol		Fluconazole
	Dofetilide		Itraconazole
	Ibutilide	Antihistamines	Diphenhydramine
	Azimalide		Terfenadine*
Psychotropic	Haloperidol		Astemizole*
	Phenothiazines	Cholinergic antagonists	Cisapride*
	Risperidone	Narcotics	Methadone
	Tricyclic antidepressants	**DRUGS FOR OTHER CONDITIONS**	
	Tetracyclic antidepressants	Bradycardia	Complete heart block or significant bradycardia
Diuretics	Furosemide		
	Hydrochlorothiazide	Electrolyte abnormalities	Hypokalemia
	Indapamide		Hypomagnesemia
	Metolazone		Hypocalcemia
Antimicrobial	Erythromycin	Nervous system injury	Subarachnoid hemorrhage
	Clarithromycin		

**No longer commercially available.*

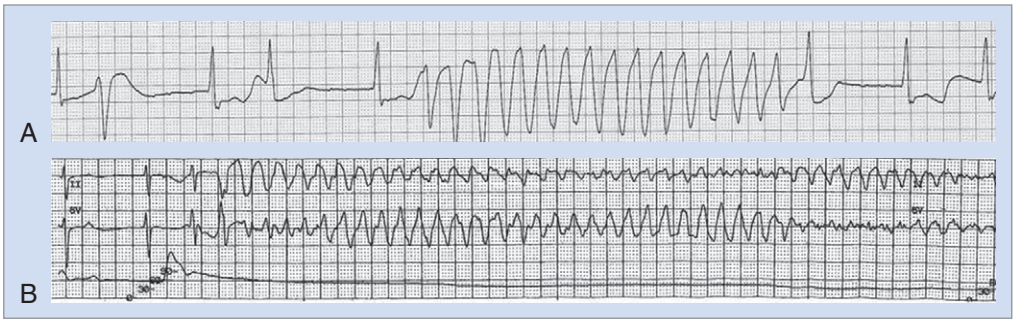

FIGURE 52-1 *Top,* Spontaneously terminating torsades de pointes ventricular tachycardia (VT). Note the bradycardia, Q-T interval prolongation, and the late coupled ventricular premature beats, which cause greater prolongation of the Q-T interval and a run of spontaneously terminating polymorphic ventricular tachyarrhythmia. *Bottom,* Torsades de pointes VT, which generates into ventricular fibrillation and sudden cardiac arrest. Note the Q-T interval prolongation and polymorphic VT triggered by a late coupled ventricular premature beat.

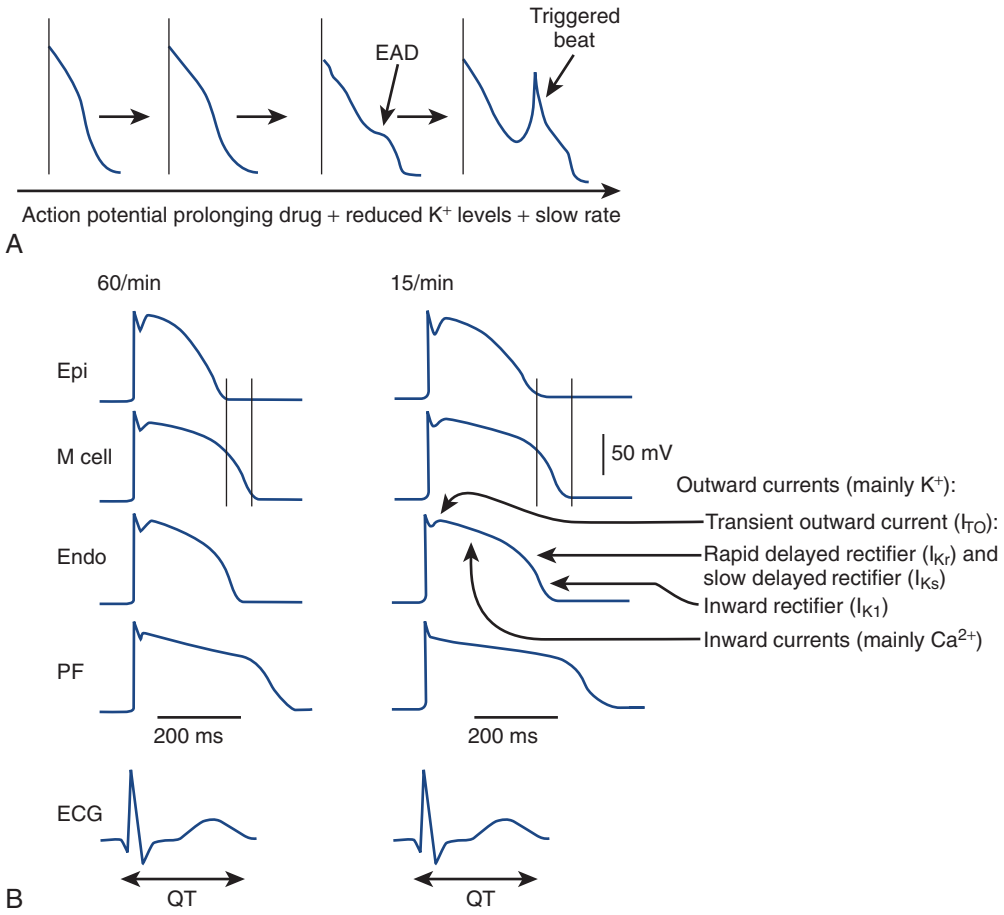

FIGURE 52-2 Mechanism of torsades de pointes ventricular tachycardia (VT). **A,** Exposure of cardiac Purkinje fibers from dogs to experimental conditions mimicking those seen in torsades de pointes results in action potential prolongation, early afterdepolarization (*EAD*), and a triggered beat arising from the EAD. **B,** Differences among the durations and configurations of action potentials recorded from epicardial (*Epi*), mid-myocardial (*M cell*), endocardial (*Endo*), and Purkinje fiber (*PF*) sites. The relationship between individual action potentials and the electrocardiogram tracings is shown at the bottom. The action potentials on the left were recorded at a stimulation rate of 60 beats/min; those on the right were recorded at a rate of 15 beats/min. The *vertical lines* denote the end of action potentials in epicardial sites (shortest) and M-cell sites (longest). At the slower rate, exaggerated heterogeneity exists in the durations of the action potentials and Q-T interval prolongation. Re-entrant excitation caused by heterogeneity in the action potentials causes torsade de pointes VT. *(From Roden DM: Drug-induced prolongation of the QT interval,* N Engl J Med *350:1013–1022, 2004.)*

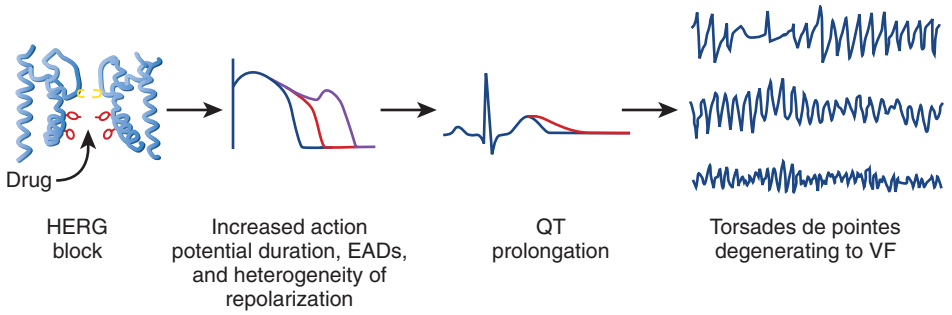

FIGURE 52-3 Mechanisms of ventricular tachyarrhythmias and sudden death secondary to *HERG* blockade. Drug blockade of the HERG channel (*left*) causes prolongation of the ventricular action potential (*blue*) followed by the development of early afterdepolarization (*red*). These changes, which are heterogeneous across the ventricular wall, result in Q-T interval prolongation and increased dispersion of the Q-T interval. A ventricular premature beat triggers torsades de pointes ventricular tachycardia, which, in this example, degenerates into ventricular fibrillation. *(From Roden DM, Viswanathan PC: Genetics of the long QT syndrome,* J Clin Invest *115:2025–2032, 2005.)*

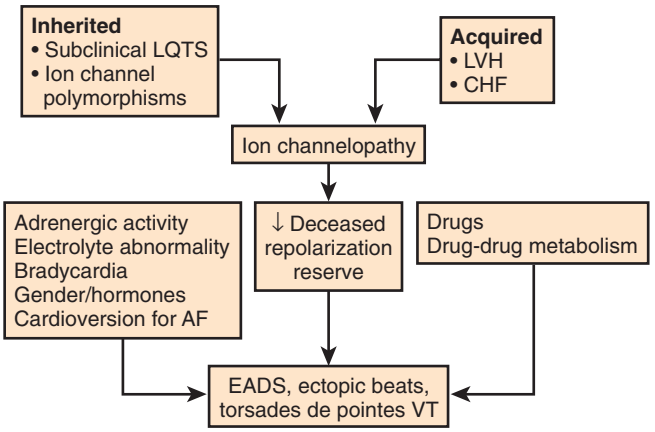

FIGURE 52-4 Factors influencing repolarization reserve and risk for torsades de pointes ventricular tachycardia. *AF*, Atrial fibrillation; *CHF*, congestive heart failure; *EADs*, early afterdepolarizations; *LQTS*, long QT syndrome; *LVH*, left ventricular hypertrophy; *VT*, ventricular tachycardia.

repolarization is increased in disease states, including ventricular hypertrophy, and may be further exaggerated by the administration of a drug that prolongs the Q-T interval.[16] Marked spatial dispersion of ventricular repolarization appears to be a prerequisite for torsades de pointes VT because it provides the functional substrate for re-entry.[19] Functional block may vary on a beat-to-beat basis, contributing to spiral re-entrant waves, which explains the polymorphic nature of the arrhythmia.[1,6,20]

Although multiple ionic mechanisms may contribute to the development of torsades de pointes VT, the vast majority of drugs associated with torsades de pointes VT are thought to act by blockade of the rapid component of I_{Kr} (Figure 52-3).[1,3,7] The *HERG* gene (also known as *KCNH2*) regulates the expression of I_{Kr}. The molecular structure of the drug-binding domain in the HERG channel makes it more vulnerable to blockade by a variety of drugs compared with other K^+ channels. A small proportion of individuals who develop drug-induced torsades de pointes may have subclinical forms of congenital LQTS.[3-6,21] Some polymorphisms of genes responsible for the expression or regulation of the ion channels involved in congenital LQTS have also been implicated in drug-induced torsades de pointes.[3,4,21] Mutations in *HERG* may enhance blockade of the channel by certain drugs.

A normal QT at the start of antiarrhythmic drug therapy does not exclude the risk for proarrhythmia.[2,5,7] The concept of reduced repolarization reserve and the risk of proarrhythmia was initially introduced by Roden.[5,22] Cardiac repolarization is determined by I_{Kr} and I_{Ks} as well as other inward and outward currents during the plateau of the action potential. A defect in one of these currents may not be apparent if other currents that contribute to repolarization are intact. Roden has hypothesized that "physiologic processes such as drug metabolism or cardiac repolarization include multiple redundancies" and that "loss of these redundancies due to congenital or acquired conditions may enhance susceptibility to proarrhythmic responses even in the absence of a baseline phenotype."[5] For example, decreased expression of I_{Ks} because of a mutation in one of the genes responsible for expression of I_{Ks}, or because of a pathophysiological state such as heart failure or atrial fibrillation (AF), may not become apparent until the individual is treated with a drug that blocks I_{Kr}, which results in marked prolongation of the Q-T interval and proarrhythmia in this setting of reduced repolarization reserve (Figure 52-4).

The period immediately after cardioversion to sinus rhythm from AF appears to be a time of great risk for torsades de pointes VT.[9,23,24] The potential mechanism underlying this event is shown in Figure 52-5. The sustained tachycardia and the neurohumoral changes associated with AF may alter some electrophysiological properties, including downregulation of repolarizing currents. Restoration of sinus rhythm is often associated with bradycardia

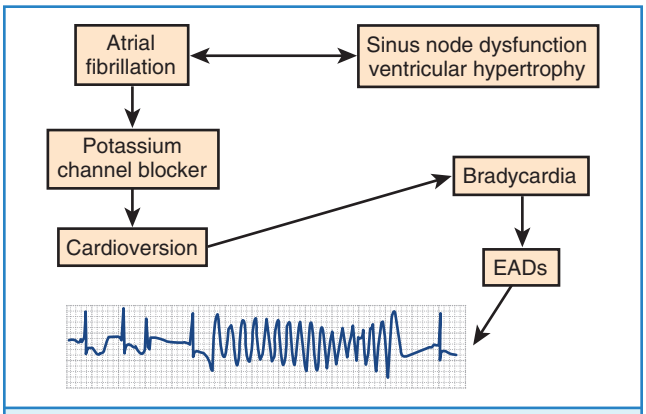

FIGURE 52-5 Conversion from atrial fibrillation to sinus rhythm increases the risk of ventricular proarrhythmia. Resumption of sinus rhythm often is associated with profound bradycardia, which, in the setting of left ventricular hypertrophy or left ventricular dysfunction, is associated with action potential prolongation. Early afterdepolarizations (*EADs*) triggering torsades de pointes ventricular tachyarrhythmia are more likely to occur in this setting.

and action potential prolongation that could be further exaggerated by the downregulation of K^+ channels. The action potential prolongation also facilitates increased sarcoplasmic calcium, predisposing to triggered activity. A similar situation may occur after atrioventricular (AV) junction ablation for the management of persistent AF. The early period after ablation is a particularly vulnerable period for SCD, which is believed to be caused by bradycardia-dependent polymorphic VT.[25] Successful AV junction ablation is associated with abrupt slowing of the heart rate. Sudden slowing of the heart rate and the associated prolongation of the ventricular APD after ablation could increase the likelihood of EADs. Consistent with this hypothesis, we have observed exaggerated bradycardia-dependent prolongation of the Q-T interval and increased Q-T interval dispersion in patients with significant left ventricular dysfunction after total AV junction ablation.[26]

Risk Factors for Torsades de Pointes Ventricular Tachycardia

The risk factors for torsades de pointes VT are summarized in Box 52-2.[1-9,27,28] The presence of multiple risk factors (e.g., female gender, cardiac hypertrophy, electrolyte abnormalities, and prior history of VT) dramatically increase the risk of developing torsades de pointes VT. Diuretic use in the setting of normal serum potassium concentrations has been reported to be a risk factor for torsades de pointes VT.[29] This may be caused by total body potassium depletion that may not be reflected by serum potassium concentrations or the direct action potential–prolonging effects of some diuretic drugs.

Women have a twofold to threefold greater risk of developing torsades de pointes VT during treatment with action potential–prolonging drugs independent of other risk factors.[27,30] In the general population, women have longer Q-T intervals compared with men. In experimental models, females have longer ventricular APDs and increased transmural dispersion of repolarization compared with males, which may be explained, in part, by reduced expression of I_{Kr} as well as other K^+ currents.[28] Testosterone shortens the ventricular APD, whereas estrogen prolongs the APD.

Box 52-2 Risk Factors for Torsades de Pointes Ventricular Tachycardia

Female gender
Baseline Q-T interval prolongation
Excessive Q-T interval prolongation on drug
Increased Q-T interval dispersion on drug
Bradycardia
Recent cardioversion from atrial fibrillation
Hypokalemia
Hypomagnesemia
Congestive heart failure or left ventricular dysfunction
Ventricular hypertrophy
History of VT or VF
Renal impairment
Ion channel polymorphisms
Subclinical long QT syndrome

VF, *Ventricular fibrillation;* VT, *ventricular tachycardia.*

Gender-specific differences in drug transport and metabolism may also contribute to the modulation of the pharmacokinetics of I_{Kr}-blocking drugs.[28]

The risk of torsades de pointes VT is generally related to drug dose.[6,31] However, torsades de pointes VT has been described as an idiosyncratic reaction that occurs during quinidine therapy, and syncope secondary to torsades de pointes occurs within hours of initiation of this drug therapy.[6,12] The development of torsades de pointes VT at low quinidine concentrations may be secondary to the I_{Kr}-blocking effects in conjunction with augmentation of the late Na^+ current resulting in a decrease in net repolarizing currents; however, at higher quinidine concentrations, the more dominant Na^+ channel–blocking effects balance the I_{Kr} block and restore the repolarization reserve.[6] The risk of torsades de pointes VT associated with sotalol or dofetilide therapy clearly increases significantly with dose, which is further exacerbated by other risk factors, including renal failure.[31] The incidence of ventricular proarrhythmia during sotalol initiation at doses up to 320 mg/day was 1.8%; this incidence increased to 4.5% at doses up to 480 mg/day and to 6.8% at doses greater than 640 mg/day.

Some cardiac disease processes such as ventricular hypertrophy or significant left ventricular dysfunction are associated with significant prolongation of the APD.[32-34] These electrophysiological changes are caused by changes in repolarizing current densities, including decreases in I_{to}, I_{K1}, I_{Kr}, and I_{Ks}.[16,35] Changes in these repolarizing currents in their densities, balance, or both may alter the response of specific channel blockers, resulting in exaggerated prolongation of the APD and increased dispersion of ventricular repolarization that provides the substrate for torsades de pointes VT.

Electrocardiographic Harbingers of Torsades de Pointes Ventricular Tachycardia

Excessive Q-T interval prolongation and morphologic changes in the T wave usually precede the development of torsades de pointes VT.[6,29,34] Figure 52-6 illustrates the changes in the Q-T interval and T-wave morphology during sotalol initiation that precede the development of torsades de pointes VT. Note the development of Q-T interval prolongation and a U wave, both of

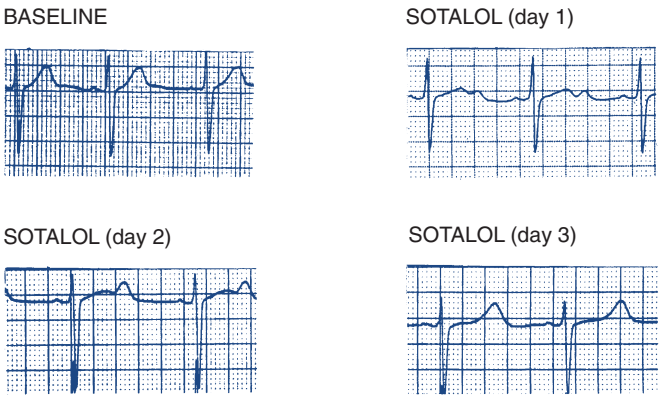

FIGURE 52-6 Serial changes in the Q-T interval after sotalol initiation. Note that the Q-T interval prolongs early after initiation of sotalol (*right upper panel*). This is followed by the development of more marked U waves, bradycardia, and further Q-T interval prolongation.

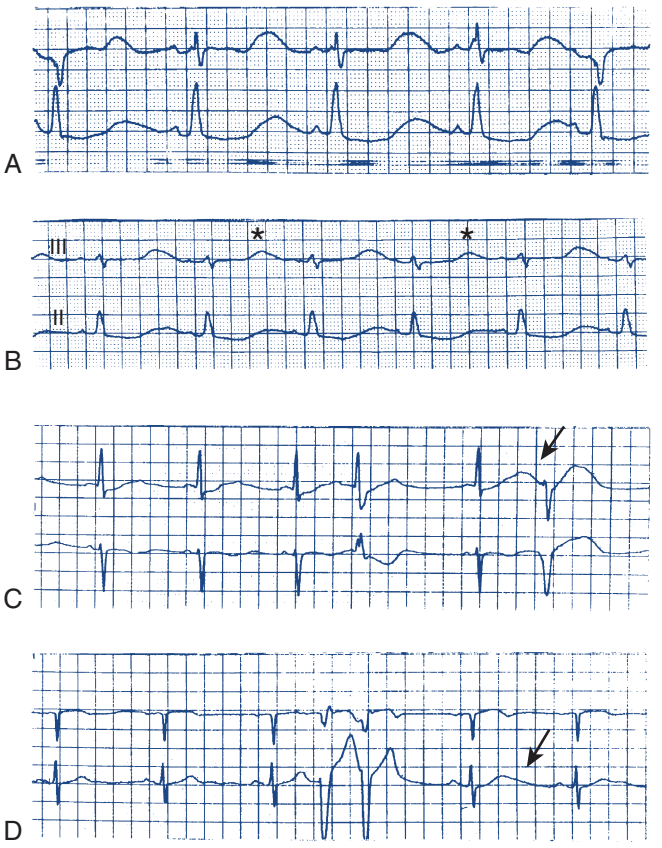

FIGURE 52-7 Electrocardiographic harbingers of torsades de pointes ventricular tachyarrhythmia. Note the marked Q-T interval prolongation (**A**), the T-wave alternans in the setting of Q-T interval prolongation (**B**), prolongation of the Q-T interval after a post-extrasystolic pause (**C**), and late coupled premature ventricular beats (**C** and **D**).

which become progressively more prominent over the 48 to 72 hours after the initiation of sotalol administration. The magnitude of the Q-T interval prolongation may be exaggerated by abrupt slowing of the heart rate (e.g., after a compensatory pause). The prominence of the U waves may vary on a beat-to-beat basis and may be modified by abrupt changes in heart rate. Figure 52-7 illustrates and Box 52-3 summarizes some of the electrocardiographic harbingers of torsades de pointes VT. Note the excessive Q-T interval prolongation, the development of prominent U waves, T-wave alternans, post-extrasystolic pause exaggeration of the Q-T interval prolongation, and T-wave morphologic changes and clustering of repetitive polymorphic ventricular premature beats.

Box 52-3 Electrocardiographic Harbingers of Torsades de Pointes Ventricular Tachycardia

QTU prolongation
Increased Q-T interval dispersion >60 ms
T-wave alternans
Post-extrasystolic pause TU changes
Late-coupled polymorphic VPBs
Repetitive polymorphic beats

QTU, *QT–U-wave interval;* TU, *T wave–U wave complex;* VPBs, *ventricular premature beats;* VT, *ventricular tachycardia.*

Dispersion of Ventricular Repolarization and Torsades de Pointes Ventricular Tachycardia

Abrupt changes in the Q-T interval and in the relationship between the Q-T interval and heart rate may develop immediately before the onset of torsades de pointes VT.[7,36] Increased Q-T interval dispersion, defined as the difference between the shortest and the longest Q-T intervals measured on the 12-lead ECG, may precede the development of torsades de pointes VT. Class Ia antiarrhythmic drugs were shown to significantly increase Q-T interval dispersion compared with the drug-free state in patients who developed torsades de pointes VT during drug therapy.[19,34] In contrast, patients who did not develop this proarrhythmia during drug therapy did not manifest a significant increase in Q-T interval dispersion compared with those in the drug-free state. Amiodarone did not increase Q-T interval dispersion in the patients who developed torsades de pointes VT on class Ia drugs. The low incidence of torsades de pointes VT observed during amiodarone therapy likely reflects its homogeneous effects on ventricular repolarization, which may, in part, be caused by calcium channel–blocking and β-adrenergic–blocking effects.[19,34] The time from the peak of the T wave to its return to baseline has been shown to correlate directly with the development of torsades de points VT.[7] Amiodarone therapy causes less bradycardia-induced prolongation of the APD of M cells isolated from patients with heart failure compared with M cells isolated from patients with heart failure who were not treated with amiodarone.[37] The reduced dispersion of ventricular repolarization likely explains the low incidence of torsades de pointes VT occurring in association with amiodarone compared with class I or other class III antiarrhythmic drugs.

Treatment

The initial treatment for torsades de pointes VT is magnesium sulfate (1 to 2 g IV bolus).[38] Magnesium should be administered even if the serum magnesium level is normal. The drug implicated should be discontinued, and other reversible causes should be corrected (e.g., electrolyte abnormalities, bradycardia). Overdrive atrial or ventricular pacing is effective when the arrhythmia recurs despite magnesium administration.[39] Isoproterenol infusion may also be used to increase heart rate and shorten the Q-T interval. Atropine has been reported to eliminate torsades de pointes VT, presumably via the increase in heart rate reversing the Q-T interval prolongation.[40] Serum K^+ should be maintained in the high normal range (4.5 to 5 mEq/L). Elevation of the extracellular K^+ concentration increases outward K^+ currents and reduces the magnitude of drug block of I_{Kr}, thus shortening ventricular repolarization.[41] Modest increases in serum K^+ may reverse the repolarization abnormalities associated with some variants of LQTS or abnormalities associated with antiarrhythmic drug use and cause Q-T interval shortening as well as reduced Q-T interval dispersion.[42] The mechanism by which magnesium prevents torsades de pointes VT is uncertain. Magnesium does not shorten the APD or the Q-T interval and likely exerts its effect by blocking Ca^{2+} channels. In experimental models, Na^+ channel blockers have been reported to antagonize the effects of class Ia and III drugs on APD and to prevent proarrhythmia.[43,44] K^+ channel–activating compounds have also been reported to prevent EAD and proarrhythmia in animal models.[45] However, these agents have not become mainstream therapies for torsades de pointes VT.

Prevention

Torsades de pointes VT may be prevented by (1) avoiding the use of class I or III antiarrhythmic drugs in patients with significant left ventricular dysfunction, (2) reducing the dose or stopping the drug if significant Q-T interval prolongation (>500 ms) or increased Q-T interval dispersion (>80 ms) is observed during drug therapy, (3) correcting electrolyte abnormalities (hypokalemia or hypomagnesemia) before antiarrhythmic drug initiation, (4) avoiding potassium-wasting diuretics or using potassium-sparing diuretics (amiloride or spironolactone), (5) considering prophylactic magnesium supplements in high-risk patients; (6) preventing significant bradycardia; (7) considering permanent pacing in patients with significant bradycardia in whom class I or III antiarrhythmic drugs are considered important therapies; and (8) monitoring high-risk patients during initiation of antiarrhythmic drug therapy in the hospital.

Should Antiarrhythmic Drug Therapy Be Initiated in the Hospital?

The safety of initiating antiarrhythmic drug therapy in the outpatient setting is still being debated.[31] Approximately 50% of episodes of ventricular proarrhythmia occur within 72 hours of initiation of antiarrhythmic drug therapy for AF. It has been estimated that 1200 patients would have to be monitored for 3 days to prevent one torsades de pointes VT–related death. The Symptomatic Atrial Fibrillation Investigative Research on Dofetilide (SAFIRE-D) investigators reported a low incidence (0.8%) of torsades de pointes VT during the initial 3 days of dofetilide therapy in patients with AF.[46] Nevertheless, the guidelines for dofetilide initiation approved by the U.S. Food and Drug Administration (FDA) require that this drug be initiated in the hospital. Similar recommendations can be found in the product monograph for sotalol approved for the treatment of AF. ECG monitoring during drug initiation should be undertaken for high-risk patients but does not appear to be cost effective for low-risk patients. Moreover, efforts at the prevention of proarrhythmia must be continued throughout the course of antiarrhythmic drug therapy.

Proarrhythmia Caused by Sodium Channel Blocking Drugs

Sudden Cardiac Death After Myocardial Infarction

Cardiac Arrhythmia Suppression Trials

The Cardiac Arrhythmia Suppression Trial (CAST) investigators reported that patients with frequent ventricular premature beats after a myocardial infarction (MI) who were treated with flecainide or encainide had a higher mortality rate compared with patients treated with placebo.[47] The proarrhythmic risk was not just limited to the early phase of drug therapy but increased over the course of the trial. Subgroup analyses suggested that recurrent myocardial ischemia played an important role in the increased risk of arrhythmic death.[48-50] Total mortality rate and risk of cardiac arrest were higher in patients who had sustained a

non–Q-wave MI and in those who had not received thrombolytic therapy. The relative risk (RR) of death or cardiac arrest was 10.6 in patients sustaining a non–Q-wave MI versus 1.45 in those patients sustaining a Q-wave MI.[49] This observation led to the hypothesis that recurrent ischemia in the setting of class Ic drug therapy altered the electrophysiological milieu in the infarct region, predisposing to a proarrhythmic response. Consistent with this hypothesis, concomitant β-blocker and flecainide or encainide use was not associated with an increased RR of death.[49]

CAST-II demonstrated the increased proarrhythmic potential of the class I antiarrhythmic drug moricizine during early dosage titration.[51] Death or nonfatal cardiac arrest during the drug initiation phase was significantly greater in patients treated with moricizine compared with those treated with placebo. The RR of death or nonfatal cardiac arrest during the initial 2 weeks of moricizine therapy was 5.6. Although survival during long-term follow-up was similar in the moricizine and placebo groups, CAST-II was terminated early because it was deemed unlikely that a survival benefit from moricizine would be observed if the trial were completed.

CAST and meta-analyses of class I anti-arrhythmic drugs in patients with ischemic heart disease, left ventricular dysfunction, or both indicate that these drugs increase the risk of lethal cardiovascular events.[52,53] Therefore such drugs are contraindicated in patients with a history of prior MI. By extension, many clinicians also believe that these drugs are relatively contraindicated in any patient with ischemic heart disease or risk factors for ischemic heart disease, as well as in patients with significant left ventricular dysfunction.

Mechanisms of Ventricular Proarrhythmia in Ischemic Heart Disease

Na^+ channel–blocking agents slow conduction in atrial and ventricular muscles in a use-dependent manner (i.e., greater conduction block occurs at faster heart rates). Some Na^+ channel–blocking agents (encainide and flecainide) produce extensive block at slow physiological heart rates, which increases the risk of proarrhythmia.[2,54] By causing excessive slowing of conduction that exceeds changes in refractoriness in diseased tissue, class Ic antiarrhythmic drugs may stabilize a re-entrant circuit that has previously been unable to sustain re-entry and thus establish the electrophysiological substrate for sustained VT or convert nonsustained VT to sustained monomorphic VT.[2,54] This model of re-entry assumes that the drug alters only conduction velocity. In reality, many Na^+ channel–blocking drugs alter conduction velocity and refractoriness in a heterogeneous manner that depends on the physiological milieu. Increased dispersion of tissue refractoriness may also promote ventricular re-entry.

Experimental studies demonstrated that encainide and flecainide enhanced induction of sustained VT in dogs with prior MI without VT inducible at baseline.[55-58] These drugs cause preferential conduction slowing in the peri-infarct zone, which results in unidirectional block or marked slowing of conduction in the direction transverse to fiber orientation that facilitates ventricular re-entry. In experimental models of acute ischemia, the presence of a Na^+ channel–blocking agent significantly increased the incidence of spontaneous ventricular fibrillation (VF).[54] Class I drugs, including lidocaine and flecainide, produce exaggerated effects on conduction velocity and repolarization in ischemic tissue, contributing to the substrate for VF.[58-61] Ranger et al evaluated the concentration dependence of flecainide proarrhythmia in dogs with acute or chronic MI.[56] Proarrhythmia was observed in 79% of dogs with chronic MI versus 55% of dogs with acute ischemia. However, the concentration dependence of flecainide proarrhythmia differed substantially between the two groups: proarrhythmia occurred at therapeutic concentrations in the setting of acute MI and most likely manifested as VF, whereas 20-fold higher concentrations of flecainide were required to induce proarrhythmia in the dogs with chronic MI, and proarrhythmia manifested as induced sustained monomorphic VT.[56]

Studies in experimental models have demonstrated that β-blockers, in the setting of acute ischemia, reduce the proarrhythmic effects of Na^+ channel blockers.[62,63] Under normal conditions, isoproterenol reverses flecainide's effect on Na^+ channel block. However, under conditions of membrane depolarization, as would be expected in ischemia, isoproterenol amplifies flecainide's effects on sodium channel block.[63] Thus an enhanced sympathetic tone in the setting of acute ischemia may further modulate the interaction between a class I drug and ischemic tissue to promote proarrhythmia.

These experimental studies demonstrate that class I antiarrhythmic drugs, when present in sufficient concentrations in the myocardium, increase the risk for VF in patients with coronary artery disease if acute ischemia develops, presumably because of spatially heterogeneous effects on conduction velocity and possibly repolarization, which provides the substrate for re-entry and VF.

Other Cardiac Disease States

Information about the proarrhythmic potential of class I Na^+ channel–blocking drugs in cardiac disease models without ischemic heart disease is limited. However, cardiac hypertrophy and ventricular dysfunction in the setting of volume overload are associated with heterogeneous abnormalities of ventricular conduction and repolarization.[17] In the setting of cardiac disease, the resting membrane potential is likely elevated in some cells, which might predispose them to greater antiarrhythmic drug-induced Na^+ channel conduction block. In addition, frequent ventricular premature beats, which may occur in the setting of left ventricular dysfunction, may be associated with greater conduction delays in the presence of class I drugs and thus predispose to ventricular re-entry. Some Na^+ channel–blocking drugs produce exaggerated slowing of conduction in models of disease states.[54,64] Thus any Na^+ channel–blocking drug may likely produce exaggerated electrophysiological responses in diseased ventricular tissue with responses occurring in a heterogeneous manner, thereby predisposing to ventricular proarrhythmia. Therefore selective Na^+ channel–blocking drugs are relatively contraindicated in all patients with significant left ventricular dysfunction.

Incessant Ventricular Tachycardia Secondary to Sodium Channel–Blocking Drugs

Some patients treated with Na^+ channel–blocking drugs, particularly class Ic drugs such as flecainide or propafenone, may develop slow, incessant VT.[2,65] This usually occurs in the setting of structural heart disease (e.g., prior MI) and marked conduction slowing because the circulating wavefront is less likely to encounter refractory tissue and be abolished. Incessant VT may be hemodynamically tolerated because of its slow rate. However, the arrhythmia may degenerate into a hemodynamically significant VT or VF and be lethal.[65] This arrhythmia is usually observed with higher or toxic drug doses or in the setting of other pathophysiological conditions that exaggerate the effects of the drug on

conduction (e.g., acidosis, hyperkalemia, or concomitant Na^+ channel blockers, including phenytoin). Incessant monomorphic VT may also be observed with overdose of tricyclic antidepressants. The anticholinergic effects of tricyclic antidepressants cause an increase in sinus rate, which results in exaggerated Na^+ channel block.

Treatment

The antiarrhythmic drug should be discontinued, and electrolyte abnormalities or acidosis should be corrected. Hypertonic saline or sodium bicarbonate may reverse the conduction slowing and terminate the arrhythmia.[66,67] However, Na^+ may exacerbate heart failure, so caution is required in patients with significant left ventricular dysfunction. β-blockers may be beneficial because the magnitude of conduction slowing is less at slower heart rates. Na^+ channel–blocking drugs should be avoided.

Ventricular Proarrhythmia in Wolff-Parkinson-White Syndrome

In the setting of ventricular pre-excitation, adenosine, digoxin, β-blockers, verapamil, and diltiazem may promote conduction of AF in an antegrade fashion across the accessory pathway. If the antegrade refractory period of the accessory pathway is short, this may provoke VF. Accordingly, these drugs are contraindicated in this setting.[68]

Atrial Flutter with 1:1 Atrioventricular Conduction

In patients with atrial flutter, Na^+ channel–blocking drugs may significantly slow the atrial flutter cycle length such that 1:1 AV conduction develops and the ventricular rate increases (Figure 52-8).[69,70] This phenomenon has been reported with quinidine and has been attributed to quinidine's vagolytic effects. Slowing of the atrial flutter cycle length also occurs in association with flecainide and propafenone, particularly when rate-controlling (AV node–blocking) antiarrhythmic drugs are not prescribed. During atrial flutter, the atrial rate typically is approximately 300 beats/min. In most individuals not on AV node blocking drugs, 2:1 AV conduction is present and the ventricular response is approximately 150 beats/min. Flecainide or propafenone may slow the atrial flutter rate to approximately 200 to 220 beats/min. This may allow the ventricular response to increase from 150 to 200 to 220 beats/min with 1:1 AV conduction. An intraventricular conduction delay pattern is often observed because of the marked rate-dependent conduction block associated with these drugs at higher heart rates. In fact, this arrhythmia may be misdiagnosed as VT. This form of proarrhythmia may occur in patients receiving class I antiarrhythmic drugs for the treatment of AF. Such patients may have intermittent atrial flutter, or the antiarrhythmic drug may alter the electrophysiological substrate in the atria to predispose to atrial flutter.

The diagnosis of atrial flutter with 1:1 AV conduction should be considered in patients with a history of AF or atrial flutter who are treated with class Ic drugs. Carotid sinus massage or intravenous adenosine may unmask atrial flutter and establish the diagnosis. Intravenous β-blockers or Ca^{2+} channel blockers (verapamil or diltiazem) should be administered to control the ventricular rate. Na^+ channel blocking drugs should be administered in conjunction with an AV node–blocking drug (e.g., a β-blocker or Ca^{2+} channel blocker) in patients with atrial flutter or AF to prevent the development of this form of proarrhythmia.

Class I or class III antiarrhythmic drugs may also convert AF to atrial flutter and may precipitate atrial flutter with 1:1 AV conduction through their effects on slowing atrial conduction in the absence of AV node–blocking drugs.

Increased Cardiac Mortality Associated with Class III Drugs

The Survival with Oral D-Sotalol (SWORD) trial investigators reported increased cardiovascular mortality with d-sotalol compared with placebo in patients with left ventricular dysfunction.[71,72] As in CAST, excess mortality rates on active drug continued to be observed through the course of follow-up. The mechanism or mechanisms of the increased mortality rate are uncertain. Torsades de pointes VT is certainly a possibility. However, VF in the setting of acute ischemia precipitated by ischemia-mediated exaggeration of antiarrhythmic drug effects (similar to the mechanism proposed in CAST) is also another plausible cause. In contrast, the Danish Investigation of Arrhythmia and Mortality on Dofetilide (DIAMOND) did not report an increased mortality rate associated with dofetilide compared with placebo in patients with left ventricular dysfunction.[73] Differences in trial design likely explain these apparently divergent outcomes. In DIAMOND, drug therapy was initiated in the hospital during ECG monitoring, and therapy was stopped if excessive Q-T interval prolongation was observed. In contrast, the SWORD trial design favored drug doses associated with Q-T interval prolongation. Furthermore, patients in the SWORD trial were generally healthy and hence less likely to benefit substantially from drug therapy.

Induced Proarrhythmia and Device Therapy

Anti-tachycardia pacing therapies for the termination of sustained VT are not always effective and may, at times, accelerate VT to VF or to a more hemodynamically unstable form of VT (Figure 52-9).[10,74] The risk of acceleration of VT is relatively small (4%) and is similar for ramp and burst pacing modalities. Syncope in the setting of an implantable cardioverter-defibrillator (ICD) may be caused by ventricular proarrhythmia provoked by anti-tachycardia pacing therapies; the risk may be reduced by careful programming of the ICD. Sometimes, concomitant antiarrhythmic drug therapy may increase the efficacy of anti-tachycardia pacing therapies by slowing the VT rate and may minimize the risk of anti-tachycardia pacing–induced proarrhythmia. The risk of ventricular arrhythmia associated with implantable atrial defibrillators has been reported to be extremely low when the cardioversion shock is synchronized to the R wave and the shock is delivered at a slow heart rate.[75] False-positive detection of AF caused by far-field R-wave oversensing can lead to inappropriate therapies, which may rarely initiate VF.[76] Atrial anti-tachycardia pacing for treatment of atrial flutter or tachycardia may initiate sustained AF, although the risk is generally low.

Normal operation of the pacing system may, at times, promote ventricular proarrhythmia. Sweeney et al analyzed the intracardiac initiation sequence of more than 1300 VT or VF episodes from two recent clinical studies.[77] They found pacing-associated short-long-short sequences at the onset of 21% to 35% of all VT or VF episodes. The short-long-short sequences were further classified as pacing-permitted or pacing-facilitated onsets. Pacing-permitted onset of VT or VF was observed more frequently with the managed ventricular pacing algorithm and the VVI mode, whereas pacing-facilitated onset of VT or VF was

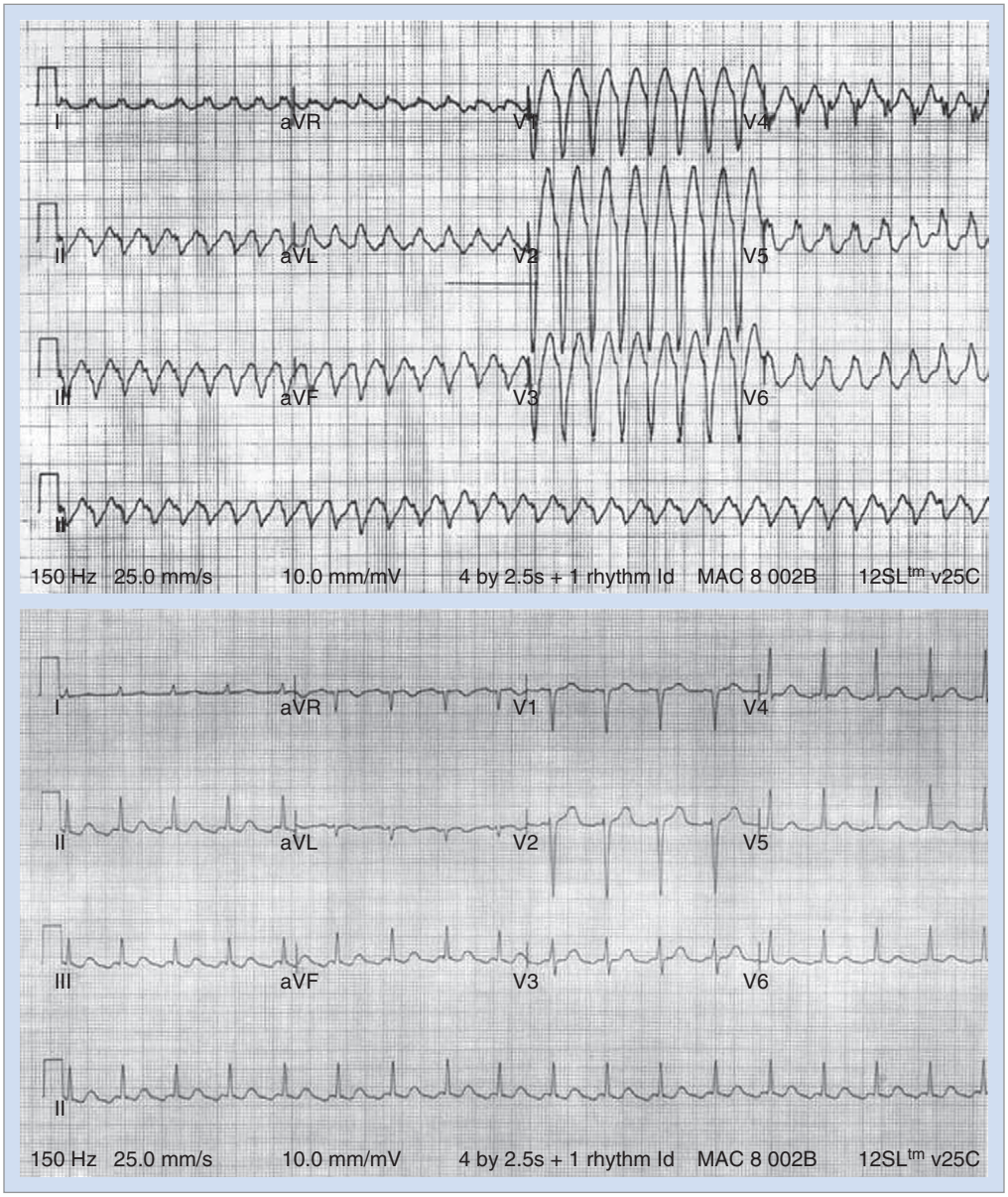

FIGURE 52-8 *Top,* Atrial flutter with 1:1 atrioventricular (AV) conduction during propafenone therapy in a patient without structural heart disease. Propafenone was prescribed for prevention of paroxysmal atrial fibrillation in the absence of AV nodal blocking drugs. Propafenone slowed the atrial flutter cycle length to 300 ms, which results in 1:1 AV conduction with an intraventricular conduction delay abnormality. *Bottom,* After administration of AV node–blocking drugs, atrial flutter with 2:1 AV conduction is apparent, the ventricular rate is now 103 beats/min, and the intraventricular conduction delay has resolved. *(Courtesy Dr. Yorgo Veenhuyzen.)*

more commonly observed with the DDD pacing mode. An example of VT initiated after a short-long-short sequence during pacing associated with the managed ventricular pacing algorithm is shown in Figure 52-10.

Precipitation of ventricular arrhythmias, including cases of VT storm immediately after cardiac resynchronization therapy (CRT), has been reported.[10,78,79] Left ventricular pacing may need to be discontinued to prevent this. Left ventricular pacing via epicardial coronary sinus lead implantation reverses the transmural activation sequence, delaying endocardial depolarization and repolarization. The resulting increased dispersion of ventricular repolarization may contribute to the ventricular proarrhythmia that is occasionally observed with cardiac resynchronization therapy. Although some clinical trial data have suggested that the risk of SCD may be increased in patients treated with CRT versus an ICD, a recent meta-analysis of 14 trials did not suggest any excess risk of SCD from CRT (RR, 1.07; 95% confidence interval [CI], 0.79 to 1.46).[80,81]

Deaths related to lead failure–induced proarrhythmia have been reported in patients with ICDs.[10]

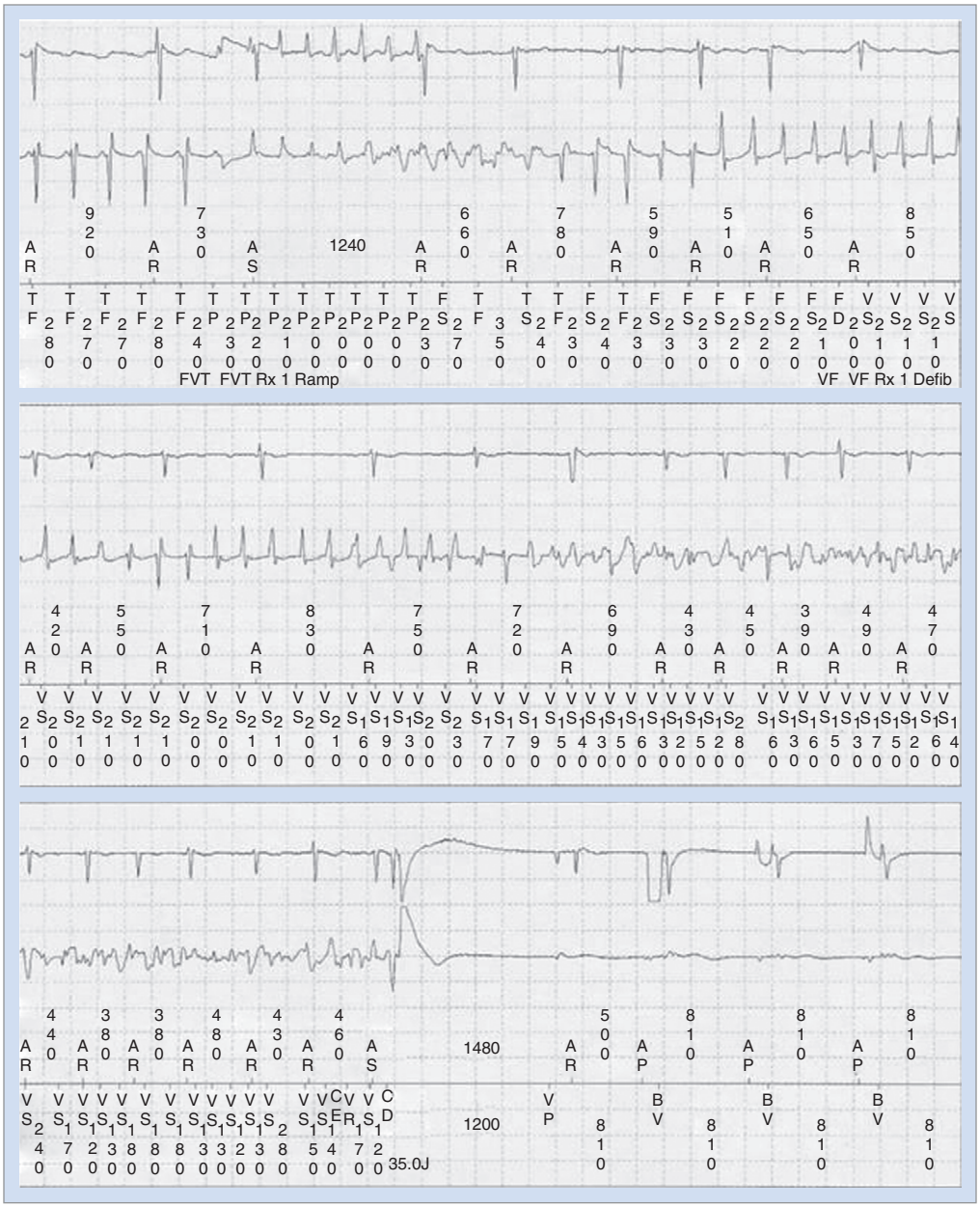

FIGURE 52-9 Example of fast ventricular tachycardia accelerated by ventricular anti-tachycardia pacing to ventricular fibrillation requiring a 35-J defibrillation shock. The atrial and ventricular intracardiac electrograms, the marker channel annotations, and atrial and ventricular cycle lengths are shown in each panel. *AR*, Atrial refractory event; *AS*, atrial sensed event; *FS*, sensed event in fibrillation detection zone; *TF*, fast VT sensed event; *TP*, anti-tachycardia paced event.

Antiarrhythmic Drug Effects on Defibrillation Thresholds

Some antiarrhythmic drugs, by virtue of their effects on passive and active membrane properties, may alter defibrillation thresholds. Na^+ channel–blocking drugs have been reported to have no effect on defibrillation thresholds and do not increase them. These divergent effects appear, in part, to depend on the experimental model or the type of anesthesia used.[82-84] In patients with left ventricular dysfunction, lidocaine has been reported to increase defibrillation thresholds.[84] Reports suggest that drugs that prolong the APD and exert predominantly class III antiarrhythmic effects (e.g., procainamide, sotalol, azimilide, dofetilide) do not have any significant effect on defibrillation energy requirements, or they reduce them.[84-89] The effects of amiodarone on defibrillation thresholds are being debated. Some studies have reported no change in defibrillation thresholds during long-term amiodarone therapy, whereas other investigators have reported an increase in defibrillation thresholds.[89] This ongoing debate concerns reassessment of marginal defibrillation thresholds at initiation of an antiarrhythmic drug known to increase the defibrillation threshold.

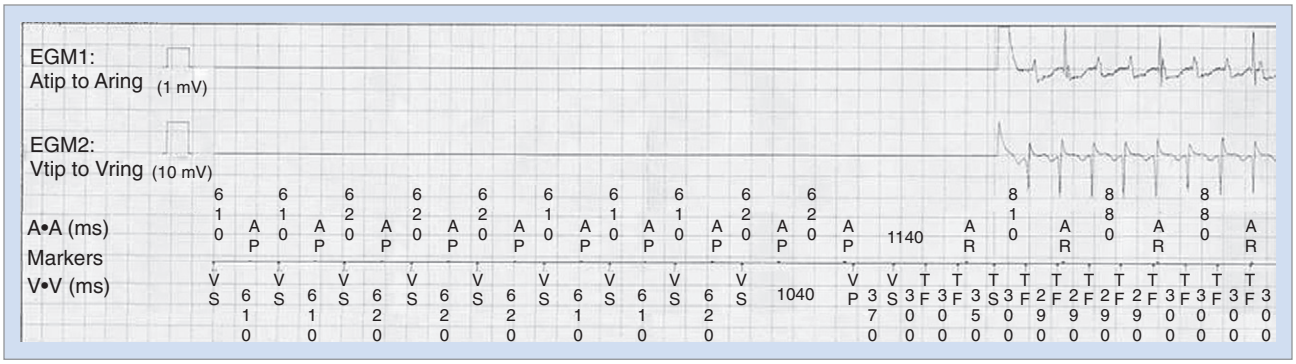

FIGURE 52-10 Pause associated monomorphic ventricular tachycardia (VT). This implantable cardioverter-defibrillator is programmed to managed ventricular pacing, which permits mode switching from the AAI to DDD mode. One atrial paced (*AP*) event fails to conduct through the atrioventricular node, resulting in a pause of 1040 ms. A ventricular premature beat occurs after the pause initiating VT. *AP*, Atrial paced event; *AR*, atrial refractory event; *ICD,* implantable cardioverter-defibrillator; *TF*, fast VT sensed event; *VP*, ventricular paced event; *VS*, ventricular sensed event.

Antiarrhythmic Drug Effects and Cardiac Pacemakers

Some antiarrhythmic drugs (e.g., β-blocking agents, Ca^{2+} channel antagonists) may cause suppression of sinus node automaticity or advanced AV node conduction abnormalities, which would result in profound sinus bradycardia, sinus arrest, or high-grade AV block requiring a permanent pacemaker insertion. These effects may be exaggerated by the concomitant use of class I or III antiarrhythmic drugs prescribed for the management of AF. Some anecdotal reports have suggested that antiarrhythmic drugs may cause an increase in pacing thresholds, particularly in the setting of ischemia, acidosis, or hypoxia. Some newer pacemakers have automatic capabilities for measuring pacing thresholds to maintain an adequate pacing safety margin. In our experience with modern pacing leads, antiarrhythmic drugs do not cause substantial changes in pacing thresholds over a 24-hour period.

Proarrhythmia After Ablation Procedures for Atrial Fibrillation

Left atrial tachycardia or flutter is a recognized complication of ablation techniques aimed at resolving AF.[11,90,91] Ostial ablation of the of the pulmonary veins may result in focal atrial tachycardias in 1% of patients, whereas circumferential ablation approaches are associated with an 18% to 25% risk of focal or re-entrant left atrial tachycardias. Many of these arrhythmias resolve during follow-up; therefore repeat ablation may not be required.

Acknowledgments

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CHAPTER 53

Exercise-Induced Arrhythmias

Senthil Kirubakaran and Jaswinder Gill

Introduction

Exercise-induced arrhythmias are defined as arrhythmias that occur during or shortly after exercise. The observation of this association was first made in 1927 by Bourne, who commented on the development of frequent ventricular premature beats (VPBs) during exercise in patients with suspected coronary artery disease (CAD).[1] Later, in 1932, Wilson et al reported the first case of ventricular tachycardia (VT) initiated during exercise.[2] Since then, exercise-induced tachyarrhythmias (both supraventricular and ventricular) and bradyarrhythmias have been reported in the literature.[3-14]

Exercise-induced supraventricular arrhythmias are common. Atrial premature beats have been reported to occur in 5% of "normal" individuals and up to 40% in patients with structural heart disease.[15] The incidence rates of atrial fibrillation (AF) and atrial tachycardia (AT) are lower and vary between 0.3% to 1.1% and 0.1% to 2.8%, respectively.[7] These have a positive relationship to age and are more frequent in those with underlying structural heart disease.

In addition to conferring a poorer prognosis, the development of ventricular arrhythmias during exercise was formerly considered representative of significant heart disease; as a result, these arrhythmias were more extensively investigated. However, it is now known to not be true for all exercise-induced arrhythmias. The incidence of VPBs during exercise has been shown to vary from 0% to 2.4% in healthy individuals to 31% in patients with structural heart disease.[15,16] The association between VPBs during exercise and the presence of ischemic heart disease was recognized early, with up to 50% of patients developing simple VPBs during exercise testing.[17,18] In addition, the complexity and number of VPBs were shown to correlate with the degree of associated ST-segment depression, disease severity, and the degree of left ventricular dysfunction, with complex VPBs or repetitive VPBs (salvos, triplets) present in 6% of patients with severe CAD.[18,19] In contrast, sustained VT during exercise is relatively uncommon, even among those with underlying CAD (0.15% to 1.7%).[20,21] A further study showed the prevalence of complex ventricular premature complexes to be between 15% and 27% in patients with CAD.[21a]

Although earlier reports clearly identified the association between these arrhythmias and structural heart disease (e.g., a previous myocardial infarction [MI], hypertrophic and dilated cardiomyopathy), more recently, there has been growing interest in inducible ventricular arrhythmias during exercise in those with structurally normal hearts (e.g., long QT syndrome [LQTS] and catecholaminergic polymorphic VT [CPVT]). These arrhythmias occur in seemingly healthy young individuals and can be inherited and associated with sudden cardiac death (SCD). Between 1983 and 1993, Van Camp et al examined 136 deaths among high school and college athletes during or within 1 hour of exercise and found that 100 deaths were likely to have a cardiac etiology: 89% had structural heart disease (hypertrophic cardiomyopathy [56%], anomalous coronary arteries [13%], aortic stenosis [6%], myocarditis [7%], and dilated cardiomyopathy [6%]), but 11% had structurally normal hearts.[22] A review of all cases of SCD at the University of Minnesota over a 13-year period found that 5% of SCDs were associated with structurally normal hearts.[23] In addition, those with normal hearts were younger (mean age, 35 years), and in 50% the first presentation was SCD following a cardiac arrest.

The clinical presentations of exercise-induced arrhythmias are variable and depend on etiology, the type of arrhythmia, and the presence of structural heart disease. Symptoms range from exertional palpitations, breathlessness, and chest pain to presyncope and syncope. In some, the initial presentation can occur after a cardiac arrest or unexplained SCD. Approximately 6% to 17% of all SCDs occur in association with exercise.[24-27]

Individuals with exercise-induced arrhythmias represent a heterogeneous group. These arrhythmias affect all ages and have a number of etiologies, some associated with structural heart disease and some in which the abnormality is at genetic and molecular levels. A wide spectrum of presenting arrhythmias is associated with different prognoses. This variability in etiology, clinical presentation, and outcomes makes diagnosis, management, and risk stratification of those affected a clinical challenge.

Normal Physiological Effects of Exercise

During exercise, an initial withdrawal of vagal tone occurs, followed by activation of the sympathetic nervous system, which causes an increase in circulating catecholamines.[28-31] The effect of this is an increase in heart rate, atrioventricular (AV) conduction, and cardiac contractility, which results in an increase in cardiac output and thus oxygen delivery to organs. These effects are mediated by activation of the α- and β-adrenoreceptors, which directly affect the ion channel currents and electrophysiological properties of cardiac cells. The predominant cardiac receptor is the β_1-adrenoreceptor. The intracellular mechanisms of β_1-adrenoreceptor activation have been extensively studied and elucidated. β_1-adrenoreceptor activation stimulates intracellular G-proteins, which, in turn, activate cyclic adenosine monophosphate (cAMP), protein kinase A, and a number of ion membrane channels. Activation of the pacemaker current (I_f) and the voltage-dependent calcium (Ca^{2+}) channel ($I_{Ca\text{-}L}$ and $I_{Ca\text{-}T}$) results in an increased rate of phase 4 depolarization of the action potential of pacemaker cells, enhancing normal automaticity and increasing sinus rate. Protein kinase A activation phosphorylates the L-type

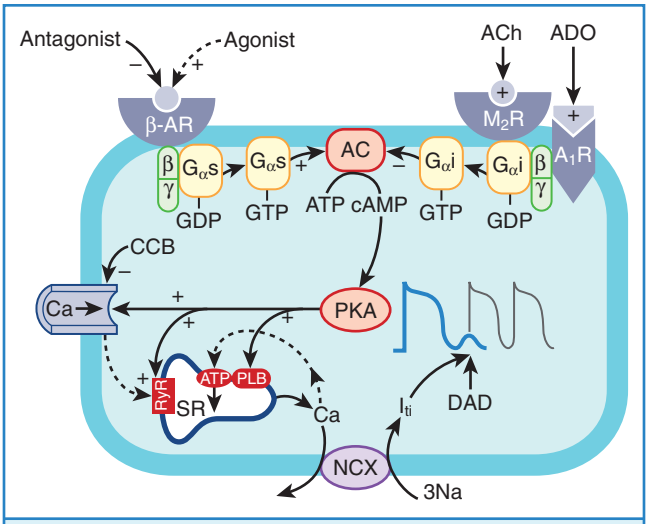

FIGURE 53-1 Signal transduction for initiation and termination of cyclic adenosine monophosphate–mediated triggered activity. *AC*, Adenyl cyclase; *Ach*, acetylcholine; *ADO*, adenosine; A_1R_1, adenosine receptor; *β-AR*, β-adrenergic receptor; *CCB*, calcium channel blocker; *DAD*, delayed afterdepolarization; I_{ti}, transient inward current; M_2R, muscarinic receptor; *NCX*, $Na^+/Ca2^+$ exchanger; *PLB*, phospholamban; *PKA*, protein kinase A; *RyR*, ryanodine receptor; *SR*, sarcoplasmic reticulum. *(From Lerman BB, Stein KM, Markowitz SM: Mechanisms of idiopathic left ventricular tachycardia,* J Cardiovasc Electrophysiol *8[5]:571–583, 1997.)*

Ca^{2+} channel, the ryanodine receptor (RyR) on the sarcoplasmic reticulum, and phospholamban. The net effect of this is increased cytosolic Ca^{2+} and activation of the sodium-calcium (Na^+-Ca^{2+}) exchange pump (Figure 53-1). Increased intracellular Ca^{2+} causes increased contractility by increasing actin and myosin interaction. Adrenergic stimulation also increases the outward repolarizing potassium (K^+) current (I_k) primarily by activation of the slow component of the delayed rectifier current, I_{ks} and the chloride current (I_{Cl^-}), resulting in rate-dependent action potential shortening.[32] The physiological effects of α-adrenoreceptor activation are less well understood. Activation of the α_1-adrenergic receptors reduces K^+ conductance primarily from a reduction in the K^+ current (I_k) and increases $I_{Ca^{2+}}$ and intracellular Ca^{2+} via the protein C and inositol phospholipid system.[33]

In addition to the direct adrenergic effects associated with exercise, electrolyte and mechanical effects caused by myocardial stretch and baroreceptor activation can affect the electrophysiological properties of cardiac cells; however, the precise mechanism of these is less well understood.[34,35]

Despite these electrophysiological changes during exercise, the initiation of arrhythmias is rare. However, if the delicate chemical balance and natural physiological response to exercise are altered, then conditions become favorable for the initiation and maintenance of arrhythmias.

Mechanisms of Arrhythmogenesis During Exercise

In the presence of an appropriate anatomic or electrophysiological substrate, the direct catecholamine effects and indirect effects of exercise can initiate abnormal automaticity, triggered activity, and re-entry.[36-38] For example, a ventricular scar caused by a previous myocardial infarct creates a stable anatomic substrate for re-entry. During exercise, catecholamine-sensitive automatic foci can be triggered, causing unidirectional block and re-entry around the scar, resulting in VT. In addition, in the presence of regional wall motion abnormalities, the mechanical stress on the heart during exercise may not be uniform, resulting in abnormal automaticity and heterogeneity of refractoriness, predisposing to re-entry.[37] In patients with CAD, exercise-induced ischemia creates an electrophysiological substrate for arrhythmias by its direct effects on ion channel currents and myocyte membrane integrity.[39] The resultant alteration in action potential characteristics alters myocyte depolarization, cell-to-cell conduction, and tissue refractoriness, which can cause abnormal automaticity, triggered activity by early afterdepolarizations (EADs) or delayed afterdepolarizations (DADs) and re-entry.[39] Genetic mutations of ion channels (LQTS types 1 or 2) or structural proteins involved with intracellular Ca^{2+} handling (CPVT) create an electrophysiological substrate for exercise-induced ventricular arrhythmias by altering the normal cellular depolarization, repolarization processes, or both during exercise.[40,41]

Although traditionally tachyarrhythmias are described as automatic, triggered or re-entry, exercise-induced arrhythmias frequently have more than one mechanism.

Abnormal Automaticity

In diseased states, cells may exhibit automatic activity and may discharge spontaneously in the presence of increased catecholamines during exercise. Abnormal automaticity occurs in patients with myocardial ischemia and electrolyte abnormalities (particularly hypokalemia). Hypokalemia and ischemia reduce the activity of the Na^+-K^+ adenosine triphosphatase, thereby reducing the background repolarizing current and enhancing phase 4 diastolic depolarization. Abnormal automaticity could be in the form of isolated ectopics or sustained tachycardias. The development of atrial or ventricular ectopy during exercise can trigger other arrhythmias (AF, atrial flutter, AV nodal re-entry tachycardia [AVNRT], AV reciprocating tachycardia, VT, VF) providing a suitable anatomic substrate is present for reentry.[3-5,42]

If the automatic focus is sustained, then an AT or VT ensues.[42,43] Automatic exercise-induced arrhythmias include atrial or ventricular ectopy, idiopathic outflow tract VT, and arrhythmias associated with myocardial ischemia and hypokalemia.

Triggered Activity

Triggered activity is initiated by afterdepolarizations. DADs occur after repolarization of the action potential and are caused by increased Ca^{2+} load in the cytosol and the sarcoplasmic reticulum.[44] Increased intracellular Ca^{2+} activates the Na^+-Ca^{2+} exchange pump and the Cl^- channel.[45,46] The effect of this is to activate the transient inward current (I_{ti}), which causes afterdepolarizations.[47] When the inward current is of sufficient threshold, another action potential is initiated, and triggered activity occurs. cAMP has an important role in regulating intracellular Ca^{2+}. Increased catecholamines during exercise activate cAMP and protein kinase A, which increases Ca^{2+} uptake by the myocyte through the L-type Ca^{2+} channel and increases release of Ca^{2+} from the sarcoplasmic reticulum by RyR2 (see Figure 53-1).

Conditions that increase intracellular Ca^{2+} can initiate DADs and triggered activity. Experimentally, DADs can be initiated during rapid pacing, increased serum Ca^{2+}, digitalis, and endogenous or exogenous catecholamines. This explains the frequent association between exercise (increased catecholamines and heart rate) and the initiation of arrhythmias caused by triggered activity such as outflow tract VTs (e.g., right ventricular outflow tract [RVOT] VT), CPVT, and LQT1 syndrome (torsades de pointes). Conversely, conditions that inhibit the β-receptor–adenyl cyclase cascade, such as vagal stimulation, β-receptor blockade, Ca^{2+} channel blockade, and adenosine, have been shown to reduce DADs. The effect of adenosine on the ventricles is mediated by the A1-adenosine receptor which causes a conformational change in the G_i-protein, which decreases cAMP levels through its inhibition of adenyl cyclase. The downstream effect of this is reduced protein kinase A–mediated phosphorylation of the L-type Ca^{2+} channels, RyR2, and phospholamban. The net effect of this is reduced intracellular Ca^{2+} and thus reduced activity of the Na^+-Ca^{2+} exchange pump and I_{ti} current as well as reduced afterdepolarizations and termination of arrhythmias (see Figure 53-1).[47] However, adenosine is unable to terminate ventricular DADs because of cAMP-independent mechanisms such as digitalis or inosine triphosphate–dependent pathways.

"Gain of function" mutations in the sarcoplasmic reticulum Ca^{2+} release channel (cardiac RyR2) have been identified in patients with the syndrome of CPVT and VF associated with a short Q-T interval.[48] Exercise has been shown to potentiate DADs in this group, resulting in polymorphic VT.[49]

EADs occur during the action potential and interrupt the normal myocyte repolarization process. LQTS types 1 (LQT1) and 2 (LQT2) are associated with EADs and can result in exercise-induced polymorphic VT, characteristically torsades de pointes.

Exercise-induced arrhythmias caused by triggered activity characteristically are initiated during fast heart rates and show acceleration during rapid rates. In addition, these arrhythmias are frequently terminated by Ca^{2+} channel blockade or the administration of adenosine.

In contrast, Ca^{2+} channel blockade or adenosine have no effect on automatic arrhythmias and EAD-mediated VT such as in LQTS.

Re-entry

Increases in catecholamines during exercise cause an increase in heart rate and an associated decrease in tissue refractoriness. If an appropriate substrate is present for re-entry arrhythmias (atrial or ventricular scar, accessory pathways, dual AV nodal pathways), the decrease in tissue refractoriness and differential effects of catecholamines on the effective refractory period of different parts of the arrhythmia circuit causes an increase in the excitable gap, which may facilitate the initiation and maintenance of atrial (AVNRT, AV reciprocating tachycardia) or ventricular re-entry arrhythmias.[42]

Exercise-induced polymorphic VT is thought to be caused by re-entry from nonstationary spiral activity within the ventricular myocardium as a result of the increased heterogeneity of myocardial refractoriness. This can rapidly degenerate into VF. It has been shown that patients with ischemic heart disease and congenital LQT1 have an abnormal adaptation of the Q-T interval during exercise. This would result in the simultaneous presence of areas of depolarized and repolarized myocardium, which creates appropriate conditions for the development of multiple wavelets or nonstationary spiral activity and polymorphic VT.[50]

Frequently, a re-entry arrhythmia is initiated during exercise by catecholamine-sensitive automatic foci or triggered activity. For example, automatic foci can trigger AVNRT, AVRT, AT, or VT, provided that an appropriate substrate is present. As previously mentioned, catecholamine-associated triggered activity can rapidly degenerate into polymorphic VT and VF.

Exercise-induced re-entry tachycardias have been implicated as the mechanism for arrhythmias caused by myocardial ischemia and arrhythmogenic right ventricular cardiomyopathy (ARVC).

Mechanism of Exercise-Induced Bradyarrhythmias

Although the majority of reported cases of exercise-induced arrhythmias are tachycardias, bradycardias have also been reported. Initial case reports described patients with pre-existing conduction disease that gave rise to the development of AV block during exercise.[14,51,52] The site of block in these cases was predominantly infra-Hisian. These authors postulated that as the distal conduction system is relatively insensitive to autonomic modulation, during exercise an attenuated increase in AV conduction would occur. Therefore, during exercise, the increased sinus rates would fail to conduct to the ventricles in a 1 : 1 manner.[53] Sumoyoshi et al[54] reviewed 14 cases of exercise-induced second-degree AV block. The mean atrial rate increased from 62.9 ± 10 beats/min before exercise to 107.1 ± 15 beats/min, but the ventricular rate decreased from 62.9 ± 10 beats/min to 53.4 ± 12.5 beats/min. They reported that the site of block was proximal to the His potential in four patients and intra-His or distal in the remainder. They also noted that AV block was initiated when the atrial rate increased above a critical level governed by the refractory period of the diseased conduction system, which was reproduced with exercise, atrial pacing, and atropine. They therefore concluded that exercise-induced AV block was not purely exercise related but was caused by atrial rate. Other reported mechanisms of exercise-induced AV block are depressed function of the sinoatrial or AV node from hypoxia or ischemia in patients with coexisting lung disease or CAD.[11-14] In addition, abrupt cessation of exercise and increased vagal tone could potentially cause bradyarrhythmias.

Conditions Associated with Exercise-Induced Arrhythmias: Structural Heart Disease

A number of conditions are associated with exercise-induced arrhythmias. These can be divided into those associated with structural heart disease and those associated with structurally normal hearts.

Ischemic Heart disease

In the United States, ischemic heart disease is the leading cause of death, with approximately 400,000 cardiac-related deaths each year. The prevalence of coronary artery disease is approximately 7.8% in men and 4.6% in women. Approximately 1.5 million cases of myocardial infarction occur annually in the

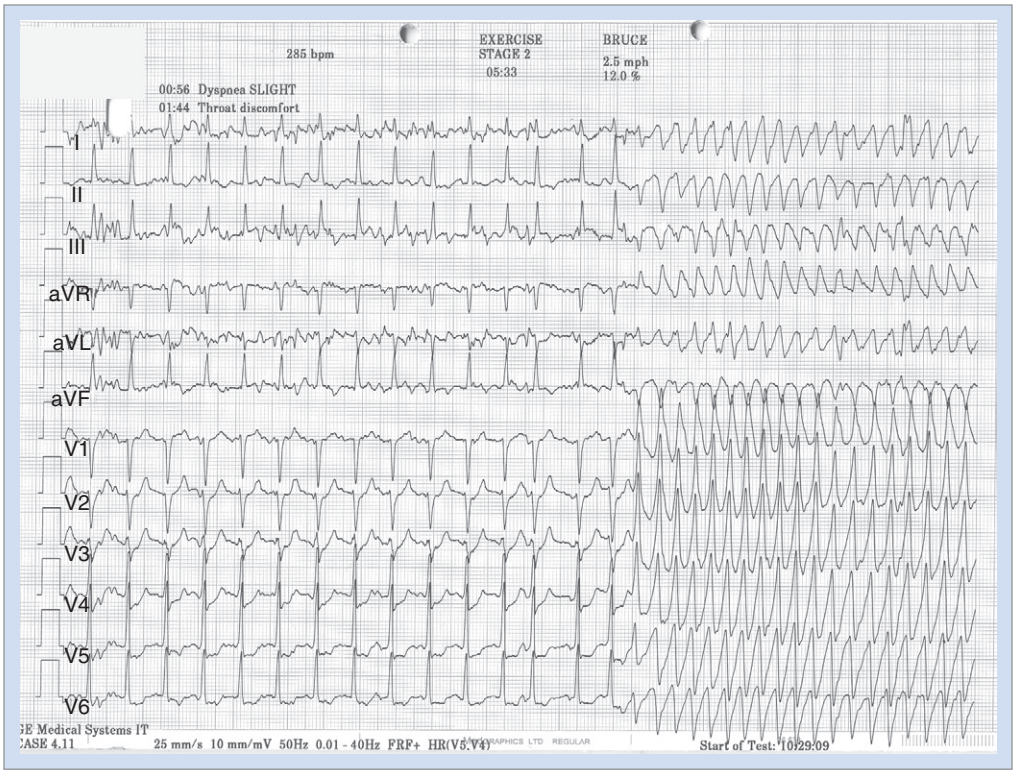

FIGURE 53-2 Exercise-induced ventricular tachycardia in a patient with coronary artery disease.

United States, with an annual incidence rate of 600 cases per 100,000 individuals.

Patients with ischemic heart disease predominantly present with symptoms of chest pain and breathlessness. In some, however, symptoms associated with an arrhythmia frequently provoked by exercise are seen at presentation (Figure 53-2).

Exercise-induced arrhythmias in patients with CAD are multifactorial. Exercise increases myocardial oxygen demand by increasing cardiac contractility, heart rate, and systolic blood pressure; therefore, if the coronary disease is flow limiting, myocardial ischemia develops. Evidence also suggests that exercise itself increases vasoconstriction at the sites of coronary stenosis. This is thought to be related to endothelial dysfunction and imbalance of endothelium-derived mediators.[56,57] Regional differences in myocardial blood flow and oxygen delivery cause changes in regional pH and electrolytes.[58,59] Myocardial ischemia results in loss of membrane integrity with K^+ efflux, increased Ca^{2+} influx, decreased amplitude and upstroke velocity of the cardiac action potential, inhomogeneous depolarization of the resting membrane potential, and shortening of the action potential.[60] This heterogeneity in the electrophysiological properties (conduction velocity, refractory period) within and around an ischemic zone causes conduction delay, unidirectional block, and re-entry arrhythmias. In experimental studies, following the onset of myocardial ischemia, polymorphic VT and VF was common.[61,62] Activation mapping showed principally re-entry arrhythmias.

Exercise itself can promote plaque rupture as the associated increased cardiac contractility and heart rate could create extra stress in the "inflexible" atherosclerotic plaque within the epicardial coronary artery.[63] In addition, it has been shown that exercise increases platelet aggregation and could contribute to the development of platelet thrombi over a ruptured plaque.[64] Black et al reported clinical, autopsy, and angiography evidence of acute plaque rupture in 13 individuals who had died or had an acute MI during vigorous exercise.[63] To determine if a difference in the size of the thrombi was present, Giri et al compared angiography findings in individuals referred for primary angioplasty who had an MI during or within 1 hour of exercise and compared them with patients who had had an MI at rest.[65] He showed that a coronary clot of more than 2 mm was present in 64% of the exercise-MI group compared with 35% in the sedentary-MI group and postulated that this difference was caused by differences in the mechanism of plaque rupture. The consequence of acute plaque rupture is myocardial ischemia, which could lead to life-threatening monomorphic or polymorphic VT or VF.[66]

In patients with a myocardial scar, the mechanism of arrhythmia induction and maintenance is different. The presence of a scar creates an anatomic substrate for re-entry. The resultant VT is monomorphic. These arrhythmias may be initiated during exercise by the sympathetic triggering of automatic ventricular ectopic beats causing unidirectional block and re-entry. Although the majority of arrhythmias associated with exercise-induced ischemia are tachyarrhythmias, bradyarrhythmias caused by myocardial ischemia and CAD have been reported.[13]

The management of patients with exercise-induced arrhythmias caused by ischemic heart disease depends on etiology. If myocardial ischemia was caused by atherosclerotic coronary disease, then prompt revascularization prevents further arrhythmia recurrence.[67,68] If the substrate for the ventricular arrhythmia is a myocardial scar, ablation is a potentially curative treatment if

the arrhythmia is incessant and refractory to anti-arrhythmic drugs and implantable cardioverter-defibrillator (ICD) therapy.

Medical management of exercise-induced arrhythmias associated with CAD primarily is with β-blockade. β-Blockers have been shown to be effective in reducing arrhythmia occurrence in patients with ischemic heart disease and after an MI.[69] The role of antiarrhythmic drugs in patients with CAD and after an MI was studied in the Cardiac Arrhythmia Suppression Trial (CAST). The hypothesis for this study was that suppression of VPBs with antiarrhythmic drugs would result in a decrease in mortality rate in patients after an MI. They showed that unfortunately, encainide and flecainide increased mortality rates and that other drugs, at best, had only a neutral effect.[70] Further meta-analysis in 1993 showed that all antiarrhythmics, with the exception of amiodarone, increased mortality rate in patients with CAD.[71,72] Therefore, at present, medical management of exercise-induced arrhythmias associated with ischemic heart disease is with β-blockers or amiodarone.

Arrhythmogenic Right Ventricular Cardiomyopathy

ARVC is characterized morphologically by fibro-fatty infiltration of the myocardium (predominantly of the right ventricle). The most frequent clinical presentation of ARVC is syncope or SCD. ARVC is well recognized as a cause of SCD in the young. A prospective investigation on SCD of the young in the Veneto region in Italy showed that nearly 20% of fatal events in young people and athletes were caused by ARVC. The remainder present with palpitations associated with ventricular ectopy or VT, with a characteristic left bundle branch block (LBBB) morphology. VT associated with ARVC is frequently associated with exercise. Thiene et al found that of the 12 patients identified with ARVC, 10 of them had died suddenly during exercise because of presumed ventricular arrhythmias.[73] Rossi et al and Palileo et al initially demonstrated that the re-entry arrhythmia was localized within the abnormal right ventricle.[74,75] The presence of widespread disruption of the myocardium by fibro-fatty infiltration creates areas of slow intraventricular conduction and thus represents an ideal substrate for re-entry and ventricular arrhythmias. The precise mechanism for arrhythmogenesis during exercise is not well understood. It is thought that the initiation of the arrhythmia by exercise is related to both hemodynamic and neurohormonal factors. Physical exercise increases right ventricular afterload, which may trigger ventricular arrhythmias by cavity enlargement and increased stretch.[76] In addition, progression of disease from the epicardium to the endocardium may cause functional or structural sympathetic denervation, decreased catecholamine reuptake, enhanced sensitivity to catecholamines, and thus increased arrhythmia induction during sympathetic activation during exercise.[77] Leclercq et al showed that a stronger sympathetic stimulation was needed to produce sustained VT than to elicit ventricular couplets and nonsustained VT.[78]

Differentiating idiopathic RVOT VT from VT associated with ARVC is critical because the diagnosis affects long-term prognosis. No pathognomonic feature of ARVC exists; to make the diagnosis, electrocardiography (ECG), echocardiography, right ventricular angiography, cardiac magnetic resonance imaging (MRI), and genetic testing are used. The most common ECG abnormality is T-wave inversion in leads V_1 to V_3; however, a normal ECG does not exclude ARVC. An ε-wave is found in approximately 50% of those affected and is caused by slowed intraventricular conduction. However, more commonly, signal-averaged ECGs are used to detect late potentials and ε-waves. Although the morphologic features of VT in ARVC and idiopathic RVOT VT are similar, QRS duration may be useful in the differential diagnosis. A QRS duration of 120 ms or more in lead I and a QRS axis less than 30 degrees were found to be predictive of ARVC.[79] These differences are caused by the presence of slowly conducting tissue in ARVC and is supported by pace-mapping studies in patients with ARVC and idiopathic RVOT VT.[79] Transthoracic echocardiography may reveal an enlarged, hypokinetic right ventricle. However, the sensitivity for the detection of ARVC on echocardiography is poor, so cardiac MRI is used frequently. Fatty infiltration and extreme thinning and akinesis of the right ventricular free wall can be seen on cardiac MRI. If the diagnosis is still in doubt after the above investigations, then a transvenous biopsy of the right ventricle can be performed, although it has a low sensitivity in spite of being highly specific for ARVC. A biopsy sample consistent with ARVC would contain more than 3% fat, more than 40% fibrous tissue, and less than 45% myocytes. Exercise stress testing may be helpful in precipitating ventricular arrhythmias in some patients with ARVC; however, response to exercise is variable, and the absence or suppression of PVCs during exercise should not be considered a conclusive factor in terms of its diagnostic exclusion.[80] Localized or diffuse wall motion abnormalities in the right ventricle in patients with ARVC may induce ST-segment elevation in response to exercise. Toyofuku and colleagues observed ST-segment elevations of more than 0.1 mV in the right precordial leads and associated right ventricular regional wall motion abnormalities in 65% of patients with ARVC.[81] Because exercise-induced ST-segment elevation is a rare phenomenon in normal subjects and in those with idiopathic RVOT VT, this observation may be helpful in diagnosing ARVC.

In view of the strong association between exercise and arrhythmia occurrence, patients with a diagnosis of ARVC are discouraged from participating in competitive sports and endurance training. As described earlier, increased sympathetic activity and sensitivity to catecholamines may play a role in the genesis of ventricular arrhythmias; therefore, β-blockers are used as the first line of treatment for symptomatic patients. Amiodarone is recommended if β-blockers prove ineffective or are contraindicated. In patients with impaired right ventricular function and dilation, anticoagulation should be considered in those with AF, marked ventricular dilation or aneurysms, and a history of pulmonary or cerebral emboli. The ICD confers protection against SCD. It is therefore implanted in survivors of a cardiac arrest, arrhythmias associated with syncope or hemodynamic compromise, and left ventricular involvement or VT resistant to medical therapy as well as in those with a history of SCD of an immediate family member.

Left Ventricular Dysfunction

Exercise-induced arrhythmias in patients with left ventricular dysfunction and heart failure are rare and, in fact, exercise has been shown to be beneficial in these patients. A meta-analysis of exercise training in patients with chronic heart failure showed that of the 156 patients in the rehabilitation program, 22 had arrhythmias during exercise.[82] One had an episode of AF that spontaneously cardioverted, 11 had premature ventricular beats, and 10 had atrial premature beats. No sustained ventricular arrhythmias were reported. A study from the Lancisi hospital of 154 consecutive patients in a cardiac rehabilitation program found that 21 patients (13.6%) had VPBs, 10 (6.5%) had atrial

premature beats, 1 (0.6%) had AF, and 1 (0.6%) had VF requiring DC cardioversion. At the Cleveland Clinic, ECG data were gathered during rest, exercise, and recovery from 2123 patients with left ventricular ejection fraction less than 35%.[83] Of these patients, 7% developed exercise-induced ventricular arrhythmias (defined as ventricular triplets, nonsustained or sustained VT, or polymorphic VT or VF) during recovery. This was associated with a 1.5-fold increased risk of death over 3 years, after adjustment for potential confounding factors. These patients are, however, at an increased risk of developing arrhythmias during exercise or recovery. This is thought to be multi-factorial and related to neurohormonal factors (increased sympathetic tone, reduced heart rate variability), electrolyte disturbances (hypokalemia, hypomagnesemia secondary to diuretics), hemodynamic factors (increased end-diastolic pressure, increased afterload, and variations in myocardial stress) and iatrogenic factors (antiarrhythmic drugs).[37] Therefore, if arrhythmias develop, it is important to ensure that these patients are on appropriate heart failure treatment (e.g., diuretics, angiotensin-converting enzyme [ACE] inhibitors) and particularly β-blockers, and that serum electrolytes are normal. In addition, patients with sustained ventricular arrhythmias and severe left ventricular systolic dysfunction should be offered ICD therapy.

Mitral Valve Prolapse

Mitral valve prolapse is defined as displacement of mitral valve leaflets by more than 2 mm above the mitral annulus. The reported incidence varies widely between 5% and 38%.[84,85] Initial studies suggested that patients with mitral valve prolapse had an increased incidence of ventricular arrhythmias and greater risk of SCD.[86,87] A later study by Kilgfield et al demonstrated no increased risk of SCD in patients with mitral valve disease compared with the general population.[88] However, patients with mitral valve prolapse do experience palpitations caused by ventricular ectopy and nonsustained VT. In the 1970s, it was appreciated that these ventricular arrhythmias occurred during exercise or during the immediate recovery period.[89] In 1986, Butrous et al demonstrated the development of VPBs during the first two stages of the Bruce protocol (increased sympathetic activity), during early recovery after exercise (increased parasympathetic and decreased sympathetic), and during performance of the Valsalva maneuver (rapid increase in parasympathetic activity), and they postulated that the development of VPBs was caused by autonomic imbalance.[90]

Patients with symptomatic palpitations associated with VPBs frequently respond to β-blockers.

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is characterized by hypertrophy of the myocardium, particularly the interventricular septum. The overall prevalence of HCM has been estimated to be between 0.05% and 0.2% of the general population. HCM is inherited as an autosomal dominant trait and is attributed to mutations in one of a number of genes that encode for one of the sarcomere proteins. HCM was recognized early as a cause of SCD in young atheletes.[91] The myocardium of patients with HCM is characterized by myocardial disarray and myocardial fibrosis, which create an ideal substrate for atrial and ventricular re-entry arrhythmias.[92,93] These arrhythmias are frequently initiated during exercise. This is thought to be caused by the development of regional ischemia and hemodynamic effects. The increased muscle mass and narrowed intramural arterioles provoke exercise-induced regional ischemia, which creates heterogeneity in conduction, thus facilitating re-entry, abnormal automaticity, and triggered activity. In addition, during exercise, abrupt increases in outflow tract obstruction increases left ventricular pressure, causing increased stretch, which potentially could induce arrhythmias. McKenna et al investigated the effects of submaximal treadmill exercise on 30 patients with HCM.[94] One patient (3%) had no arrhythmia, 14 (46%) had supraventricular tachycardia or paroxysmal AF, 13 (43%) had multi-form or paired ventricular extrasystoles, and 8 (26%) had VT. Routine echocardiographic or hemodynamic measurements did not predict the development of serious ventricular arrhythmias. It was concluded that asymptomatic exercise-induced ventricular arrhythmia is a common occurrence in patients with HCM.

The consensus is that young patients with HCM should be restricted from intense competitive sports to reduce the risk of SCD. Medical therapy consists of β-blockers, verapamil, and disopyramide in symptomatic patients. ICDs should be offered to patients with a major risk factor for SCD. This includes a prior cardiac arrest or sustained VT; family history of SCD in a first-degree relative; unexplained syncope, particularly exertional; multiple repetitive nonsustained VT recorded on a 24-hour Holter monitor; abnormal blood pressure response during exercise; and severe left ventricular hypertrophy (left ventricle thickness >30 mm).

Conditions Associated with Exercise-Induced Arrhythmias Without Structural Heart Disease

Approximately 10% of patients presenting at the hospital with VT have no obvious evidence of underlying structural heart disease or CAD.[95]

Catecholaminergic Polymorphic Ventricular Tachycardia

Familial CPVT is a rare cause of exercise-induced VT. Sporadic cases were initially reported in the 1970s; however, in the past decade, a genetic etiology has become apparent.[96] The prevalence of CPVT is unknown but is estimated to be approximately 1 per 10,000. CPVT diagnosis is frequently missed because individuals are often young with structurally normal hearts. Approximately 30% of probands present with a family history of stress-related syncope, seizure, or SCD.[97] SCD can be the first manifestation of CPVT.

CPVT is inherited as an autosomal dominant or recessive trait, usually with high penetrance. In the dominant form, the disease-causing gene has been mapped to chromosome 1q42 to 43, which codes for the cardiac RyR gene *RyR2*, which is a tetrameric intracellular Ca^{2+} release channel on the sarcoplasmic reticulum required for excitation-contraction coupling. In addition, *RyR2* gene mutations have been identified in patients affected by ARVC2, a variant form of ARVC.[98] Mutations of the RyR2 channel result in a "gain of function" thought to be caused by either the decreased binding affinity of the stabilizing FKBP 12.6 protein or the increased sensitivity of the channel to Ca^{2+} and increased propensity to spontaneous release of Ca^{2+} from the sarcoplasmic reticulum.[99-102] In the recessive form, a missense mutation on the locus of chromosome 1p13-21 has been identified.[102,103] This

codes for CASQ2, which is the major Ca^{2+} reservoir within the sarcoplasmic reticulum of cardiac myocytes. Abnormalities in the RyR2 channel proteins and CASQ2 result in increased intracellular Ca^{2+} and cytosolic Ca^{2+} overload; this, in turn, generates a net transient inward current (I_{ti}), which underlies diastolic membrane depolarization, which, if sufficient, could reach the threshold for Na^+ current activation and triggered activity.[44]

During exercise, increased catecholamines activate the β_1-receptors, cAMP, and protein kinase A, which triggers Ca^{2+} release from the sarcoplasmic reticulum. In patients with CPVT, the abnormal RyR2 channel and CASQ2 result in an abnormally high intracellular Ca^{2+} release, causing DADs or triggered activity and polymorphic VT. Liu et al, in their transgenic CPVT murine model, demonstrated the enhancement of DADs after β-adrenergic stimulation and the development of multiple triggered action potentials.[104] Subsequently, a number of other studies have confirmed these findings.[105-108] In humans, Paavola et al showed that in humans, those with the *RyR2* mutation developed more DADs after the administration of adrenaline compared with control subjects.[49]

The clinical manifestations of CPVT are exercise-induced polymorphic, monomorphic, or bidirectional VT in patients with structurally normal hearts. Although, classically, CPVT is associated with bi-directional VT, this is the presenting arrhythmia in only 35% of patients.[109] The ventricular arrhythmias that occur during exercise stress testing appear quite consistently at heart rates of 110 to 130 beats/min. They initially start as polymorphic premature ventricular complexes, and then at increasing workload, an increased complexity of ventricular arrhythmia is observed (i.e., bigeminy and couplets leading to bi-directional VT, polymorphic VT, or both). When the exercise stops, the arrhythmias gradually disappear. Monteforte et al analyzed ventricular arrhythmias developing during exercise stress testing in 61 consecutive patients with CPVT before therapy.[110] They demonstrated a positive direct correlation between the coupling interval of ventricular arrhythmias and the preceding R-R interval, supporting the view that triggered activity is the mechanism underlying arrhythmias in CPVT.

The mechanism for bi-directional VT has been the subject of much debate. Since its initial description in 1922, several hypotheses have been suggested, including two separate foci and re-entry.[111,112] Cerrone et al demonstrated, in their CPVT mouse model, the development of monomorphic, polymorphic, and bi-directional VTs during adrenergic stimulation and Ca^{2+} overload.[108] Endocardial mapping during the arrhythmia showed that the foci were predominantly from the specialized conduction system. Monomorphic VT was unifocal, and polymorphic VT was multifocal, later degenerating into re-entry and VF. A case report by Mok et al demonstrated the development of unifocal ventricular ectopy, followed by polymorphic VT and then bi-directional VT during adrenaline infusion (Figure 53-3).[113]

Bi-directional VT was associated with the occurrence of alternating right and left ventricular epicardial breakthroughs, which accompanied the changes in the axis of the QRS. In addition, chemical ablation of the right ventricular endocardium induced complete right bundle branch block (RBBB) and converted bi-directional VT into monomorphic VT.

CPVT presents with a significant mortality rate, reaching 30% by age 30 years if left untreated.[114] Treatment with β-blockers is effective; however, some patients may require ICD therapy.[114,115] Some studies showed that verapamil may be an alternative option for the treatment of CPVT. Sumitomo et al and Swan et al reported that verapamil could significantly decrease the prevalence of ventricular arrhythmia in patients with CPVT during exercise stress testing, although it did not completely suppress CPVT.[116,117] Rosso et al reported that combining β-blockers and verapamil would be better than β-blockers alone for preventing exercise-induced arrhythmias in CPVT.[118] Recent studies and case reports of murine models of CPVT as well as clinically in three patients with CPVT have demonstrated that flecainide can effectively suppress arrhythmia.[119-121] Facchini et al also explored the therapeutic value of left cardiac sympathetic denervation (LCSD) in two patients with CPVT who had ventricular arrhythmias despite β-blockade.[122] After LCSD, the two patients remained asymptomatic, VT could only be induced at high workloads, and the quality of life was improved. However, despite these studies, the consensus at present is for ICD therapy. However, both appropriate and inappropriate ICD shocks can trigger catecholamine release, precipitating arrhythmic storms and death.[123,124]

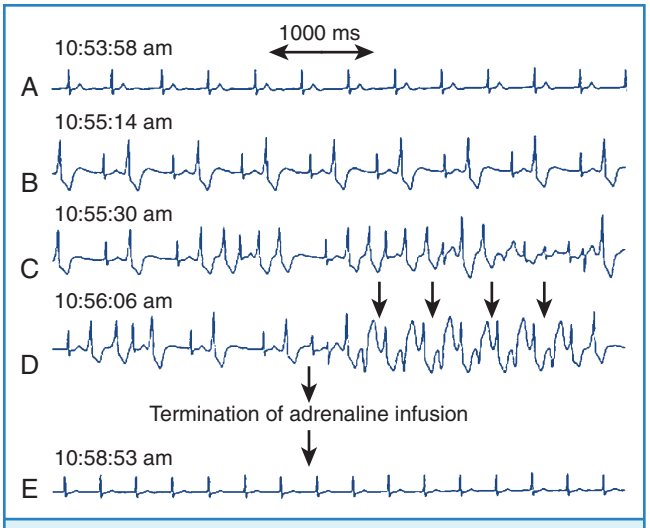

FIGURE 53-3 Demonstration of unifocal ventricular ectopy, polymorphic ventricular tachycardia (VT) and bi-directional VT in a patient with catecholaminergic polymorphic VT during adrenaline infusion. *(From Mok NS, Lam CW, Fong NC, et al: Cardiac ryanodine receptor gene* (hRyR2) *mutation underlying catecholaminergic polymorphic ventricular tachycardia in a Chinese adolescent presenting with sudden cardiac arrest and cardiac syncope,* Chin Med J [Engl] *119[24]:2129–2133, 2006.)*

Long QT Syndrome

The Q-T interval is influenced by a number of factors, including heart rate, autonomic nervous system activity, electrolyte disturbances, drugs, and genetic mutations in ion channel proteins (LQTS).[125]

In the United States, the prevalence of LQTS is estimated at 1 per 7000 persons, causing 2000 to 3000 deaths in children and young adults each year. At present, at least seven genes for LQTS have been identified, with more than 200 mutations discovered so far.[126] The genes have been numbered in order of discovery (*LQT1* to *LQT9*).

LQT1 is characterized by ventricular arrhythmias precipitated by exercise and LQT2 by acute arousal such as a sudden loud noise. Symptoms of palpitations, presyncope or syncope, or SCD can present from birth to the fourth decade of life. SCD typically

presents in the preteen or early teenage period in LQT1 and slightly later (teenage years or early twenties) in LQT2. Sixty percent of patients with LQTS have the LQT1 type. A study demonstrated that 62% of symptomatic patients with LQT1 genotype had events triggered by exercise.[127] The mean QTc of these patients is 490 ms; the T wave typically has a broad base. Patients with LQT2 syndrome have a mean QTc of 480 ms, and approximately 17% have a normal QTc at rest. Characteristically, the T wave is bifid. Sixty percent of patients with LQT2 have cardiac events triggered by exercise, strong emotions, and loud noises.

Mutations in *KCNQ1* and *HERG* are most commonly identified and cause the LQT1 and LQT2 forms of LQTS, respectively. These mutations induce functional defects in either the slow (I_{Ks}) or rapid (I_{Kr} [LQT2]) component of the delayed rectifier K^+ current. I_{Ks} is regulated by β-adrenoreceptors; therefore arrhythmias are precipitated during activities that increase sympathetic activity, such as exercise. Conversely, LQT3, in which the abnormality appears to be within the Na^+ channel, is associated with ventricular arrhythmias at rest, frequently during sleep when the resting heart rate is low.

A prolonged Q-T interval reflects dispersion of repolarization within the myocardium increasing the susceptibility to re-entry and ventricular arrhythmias, characteristically torsades de pointes (Figure 53-4).

It has been shown that impaired adaptation of the Q-T interval to changes in heart rate during exercise is important in the genesis of exercise-induced ventricular arrhythmias.[128-130] Paavonen et al studied the effects of mental and physical stress on patients with congenital LQT1 and LQT2.[131] During exercise, in healthy controls, a reduction occurred in the Q-T interval by 47 ms compared with 38 ms in patients with LQT1 or LQT2. Furthermore, it appeared that different mutations on the same ion channel resulted in different effects on the Q-T interval during exercise. The longest Q-T interval during exercise as well as the most impaired heart rate response to exercise was associated with a mutation in the pore region of the K^+ channel gene *KvLQT1*, which is characteristically associated with exercise-induced torsades de pointes.[132] These findings were later confirmed by a number of other studies.[129,130,132-134] This abnormal adaptation of the Q-T interval during exercise results in simultaneous depolarized and repolarized areas of the myocardium, which sets up the appropriate conditions for re-entry. A number of studies have tried to elucidate the precise mechanism for this impaired rate-dependent Q-T interval shortening during exercise. It has long been recognized that some forms of LQTS are sensitive to β-adrenergic stimulation; however, the cellular basis for this arrhythmogenic effect is poorly understood. As previously described, during increased sympathetic activity during exercise, the Cl^--K^+ (I_{KS}) current and the L-type Ca^{2+} channel are activated. The response to action potential shortening and therefore the Q-T interval depends on the balance between the outward currents (primarily I_{Cl^-} and I_{Ks}) and the inward currents (Ca^{2+}). A defect in I_{Ks} (in LQT1) offsets this balance, resulting in a net inward current and therefore failure of β-adrenergic stimulation (and therefore exercise) to abbreviate the action potential duration and the Q-T interval.[135] In LQT2, arrhythmogenesis is thought to be caused by a different mechanism. Shimizu et al demonstrated, in their LQT2 mouse model (reduced I_{Kr}), that β-adrenergic stimulation with isoproterenol causes an abrupt increase in action potential duration associated with intracellular Ca^{2+} loading, which was associated with the development of EADs.[135] This, together with a study by Priori et al, who demonstrated the same effect in guinea pig myocytes pretreated with the I_{Kr} blocker dofetilide, led to the conclusion that increased adrenergic stimulation contributes to the development of torsades de pointes in LQT2 by producing transient increases in action potential duration and repolarization dispersion leading to the induction of EAD-mediated activity.[135,136]

The diagnosis of LQTS can be difficult because 2.5% of the healthy population have a prolonged Q-T interval, and patients with LQTS may have a normal Q-T interval. In view of this, a scoring system was developed by Schwarz et al to determine the probability of an individual having LQTS (Table 53-1).[137] However, this diagnostic criterion, although being specific, is not very

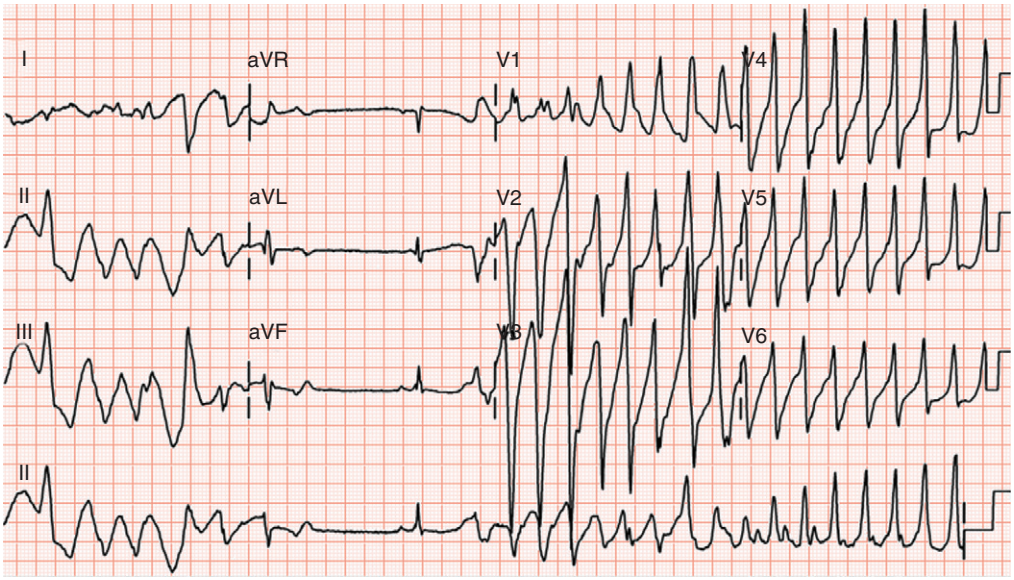

FIGURE 53-4 Initiation of polymorphic ventricular tachycardia in a patient with long QT syndrome.

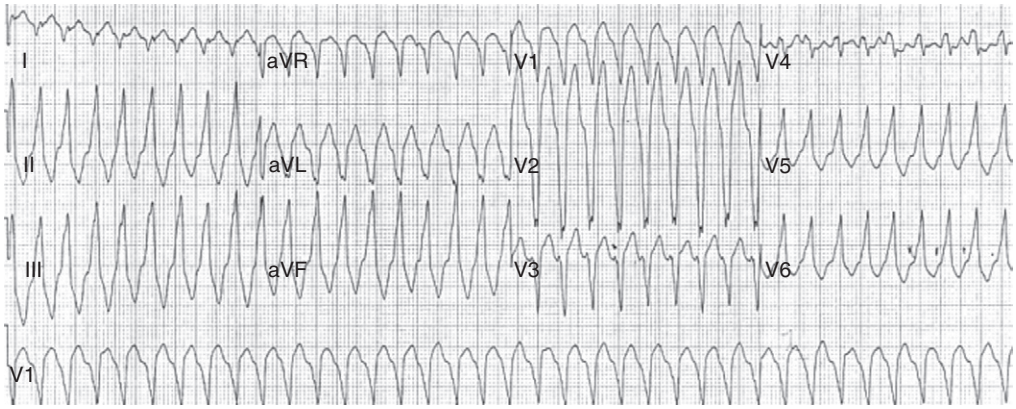

FIGURE 53-5 Right ventricular outflow tract ventricular tachycardia.

Table 53-1 Diagnostic Criteria for Long QT Syndrome

ECG FINDINGS*	
(A) QTc†	
≥480 ms	3 points
460 to 479 ms	2 points
450 to 459 ms (in males)	1 point
(B) Torsades de pointes‡	2 points
(C) T-wave alternans	1 point
(D) Notched T wave in three leads	1 point
(E) Low heart rate for age§	0.5 point
CLINICAL HISTORY	
(A) Syncope‡	
With stress	2 points
Without stress	1 point
(B) Congenital deafness	0.5 point
FAMILY HISTORY¶	
(A) Family members with definite LQTS‖	1 point
(B) Unexplained sudden cardiac death at <30 years among immediate family members	0.5 point

**In the absence of medications or disorders known to affect these ECG features.*
†Calculated by Bazett's formula, where QTc = QT/$\sqrt{RR}$.
‡Mutually exclusive.
§Resting heart rate below the second percentile for age.
¶The same family member cannot be counted in A and B.
‖Definite LQTS is defined by an LQTS score ≥4. Scoring: ≤1 point, low probability of LQTS; 2-3 points, intermediate probability of LQTS; ≥4 points, high probability of LQTS.
From Schwartz PJ, Moss AJ, Vincent GM, Crampton RS: Diagnostic criteria for the long QT syndrome. An update, Circulation *88(2):782–784, 1993.*

sensitive. Hofman et al found that analysis of the QTc duration alone was more useful to screen for LQTS carriers.[138] In addition, with the recognition of the genes involved, genetic testing will become the preferred diagnostic tool in genotyped families.

The role of increased adrenergic activity in the genesis of ventricular arrhythmias in patients with LQT1 and LQT2 explains the efficacy of β-blockers and their lack of effect in patients with LQT3. Therefore β-blockers are the first-line treatment for patients with LQT1 and LQT2. In addition, ICDs should be considered, particularly in high-risk patients, including those having symptoms before puberty, a very prolonged QTc interval (>500 ms), and recurrent syncope or arrhythmias despite adherence to β-blocker treatment.

Idiopathic Ventricular Tachycardia

Idiopathic monomorphic VT represents 10% of all cases of VT. Three types have been described: RVOT and LVOT VT, fascicular or verapamil-sensitive VT, and nonspecific (normal heart) VT.

Outflow Tract Ventricular Tachycardia

Two types of outflow tract VT have been described: RVOT and LVOT. In North America, 70% of idiopathic VTs arise from the RVOT just inferior to the pulmonary valve.[139] RVOT VT is more common in females and is typically diagnosed in the third to fifth decades of life.

The clinical presentation of RVOT or LVOT VT is highly variable. Patients can present with intermittent palpitations caused by RVOT or LVOT ectopy or sustained palpitations, near syncope, or syncope.

The characteristic ECG of RVOT VT was initially described by Buxton in 1983.[20] The ECG shows LBBB morphology with an inferior axis (Figure 53-5).

LVOT VT can be differentiated from RVOT VT by an earlier R-wave transition (V3 compared with V5), more rightward axes, taller R waves inferiorly, and a small R wave in V1 (Figure 53-6).[140]

Outflow tract VTs frequently are initiated during exercise or conditions of increased sympathetic nervous system activity.[141] A characteristic of this arrhythmia is that acceleration of heart rate facilitates its initiation, which explains its propensity to occur during exercise. Forty percent of patients with repetitive monomorphic VT have inducible ventricular arrhythmias during isoprenaline infusion, which suggests the important role of activation of the sympathetic nervous system and increased catecholamines in the genesis of the arrhythmia.[95,142] Patients with this form of VT have also been shown to have relative sympathetic denervation, which could lead to sympathetic and parasympathetic imbalance

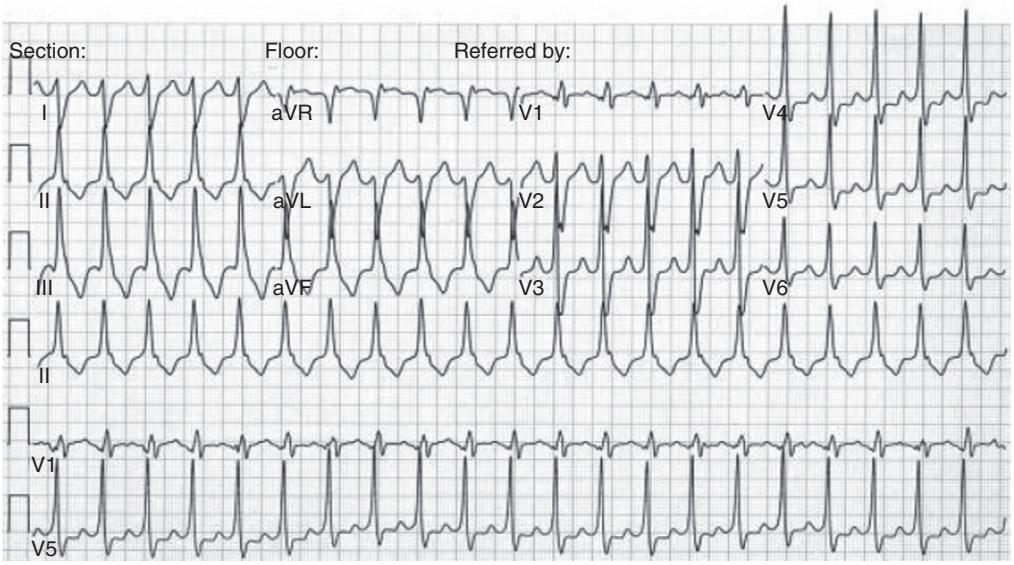

FIGURE 53-6 Left ventricular outflow tract ventricular tachycardia. *(From Srivathsan K, Lester SJ, Appleton CP, et al: Ventricular tachycardia in the absence of structural heart disease,* Indian Pacing Electrophysiol J *5[2]:106–121, 2005.)*

that could contribute to the genesis of VT.[143,144] This is supported by the fact that maneuvers to lower cAMP levels (an effect of sympathetic nervous system activation), such as vagal stimulation, β-receptor blockade, or activation of the A1-adenosine receptor with adenosine, frequently terminate the arrhythmia.[145-147]

Abnormal automaticity, re-entry, and triggered activity have been implicated as mechanisms for this arrhythmia.[148,149] However, triggered activity is thought to be the predominant mechanism caused by EADs and DADs.[150] Insights into the mechanism of outflow tract VT initially were drawn from patients who had exercise-induced sustained VT of right ventricular origin. Lerman et al[145] demonstrated the effectiveness of adenosine in terminating idiopathic VT, postulating that its effects were caused by its antagonism of the stimulatory effects of β-adrenergic activation and cAMP on intracellular Ca^{2+}. The effect of this was to reduce the amplitude of DADs, which confirmed cAMP-mediated triggered activity as the predominant mechanism responsible for this arrhythmia. Conversely, conditions that increase intracellular Ca^{2+} increase triggered activity, such as increased heart rates and catecholamines, which explains the association with exercise. Further support for triggered activity came from Gill et al, who suggested both EADs and DADs as possible mechanisms on the basis of the initiating sequences of LBBB-type VT during exercise. VT initiated without a cycle length change, suggestive of DADs, had an inferior axis (outflow tract VT), whereas long-short sequences suggested EADs, which were more common in VT with a superior axis (body or septal origin).

Investigation of patients with suspected outflow tract VT is initially aimed at determining if evidence of structural heart disease exists. RVOT VT should be distinguished from ARVC because both present with similar VT morphologies and because ARVC is associated with a more serious clinical outcome. Therefore echocardiography and cardiac MRI should be performed, with particular assessment of right ventricular size, morphology, and function. As mentioned earlier, in ARVC, the resting ECG may show features of right ventricular conduction delay (ε-waves or late potentials). Exercise testing is frequently used to initiate and evaluate RVOT or LVOT VT. During exercise testing, 30% to 50% of patients develop outflow tract VT. During electrophysiology testing, outflow tract VT can be induced, in most cases, with ventricular burst pacing or programmed electrical stimulation in combination with pharmacologic agents such as isoprenaline, atropine, or aminophylline. The arrhythmia cannot be entrained, and termination is with adenosine, verapamil, vagal maneuvers, or β-blockers.

Treatment options for RVOT or LVOT VT include medical therapy or radiofrequency (RF) ablation. First-line medical therapy is with either β-blockers, calcium channel blockers (verapamil or diltiazem), or sotalol and has been shown to have a 25% to 50% efficacy rate.[20,151-153] Second-line therapy includes class Ia, Ic, and III drugs, including amiodarone.[20] However, RF ablation is now at least 90% effective and, in view of the young age of individuals affected, is the preferred treatment.[154,155] In addition, ablation of LVOT VT near the aortic sinus cusps appears to be equally effective; however, serious complications, including left main coronary artery occlusion, may occur; therefore coronary angiography is recommended before and after ablation.

Verapamil-Sensitive Ventricular Tachycardia

This form of VT typically presents between the second and fourth decades of life and occurs more often in men (60% to 80%).[156] Symptoms during tachycardia include palpitations, presyncope, and syncope. On occasion, this tachycardia can be associated with tachycardia-induced cardiomyopathy. SCD is rare; however, a polymorphic form that degenerates into VF can occur.

Focal re-entry involving the fascicles or abnormal Purkinje tissue appears to be the principal mechanism. QRS morphology depends on which branches of the fascicles provide the exit point. The most common has a right bundle branch morphology (RBBB) and left-axis deviation associated with left posterior fascicle exit (90% to 95%) (Figure 53-7).

Typically, diagnosis involves the demonstration of induction with atrial pacing, tachycardia with an RBBB and left- or right-axis

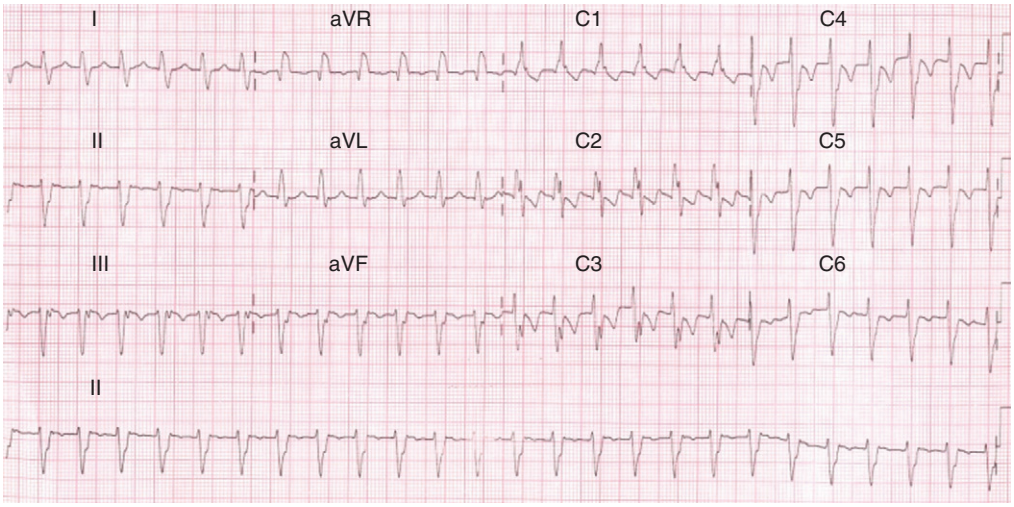

FIGURE 53-7 Fascicular ventricular tachycardia (right bundle branch block and left-axis deviation) with posterior exit.

deviation, no evidence of structural heart disease, and verapamil sensitivity.[157,158]

Intrafascicular VT was described as occurring at rest; however, more recently, sensitivity of the tachycardia to catecholamines (during exercise) or emotional stress has been appreciated.[158-160]

First-line treatment of patients with verapamil-sensitive VT is with verapamil. RF ablation, however, has been shown to be 85% to 90% effective. Ablation is targeted at sites of earliest ventricular activation and the presence of Purkinje potentials.

Idiopathic Ventricular Tachycardia (Nonspecific Normal Heart Ventricular Tachycardia)

This form of VT, which occurs in the fifth decade of life, arises from the left or right ventricle and is thought to be caused by abnormal automaticity.[156] This tachycardia may be monomorphic or polymorphic and typically is not inducible with programmed stimulation, whereas it is inducible with catecholamines (exercise) and is sensitive to β-blockade. As a result, this form of VT has previously been described as automatic "propranolol sensitive" VT.[161]

In view of the sensitivity of the arrhythmia to β-blockers, they are used as first-line treatment. Currently, data regarding other treatment options for these patients are insufficient; however, survivors of a cardiac arrest should be offered ICD therapy.

Drugs

Class Ia and Ic antiarrhythmic drugs have been implicated as being proarrhythmic during exercise.[162] After the introduction of flecainide, an investigation was carried out to study the potential proarrhythmic effects of the drug.[163] Class Ic drugs slow intraventricular conduction, which is manifested on the ECG by an increased QRS width.[164-166] This slowing of ventricular conduction, particularly in the presence of diseased myocardium, could facilitate re-entry. Of the 55 patients who took the drug, 5 had inducible VT during exercise. Ranger et al hypothesized that sinus tachycardia during exercise may enhance flecainide-induced conduction slowing by increasing Na^+ channel blockade, facilitating ventricular re-entry.[167] Their study showed that the patients who developed the greatest QRS width increase during exercise developed monomorphic VT. Conversely, Hirsowitz et al postulated that concurrent administration of β-blockers and thus a lower heart rate response to exercise should reduce the incidence of exercise-induced VT.[168] They demonstrated a reduction in inducible VT from 39% to 7% during exercise in patients taking class Ic drugs. Other drugs implicated as proarrhythmic during exercise include quinidine, moricizine, procainamide, encainide, and propafenone.[128,169,170]

Class III antiarrhythmics cause torsades de pointes because of their effects on cardiac repolarization and the associated increased Q-T interval. This effect is augmented during slow rates and therefore do not occur during exercise. However, a recent case report described a patient who developed polymorphic VT during exercise while on dofetilide. This was provoked by an exercise-induced post-ectopic pause following significant Q-T prolongation.[171]

Prognostic Significance of Exercise-Induced Arrhythmias

Exercise-Induced Supraventricular Arrhythmias

Few studies have looked at the prognostic significance of exercise-induced supraventricular arrhythmias. Atrial arrhythmias precipitated during exercise are often a result of an underlying substrate such as left ventricular dysfunction or left atrial enlargement, which, in themselves, are both prognostic. Bunch et al looked at the prognostic significance of atrial arrhythmias induced during exercise testing in patients with suspected CAD.[172] Of the 5375 patients (aged 61 ± 12 years), 1275 (24%) developed atrial ectopy, 185 (3.4%) developed supraventricular tachycardia, and 43 (0.8%) developed AF. The 5-year cardiac mortality rate was not different among these groups compared with those with no inducible atrial arrhythmias; however, the 5-year incidence of MI was higher in the AF group. This suggests that exercise-induced atrial arrhythmias appear to be benign except for the possible relationship with induced AF, which likely represents underlying structural heart disease.

Exercise-Induced Ventricular Arrhythmias

The underlying cause and associated structural heart disease often determine the prognosis associated with exercise-induced ventricular arrhythmias. Among patients without evidence of CAD, an increase in cardiovascular morbidity and mortality seems to be associated with individuals with exercise-induced ventricular arrhythmias. An analysis of the Framingham Heart study reported the results of 1397 men without known cardiovascular heart disease and who underwent a routine exercise testing.[173] Exercise test–induced ventricular arrhythmias were noted in 792 (27%) of the subjects. During a mean follow-up of 15 years, this was associated with an increase in all-cause mortality (hazard ratio, 1.9). Exercise-induced ventricular arrhythmias were not associated with left ventricular function or ischemic ST-segment responses. In 2000, Jouven et al evaluated 6101 asymptomatic men who underwent exercise stress testing.[174] The subjects were followed up for 23 years. The investigators concluded that frequent VPBs (a run of two or more making up 10% of any 30 seconds) during exercise in men without detectable cardiovascular disease is associated with long-term increase in cardiovascular mortality (relative risk, 2.53%; 95% confidence interval, 1.65 to 3.88). This group included those with genetic diseases (LQTS, CPVT) and ischemic heart disease with preserved left ventricular function.

In patients with CAD, the presence of exercise-induced ventricular arrhythmias is associated with increased cardiovascular mortality. In patients undergoing predischarge exercise testing after MI, induced ventricular arrhythmias had a mortality rate of 15% at 1 year compared with 7% in those with no inducible ventricular arrhythmias.[175] The most accurate predictor of mortality was left ventricular function. In a similar study following MI, the 1-year mortality rate in those with and without VPBs during exercise was 12% and 4%, respectively.[176] The presence of simple or complex VPBs in patients with CAD and ischemic ST depression during exercise appears to allow further risk stratification at 1-year follow up.[177]

Management

A number of causes of exercise-induced arrhythmias exist. Initial management should be focused on identifying the etiology and treating any reversible causes. If myocardial ischemia is caused by atherosclerotic coronary disease, then prompt revascularization prevents further arrhythmia recurrence.[67,68] Other considerations include ensuring treatment is provided for other factors that may precipitate these arrhythmias, for example, electrolyte disturbances and optimization of hemodynamics, which are particularly important in patients with impaired ventricular function.

A number of conditions described are caused by genetic mutations, and therefore genetic testing and family screening become important in risk stratification for individuals and family members. Because of the association of these conditions with SCD, individuals affected are discouraged from endurance exercises and strenuous exertion.

As described, increased sympathetic activity plays a central role in the genesis of exercise-induced arrhythmias. Therefore, the mainstay of treatment for the prevention of these arrhythmias is with β-adrenoreceptor–blocking agents. In addition Ca^{2+} channel blockers have been shown to be effective in patients with repetitive monomorphic VT and CPVT, particularly in combination with β-blockers.[117,118,178]

RF catheter ablation has a role in patients with outflow tract VT and verapamil-sensitive VT. Success rates have been reported to be between 80% and 100%. In addition, ablation has a role in scar-related VT that is refractory to drug treatment.

Despite medical management and catheter ablation, the associated increased incidence of SCD in individuals affected often necessitates the implantation of ICDs.

Conclusion

Individuals with exercise-induced arrhythmias represent a heterogeneous group, involving a number of etiologies, clinical manifestations, and treatments. Current management is limited to pharmacotherapy (mainly β-blockers and Ca^{2+} channel blockers), RF ablation, and implantation of ICDs. Currently, considerable research is being undertaken to understand the precise mechanism of arrhythmogenesis at genetic and molecular levels, which could, in the future, provide more targeted and efficacious treatments.

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CHAPTER 54

Genetics and Cardiac Arrhythmia Syndromes

Jeffrey A. Towbin, Matteo Vatta, Hua Li, and Neil E. Bowles

Cardiac arrhythmias are major causes of morbidity and mortality, including sudden cardiac death (SCD). SCD in the United States occurs with a reported incidence of more than 300,000 persons per year.[1] Although coronary heart disease is a major cause of death, other etiologies contribute to this problem. In many of these non–ischemia-related cases, autopsies are unrevealing. Interest in identifying the underlying cause of the death in these instances has been focused on cases of unexpected arrhythmogenic death, which is estimated to represent 5% of all SCDs. In cases in which no structural heart disease can be identified, long QT syndrome (LQTS), ventricular pre-excitation (Wolff-Parkinson-White syndrome), and idiopathic ventricular fibrillation (IVF) or Brugada syndrome (characterized by ST-segment elevation in the right precordial leads with or without right bundle branch block [RBBB]) are most commonly considered as likely causes.[1-3] Another important disease in which arrhythmias are believed to play a central role is sudden infant death syndrome (SIDS), a disorder with no structural abnormalities.[4]

Arrhythmogenic right ventricular dysplasia (ARVD) is also a significant cause of SCD and is considered a primary electrical disease despite being associated with fibrosis and fatty infiltration of the right ventricle.[5] The arrhythmias associated with ARVD also occur in other disorders in which structurally normal myocardium is seen, such as catecholaminergic ventricular tachycardia (VT).[6]

This chapter describes the current understanding of the clinical and molecular genetic aspects of inherited diseases in which arrhythmias are prominent features. The discussion should serve as an introduction and overview to these conditions. Newer disorders are rapidly being added to this list and are discussed in more detail elsewhere in this textbook. A more detailed treatment of the current state of knowledge regarding the molecular basis and basic electrophysiological mechanisms of inherited arrhythmia syndromes is discussed in Chapters 6 and 7. Individual clinical syndromes are discussed in Chapters 62 to 65.

Long QT Syndrome

Clinical Description

LQTS is an inherited or acquired disorder of repolarization identified by the electrocardiographic abnormalities of prolongation of the Q-T interval corrected for heart rate (QTc), usually above 460 to 480 ms; relative bradycardia; T-wave abnormalities (Figure 54-1); and episodic ventricular tachyarrhythmias, particularly *torsades de pointes* (Figure 54-2).[7] The inherited form of LQTS is transmitted as an autosomal dominant or autosomal recessive trait. Acquired LQTS may be seen as a complication of various drug therapies or electrolyte abnormalities. Whether the abnormality is genetic or acquired, the clinical presentation is similar.[1,7] The initial presentation of LQTS is heterogeneous and most commonly includes syncope, which, in many instances, is triggered by emotional stress, exercise, or auditory phenomena. Other presenting features include seizures or palpitations. SCD is the first symptom in some individuals, but some other cases are diagnosed by surface electrocardiogram (ECG) as a family screening evaluation necessitated by family history of LQTS or SCD.

Clinical Genetics

Two differently inherited forms of familial LQTS have been reported. *Romano-Ward syndrome* is the most common of the inherited forms of LQTS and appears to be transmitted as an autosomal dominant trait.[8,9] In this disorder, the disease gene is transmitted to 50% of the offspring of an affected individual. However, low penetrance has been described, so gene carriers may, in fact, have no clinical features of disease.[10] Individuals with Romano-Ward syndrome have the pure syndrome of prolonged Q-T interval on ECG, with the associated symptom complex of syncope, SCD, and, in some patients, seizures.[11,12] Occasionally, other noncardiac abnormalities such as diabetes mellitus, asthma, or syndactyly may also be associated with QT prolongation.[13-16] LQTS may also be involved in some cases of SIDS, which, in some cases, appear in several family members.[5,17,18]

Jervell and Lange-Nielsen syndrome (JLNS) is a relatively uncommon inherited form of LQTS. Classically, this disease has been described as having apparent autosomal recessive transmission.[19-21] These patients have a clinical presentation identical to that in patients with Romano-Ward syndrome but also have associated sensorineural deafness. Clinically, patients with JLNS usually have longer Q-T intervals compared with individuals with Romano-Ward syndrome and also have a more malignant course. Priori and colleagues have reported autosomal recessive cases of Romano-Ward syndrome as well, thus changing one of the sine qua non of JLNS.[22]

Gene Identification in Romano-Ward Syndrome

KVLQT1 or *KCNQ1*: The *LQT1* Gene

The first of the genes mapped for LQTS, termed *LQT1*, required 5 years from the time that mapping to chromosome 11p15.5 was first reported to gene cloning.[23] This gene, originally named

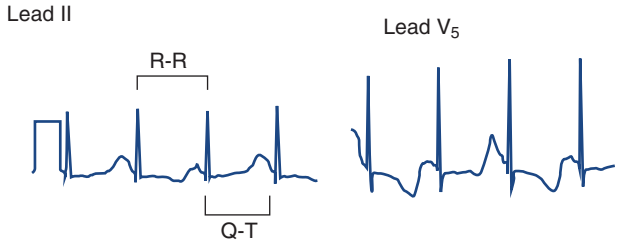

FIGURE 54-1 Electrocardiogram leads II and V5 demonstrating prolonged Q-T intervals and T-wave alternans. Bazett's formula, used to calculate the Q-T interval corrected for heart rate (QTc), is noted.

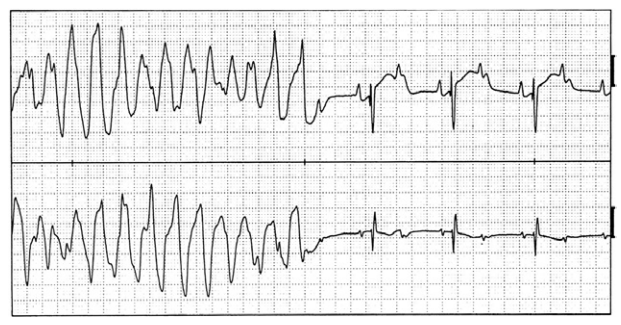

FIGURE 54-2 Polymorphic ventricular tachycardia in a patient with long QT syndrome.

KVLQT1, but more recently called *KCNQ1* (Table 54-1), is a novel potassium channel gene that consists of 16 exons, spans approximately 400 kb, and is widely expressed in human tissues, including the heart, inner ear, kidney, lung, placenta, and pancreas but not in the skeletal muscle, liver, or brain.[24] Although most of the mutations are "private" (i.e., only seen in one family), at least one frequently mutated region (called a "hot spot") of *KVLQT1* exists.[25-27] This gene is the most commonly mutated gene in LQTS.

Analysis of the predicted amino acid sequence of *KVLQT1* suggests that it encodes a potassium channel α-subunit with a conserved potassium-selective pore-signature sequence flanked by six membrane-spanning segments similar to shaker-type channels (Figure 54-3).[24,27-29] A putative voltage sensor is found in the fourth membrane-spanning domain (S4), and the selective pore loop is located between the fifth and sixth membrane-spanning domains (S5,S6). Biophysical characterization of the KVLQT1 protein confirmed that *KVLQT1* is a voltage-gated potassium channel protein subunit, which requires coassembly with a β-subunit called *minK* to function properly.[28,29] Expression of either *KVLQT1* or *minK* alone results in either inefficient or no current development. When *minK* and *KVLQT1* are co-expressed in either mammalian cell lines or *Xenopus* oocytes, however, the slowly activating potassium current (I_{Ks}) is developed in cardiac myocytes.[28,29] The combination of normal and mutant *KVLQT1* subunits forms abnormal I_{Ks} channels, and these mutations are believed to act through a dominant-negative mechanism (the mutant form of *KVLQT1* interferes with the function of the normal wild-type form through a "poison pill" type mechanism) or a loss-of-function mechanism (only the mutant form loses activity).[30]

Because *KVLQT1* and *minK* form a unit, mutations in *minK* could also be expected to cause LQTS. This fact was subsequently demonstrated (discussed below).[31]

HERG or *KCNH2*: The *LQT2* Gene

The *LQT2* gene was initially mapped to chromosome 7q35-36 by Jiang et al, and subsequently, candidate gene screening identified the disease-causing gene *HERG* (***h***uman ***e***ther-a-go-go-***r***elated ***g***ene), a cardiac potassium channel gene to be the *LQT2* gene (see Table 54-1).[27,32] *HERG* was originally cloned from a brain cDNA library and found to be expressed in neural crest–derived neurons, microglia, a wide variety of tumor cell lines, and the heart.[33-37] LQTS-associated mutations were identified in *HERG* throughout the gene, including missense mutations, intragenic deletions, stop codons, and splicing mutations.[27,37,38] Currently, this gene is thought to be the second most common gene mutated in LQTS (second to *KVLQT1*). As with *KVLQT1*, "private" mutations that are scattered throughout the entire gene without clustering preferentially are seen.

HERG consists of 16 exons and spans 55 kb of genomic sequence.[37] The predicted topology of *HERG* (see Figure 54-3) is similar to that of *KVLQT1*. Unlike *KVLQT1*, *HERG* has extensive intracellular amino-and-carboxyl termini, with a region in the carboxyl-terminal domain having sequence similarity to nucleotide binding domains (NBDs).

Electrophysiological and biophysical characterization of expressed *HERG* in *Xenopus* oocytes established that *HERG* encodes the rapidly activating delayed rectifier potassium current I_{Kr}.[39-41] Electrophysiological studies of LQTS-associated mutations showed that they act through either a loss of function or a dominant negative mechanism.[41,42] In addition, protein trafficking abnormalities have been shown to occur.[43,44] This channel has been shown to coassemble with β-subunits for normal function, similar to that seen in I_{Ks}. McDonald et al initially suggested that the complexing of *HERG* with *minK* is needed to regulate the I_{Kr} potassium current.[45] Bianchi et al provided confirmatory evidence that *minK* is involved in the regulation of both I_{Ks} and I_{Kr}.[46] Abbott et al identified *MiRP1* as a β-subunit for *HERG* (discussed below).[47]

SCN5A: The *LQT3* Gene

The positional candidate gene approach was also used to establish that the gene responsible for chromosome 3–linked LQTS (*LQT3*) is the cardiac sodium channel gene *SCN5A* (see Table 54-1).[48,49] *SCN5A* is highly expressed in the human myocardium and brain but not in the skeletal muscle, liver, or uterus.[50-52] It consists of 28 exons that span 80 kb and encodes a protein of 2016 amino acids with a putative structure that consists of four homologous domains (DI to DIV), each of which contains six membrane-spanning segments (S1 to S6) similar to the structure of the potassium channel α-subunits (see Figure 54-3).[27,39] Linkage studies with *LQT3* families and *SCN5A* initially demonstrated linkage to the *LQT3* locus on chromosome 3p21-24, and multiple mutations were subsequently identified.[50,51] Biophysical analysis of the initial three mutations were expressed in *Xenopus* oocytes,

Table 54-1 Common Arrhythmia Syndromes and Their Genetic Basis

DISEASE	RHYTHM ABNORMALITY	INHERITANCE	CHROMOSOME LOCATION	GENE
VENTRICULAR ARRHYTHMIAS				
Romano-Ward syndrome	TdP, VF	AD	11p15.5, 7q35, 3p21	*KVLQT1* (11p15.5); *4q25*, *21q22* HERG* (7q35); *SCN5A*; (3p21); *minK* (21q22); *MiRP1* (21q22)
Jervell and Lange-Nielsen syndrome	TdP, VF	AD/AR†	11p15.5, 21q22	*KVLQT1* (11p15.5); *minK* (21q22)
Brugada syndrome	VT, VF	AD	3p21	*SCN5A*
Sudden infant death syndrome	VT/VF	AD	3p21	*SCN5A*
Familial VT	VT	AD	?	?
Familial bidirectional VT	VT	AD	1q42	*RYR2*
Familial polymorphic VT	VT	AD	1q42*	*RYR2*
Arrhythmogenic right ventricular dysplasia	VT	AD	1q42	*RYR2*
Naxos disease	VT	AR	17q21, 6p24	Plakoglobin (17q21); desmoplakin (6p24)
SUPRAVENTRICULAR ARRHYTHMIAS				
Familial atrial fibrillation	AF	AD	10q22	*NUP155*, *KCNQ1*, and others (?)
Familial total atrial standstill	SND, AF	AD	?	?
Familial absence of sinus rhythm	SND, AF	AD	?	?
Wolff-Parkinson-White syndrome	AVRT, AF, VF	AD	7q3	*AMPK*
Familial PJRT	AVRT	AD	?	?
CONDUCTION ABNORMALITIES				
Familial AV block	AVB, AF, SND, VT, SD	AD	19q13	?
Isolated AV block	AVB, AF, SND, VT, SD	AD	3p21	*SCN5A*
Lev-Lenègre syndrome	AVB, AF, SND, VT, SD	AD	3p21	*SCN5A*
Familial bundle branch block	RBBB	?	?	?

AD, *Autosomal dominant;* AF, *atrial fibrillation;* AR, *autosomal recessive;* AV, *atrioventricular;* AVB, *atrioventricular block;* AVRT, *atrioventricular reciprocating tachycardia;* PJRT, *permanent form of junctional reciprocating tachycardia; RBBB, right bundle branch block;* SD, *sudden death;* SND, *sinus node dysfunction;* TdP, *torsades de pointes;* VF, *ventricular fibrillation;* VT, *ventricular tachycardia.*
**At least one other unknown.*
†Jervell and Lange-Nielsen syndrome: autosomal dominant rhythm abnormality and autosomal recessive sensorineural deafness.

and it was found that all mutations generated a late phase of inactivation-resistant, mexiletine- and tetrodotoxin-sensitive whole-cell currents through multiple mechanisms.[53,54] Two of the three mutations showed dispersed reopening after the initial transient current, but the other mutation showed both dispersed reopening and long-lasting bursts.[54] These results suggested that *SCN5A* mutations act through a gain of function mechanism (the mutant channel functions normally, but with altered properties such as delayed inactivation) and that the mechanism of chromosome 3–linked LQTS is persistent non-inactivated sodium current in the plateau phase of the action potential. Later, An et al showed that not all mutations in *SCN5A* are associated with persistent current and demonstrated that *SCN5A* interacted with β-subunits.[55]

minK or *KCNE1*: The *LQT5* Gene

minK (*IsK* or *KCNE1*) was initially localized to chromosome 21 (21q22.1) and found to consist of three exons that span approximately 40 kb (see Table 54-1). It encodes a short protein consisting of 130 amino acids and has only one transmembrane-spanning segment with small extracellular and intercellular regions (see Figure 54-3).[30,31,56] When expressed in *Xenopus* oocytes, it produces potassium current that closely resembles the slowly activating delayed-rectifier potassium current I_{Ks} in cardiac cells.[56,57] The fact that the *minK* clone was only expressed in *Xenopus* oocytes and not in mammalian cell lines raised the question whether *minK* is a human channel protein. With the cloning of *KVLQT1* and the coexpression of *KVLQT1* and *minK* in both mammalian

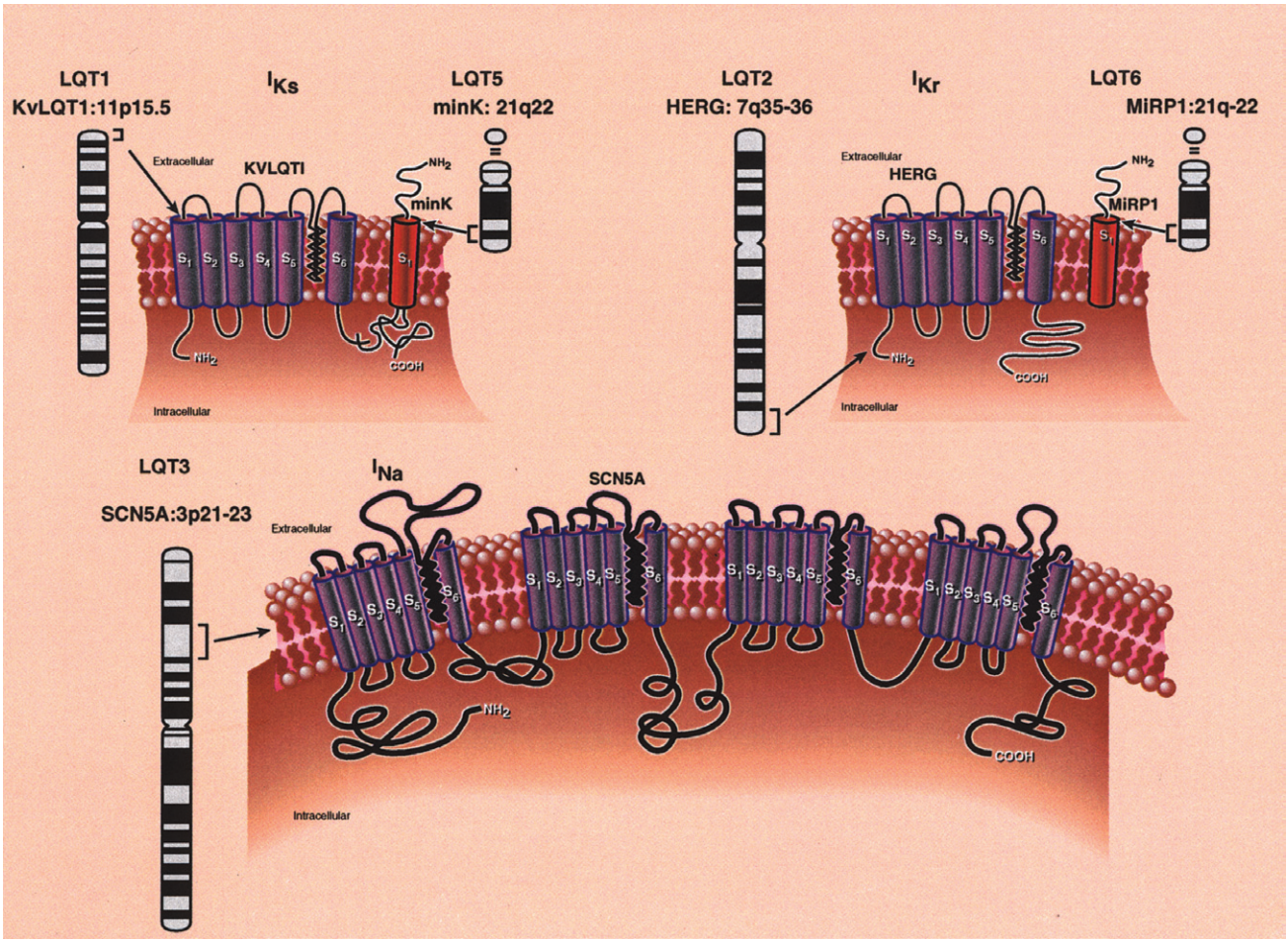

FIGURE 54-3 Genetics of ventricular arrhythmias. The genetic loci and known genes identified for long QT syndrome are shown along with the ion channel protein structure. Note that the potassium channel α-subunits *KvLQT1* and *HERG* require association with β-subunits (*minK* and *KVLQT1*=IKs; *MiRP1* and *HERG*=IKr for normal function).

cell lines and *Xenopus* oocytes, it became clear that *KVLQT1* interacts with *minK* to form the cardiac slowly activating delayed rectifier I_{Ks} current.[28,29] *minK* alone cannot form a functional channel but induces the I_{Ks} current by interacting with endogenous *KVLQT1* protein in *Xenopus* oocytes and mammalian cells. Bianchi et al showed that mutant *minK* results in abnormalities of I_{Ks}, I_{Kr} as well as protein trafficking abnormalities.[46] McDonald et al showed that *minK* also complexes with *HERG* to regulate the I_{Kr} potassium current.[45] Splawski et al demonstrated that *minK* mutations cause *LQT5* when they identified mutations in two families with LQTS.[31] In both cases, missense mutations (S74L, D76N) were identified; they reduced I_{Ks} by shifting the voltage dependence of activation and accelerating channel deactivation. This was supported by the fact that a murine model of *minK*-defective LQTS was also created.[58] The functional consequences of these mutations include delayed cardiac repolarization and, hence, an increased risk of arrhythmias.

MiRP1 or *KCNE2*: The *LQT6* Gene

MiRP1, the *minK*-related peptide 1, or *KCNE2* (see Table 54-1), is a novel potassium channel gene recently cloned and characterized by Abbott and colleagues.[47] This small integral membrane subunit protein assembles with *HERG* (*LQT2*) to alter its function, enabling full development of the I_{Kr} current (see Figure 54-3). *MiRP1* is a 123–amino acid channel protein with a single predicted transmembrane segment similar to that described for *minK*.[56] Chromosomal localization studies mapped this *KCNE2* gene to chromosome 21q22.1, within 79kb of *KCNE1* (*minK*) and arrayed in opposite orientation.[47] The open reading frames of these two genes share 34% identity, and both are contained in a single exon, suggesting that they are related through gene duplication and divergent evolution.

Three missense mutations associated with LQTS and ventricular fibrillation (VF) were identified in *KCNE2* by Abbott et al, and biophysical analysis demonstrated that these mutants form channels that open slowly and close rapidly, thus diminishing potassium currents.[47] In one case, the missense mutation, a C-to-G transversion at nucleotide 25, which produced a glutamine (Q) to glutamic acid (E) substitution at codon 9 (Q9E) in the putative extracellular domain of *MiRP1*, led to the development of torsades de pointes and VF after intravenous clarithromycin infusion (i.e., drug induced).

Therefore, like *minK*, this channel protein acts as a β-subunit but, by itself, leads to ventricular arrhythmia risk when mutated. These similar channel proteins (i.e., *minK* and *MiRP1*) suggest

that a family of channels that regulates ion channel α-subunits exists. The specific role of this subunit and its stoichiometry remain unclear and are currently being hotly debated.

Genetics and Physiology of Autosomal Recessive Long QT Syndrome (Jervell and Lange-Nielsen Syndrome)

Neyroud et al reported the first molecular abnormality in patients with JLNS when they reported on two families in which three children were affected by JLNS and in whom a novel homozygous deletion-insertion mutation of *KVLQT1* was found.[59] A deletion of 7 bp and an insertion of 8 bp at the same location led to premature termination at the C-terminal end of the *KVLQT1* channel. At the same time, Splawski et al identified a homozygous insertion of a single nucleotide that caused a frameshift in the coding sequence after the second putative transmembrane domain (S2) of *KVLQT1*.[60] Together, these data strongly suggested that at least one form of JLNS is caused by homozygous mutations in *KVLQT1* (see Table 54-1). This has been confirmed by others.[27,30,61,62]

As a general rule, heterozygous mutations in *KVLQT1* cause Romano-Ward syndrome (LQTS only), whereas homozygous (or compound heterozygous) mutations in *KVLQT1* cause JLNS (LQTS and deafness). The hypothetical explanation suggests that although heterozygous *KVLQT1* mutations act by a dominant-negative mechanism, some functional *KVLQT1* potassium channels still exist in the stria vascularis of the inner ear. Therefore congenital deafness is averted in patients with heterozygous *KVLQT1* mutations. For patients with homozygous *KVLQT1* mutations, no functional *KVLQT1* potassium channels can be formed. It has been shown by in situ hybridization that *KVLQT1* is expressed in the inner ear, suggesting that homozygous *KVLQT1* mutations can cause the dysfunction of potassium secretion in the inner ear and lead to deafness.[60] However, it should be noted that incomplete penetrance exists, and not all heterozygous or homozygous mutations follow this rule.[11,22]

As with Romano-Ward syndrome, if *KVLQT1* mutations can cause the phenotype, it could be expected that *minK* mutations could also be causative of the phenotype (JLNS). Schulze-Bahr et al, in fact, showed that mutations in *minK* result in JLNS syndrome as well, and this was confirmed subsequently (see Table 54-1).[60,63] Hence, abnormal I_{Ks} current, whether caused by homozygous or compound heterozygous mutations in *KVLQT1* or *mink,* results in LQTS and deafness.

Genotype-Phenotype Correlations in Long QT Syndrome

Clinical Features

To a significant extent, the clinical features of LQTS depend on the mutated gene as well as on the intragenic position of the mutation and its effect on the channel protein. Several studies have clarified the specific associations, including the clinical severity in the probands and their parents and siblings, as well as the modifying influences on severity.

Kimbrough et al recently reported on the study of 211 probands with LQTS and classified the severity in the probands, affected parents, and siblings.[64] Importantly, they showed that the severity of the disease in the proband did not correlate with the clinical severity seen in first-degree relatives, specifically their parents and siblings. In fact, variable intrafamily penetrance was noted, consistent with other genetic and environmental factors playing a role in modulating and modifying clinical manifestations in members of the same family. Several stratifiers were identified as important.

The length of the QTc in affected parents and siblings was shown to be associated with significant risk of LQTS-related cardiac events. They also confirmed that genotype, age, and gender influence the course of disease in affected family members. For instance, male probands were found to have their first cardiac event at younger mean age compared with female probands (13 years vs. 19 years), but female probands had a higher frequency of cardiac arrest or LQTS-related death by 40 years of age. In the case of affected parents, they found that female gender and QTc length were risk factors for events, whereas QTc duration was the only risk factor in siblings. Affected mothers of LQTS probands displayed an ongoing cardiac event risk well after the birth of the proband, but affected fathers did not display this ongoing risk.

These findings complement the findings previously described by Zareba et al.[65] In this study, the authors provided evidence of clinical outcome, age of onset, and frequency of events based on genotype. Patients with mutations in *LQT1* had the earliest onset of events and the highest frequency of events followed by mutations in *LQT2*. The risk of SCD in these two groups was relatively low for any event. Mutations in *LQT3* resulted in a paucity of syncopal events, but events commonly resulted in SCD. In addition, mutations in *LQT3* resulted in the longest QTc duration. Mutations in *LQT1* and *LQT2* appeared to be associated with stress-induced symptoms, with *LQT1* associated with exercise and swimming and *LQT2* associated with auditory triggers.[66-71] *LQT3* appeared to be associated with sleep-associated symptoms and events.

Electrocardiographic and Biophysical Features

In 1995, Moss and colleagues provided the first evidence that mutations in different genes cause differing ECG features.[72] Specifically, these authors focused on the different types of T waves seen in patients with *LQT1* versus *LQT2* versus *LQT3*. ECGs of patients with *LQT1* were shown to display broad-based T waves, those with *LQT2* had low-amplitude T waves, and those with *LQT3* mutations had distinctive T waves with late onset. More recently, Zhang et al showed that there are actually four different ST-T wave patterns.[73] Using these definitions, they were able to identify 88% of patients with *LQT1* and *LQT2* accurately by surface ECG and 65% of *LQT3* carriers. Prospectively, these authors correctly predicted the genotype in 100% of patients.

Further insight into ECG findings and genotype were reported by Lupoglazoff et al using Holter monitor analysis.[74] Analysis of 133 patients with *LQT1* 57 *LQT2* carriers, and 100 control individuals, led the authors to conclude that T wave morphology was normal in most patients with *LQT1* (92%) and in normal controls (96%), but the vast majority of patients with *LQT2* had abnormal T waves (19% normal, 81% abnormal). In the largest percentage of patients with *LQT2*, T-wave notching was identified, with the T-wave protuberance seen above the horizontal, whereas another subset had a bulge at or below the horizontal. In the former case, young age, missense *LQT2* mutations, and mutations in the core domain of *HERG* predicted morphology, whereas potential diagnostic clues gained by the latter morphology included amino-terminal or carboxy-terminal mutations or frameshifts in *HERG*.

Animal Models of Long QT Syndrome

By using an arterially perfused canine left ventricular wedge preparation developed pharmacologically, induced animal models of *LQT1, LQT2,* and *LQT3* have been created.[75,76] By using chromanol 293B, a specific I_{Ks} blocker, a model that mimics *LQT1* was produced.[75] In this model, I_{Ks} deficiency alone was not enough to induce torsades de pointes, but the addition of β-adrenergic influence (i.e., isoproterenol) predisposed the myocardium to torsade by increasing trans-mural dispersion of repolarization. The addition of a β-blocker or mexiletine reduced the ability to induce torsades de pointes, suggesting that these medications might improve patient outcomes.

Models for *LQT2* and *LQT3* were created by using D-sotalol *(LQT2)* or ATX-II (*LQT3*) in this wedge preparation.[76] Both drugs preferentially prolong M cell action potential duration (APD), with ATX-II also causing a sharp rise in trans-mural dispersion. Mexiletine therapy abbreviated the Q-T interval prolongation in both models and reduced dispersion. Spontaneous torsades de pointes was suppressed, and the vulnerable window during which torsades de pointes induction occurs was also reduced in both models. These models support the current understanding of the different subtypes of LQTS and provide an explanation for potential therapies.

Therapeutic Options in Long QT Syndrome

Currently, the standard therapeutic approach in LQTS is the initiation of β-blockers at the time of diagnosis.[7] Recently, Moss et al demonstrated significant reduction in cardiac events using β-blockers.[77] However, syncope, aborted cardiac arrest, and SCD do continue to occur. When β-blockers cannot be used, such as in patients with asthma, other medications such as mexiletine have been tried.[78] When medical therapy has failed, left sympathectomy or therapy with an implantable cardioverter-defibrillator (ICD) has been used.[7]

Genetics-based therapy has also been described. Schwartz et al showed that sodium channel blocking agents (i.e., mexiletine) shorten the QTc in patients with *LQT3*, whereas exogenous potassium supplementation or potassium channel openers have been shown to be potentially useful in patients with potassium channel defects.[78-80] However, long-term potassium therapy with associated potassium-sparing agents has been unable to keep the serum potassium above 4 mmol/L because of renal potassium homeostasis. This suggests that long-term potassium therapy may not be useful. In addition, no definitive evidence that these approaches (i.e., sodium channel blockers, exogenous potassium, or potassium channel openers) improve survival has been published.

Andersen Syndrome (LQT7)

Clinical Aspects

Andersen and colleagues (1971)[81] identified a complex phenotype, including ventricular arrhythmias, potassium-sensitive periodic paralysis, and dysmorphic features. The dysmorphisms included hypertelorism, broad nasal root, defects of the soft and hard palate, as well as short stature. More recently, skeletal abnormalities have broadened the phenotype (Andelfinger et al).[82] The associated cardiac abnormalities include QTC prolongation, ventricular tachycardia (VT), ventricular fibrillation (VF), and atrial arrhythmias. Torsades de pointes and bi-directional VT have been seen. In addition, repolarization abnormalities affecting late repolarization and resembling giant U waves are common. SCD has not been reported as a major risk in this disorder.

Genetic Aspects

Andersen syndrome was originally mapped to chromosome 17q23-q24.2 by Plaster et al[83] who used genome-wide linkage analysis. The critical region within this locus was narrowed, and candidate gene mutation screening identified mutations in *KCNJ2*, which encodes an inward rectifier potassium channel called Kir2.1 (Tristani-Firouzi et al).[84] This channel is highly expressed in the heart and plays a role in phase 3 repolarization and in the resting membrane potential. Multiple gene mutations have been identified, to date, with relatively high penetrance noted. Functional studies have demonstrated reduction or suppression of Ik_1, by a haplo insufficiency or dominant negative effect. This gene may play a role in developmental signaling pathways as well, which is believed to cause dysmorphisms.

Brugada Syndrome

Clinical Aspects of Brugada Syndrome

The first identification of the electrocardiographic pattern of RBBB with ST elevation in leads V1 to V3 was reported by Osher and Wolff.[85] Shortly thereafter, Edeiken identified persistent ST elevation without RBBB in 10 asymptomatic males, and Levine et al described ST elevation in the right chest leads and conduction block in the right ventricle in patients with severe hyperkalemia.[86,87] The first association of this ECG pattern with SCD was described by Martini et al and later by Aihara et al.[88,89] This association was further confirmed in 1991 by Pedro and Josep Brugada, who described four patients with SCD and aborted SCD, with ECGs demonstrating RBBB and persistent ST elevation in leads V1 to V3 (Figure 54-4).[90] In 1992 these authors characterized what they believed to be a distinct clinical and electrocardiographic syndrome.[3]

The finding of ST elevation in the right chest leads has been observed in various clinical and experimental settings and is not unique to or diagnostic of Brugada syndrome by itself.[91] Situations in which these ECG findings occur include electrolyte or metabolic disorders, pulmonary or inflammatory diseases, and abnormalities of the central or peripheral nervous system. In the absence of these abnormalities, the term *idiopathic ST elevation* is often used and may identify patients with Brugada syndrome.

The ECG findings and associated sudden and unexpected death have been reported as common problems in Japan and Southeast Asia, where it most commonly affects men during sleep.[92] This disorder, known as *sudden and unexpected death syndrome* (SUDS) or *sudden unexpected nocturnal death syndrome* (SUNDS), has many other names in Southeast Asia: *bangungut* (to rise and moan in sleep) in the Philippines; *non-laitai* (sleep-death) in Laos; *lai-tai* (died during sleep) in Thailand; and *pokkuri* (sudden and unexpectedly ceased phenomena) in Japan. General characteristics of SUNDS include young, healthy males in whom sudden death, preceded by a groan, occurs usually during sleep late at night. No precipitating factors are identified, and autopsy findings show no structural heart disease.[93] Life-threatening

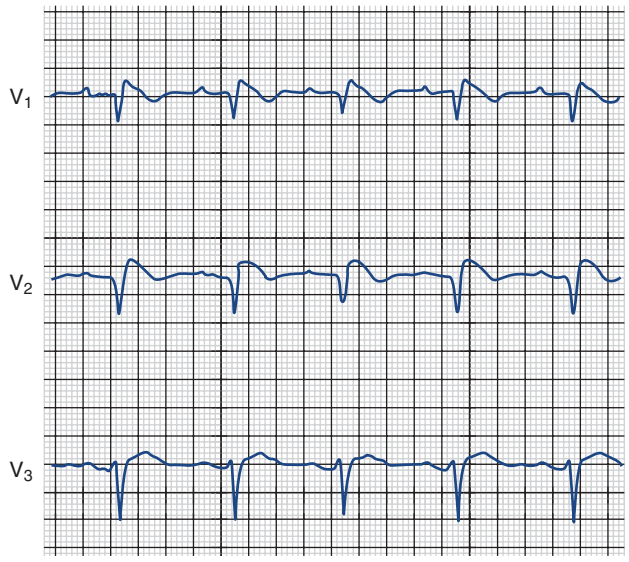

FIGURE 54-4 Electrocardiographic features of Brugada syndrome. Note the ST-segment elevation (cove type) in leads V1 and V2.

ventricular tachyarrhythmias as a primary cause of SUNDS have been demonstrated, with VF occurring in most cases.[94]

The risk of SCD associated with Brugada syndrome and SUNDS in European and Southeast Asian individuals has been reported to be extremely high; approximately 75% of patients, as reported by Brugada et al, survived cardiac arrest.[3,90,95] In addition, symptomatic and asymptomatic patients have been considered to be at equal risk. Priori et al have, however, disputed this claim.[96] In a study of 60 patients with Brugada syndrome, asymptomatic patients had no episodes or events. The importance of this difference is its impact on therapeutic decision making, as currently all patients receive ICD therapy. Should the data of Priori et al hold up, selective use of ICDs would be appropriate.[96] If selective use of ICDs were to be considered, other diagnostic tests for risk stratification would be necessary.

Kakishita et al studied a high-risk group of patients, 37% of whom had experienced spontaneous episodes of VF.[97] As the majority of patients had ICDs, the authors were able to show that 65% of episodes were preceded by premature ventricular complexes (PVCs), which were essentially identical to the initiating PVCs of VF in morphology. In fact, the PVCs initiating all VF episodes arose from the terminal portions of the T wave, and pause-dependent arrhythmias were rare. This suggests that vigilant evaluation by Holter monitoring could identify at-risk patients. In addition, the authors suggested that the use of radiofrequency (RF) ablation targeting the initiating PVCs could be helpful in reducing risk and reducing the need for ICD placement.

Clinical Genetics of Brugada Syndrome

Most of the families thus far identified with Brugada syndrome have apparent autosomal dominant inheritance.[98-100] In these families, approximately 50% of offspring of affected patients develop the disease. It is likely that the number of families reported has been small because of under-recognition as well as the occurrence of premature and unexpected deaths.[91,101,102]

Molecular Genetics of Brugada Syndrome

In 1998, our laboratory reported the findings on six families and several sporadic cases of Brugada syndrome.[100] The families were initially studied by linkage analysis by using markers to the known ARVD loci and LQT loci, and linkage was excluded. Candidate gene screening using the mutation analysis approach of single-strand conformation polymorphism (SSCP) analysis and deoxyribonucleic acid (DNA) sequencing was performed, and *SCN5A* was chosen for study on the basis of the suggestions of Antzelevitch.[91,99,101-103] In three families, mutations in *SCN5A* were identified (see Table 54-1): (1) a missense mutation (C-to-T base substitution) causing a substitution of a highly conserved threonine by methionine at codon 1620 (T1620M) in the extracellular loop between transmembrane segments S3 and S4 of domain IV (DIVS3-DIVS4), an area important for coupling of channel activation to fast inactivation; (2) a two-nucleotide insertion (AA), which disrupts the splice-donor sequence of intron 7 of *SCN5A*; and (3) a single nucleotide deletion (A) at codon 1397, which results in an in-frame stop codon that eliminates DIIIS6, DIVS1-DIVS6, and the carboxy-terminus of *SCN5A* (Figure 54-5).[100] Since the initial report, multiple confirming mutations have been identified. *SCN5A* mutations have also been found in the case of SCD in children.[104]

Biophysical analysis of the mutants in *Xenopus* oocytes demonstrated a reduction in the number of functional sodium channels in both the splicing mutation and the one-nucleotide deletion mutation, which should promote development of re-entrant arrhythmias. In the missense mutation, sodium channels recover from inactivation more rapidly than normal. Subsequent experiments conducted in modified HEK cells revealed that at physiological temperatures (37° C), reactivation of the T1620M mutant channel was actually slower, whereas inactivation of the channel was significantly accelerated. These alterations leave the transient outward current unopposed and thus able to effect an all-or-none repolarization of the action potential at the end of phase 1.[105] Failure of the sodium channel to express, as with the insertion and deletion mutations, results in similar electrophysiological changes. Reduction of the sodium channel I_{Na} current causes heterogeneous loss of the action potential dome in the right ventricular epicardium, leading to a marked dispersion of depolarization and refractoriness, an ideal substrate for development of re-entrant arrhythmias. Phase 2 re-entry produced by the same substrate is believed to provide the premature beat necessary for the initiation of the VT and VF responsible for symptoms in these patients. Interestingly, however, Kambouris et al identified a mutation in essentially the same region of *SCN5A* as the T1620M mutation (R1623H), but the clinical and biophysical features of this mutation were found to be consistent with *LQT3* and not Brugada syndrome.[106] More recently, mutations in *SCN5A*, in which both Brugada syndrome and LQT3 features were seen in the same patient, has been described.[107] Hence, there clearly remains a gap in our understanding of these entities.

Risk Stratification in Brugada Syndrome

Most symptomatic or at-risk patients with Brugada syndrome manifest an ECG with a coved-type ST-segment elevation with or without provocation with sodium channel blocking agents such as ajmaline or flecainide (Figure 54-6).[108] The other form of ST-segment elevation, the so-called *saddle type,* is not associated

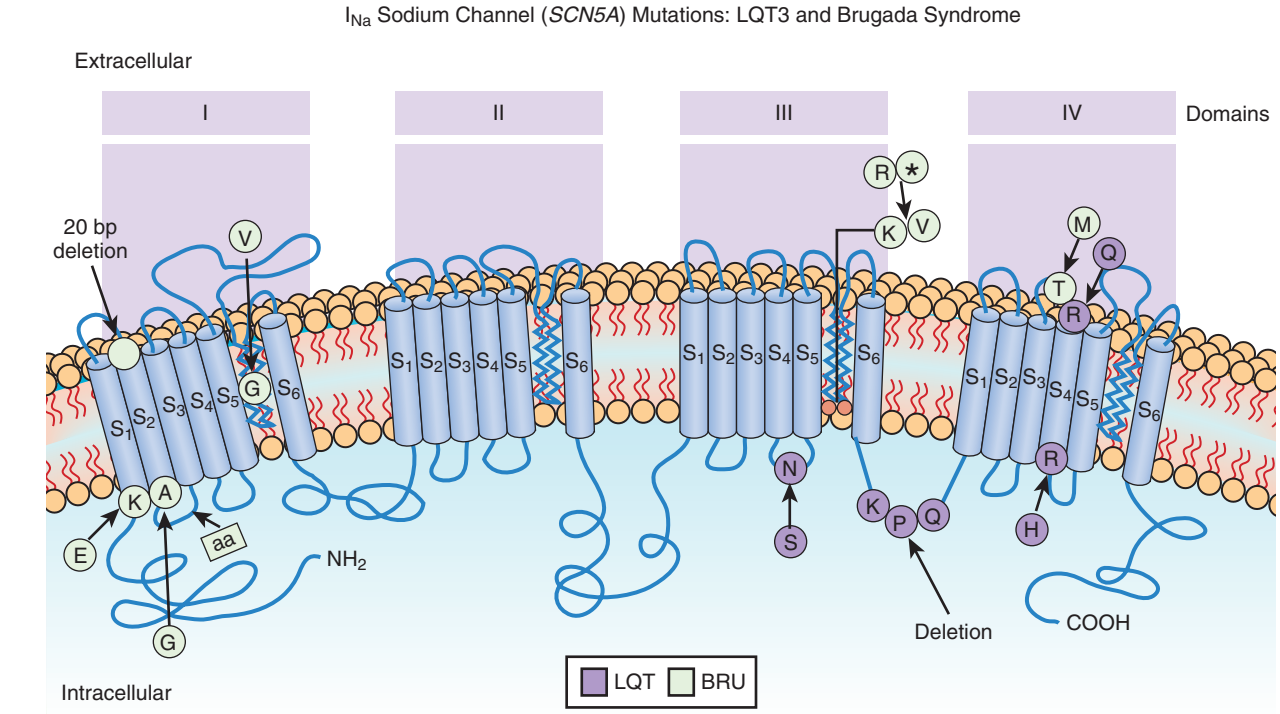

FIGURE 54-5 The molecular architecture of the cardiac INa sodium channel encoded by *SCN5A* and the mutations causing *LQT3* (*purple*) and Brugada syndrome (*white*).

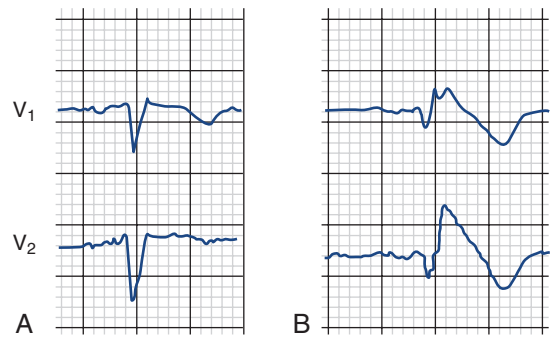

FIGURE 54-6 Ajmaline provocation in Brugada syndrome. **A,** Normal electrocardiographic findings in leads V1 and V2 in an individual with asymptomatic concealed Brugada syndrome and an *SCN5A* mutation. **B,** The response to ajmaline, identifying ST-segment elevation in leads V1 and V2.

with definitive Brugada syndrome unless it transitions into a coved type by provocation or independently. Brugada et al have suggested, however, that the risk of SCD is not different between symptomatic patients and asymptomatic patients, including those with concealed forms of disease.[90,95,108]

Various other risk stratifiers have also been identified.[109-112] Assessment of noninvasive markers by Ikeda et al demonstrated that late potentials noted using signal-averaged ECGs were present in 24 (73%) of 33 patients with a history of syncope or aborted SCD.[110] Using multivariate logistic regression, the authors showed that the presence of late potentials were significantly correlated with the occurrence of life-threatening events in patients with Brugada syndrome. The evaluation of these same patients with microvolt T-wave alternans and corrected Q-T interval dispersion failed to correlate with outcome. These findings were supported by others as well.[112]

Finally, spontaneous episodes of VF in patients with Brugada syndrome were shown to be triggered by PVCs with specific morphologies. Kakishita et al suggested that the use of ICD therapy not only could be lifesaving but also could record the specific triggering events.[97] They suggested that this knowledge could define risk and potentially lead to either ablative therapy or the ability to stratify the risk of SCD.

Hence, the identification of coved-type ST-segment elevation on surface ECG, the identification of late potentials on signal-averaged ECG, and the finding of triggering PVCs could provide insight into those patients with Brugada syndrome at high risk. Addition of family history could allow for further improvements of risk stratification.

Cardiac Conduction Disease

Syncope and SCD may also be caused by bradycardia. The most common form of life-threatening bradycardias include disorders in which complete atrioventricular (AV) block occurs.[113] These disorders require pacemaker implantation for continued well-being. Two major forms of conduction system disease in which no congenital heart disease is associated include isolated forms of conduction disease associated with dilated cardiomyopathy.[113-115]

Progressive cardiac conduction defect, also known as *Lev-Lenègre disease*, is one of the most common cardiac conduction disorders.[113-116] This disorder is characterized by progressive alteration of conduction through the His-Purkinje system with development of RBBB or left bundle branch block (LBBB) with widening of the QRS complexes. Ultimately, complete AV block occurs, resulting in syncope and SCD. Lev-Lenègre disease represents the most common reason for pacemaker implantation worldwide, accounting for 0.15 implants per 1000 population yearly in developed countries. This disorder has been considered a primary degenerative disease, an exaggerated aging process with sclerosis of the conduction system, or an acquired disease. The first gene identified for Lev-Lenègre disease was reported in 1999 by Schott et al.[116] They identified a missense mutation and deletion mutation, respectively, in *SCN5A* (see Table 54-1), the cardiac sodium channel gene, in two families with autosomal-dominant inheritance (Figure 54-7). Although the authors suggested that the biophysical abnormality was channel loss of function, no electrophysiological analysis was provided. As *SCN5A* also causes *LQT3*, Brugada syndrome, and SIDS (see Figure 54-7), all diseases in which ventricular tachyarrhythmias result in syncope and SCD, the association of conduction disturbance with *SCN5A* mutations was initially surprising.[107,114,117,118] However, it is now known that conduction disturbance occurs in these disorders as well.

A similar disorder, known as *isolated cardiac conduction disease*, also results in complete AV block, syncope, and SCD. This disorder has been considered to be genetically inherited (autosomal dominant trait) and not acquired. Brink et al and de Meeus et al independently mapped a gene to chromosome 19q13.3 in families with isolated conduction disturbance in 1995, but the gene has remained elusive (see Table 54-1).[119,120] Recently, however, Tan and colleagues identified a mutation in *SCN5A* in this disorder (see Figure 54-7) and also presented biophysical analysis (see Table 54-1).[114] This mutation, a G-to-T transversion in exon 12 of *SCN5A*, resulted in a change from glycine to cysteine at position 514 (G514C) encoding an amino acid within the DI-DII intercellular linker of the cardiac sodium channel. Biophysical characterization of the mutant channel demonstrated abnormalities in voltage-dependent gating behavior. The sodium current (I_{Na}) was found to decay more rapidly than the wild-type channel. In the mutant, open-state inactivation was hastened, but closed state inactivation was reduced and destabilized. Computational analysis predicted that the gating defects selectively slowed myocardial conduction without provoking the rapid cardiac arrhythmias seen in LQTS and Brugada syndrome. When comparing Brugada syndrome, LQT3, and conduction disease biophysics, the following findings are notable. In Brugada syndrome, *SCN5A* mutations cause reduction in I_{Na}, hastening epicardial repolarization and causing the development of VT and VF. In contradistinction, LQT3 mutations in *SCN5A* result in excessive I_{Na}, delaying repolarization and torsades de pointes VT. Importantly, the G514C mutation evokes gating shifts reminiscent of both LQT3 and Brugada syndrome, including an activation gating shift responsible for reducing I_{Na} and destabilization of inactivation that causes an increase in I_{Na}. Tan et al showed that these voltage-dependent gating abnormalities may be partially corrected by dexamethasone, consistent with the known salutary

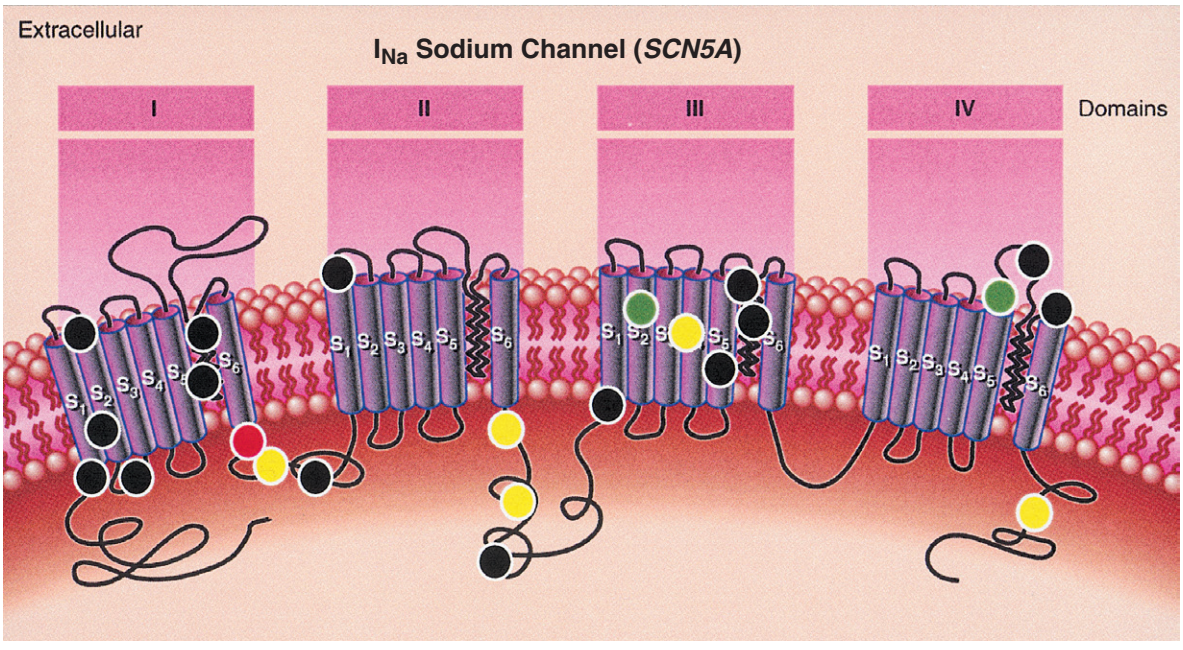

FIGURE 54-7 Cardiac sodium channel (*SCN5A*) gene mutations associated with cardiac arrhythmias and conduction system diseases. Cardiac arrhythmias: sudden infant death syndrome (*yellow*), Brugada syndrome (*black*), Lev syndrome (*green*), and isolated conduction disease (*red*). Note that mutations for all the disorders are scattered throughout the channel protein domains. They are found within the transmembrane portions and pore regions of the channel as well as within intracellular and extracellular regions of the protein.

effects of glucocorticoids on the clinical phenotype.[114] It is also worth noting that some patients with LQT3 and Brugada syndrome have been reported to have conduction disturbances.

Finally, patients with conduction disease and dilated cardiomyopathy present a conundrum with regard to what comes first—conduction abnormalities leading to cardiomyopathy, or vice versa.[115] Clinically, these patients tend to develop variable degrees of AV block in their teen years or 20s, with progression of this block over another 1 or 2 decades before developing the signs and symptoms of heart failure consistent with the cardiomyopathic phenotype. To date, only the gene *lamin A/C* located on chromosome 1q21 has been confirmed to cause this disease.[121,122] *Lamins A* and *C* are members of the intermediate filament multigene family, which are encoded by a single gene. *Lamins A* and *C* polymerize to form part of the nuclear lamina, a structural filamentous network on the nucleoplasmic side of the inner nuclear membrane. The specific causes of conduction disease and myocardial dysfunction are not currently known but could be attributed to the progressive degeneration of cardiac tissue analogous to that described in Lev-Lenègre disease.

Sudden Infant Death Syndrome

SIDS is defined as the sudden death of an infant younger than 1 year of age that remains unexplained after performance of a complete autopsy, review of clinical and family histories, and examination of the death scene. Although the incidence of SIDS has been dramatically reduced from 1.6 per 1000 live births to 0.64 per 1000 live births as reported in 1998 in the United States, it is still one of the most common causes of death among babies between 1 and 6 months of age. Death usually occurs during sleep.[123]

The potential causes of sudden death in infants are many, including cardiac disorders, respiratory abnormalities, gastrointestinal diseases, metabolic disorders, traumatic injury, brain abnormality, or child abuse. One of the most referenced etiologic speculations was that described by Schwartz in 1976. He proposed that a developmental abnormality in cardiac sympathetic innervation predisposed some infants to lethal cardiac arrhythmias. Specifically, an imbalance in the sympathetic nervous system was speculated to result in prolongation of the Q-T interval on the ECG and in potentially lethal ventricular arrhythmias.[17,18] In 1998, Schwartz et al published data collected from 1976 to 1994, in which ECGs were recorded on the third or fourth day of life in 34,442 Italian newborns.[4] These babies were followed up for 1 year; during that period, 34 babies died. Evaluation of these 34 babies demonstrated that 24 died of SIDS. These 24 SIDS victims were found to have longer QTc measurements compared with controls or other infants dying of other causes. In 12 of these 24 cases, the QTc was clearly prolonged, and the authors suggested that QTc prolongation during the first week of life is associated with SIDS.[125]

Although this suggestion linking SIDS and LQTS was roundly criticized, the authors were subsequently able to identify a mutation in *SCN5A* (see Table 54-1) in one patient with aborted SIDS.[118,126-132] In addition, Priori et al reported identification of an *SCN5A* mutation in an infant with Brugada syndrome.[133] More recently, Ackerman et al reported a molecular epidemiology study of 95 cases of SIDS, in which the myocardium obtained at autopsy was screened for ion channel gene mutations.[134] In 4 of 93 cases, mutations in *SCN5A* were identified in postmortem analysis, and the authors suggested that in 4.3% of this cohort SIDS was caused by mutations in this known arrhythmia-causing gene. Hence, it appears that ion channel mutations, particularly *SCN5A*, result in SIDS in some infants (see Figure 54-7). Biophysical analysis identified a sodium current characterized by slower delay, and a twofold to threefold increase in late sodium current similar to that seen in LQTS. The fact that these SIDS occurs during sleep is consistent with the features seen for this channel when mutations result in LQTS (LQT3). *SCN5A* mutations in SIDS have been further confirmed recently.[134] It is likely that other ion channel gene abnormalities will be found in infants with SIDS and that there is wide etiologic heterogeneity.

Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is characterized by fatty infiltration of the right ventricle, fibrosis, and ultimately thinning of the wall with chamber dilatation (Figure 54-8).[5] It is the most common cause of SCD in the young in Italy and is said to account for about 17% of SCD in the young in the Unites States.[135,136] Rampazzo et al mapped this disease in two families, one to 1q42-q43 and the other on chromosome 14q23-q24.[137,138] A third locus was mapped to 14q12.[139] A large Greek family with ARVD and Naxos disease was recently mapped to 17q21.[140] Two loci responsible for ARVD/C in North America were subsequently mapped at 3p23 and the other at 10p12.[141,142]

ARVD/C is a devastating disease because the first symptom is often SCD. Electrocardiographic abnormalities include inverted T waves in the right precordial leads, late potentials, and right ventricular arrhythmias with LBBB. In many cases, the ECG looks similar to that seen in Brugada syndrome, with ST elevation in V1 to V3.[143] The issue of SCD is compounded by the great difficulty in making the diagnosis of ARVD/C even when occurring in a family with a history of the disease. Since the disease affects only the right ventricle, it is difficult to detect it by using most diagnostic modalities. No diagnostic definitive standard is available at present. The right ventricular biopsy may be definitive when positive but often gives a false-negative result, since the disease initiates in the epicardium and spreads to the endocardium of the right ventricular free wall, making it inaccessible to biopsy. A consensus diagnostic criteria that includes right ventricular biopsy, magnetic resonance imaging (MRI), echocardiography, and electrocardiography was developed.[144]

The genetic basis of ARVD/C has started to unravel recently. The first gene causing ARVD/C was identified by Tiso et al for the chromosome 1q42-1q43-linked ARVD2 locus in 2001 (Figure 54-9).[145] This gene (see Table 54-1), the cardiac ryanodine receptor gene (*RYR2*), a 105 exon gene that encodes the 565 kd monomer of a tetrameric structure interacting with four FK-506 binding proteins called FKBP12.6, is fundamental for intracellular calcium homeostasis and for excitation–contraction coupling. This large protein physically links to the dihydropyridine (DHP) receptor of the t-tubule, where the DHP receptor protein, a voltage-dependent calcium channel, is activated by plasma membrane depolarization and induces a calcium influx.[146,147] The *RYR2* protein, activated by calcium, induces release of calcium from the sarcoplasmic reticulum into the cytosol. Hence, mutations in *RYR2* would be expected to cause calcium homeostasis imbalance and result in abnormalities in rhythm as well as excitation-contraction coupling and myocardial dysfunction.[147] This

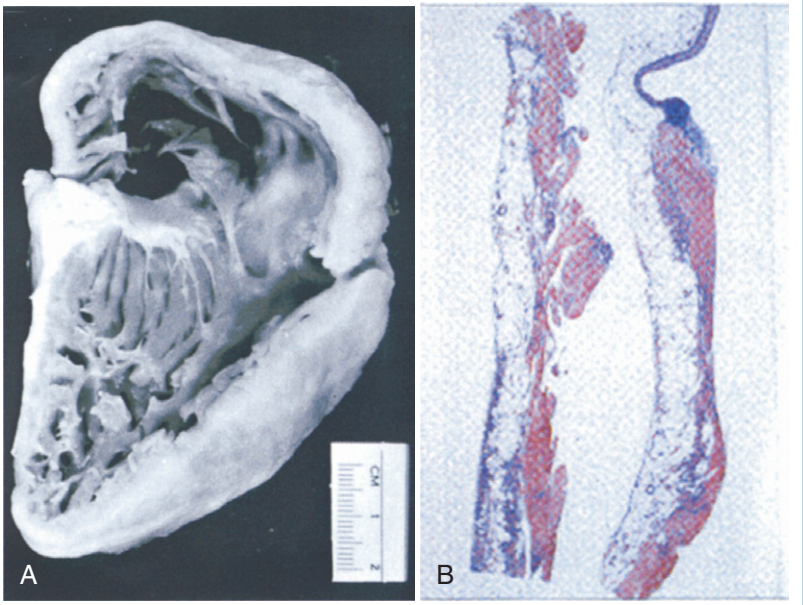

FIGURE 54-8 Arrhythmogenic right ventricular dysplasia/cardiomyopathy. **A,** Gross anatomy with thinned right ventricle and fatty infiltration. **B,** Histology identifying fibro-fatty infiltration of right ventricle.

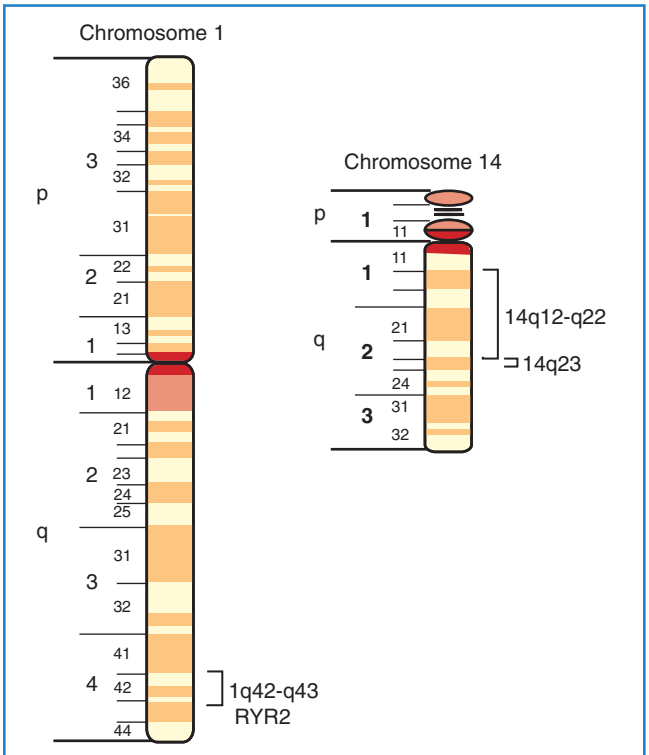

FIGURE 54-9 Chromosomal positions of *ARVD1* (chromosome 14q23), *ARVD2* (chromosome 1q42-q43), and *ARVD3* (chromosome 14q12-q22) with identification of the *ARVD2* gene, ryanodine receptor (*RYR2*).

causative gene is therefore, in many ways, similar to the mutant genes responsible for the ventricular arrhythmias of LQTS, Brugada syndrome, and SIDS, in which ion channel mutations cause the clinical phenotype. In those instances, potassium channel dysfunction and sodium channel dysfunction occur, whereas in ARVD2, intracellular calcium channel dysfunction plays a central role.

Two other genes associated with arrhythmogenic cardiomyopathy have also been described. The first of these, plakoglobin, was shown to cause the chromosome 17q21-linked autosomal recessive disorder called *Naxos disease* (see Table 54-1).[148] This disorder is characterized by ARVD/C in association with abnormalities of skin (palmoplantar keratoderma) and hair (woolly hair) and, therefore, is not exactly the same as isolated ARVD/C, being a more complex phenotype.

Plakoglobin is a cell adhesion protein thought to be important in providing functional integrity to the cell. This protein is found in many tissues, including the cytoplasmic plaque of cardiac junctions and the dermal-epidermal junctions of the epidermis, and it has a potential signaling role in the formation of desmosomal junctions. It is believed that plakoglobin serves as a linker molecule between the inner and outer portions of the desmosomal plaque by binding tightly to the cytoplasmic domains of cadherins. The mutations identified, a homozygous 2 bp deletion, resulted in a frameshift and premature termination of the protein.[148] Support for this gene being causative of Naxos disease comes from a murine model with null mutations, which exhibit the heart and skin abnormalities seen in affected patients. The mutated protein is thought to cause disruption of myocyte integrity, leading to cell death and fibro-fatty replacement, with secondary arrhythmias being caused by the abnormal myocardial substrate.

The last gene identified, desmoplakin, is another desmosomal protein with similarities to plakoglobin (see Table 54-1).[149] Homozygous mutations in this gene resulted in a Naxos-like disorder, although the cardiac features occurred in the left ventricle instead of the right ventricle. The affected protein is an important protein in cell adhesion and appears to function similarly to that described for plakoglobin. Although it is easy to speculate that mutation in this gene and in plakoglobin causes the myocardial abnormalities, it remains unclear why differences in ventricular chamber specificity occurs and how the ventricular tachyarrhythmias develop.

Brugada Syndrome and Arrhythmogenic Right Ventricular Dysplasia

Controversy exists concerning the possible association of Brugada syndrome and ARVD, with some investigators arguing that these are the same disorder or at least one is a forme fruste of the other.[143,150-156] However, the classic echocardiographic, angiographic, and MRI findings of ARVD are not seen in patients with Brugada syndrome. In addition, patients with Brugada syndrome typically do not exhibit the histopathologic findings of ARVD. Further, the morphology of VT or VF differs.[91,143] Finally, the genes identified so far differ.[61,144,145,149,152]

Polymorphic Ventricular Tachycardia

Familial polymorphic VT, an autosomal-dominant disorder characterized by episodes of bi-directional (Figure 54-10) and polymorphic VT, typically in relation to adrenergic stimulation or physical exercise, was first described by Coumel et al in 1978.[155] This disorder most commonly occurs in childhood and adolescence, presenting with syncope and SCD.[6,156] Mortality rates of 30% to 50% in patients aged 20 to 30 years have been reported, suggesting this is a highly malignant disorder. Autopsy data demonstrate this disorder to have no associated structural cardiac abnormalities.

Mutations in the cardiac ryanodine receptor (*RYR2*), the same gene responsible for ARVD2 (see Figure 54-9), were recently independently identified by Laitinen et al and Priori et al in multiple families linked to chromosome 1q42 (see Table 54-1).[157-160] Interestingly, ARVD2 typically is considered to be the one form of ARVD/C in which catecholaminergic input is important in the development of symptoms. It is not clear at this time why patients with familial polymorphic VT have no associated structural cardiac abnormalities and patients with ARVD/C have classic fibro-fatty replacement in the right ventricle.

Mutations in another member of the ryanodine receptor gene family, *RYR1*, which is expressed in skeletal muscle, result in malignant hyperthermia and central core disease.[161] The mutations in this gene appear to cluster in three regions of the gene, regions similar to the mutations found in *RYR2* in the cases of VT reported, suggesting these to be functionally critical regions.

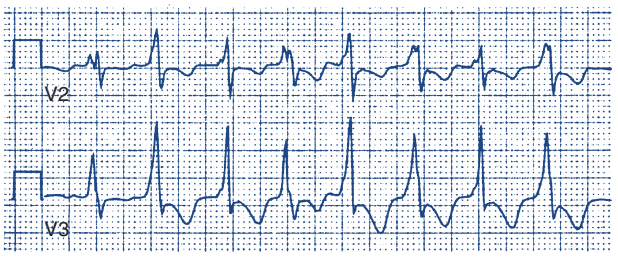

FIGURE 54-10 Bi-directional ventricular tachycardia. The genetic cause, mutations within the ryanodine receptor gene (*RYR2*), is the same gene responsible for the chromosome 1–linked arrhythmogenic right ventricular dysplasia cardiomyopathy.

Wolff-Parkinson-White Syndrome

Wolff-Parkinson-White syndrome (WPW) is the second most common cause of paroxysmal supraventricular tachycardia (SVT), with a prevalence of 1.5 to 3.1 per 1000 individuals.[2] In some parts of the world such as China, WPW is even more common, being responsible for up to 70% of cases of SVT.[162] Tachycardia presents typically in a bi-modal fashion, with onset common in infancy as well as during the teen years. Symptoms most commonly include syncope, presyncope, shortness of breath, palpitations, and SCD.[113]

WPW has long been described to be caused by accessory pathways derived from muscle fibers providing direct continuity between the atrial and ventricular myocardia.[2,163] These accessory pathways may be identified by the peculiar ECG findings seen in WPW, including short P-R interval, widened QRS complexes, and the classic δ wave in which an abnormal initial QRS vector is notable (Figure 54-11).[2,163-165] In a significant percentage of patients, conduction abnormalities including high-grade sinoatrial or AV block occur, necessitating pacemaker implantation. In most patients with WPW and SVT, RF ablation of the accessory pathways is curative.[166,167]

Some cases of WPW are associated with other primary disorders such as hypertrophic cardiomyopathy or left ventricular noncompaction cardiomyopathy, or the congenital cardiac disorder Ebstein's anomaly.[166,168,169] Whether the underlying cause of WPW is similar in these cases compared with pure cases of WPW has been discussed for many years, but no definitive answers have been provided.

The first gene in patients with WPW was recently identified by Gollob et al and Blair et al independently in familial forms of WPW.[170,171] In both reports, autosomal-dominant inheritance was reported. Interestingly, this gene, which maps to chromosome 7q34-7q36, was found to cause WPW and hypertrophic cardiomyopathy in a significant percentage of patients in both reports (see Table 54-1).[168] The gene, the γ2 subunit of adenosine monophosphate–activated protein kinase, consists of 569 amino acids, is 63 kD in size, and functions as a metabolic sensor in cells, responding to cellular energy demands by regulating adenosine triphosphate (ATP) production and utilization.[172] It is not clear whether this is a primary hypertrophic cardiomyopathy–causing gene or a WPW gene, particularly since the initial mapping of this locus was in patients with hypertrophic cardiomyopathy and associated WPW. Clearly, this is not the only gene responsible for WPW, and the functional and physiological abnormalities responsible for the resultant WPW are not yet obvious.

Summary

Ventricular arrhythmias appear to result from ion channel abnormalities. Whether this is necessarily a primary abnormality or a secondary one is becoming better understood. Therapeutic options including drug and device therapy are likely to be expanded once this knowledge has matured. These are detailed in Chapters 84, 94, and 95. Similarly, conduction system abnormalities have been shown to occur secondary to mutations in the ion channel gene and are widely but empirically treated with device therapy as discussed in Chapter 38. The individual disorders are now exhaustively discussed in Chapters 62 to 65.

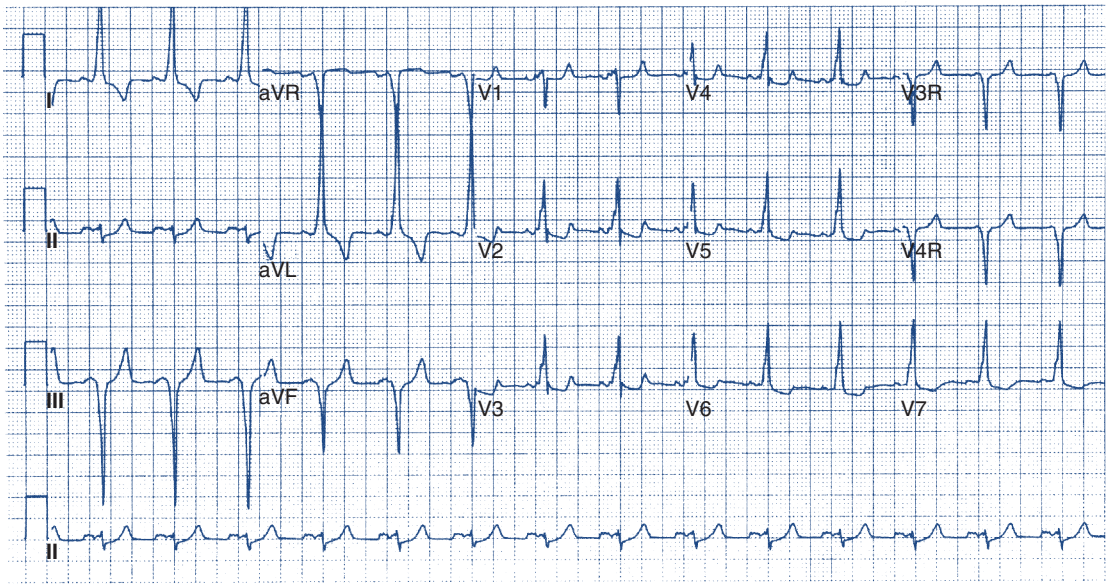

FIGURE 54-11 Electrocardiogram showing the short P-R interval and δ wave associated with Wolff-Parkinson-White syndrome.

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CHAPTER 55

Ventricular and Supraventricular Tachyarrhythmias Associated with Hypertrophic Cardiomyopathy

Barry J. Maron, Iacopo Olivotto, and Franco Cecchi

Hypertrophic cardiomyopathy (HCM) is a genetic cardiac disease with a particularly heterogeneous clinical presentation and diverse natural history.[1-5] Sudden and unexpected death has been recognized as a prominent and devastating complication of HCM since the initial contemporary description of this disease over 50 years ago.[6] Ventricular tachyarrhythmias have always represented a focus of concern in this disease because of an apparent causal relationship to sudden cardiac death (SCD).[7-22] In addition, it is now evident that supraventricular tachyarrhythmias (particularly atrial fibrillation [AF]) commonly occur in HCM and can also represent important determinants of clinical course.[23] This chapter discusses the linkage of tachyarrhythmias to SCD, disease progression in HCM, and the role of preventive interventions.

Ventricular Arrhythmias and Sudden Cardiac Death

Historical Context

Recognition that a small but important subgroup of patients with HCM is at increased risk for SCD has for many years generated considerable interest in the role of arrhythmias and the process of risk stratification.[1,3,5,8-10,12,17,20,22] This focus is now particularly acute with the availability of implantable cardioverter defibrillators (ICDs) for the effective prevention of these unpredictable catastrophes.[16,24] It has been emphasized that SCD in HCM usually occurs in young asymptomatic patients, with annual mortality rates initially reported as up to 4% to 6% in tertiary-center referral populations, which are disproportionately composed of high-risk patients, and more recently 1% per year in less selective community-based cohorts.[3,5,1-22,25-27]

On routine ambulatory (Holter) monitoring, more than 90% of HCM patients demonstrate frequent and complex ventricular tachyarrhythmias, including premature ventricular depolarizations or couplets and nonsustained ventricular tachycardia (VT) (Figure 55-1).[7,8,10,12,19,20] Although the frequency of these ventricular arrhythmias appears disproportionate to the occurrence of SCD in HCM, short bursts of nonsustained VT were identified 25 years ago as markers for SCD risk, focusing attention at that time on 24-hour ambulatory (Holter) electrocardiogram (ECG) monitoring for occult arrhythmia detection before major adverse cardiac events, an observation that triggered an era of prophylactic anti-arrhythmic drug treatment.[7,8,10,12,18-20]

Nonsustained Ventricular Tachycardia

Ventricular arrhythmias in patients with HCM are largely clinically silent. Indeed, short runs of asymptomatic nonsustained VT commonly occur in 20% to 25% of HCM patients on 24-hour ambulatory ECG monitoring.[7-9,11,12,17] Nonsustained VT confers about an eightfold increased risk for SCD—that is, 8% per year compared with 1% per year in the absence of VT, high negative predictive values, and low positive predictive values for events (i.e., 96% and 26%, respectively).[11,12,18] These relatively low positive predictive values are largely attributable to the low event rate characteristic of HCM and similar to that of other risk markers in this disease.[28]

Nevertheless, nonsustained VT on ambulatory Holter monitoring as a risk factor has been fraught with particular ambiguity over the years.[28-30] For example, a single brief isolated burst of nonsustained VT on a random Holter ECG is no longer regarded, per se, as a risk marker that should trigger ICD implantation for primary prevention.[1,20] However, longer VT runs (>10 beats/min) intuitively carry greater weight in these clinical circumstances. One potentially useful (but non–evidence-based) strategy that may be considered following the identification of a short run of VT on the initial 24-hour Holter ECG involves a more extended ambulatory monitoring period of 7 to 21 days. This approach achieves a more measured assessment of an individual patient's day-to-day ectopy profile, potentially influencing or clarifying decisions concerning prophylactic ICDs. Conversely, and of particular importance, the absence of VT on Holter monitoring in patients with otherwise low-risk clinical profiles dictates a large measure of reassurance with regard to prognosis.

Selection of Patients for Implantable Cardioverter-Defibrillators

Conventional Risk Markers

It is universally agreed that HCM patients should be afforded secondary prevention ICDs following cardiac arrest or sustained episodes of VT (with or without hemodynamic instability), including recommendations from the American College of Cardiology/European Society of Cardiology (ACC/ESC) expert consensus HCM panel.[3,5] However, selection of patients most likely to benefit from prophylactic ICD therapy is less certain, with implantation

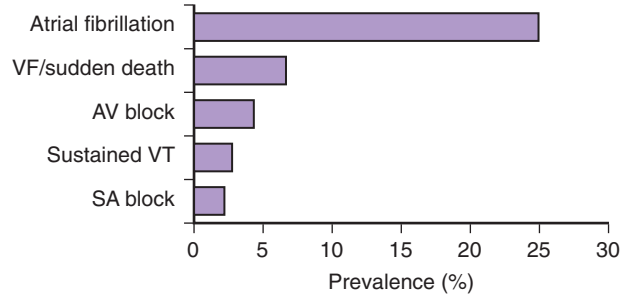

FIGURE 55-1 Estimated prevalence of arrhythmias and conduction abnormalities occurring in a hypertrophic cardiomyopathy population, assembled from previously published reports. *VF*, Ventricular fibrillation; *VT*, ventricular tachycardia; *AV*, atrioventricular; *SA*, sinoatrial.

guidelines being a long-evolving and sometimes contentious issue for which definitive resolution has been elusive.

Risk stratification in HCM is predicated on the assessment of noninvasive risk markers, usually in clinically stable patients, which have emerged from observational studies and achieved general acceptance.[1,3,5,10-22,24] In this respect, the ICD strategy differs from that used in patients with coronary artery disease (CAD)—that is, with primary prevention being based largely on a single predominant risk marker emanating from a major clinical event (i.e., myocardial infarction [MI]), leading to left ventricular (LV) remodeling and impaired cardiac function with ejection fraction of 30% to 35% or less and frequently adverse disease progression.[30-32]

The acknowledged primary prevention HCM risk factors are: (1) family history of one or more HCM-related SCDs; (2) one or more episode of unexplained, recent syncope; (3) multiple, repetitive, or prolonged nonsustained VT on more than one ambulatory 24-hour ECG; (4) hypotensive or attenuated blood pressure response to exercise; (5) massive LV hypertrophy (wall thickness ≥30 mm on echocardiography) (see Figure 55-6). Each of these risk markers applies largely to patients younger than 50 years, and only one (the ambulatory ECG) explores the arrhythmogenic substrate.

Patients in other HCM subgroups who may also be selectively considered at increased risk are those with (1) LV apical aneurysm with regional scarring; (2) end-stage phase with systolic dysfunction; (3) transmural MI following alcohol septal ablation.[33-35]

One risk factor judged to be major in a given HCM patient can be sufficient to justify consideration for a primary prevention ICD.[22,24,29] However, the presence of multiple risk factors certainly creates a clinical environment in which decision making regarding ICD implantation becomes much more intuitive and easier. Nevertheless, it should be underscored that not all patients with one risk factor require prophylactic implants.[22,24,29] Indeed, numerous complex clinical scenarios exist in HCM, with ambiguities and gray areas that arise with respect to the presence, strength, and number of risk factors ultimately affecting those decisions regarding prophylaxis. One specific example in this regard would be older HCM patients with unexplained syncope as a single risk factor. Such patients may not be candidates for primary prevention, given that HCM-related SCD is uncommon in this age group, survival to advanced age itself determines the lower risk status in this disease, and syncope is not uncommon at advanced ages.[24,29] However, syncope as a single risk factor necessitating primary prevention ICDs has been associated with appropriately high intervention rates in HCM.[22,24,29] Finally, the available data do not permit assessment of the relative weight that each risk factor can be assigned in the individual patient.

Potential Mechanisms of Sudden Cardiac Death

While the pathogenesis of SCD in HCM is likely complex and multi-factorial (and remains incompletely defined), such events emanate from primary ventricular tachyarrhythmias.[1-24,36-38] These arrhythmia sequences have been documented by stored electrocardiographic recordings in patients with ICDs experiencing appropriate device interventions (Figure 55-2).[16,22,24] These observations offer a unique window to understanding the mechanisms responsible for SCD in HCM. It has not been possible, however, to exclude bradycardia-mediated events conclusively because of the backup pacing capability operative in many of the devices, and it is possible that other more diverse arrhythmia mechanisms may ultimately prove to be involved.[37,38] Complete heart block and accelerated atrioventricular (AV) conduction caused by accessory pathways are acknowledged, even though particularly rare, as causes of syncope or SCD in HCM.[39]

Ventricular tachyarrhythmias in HCM probably emanate primarily from a substrate of electrical instability and disordered electrophysiological transmission caused by disorganized left ventricular cellular architecture.[6,40,41] Alternatively, they may be caused by bursts of myocardial ischemia (probably because of structurally abnormal, narrowed intramural arterioles), leading to myocyte necrosis and repair in the form of replacement fibrosis (Figure 55-3).[42] This myocardial substrate may be vulnerable to a variety of triggers, either intrinsically—related to the HCM disease process—or to extrinsic environmental factors such as intense physical exertion (including in athletes). In addition, a variable and defined component of individual patient susceptibility undoubtedly plays a role in determining which HCM patients experience clinical events at particular moments in their lives.[43]

Prevention of Sudden Cardiac Death

Pharmacologic Treatment

Historically, the management of high-risk HCM patients was limited to prophylactic pharmacologic treatment with β-blockers, verapamil, antiarrhythmic agents such as procainamide and quinidine, and more recently amiodarone.[44-46] However, no convincing data in HCM support the efficacy of prophylactic drug treatment for SCD.[1,5] For example, no controlled studies address the effects of β-blockers or verapamil on SCD. Type IA antiarrhythmic agents (such as procainamide and quinidine) have long been abandoned in the treatment for isolated or infrequent bursts of nonsustained VT on ambulatory Holter monitoring in HCM patients because of the potential proarrhythmic effects of these drugs.[12,44]

Furthermore, the efficacy of amiodarone in preventing SCD in HCM has been called into question by observations in studies in which this drug did not offer complete protection against appropriate ICD shocks or cardiac arrest.[16,22,24,46] Also, the frequent adverse consequences associated with the long-term

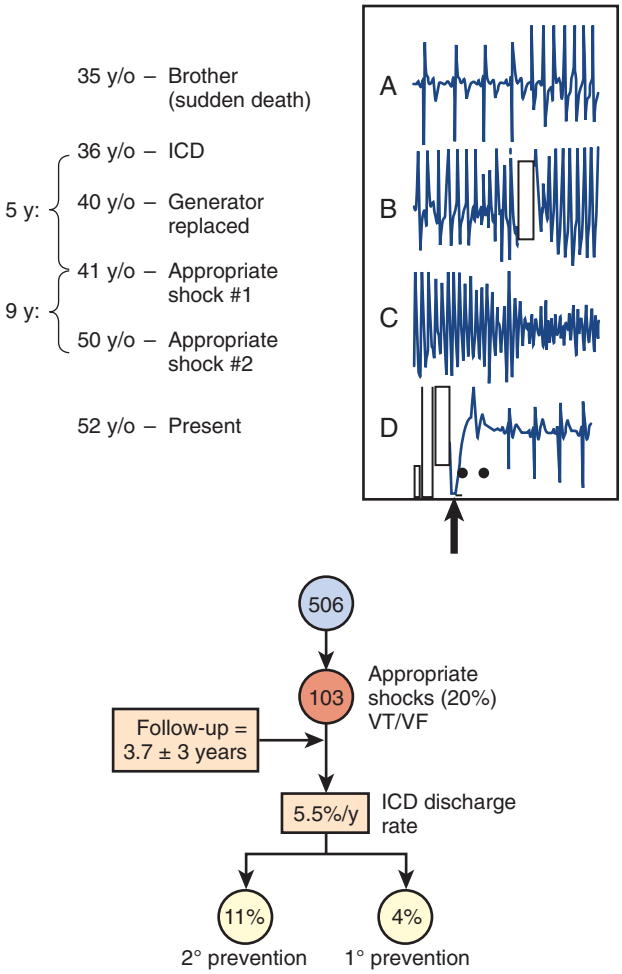

FIGURE 55-2 *Top*, Primary prevention of sudden cardiac death in hypertrophic cardiomyopathy (HCM). Stored ventricular electrogram from an asymptomatic 35-year-old man who received an implantable cardioverter-defibrillator (*ICD*) prophylactically because of a family history of HCM-related sudden death and marked ventricular septal hypertrophy (i.e., wall thickness of 31 mm). Intracardiac electrogram was triggered 4 years and 8 months after the defibrillator implantation (at 1:20 AM during sleep). Continuous recording at 25 mm/s is shown in four contiguous panels with the tracing recorded left to right in each segment. **A,** Begins with four beats of sinus rhythm and, thereafter, ventricular tachycardia (*VT*) begins abruptly (at 200 beats/min). **B,** The device senses VT and charges. **C,** VT deteriorates into ventricular fibrillation (*VF*). **D,** The defibrillator discharges appropriately (20-J shock) during VF and restores sinus rhythm immediately. *Bottom*, Flow diagram showing outcomes of 506 high-risk patients with HCM with implantable defibrillators for primary prevention with one or more risk factors) or for secondary prevention (following cardiac arrest or sustained VT. *(Top, From Maron BJ, Shen W-K, Link MS, et al: Efficacy of implantable cardioverter-defibrillators for the prevention of sudden death in patients with hypertrophic cardiomyopathy,* N Engl J Med *342:365–373, 2000. Copyright Massachusetts Medical Society.)*

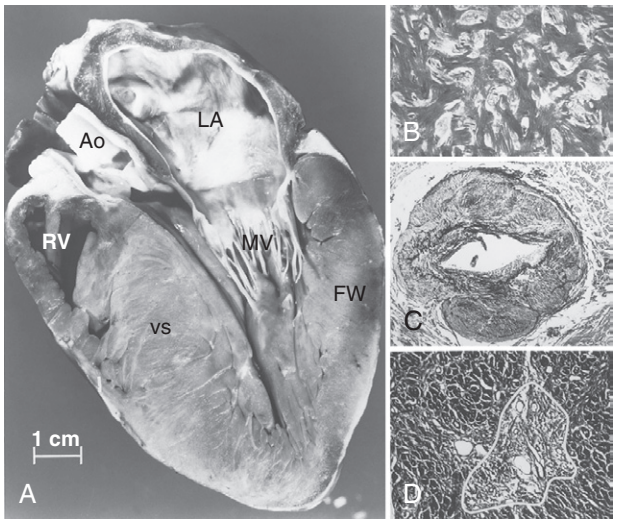

FIGURE 55-3 Morphologic components of the disease process in hypertrophic cardiomyopathy (HCM), which is the most common cause of sudden cardiac death in the young. **A,** Gross heart specimen sectioned in a cross-sectional plane similar to that of the echocardiographic (parasternal) long axis; left ventricular wall thickening shows an asymmetrical pattern and is confined primarily to the ventricular septum (*vs*), which bulges prominently into the left ventricular outflow tract. Left ventricular cavity appears reduced in size. **B, C,** and **D,** Histologic features characteristic of left ventricular myocardium and representative of the arrhythmogenic substrate in HCM. **B,** Markedly disordered architecture with adjacent hypertrophied cardiac muscle cells arranged at perpendicular and oblique angles. **C,** Intramural coronary artery with thickened wall, caused primarily by medial hypertrophy, and an apparently narrowed lumen. **D,** Replacement fibrosis (after cell death) in an area of ventricular myocardium adjacent to an abnormal intramural coronary artery. *Ao*, Aorta; *FW*, left ventricular free wall; *LA*, left atrium; *MV*, mitral valve; *RV*, right ventricle. *(From Maron BJ: Hypertrophic cardiomyopathy,* Lancet *350:127–133, 1997.)*

administration of amiodarone greatly limit its application to SCD prevention in young patients with HCM who characteristically have long periods of risk.

Implantable Defibrillators

Since its introduction by Mirowski and Mower 30 years ago,[47] the ICD has achieved widespread acceptance as a preventive treatment for SCD by virtue of the indisputable evidence of its efficacy in terminating life-threatening ventricular tachyarrhythmias and prolonging life, principally in high-risk patients with ischemic heart disease.[30-32,47,48]

In HCM, evidence assembled over the past 10 years substantiates that ICD interventions are frequent and highly effective in terminating potentially lethal ventricular tachyarrhythmia.[16,22,24] Indeed, experience with ICDs has created a new strategy within the HCM armamentarium as the most reliable treatment currently available for SCD prevention. The most reliable data are largely confined to an international multicenter registry of 506 HCM patients with ICDs implanted for secondary and primary prevention (n = 42), on the basis of the clinical judgment of managing electrophysiologists and cardiologists (see Figure

55-2), with more than twofold the number of participants in the first Multicenter Automatic Defibrillator Implantation Trial (MADIT I).[30]

Over an average follow-up of 3.7 years, 20% of patients experienced appropriate device therapy for VT or ventricular fibrillation (VF), equivalent to five ICDs implanted per intervention. Appropriate ICD discharge rates were 5.5% per year, 11% per year for secondary prevention (in patients with cardiac arrest and sustained VT, respectively), and 4% per year for primary prevention (in patients with one or more risk factors) (see Figure 55-3). The highest rates are among children and adolescents (up to 11% per year), consistent with the known predilection of SCD in young patients with HCM.[1-6,16,21,22,24,49] Of note, primary prevention intervention rates in high-risk patients (i.e., 4%) are similar to those previously reported for SCD from tertiary HCM centers with skewed high-risk referral patterns, and four times the SCD rates from less selective community-based patient populations.[5,25,26] It should be emphasized that ICDs were effective in terminating VT or VF despite the complex HCM phenotype, which may include extreme LV hypertrophy, subaortic obstruction, microvascular ischemia, and diastolic dysfunction.[1-5]

Risk Period in Hypertrophic Cardiomyopathy

In contrast to those with ischemic heart disease, patients with HCM are exposed to an extended period of risk for SCD, which is predominant in patients younger than 30 years, but, importantly, including those in mid-life and even beyond; indeed, no particular age itself appears to confer immunity to SCD.[9] Mean age at implantation is about only 40 years (almost 25% <30 years old), and the age at the time of first appropriate device intervention is also 40 years.[16,22,24] An important principle related to ICDs in HCM surrounds the highly unpredictable timing of life-threatening ventricular tachyarrhythmias, which commonly have long periods of dormancy (Figure 55-4). Substantial delays of many years between implantation and initial appropriate device intervention are not uncommon (see Figure 55-4)[1] and circadian patterns of ICD-terminated events do not show a discrete hourly predilection, and also occur frequently during sleep.[6,22,24,50,51]

Inducible Ventricular Arrhythmias

The strategy of using electrophysiological testing with programmed ventricular stimulation and inducible ventricular tachyarrhythmias to identify the substrate for and the mechanisms of SCD and to target those HCM patients at increased SCD risk has been largely abandoned.[5] Limitations to this technique include the infrequency with which monomorphic VT is inducible in HCM (in only 10% of patients), and the observation that the electrical responses of the HCM substrate appear to be highly dependent on the precise stimulation protocol used.[5,22,52]

Complications and Other Considerations

Although ICD components have proved generally safe and effective, a number of device-related complications, including infection, pocket hematoma, pneumothorax, and venous thrombosis, do occur rarely.[16,22,24,53] More frequently, about 25% of patients with HCM experience inappropriate shocks (5.3% per year) resulting from lead fracture or dislodgment, oversensing, double counting of QRS complexes, or T-wave oversensing or when triggered by sinus tachycardia or AF; multiple-shock "storms" are rare.[16,22,24,53] Such complications most commonly occur in younger patients, largely because of activity level and body growth.[54] Of note, young patients will require many generator changes over their lifetime, which exposes those patients to a much higher risk, on average, of lead complications and infection compared with high-risk patients with CAD.

Atrial Fibrillation

AF is the most frequent sustained arrhythmia in HCM (Figure 55-5).[23] When expressed clinically, AF may have substantial prognostic importance in a considerable proportion of patients with HCM by virtue of its association with heart failure and embolic stroke in the long term and also occasionally acute hemodynamic

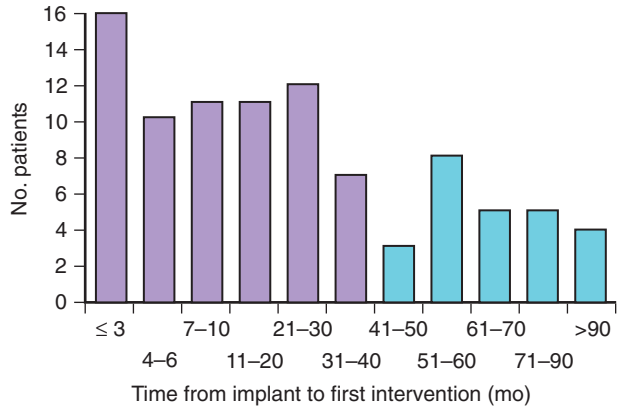

FIGURE 55-4 Interval between implantation of the defibrillator and the first appropriate implantable cardioverter-defibrillator discharge. Note the substantial proportion of patients with initial defibrillation shock occurring 5 to 10 years after implantation (*blue bars*).

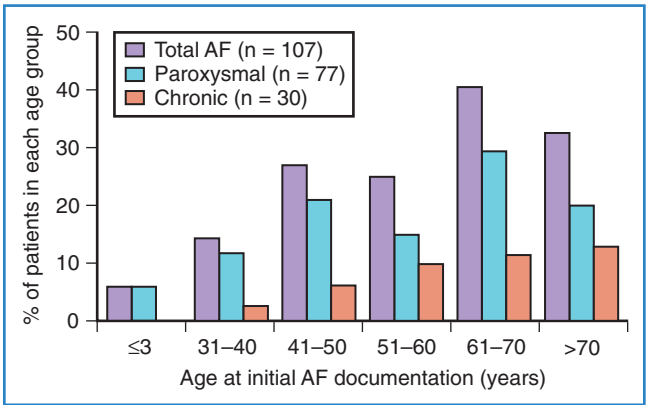

FIGURE 55-5 Age at development of atrial fibrillation (*AF*) in hypertrophic cardiomyopathy. Bars express the proportion of patients in each age group with paroxysmal or chronic AF. Patients evolving from paroxysmal to chronic AF are considered paroxysmal (i.e., as the initial manifestation of the arrhythmia). *(From Olivotto I, Cecchi F, Casey SA, et al: Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy,* Circulation *104:2517–2524, 2001.)*

Table 55-1 Prevalence of Atrial Fibrillation Reported in Hypertrophic Cardiomyopathy Populations

STUDY	NO. PATIENTS	PREVALENCE OF AF (%)	FOLLOW-UP (YR)
Glancy et al[55]	167	10	3
Savage et al[19]	100	12	Not available
McKenna et al[18]	86	14	2.6
Cecchi et al[27]	202	28	10.1
Maron et al[25]	277	18	8.1
Olivotto et al[23]	480	22	9.1

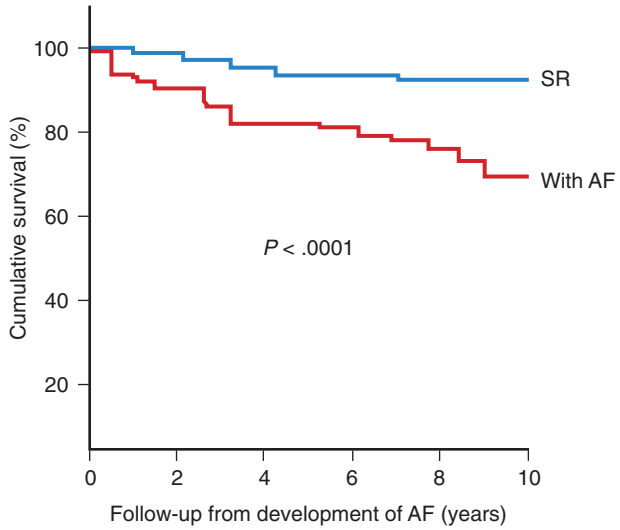

FIGURE 55-6 Impact of atrial fibrillation (*AF*) on overall hypertrophic cardiomyopathy (HCM)–related mortality. Cumulative survival of patients with HCM and AF compared with a matched group of patients with HCM in sinus rhythm (*SR*). *(From Olivotto I, Cecchi F, Casey SA, et al: Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy,* Circulation *104:2517–2524, 2001.)*

decompensation.[23,25,27,55,56] It has not, however, been conclusively determined whether AF in HCM causes heart failure or, alternatively, is a reflection of more severe disease.

Prevalence and Demographics

A number of centers have reported that AF occurs in HCM with a prevalence of approximately 20% to 25% and that a 2% incidence of new cases is seen annually (Table 55-1).[23,27] Patients with HCM appear to have an overall four to six times greater likelihood of developing AF compared with the general population.[57-61] The average age for AF onset in HCM is 55 ± 15 years, progressively increasing in frequency with age, and is predominant in those older than 60 years (see Figure 55-5). However, AF appears to be exceedingly uncommon in patients with HCM who are younger than 25 years.

Predisposing Factors

AF has some measure of predictability as a complication of HCM in that it is related to advanced age and to increased left atrial size, which is the most powerful AF predictor. Modest enlargement of the left atrium (i.e., in the range of transverse dimension 40 to 45 mm) is common, even in patients with no history of AF, probably largely as a consequence of impaired diastolic function caused by the thickened and poorly compliant ventricular chambers.[23,55,62,63] However, the determinants of marked and progressive left atrial enlargement, which ultimately predispose to AF in some patients with HCM, remain unresolved (i.e., factors responsible for increased left atrial dimension >50 mm). In addition to left atrial size, atrial systolic dysfunction, which can be easily assessed by trans-thoracic echocardiography, has been shown to be a predictor of AF.[64] Conversely, neither the degree of mitral regurgitation nor the presence of outflow obstruction reliably predicts the development of AF in HCM. Indeed, moderate to severe mitral regurgitation occurs in only a minority of HCM patients with AF (i.e., approximately 15%), and the proportion of patients with outflow obstruction is similar among patients with or without AF.[23]

Alternatively, it is possible that specific HCM-causing mutations may increase the predisposition to AF, possibly by creating an intrinsic atrial myopathy associated with prolonged and fragmented atrial conduction.[65] Families commonly showing coexistence of HCM and AF have been reported to be linked to β-myosin heavy chain mutations.[66] Such a hypothesis could also help explain the development of AF in the absence of left atrial enlargement, a scenario observed in about 10% of patients with HCM.[23]

It is not possible, on the basis of available evidence, to reliably identify those patients with HCM in sinus rhythm who will ultimately develop AF—or at least not to a degree sufficient to justify prophylactic intervention. Nevertheless, three noninvasive parameters (left atrial enlargement, P-wave prolongation on signal-averaged ECG, and supraventricular tachyarrhythmias on Holter ECG) may allow identification of a patient subset with the highest risk for developing AF in the future.[67]

Atrial Fibrillation–Related Mortality and Morbidity

The development of AF is a powerful predictor of HCM-related mortality and limiting symptoms; this may represent a clinical turning point by dominating the natural history and decisively influencing the long-term outcome. Indeed, patients with AF demonstrate a fourfold increase in the risk for HCM-related mortality compared with matched control patients with HCM in sinus rhythm, independent of age and symptomatic state; this reflects an increase in progressive heart failure and stroke-related mortality (Figure 55-6).[23,68]

HCM-related complications, clinical deterioration, and death are not distributed uniformly in an AF cohort but, rather, appear to preferentially affect certain patient subgroups such as those with early development of the arrhythmia (age <50 years) or those with outflow tract obstruction (Figures 55-7 and 55-8).[23] Although why the more severe consequences of AF are associated with its development earlier in life has not yet been determined, it is possible that this arrhythmia is a marker of a generally more aggressive disease state.[23,65] In this regard, the dependence of patients with obstructive HCM on left atrial contraction for adequate left

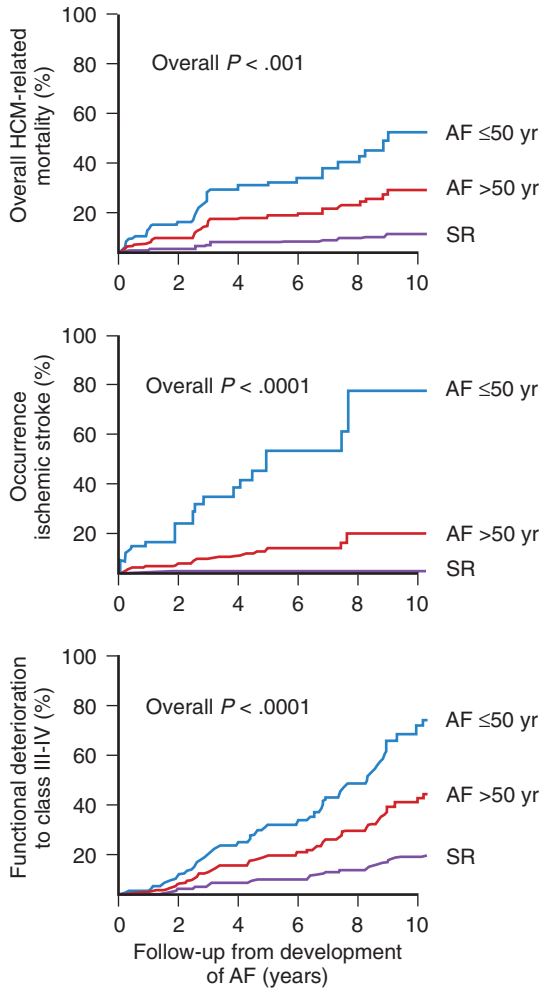

FIGURE 55-7 Relation of early (<50 years) versus late (>50 years) development of atrial fibrillation (*AF*) to overall hypertrophic cardiomyopathy (*HCM*)–related mortality (*top*), stroke (*middle*), and progression of New York Heart Association class III-IV (*bottom*) compared with patients remaining in sinus rhythm (*SR*). *(From Olivotto I, Cecchi F, Casey SA, et al: Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy,* Circulation *104:2517–2524, 2001.)*

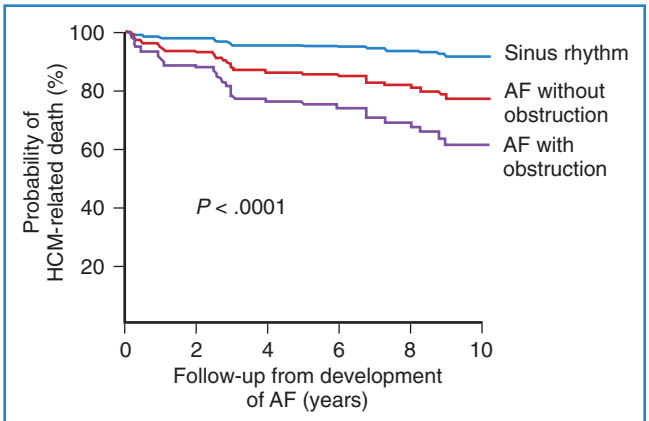

FIGURE 55-8 Combined impact to atrial fibrillation (*AF*) and basal outflow obstruction (gradient ≥30 mm Hg) to overall hypertrophic cardiomyopathy (*HCM*)–related death in patients with HCM and AF compared with a control group of patients in sinus rhythm with HCM. *(From Olivotto I, Cecchi F, Casey SA, et al: Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy,* Circulation *104:2517–2524, 2001.)*

ventricular filling may exceed that of patients with nonobstructive HCM; this greater dependence increases the likelihood of long-term deterioration following the development of AF.[64,65,69] The pathophysiological mechanisms by which recurrent or persistent AF may develop (Figure 55-9) and ultimately can affect the long-term clinical outcomes of HCM patients are undoubtedly complex and incompletely understood. However, the substantial increase in mean ventricular rate—associated with reduced cardiac output on effort and, potentially, with recurrent microvascular ischemia—is likely to play an important role (Figure 55-10). In a recent study, patients with HCM with paroxysmal or chronic AF showed substantially more severe impairment of coronary microvascular function compared with patients in stable sinus rhythm.[70] Of note, the association between microvascular dysfunction and AF in patients with HCM was independent of other known predictors of AF such as left atrial enlargement and age, which raises the novel possibility of a direct causal link between these two unfavorable disease features.[70]

Conversely, a clear linkage between clinically evident AF and the occurrence of SCD does not seem to exist. Although a causal link between AF and potentially lethal ventricular tachyarrhythmias is suggested in a few patients with HCM, cohort-based data do not support AF as a consistent trigger for SCD in an HCM patient population.[23,38,56,71,72] For example, Stafford and coworkers described the case of an adolescent boy who survived cardiac arrest with documented VF.[38] During a subsequent electrophysiological study, AF with rapid ventricular response was induced, eliciting evidence of myocardial ischemia (on ECG) and rapidly degenerating into VF. A potential association between AF and SCD is also suggested by the observation that 20% of patients with HCM who survived a documented cardiac arrest had demonstrated supraventricular arrhythmias (including AF) at the onset of symptoms preceding collapse.[56] Furthermore, several patients have been reported to have bursts of AF immediately preceding appropriate ICD interventions for VT or VF.[72,73]

Patients with HCM, AF, and preserved systolic function often show modest and localized LV hypertrophy—that is, 18- to 22-mm wall thickness in the anterior basal septum.[73] Therefore, the morphologic imagery in such patients is dominated by left atrial enlargement rather than left ventricular hypertrophy. Chronic AF is rarely observed in the presence of extreme left ventricular hypertrophy.[17]

Clinical Variability

The impact of AF on long-term prognosis in individual patients with HCM shows substantial heterogeneity and is not invariably unfavorable.[1,23,65] Although AF is strongly associated with HCM-related mortality and clinical deterioration, about one third of patients can tolerate AF (free of stroke or severe symptoms) and may experience a generally uneventful course. The likelihood of a benign outcome is significantly higher in patients with exclusively paroxysmal AF compared with those patients progressing to

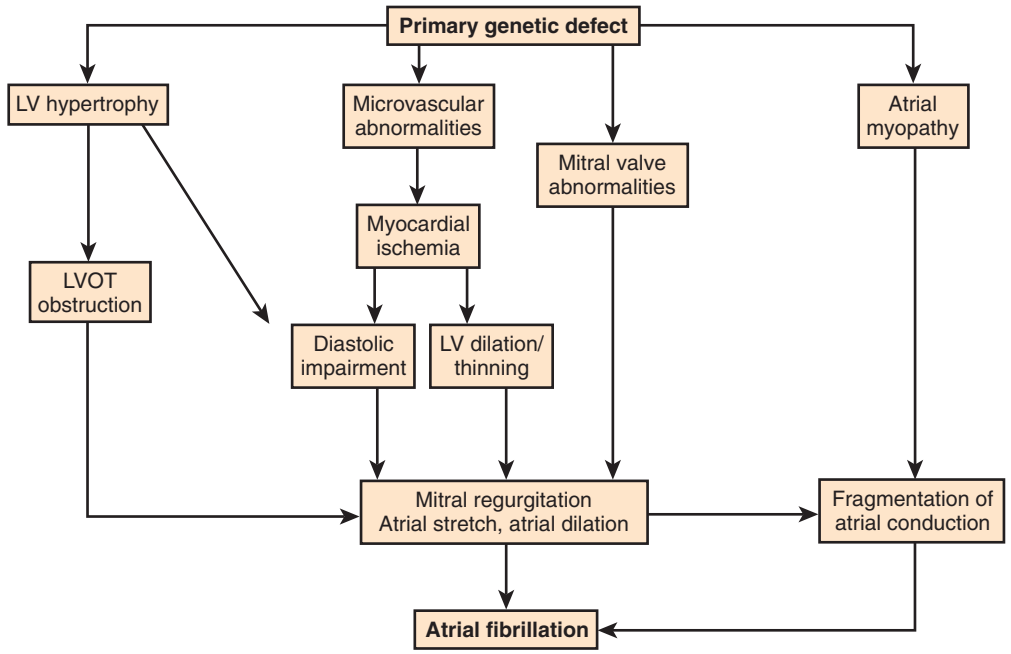

FIGURE 55-9 Arrhythmogenic substrates and potential triggers for AF in patients with hypertrophic cardiomyopathy. Proposed hypothetical sequence of events evolving from the primary gene mutation to the development of atrial fibrillation via multiple pathophysiological processes known to occur in HCM. *LV*, Left ventricular; *LVOT*, left ventricular outflow tract.

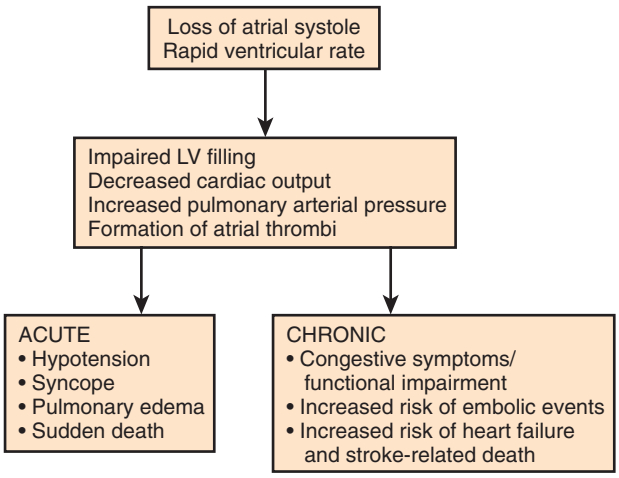

FIGURE 55-10 Acute and chronic pathophysiological consequences of atrial fibrillation in patients with hypertrophic cardiomyopathy. *LV*, Left ventricular.

chronic AF (not uncommonly associated with the end-stage of HCM).[23,34] Therapeutic efforts aimed at preventing or delaying the transition from paroxysmal AF to chronic AF carry the potential to improve patient outcome.

The question of whether the clinical importance of AF can be explained primarily by its hemodynamic impact on left ventricular filling, myocardial ischemia, or a more aggressive underlying cardiomyopathic process also remains unresolved.[63,74] However, the substantial clinical diversity associated with AF in HCM suggests that multiple variables probably affect individual patients differently in determining the clinical outcome following the onset of AF.

Risk of Stroke

Patients with HCM with AF show as much as an eightfold increase in the risk for cardioembolic stroke compared with patients with HCM in sinus rhythm.[23,62,68,75,76] The risk of stroke is similar in patients with chronic or paroxysmal AF and is not directly related to the number of clinically documented episodes.[23] Therefore, patients with a single paroxysm of AF appear to have a risk for stroke similar to that of patients with multiple episodes. Such observations suggest that the threshold for the initiation of anticoagulant treatment in patients with HCM should be low, consistent with the findings in a wide range of clinical studies in patients with AF and heart diseases other than HCM.[23,57-61] Although warfarin treatment for the primary prevention of stroke should be strongly considered (regardless of the number of documented AF episodes), such clinical decisions should be tailored to the individual patient after considering the risk for hemorrhagic complications, such as lifestyle modifications, and expectations with regard to compliance.[57,61]

Acute Deterioration

Occasionally, patients with HCM may have acute and severe hemodynamic deterioration with abrupt and unexpected onset of AF; this may be associated with heart failure, pulmonary edema, and marked functional impairment (see Figure 55-10).[23,55,77] This dramatic change in the clinical condition is attributable to the sudden loss of atrial systole (and its contribution to ventricular

filling) and a rapid increase in ventricular rate, which necessarily accompanies AF onset, triggering a fall in cardiac output when superimposed on diastolic dysfunction.[23,38,78] Urgent direct current (DC) cardioversion is mandatory in the presence of hemodynamic instability.

Medical Treatment for Atrial Fibrillation

Prospective and randomized studies addressing the optimal management of AF are not available in HCM. As a consequence, current treatment strategies for AF are largely based on standard guidelines developed for patients with other cardiac conditions including lone AF.[57-61,79]

For rhythm control in patients with HCM and recent onset of AF, early reversal to sinus rhythm is desirable for its beneficial hemodynamic effects. Therefore, an aggressive approach to AF with pharmacologic or electrical cardioversion in association with prophylactic antiarrhythmic treatment (and anticoagulation) may prevent or delay AF-related complications.[5,23,65,68,79] In a retrospective, nonrandomized study in patients with HCM and AF, long-term, low-dose amiodarone (200 mg/day) had several advantages over conventional drug treatment (including digoxin, verapamil, β-blockers, and class I agents)—that is, fewer cardioversion attempts and embolic complications and longer intervals of sinus rhythm maintenance before AF recurrence.[62,80] Also, by inference from data obtained in patients with other cardiac conditions, administration of low-dose amiodarone (200 mg/day) may represent the most efficacious strategy for maintaining sinus rhythm in patients with HCM following the development of paroxysmal AF.[23,56,80] The efficacy of other class III agents, including sotalol and dofetilide, remains undetermined in these patients.

In patients with persistent AF, in whom maintenance of sinus rhythm is not feasible, conservative strategies directed toward ventricular rate control is desirable.[5,61,65] Large multi-center trials in non-HCM diseases consistently show that optimal control of ventricular rate in AF is equivalent to sinus rhythm maintenance with respect to clinical outcome.[81,82] However, these principles cannot easily be extrapolated to HCM in the absence of specific evidence. However, at present, the favored view is that maintenance of sinus rhythm is probably preferable, whenever possible, because of the common occurrence of diastolic dysfunction and the important role of atrial contraction in patients with HCM.[23,65]

When AF becomes permanent, adequate rate control should be pursued by aggressive management with the β-adrenergic blocking agents verapamil or diltiazem, each alone or in combination. Amiodarone could be added as a second-line agent, particularly in those patients with documented ventricular arrhythmias on ambulatory ECG Holter monitoring.[5] Digitalis, which is contraindicated in patients with outflow obstruction, may be used in those developing systolic dysfunction and are in the end-stage phase, but it often fails to maintain adequate rate control during exercise in patients with HCM.[5,34] Ambulatory 24-hour Holter monitoring and exercise testing may be useful in assessing ventricular rate control during daily activities. In patients with persistently elevated ventricular rates associated with functional limitation, atrioventricular node ablation with rate-responsive pacing, although rarely necessary, may represent the only effective option to achieve rate control.[5,61]

Both paroxysmal and chronic AF represent clear indications for oral anticoagulation.[5,23,61,65,68] Among 190 patients with HCM and a history of AF followed at four institutions in Italy and the United States, the cumulative incidence of systemic thromboembolism in those untreated with anticoagulants was two times that of patients receiving warfarin (31% vs. 15%; $P = .01$).[68] Such observations are in agreement with a wide range of clinical studies on AF in patients with heart diseases other than HCM.[60,61,65,79] Thus, the threshold for the initiation of anticoagulant treatment in HCM should be low and probably independent of the number of documented AF episodes.[72,79] Nevertheless, such clinical decisions often need to be tailored to the individual patient with due consideration of the risk of hemorrhagic complications, lifestyle modifications, and expected compliance. Low-dose aspirin or other anti-platelet agents are expected to provide a lower degree of protection from cardioembolism compared with warfarin, and no data assessing their efficacy, specifically in patients with HCM, are currently available. Nevertheless, it may be reasonable to use anti-platelet agents as an alternative to warfarin in patients with HCM who are young and have normal (or near-normal) left atrial dimensions, have had no prior episodes of transient ischemic attacks or stroke, and have no additional comorbidity, particularly if they are unable or unwilling to take warfarin and manage their international normalized ratio on a regular basis.

Surgical and Catheter-Based Therapies

Management of AF is particularly challenging in relatively young patients, for whom rhythm control and prevention of AF-related complications must be weighed against the adverse effects and potential hazards of pharmacologic treatment, including long-term anticoagulation.[5,61,79] Thus, the possibility of reducing or postponing life-long pharmacologic treatment for AF is highly desirable in patients with HCM. Following experiences with treatments for structural heart diseases other than HCM, encouraging preliminary reports have shown the efficacy of surgical ablation of AF (the Cox-Maze procedure) in patients undergoing septal myectomy.[83] However, myectomy is performed in only a minority of patients with HCM, whereas AF is very common and frequently present in patients with nonobstructive HCM.[5,23,65] Therefore, radiofrequency catheter ablation has become a rapidly emerging management option for AF.

Although the overall clinical experience with radiofrequency catheter ablation has expanded,[84-93] this has been limited in HCM to early small cohort studies.[89-93] In the first published series, Liu et al reported no recurrences of AF within a 6-month period after circumferential pulmonary vein catheter ablation in a small group of four patients with HCM with paroxysmal AF.[89] A more sizable series of 27 patients with paroxysmal AF showed a 70% success rate in about 1 year following pulmonary vein isolation.[90] A more recent report described 26 HCM patients with severe symptomatic paroxysmal (n = 13) or permanent (n = 13) AF, refractory to antiarrhythmic therapy who had RF ablation (Figures 55-11 and 55-12).[91] Almost 60% of the patients had a left atrial transverse diameter of 50 mm or greater. The ablation scheme involved complete electrical isolation of pulmonary veins and creation of linear lesions interconnecting the upper pulmonary vein ostia and the left inferior vein down to the mitral annulus. Despite unfavorable baseline features (long duration of the arrhythmia and extreme left atrial dilation), successful restoration of sinus rhythm was finally maintained in two thirds of the patients over 19 ± 10 months. The success rate was greater than 75% among patients with prior paroxysmal AF and 50% in the permanent AF group, suggesting that lesser degrees of left atrial remodeling may make favorable outcome more likely.[91] Restoration of stable sinus

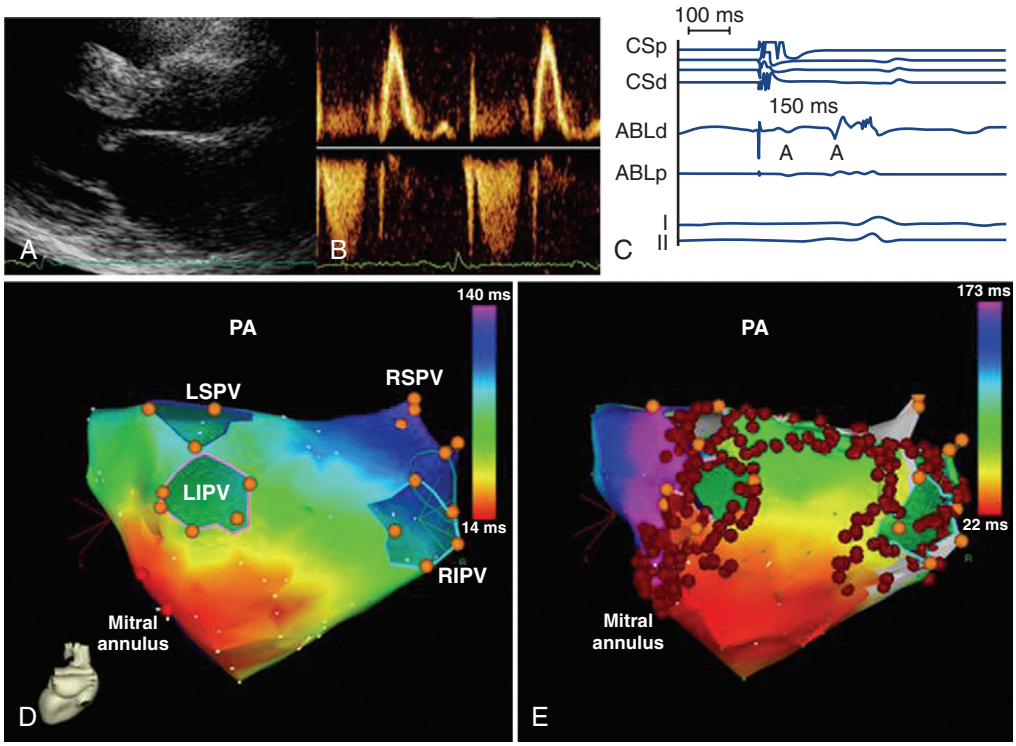

FIGURE 55-11 Echocardiographic and radiofrequency ablation procedural data in a 25-year-old woman with hypertrophic cardiomyopathy (HCM) caused by a double mutation of the cardiac troponin I and β-myosin genes [*A86fs*/27(delC) and *R869H*, respectively], with diastolic dysfunction, left atrial dilation and paroxysmal atrial fibrillation refractory to antiarrhythmic treatment. **A,** Echocardiographic parasternal long-axis view showing asymmetric hypertrophy of the left ventricle and marked left atrial dilation. **B,** Transmitral pulsed-wave Doppler image showing a restrictive left ventricular filling pattern. **C,** Endocavitary recordings on the ablation catheter, during proximal coronary sinus pacing, of double atrial (*A*) potential along the isthmus line with a wide delay of 150 ms. **D,** Three-dimensional shell activation map during coronary sinus pacing representing the left atrium and pulmonary vein ostia. **E,** Electroanatomic re-map showing the activation pattern after creation of the pulmonary vein isolation plus linear lesions (*red dots*). Color-coded activation shows complete conduction block along mitral isthmus; *red zones* represent sites of early activation, *purple zones* represent sites of late activation. *CS*, Coronary sinus; *ABL*, ablation catheter; *p*, proximal; *d*, distal; *I-II*, electrocardiogram surface leads; *PA*, posteroanterior; *PV*, pulmonary vein; *RI*, right inferior; *RS*, right superior; *LI*, left inferior; *LS*, left superior. *(From Gaita F, Di Donna P, Olivotto I, et al: Usefulness and safety of transcatheter ablation of atrial fibrillation in patients with hypertrophic cardiomyopathy,* Am J Cardiol *99:1575–1581, 2007.)*

rhythm was associated with general and marked improvement of heart failure symptoms. Moreover, long-term antiarrhythmic therapy could be discontinued in one half of patients who had successful procedures.

These findings have been subsequently confirmed in a series of 33 patients with HCM with AF refractory to medical therapy, of whom 21 had paroxysmal AF and 12 had persistent AF, with a more than 60% 1-year rate of AF abolition (i.e., stable sinus rhythm without anti-arrhythmic therapy), and a 75% rate of AF control.[92] Quality-of-life scores improved from baseline at 12 months following ablation. Of note, AF control was less likely in patients with persistent or chronic AF, larger left atrial volumes, and marked diastolic dysfunction.

Overall, these preliminary studies should be regarded with cautious optimism. First, catheter ablation represents an effective and sufficiently safe procedure in patients with HCM, effectively restoring stable sinus rhythm and improving limiting symptoms.[91,92] Success rates for ablation in HCM patients are similar to those reported for other structural heart diseases but inferior to those for "lone" AF.[84-88] Moreover, a significant proportion of patients with HCM will probably require long-term antiarrhythmic therapy following ablation.

For the same reasons, accurate patient selection becomes crucial to maximizing the likelihood of success from catheter ablation. Patients with advanced age, extreme atrial dilation, and long-standing permanent AF are less likely to benefit from this procedure. Conversely, younger patients with HCM with only mildly increased atrial size have the greatest expectation of maintaining sinus rhythm (in the absence of antiarrhythmic treatment).[91,92] However, the long-term consequences of ablation procedures in patients with HCM are presently unresolved.

Finally, the risks of catheter ablation should be carefully weighed against its potential benefits. In a recent worldwide registry, major peri-procedural complications (death, ischemic stroke, or tamponade) were reported in 6% of more than 8700 patients undergoing ablation for AF unrelated to HCM.[93] Referral of patients to centers with established expertise in the procedure with high patient volumes represents the most effective way of reducing complication rates and ensuring optimal procedural outcome.[5]

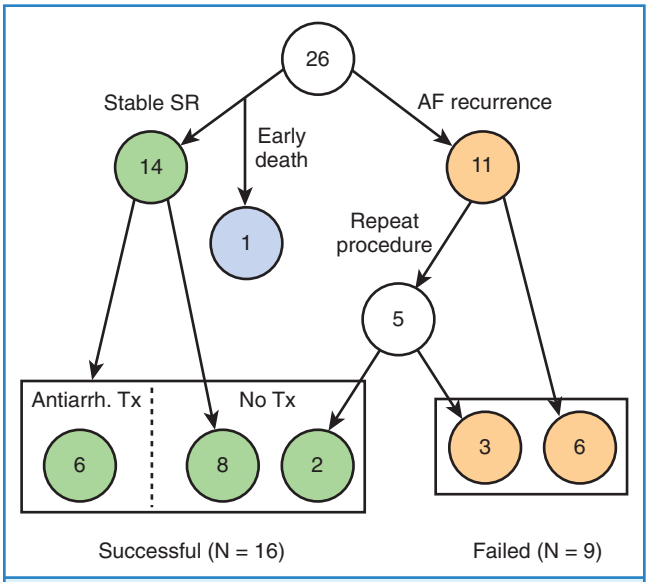

FIGURE 55-12 Outcome of 26 patients with hypertrophic cardiomyopathy undergoing radiofrequency transcatheter ablation of atrial fibrillation. The final success rate for the study group was 64% and was higher among patients with a prior history of paroxysmal atrial fibrillation (10 of 13; 77%) compared with those with prior permanent atrial fibrillation (6 of 12; 50%). *Antiarrh. Tx*, On antiarrhythmic medications at end of follow-up; *SR*, sinus rhythm. *(From Gaita F, Di Donna P, Olivotto I, et al: Usefulness and safety of transcatheter ablation of atrial fibrillation in patients with hypertrophic cardiomyopathy,* Am J Cardiol *99:1575–1581, 2007.)*

Summary

Primary ventricular tachyarrhythmias arising from an unstable myocardial substrate are the triggers for SCD in HCM. Prevention of SCD is now an achievable goal for high-risk patients with HCM, given the application of the ICD to this genetic disease. It is now evident that the ICD is efficacious and life saving in HCM, with an important role established for primary as well as secondary prevention of SCD.

AF, the most common sustained arrhythmia encountered in the HCM patient population, is caused by complex arrhythmogenic pathophysiology (see Figures 55-9 and 55-10). AF is more common in older patients but, paradoxically, has more adverse outcomes when the onset is earlier in life. Although the long-term consequences of AF are not uniformly unfavorable, the powerful independent association of paroxysmal or chronic AF with HCM-related mortality, stroke, and severe functional disability from heart failure (particularly in the presence of outflow obstruction) underlines the necessity for aggressive therapeutic strategies. Novel therapeutic initiatives such as catheter-based RF ablation show promise for the control of recurrent AF in selected patients with HCM.

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CHAPTER 56

Evaluation and Management of Arrhythmias Associated with Congestive Heart Failure

Steven Singh

Introduction

Heart failure is characterized by a failure to pump an adequate volume of blood to meet the metabolic needs of the body. Systolic failure deals with expulsion of blood from the heart, and diastolic failure is defined as an abnormality in relaxation leading to impaired filling. This chapter, because of limited data on isolated diastolic heart failure, will provide only a comprehensive discussion of systolic heart failure, with the consideration that most patients with systolic dysfunction have concomitant diastolic dysfunction.

The etiologies of systolic heart failure are multi-factorial and include associated coronary artery disease, valve pathology, primary myopathy (toxins, infection, etc.), and related tachyarrhythmias.

Both atrial and ventricular arrhythmias can not only lead to heart failure but can also occur as a consequence of heart failure. Arrhythmias commonly seen in heart failure include sinus tachycardia, atrial fibrillation (AF), premature ventricular contractions (PVCs), nonsustained ventricular tachycardia (NSVT), sustained ventricular tachycardia (VT), torsades de pointes (TdP), and ventricular fibrillation (VF) (Box 56-1).

Mechanisms

The mechanisms of arrhythmias in heart failure include re-entry, triggered activity, abnormal automaticity, and altered stretch (Box 56-2).

Re-entry is often seen in heart failure and may be related to conduction slowing caused by functional or anatomic barriers. The underlying mechanisms include reduced myocardial excitability and increases in resistance.[1] Moreover, downregulation of the gap junction protein connexin 43 promotes cell-to-cell uncoupling, a milieu for re-entrant arrhythmia.[2]

Patients with heart failure often develop left ventricular hypertrophy, a compensatory mechanism for inadequate cardiac output. Left ventricular hypertrophy is associated with increased action potential duration that provides a potential for increased dispersion of repolarization leading to TdP or VF as a result of triggered activity, especially early afterdepolarization.[3] Also of note, because of the downregulation of potassium (K^+) currents and increased late sodium (Na^+) current, the action potential duration is further prolonged, with a greater propensity for triggered activity.[4] Increases in intracellular calcium (Ca^{2+}) from enhanced sympathetic stimulation from the heart failure itself or from the use of digitalis may cause triggered arrhythmias by inducing delayed afterdepolarization.[5,6]

Abnormal automaticity stems from ischemia and is related to abnormal Ca^{2+} handling, leading to non–re-entrant arrhythmias.[6]

Stretch-activated channels may play an important role in arrhythmia genesis. This observation has been noted mostly in animal studies. Stretch affects both conduction and refractoriness. Any such alterations may predispose to arrhythmias in patients with heart failure. Electromechanical feedback can lead to electrical remodeling with changes in conduction and repolarization, creating heterogeneity and dispersion, with enhancement of atrial and ventricular arrhythmias.[7,8]

A reduction in the sinoatrial node I_f current ("funny" current) and its hyperpolarizing cyclic nucleotide (HCN) channel gene leads to sinus bradycardia from sinoatrial node dysfunction. In heart failure, however, increases may occur in atrial and ventricular tissue I_f currents that may lead to arrhythmias.[9]

Atrial Fibrillation

AF is quite commonly seen in patients with heart failure (30%). The tachycardia itself may predispose to heart failure but may occur as a result of heart failure. The risk of emboli is related to etiology and the CHADS 2 (Cardiac Failure, Hypertension, Age, Diabetes, Stroke [Doubled]) score. Valvular AF carries a higher risk of stroke. Compared with sinus rhythm, after adjustments for comorbidities, AF does not seem to have an independent mortality risk in heart failure.[10] Mechanisms of AF in heart failure, which are complex and multi-factorial, include re-entry, triggered activity, automaticity, and activation of stretch receptors. In addition, atrial interstitial fibrosis, increased collagen synthesis, and altered connexin expression predispose to heterogeneities and electrical uncoupling and eventually AF. Of note, experimental heart failure in dogs has been shown to promote AF by causing fibrosis, interfering with local conduction, and not by altering atrial refractory period, refractoriness heterogeneity, or conduction velocity as seen with rapid atrial pacing.[11]

Box 56-1 Common Arrhythmias in Heart Failure

Atrial fibrillation
Premature ventricular contraction
Nonsustained ventricular tachycardia
Sustained ventricular tachycardia
Ventricular fibrillation
Torsades de pointes

Box 56-2 Mechanisms

Re-entry
Abnormal automaticity
Triggered activity
Altered stretch

Box 56-3 Evaluation

Electrocardiogram
Ambulatory recording (Holter)
Microvolt T-wave alternans
Baroreflex sensitivity
Electrophysiology testing
Left ventricular ejection fraction

Ventricular Arrhythmias

PVCs are very common in patients with heart failure, and in those with more than 10 per hour, the incidence of NSVT is about 90%.[12] In patients with prior myocardial infarction (MI), PVCs are associated with an increased risk of death, especially in those with left ventricular dysfunction. The presence of NSVT does not seem add any more risk over PVCs.[13]

Sustained VT and VF may account for 50% of all deaths in patients with heart failure and is often classified as sudden cardiac death (SCD). However, all SCDs may not be tachyarrhythmia related. Death from bradycardia or electromechnical dissociation is common, especially in severe heart failure.[14,15] Bundle branch re-entry is a form of sustained VT that may be reproduced in the electrophysiology laboratory and is important to recognize, since this arrhythmia can be successfully treated with ablation (see below).

TdP is seen with antiarrhythmic drug toxicity. Drugs that prolong the Q-T interval may predispose to this potentially lethal arrhythmia, especially in those with heart failure.

Evaluation

Numerous tests have been used to evaluate the excessive risks of patients with heart failure (Box 56-3). The electrocardiogram is extremely useful in determining etiologies and important prognostic factors. Sinus bradycardia in response to β-blocker therapy has been shown to be beneficial in patients with heart failure. However, sinus bradycardia may be profibrillatory in the atrium because of increased dispersion (atrial torsades) or in the ventricle, especially in the presence of class III (K^+ channel blockers) antiarrhythmic drugs (see below).[16] Wide QRS or bundle branch block is an independent risk factor for premature death, that is, independent of ejection fraction (EF).[17,18] A fragmented QRS has been shown to be predictive of mortality and SCD in both ischemic and nonischemic cardiomyopathy. An acquired prolonged Q-T interval is also quite important and may be a harbinger of TdP, especially when associated with K^+ channel blockers, bradycardia, female gender, and electrolyte imbalance.

T-wave alternans, that is, a beat-to-beat variation in T-wave morphology, although subtle, has been associated with potentially lethal arrhythmias. A more sensitive technique is microvolt T-wave alternans (MTWA). A positive test carries a poor prognosis compared with a negative test, as shown in Multicenter Automatic Defibrillator Implantation Trial II (MADIT II), in which patients with prior MI and left ventricular dysfunction were randomized to implantable cardioverter-defibrillator (ICD) or not.[19] However, in the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) substudy, a positive MTWA was not predictive of excess mortality in patients with heart failure.[20] Of note, a wide QRS and the use of β-blockers may affect the results. It appears that MTWA testing should not be used to make decisions on implantation of an ICD.

Baroreflex sensitivity (BRS), a measure of autonomic nervous system activity that is independent of β-blocker usage, has been used to identify patients at high risk, especially those with previous MI. A low BRS is associated with a poor outcome. In the Autonomic Tone and Reflexes after Myocardial Infarction (ATRAMI) trial, a depressed BRS predicted cardiac mortality after MI.[21]

The role of the electrophysiology study (EPS) in nonischemic cardiomyopathy has not been established, and the chance of inducing a sustained ventricular arrhythmia is quite low.[22] VT caused by bundle branch re-entry is sometimes seen in patients with nonischemic cardiomyopathy, and ablation of the right bundle, if electrophysiologically induced, is curative.[23] Patients with ischemic cardiomyopathy and NSVT in whom sustained VT can be provoked at EPS carry a high risk of SCD compared with those in whom the arrhythmia is not inducible. However, because of a low EF, noninducibility still carries a substantial risk.[24] Thus the role of EPS is limited. Left ventricular ejection fraction is the most powerful predictor of outcome and is used frequently to guide therapy, especially nonpharmacologic therapy.

Therapy

Box 56-4 provides a brief outline of the various treatment modalities for the patient with heart failure and left ventricular dysfunction.

Pharmacologic Therapy: Antiarrhythmics

The Vaughn Williams class I antiarrhythmics (Na^+ channel blockers) are contra-indicated in patients with heart failure because of the excessive risk of proarrhythmic effects.

β-Blockers have been consistently shown to reduce SCD and total mortality in patients with heart failure.[25-27] This effect is independent of PVC suppression.[28] β-Blockers are very effective in slowing the ventricular response in AF. Not all β-blockers are created equal, and those with intrinsic sympathomimetic activity may be of limited use or harmful. Noncardioselective β-blockers may be superior to cardioselective ones; in the Carvedilol or

Box 56-4 Therapy

PHARMACOLOGIC

Antiarrhythmics: sodium, calcium, potassium channel blockers, β-blockers
Angiotensin-converting enzyme and receptor blockers
HMG-CoA reductase inhibitors
Omega-3 polyunsaturated fatty acids

NONPHARMACOLOGIC

Implantable cardioverter defibrillator
Biventricular pacing
Revascularization
Ablation

HMG-CoA, *3-hydroxy-3-methylglutaryl-coenzyme A*

Metoprolol European Trial (COMET), carvedilol was found to be superior to metoprolol with regard to outcome in patients with heart failure. This could be explained by the low daily cardioselective dose of 89 mg of metoprolol. Of note, the incidence of AF was lower with carvedilol.

Class III drugs such as sotalol and dofetilide can suppress both supraventricular and ventricular arrhythmias and may be considered safe, although they have no beneficial effects on mortality. However, the risk of a proarrhythmic effect is high in patients with heart failure, so extreme caution must be exercised. Amiodarone is unique and is a very complex antiarrhythmic agent with the capability of blocking Na^+, Ca^{2+}, and K^+ channels. Amiodarone is also an α- and β-blocker and is very effective in suppressing atrial and ventricular arrhythmias. Proarrhythmia is not often seen with this compound. However, it has many noncardiac adverse effects, so its use may be limited. It shows no benefit on survival in patients with prior MI, those with prior MI and left ventricular dysfunction, those with heart failure, and those with AF and heart failure.[12,29-31] Dronedarone has a molecular structure similar to that of amiodarone but without the iodine.

In Antiarrhythmic Trial with Dronedarone in Heart Failure (ANDROMEDA), dronedarone was associated with increased mortality caused by worsening heart failure.[32] Of note, however, in the recently published 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 (ATHENA) trial, dronedarone was effective in reducing cardiovascular hospitalization or death.[33]

The Ca^{2+} channel blockers are of no benefit and may be harmful in patients with heart failure.[34,35]

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, in addition to β-blockers, are mandated in the treatment algorithm of patients with heart failure. These agents suppress both ventricular and supraventricular arrhythmias.[36] They are thought to accomplish this effect by structural, functional, and electrical remodeling. Incidentally, two large prospective trials have shown that angiotensin receptor blockers have no benefit in patients with diastolic heart failure.[37,38]

The aldosterone receptor blockers aldactone and eplerenone have been shown to improve survival in patients with heart failure.[39,40] Both drugs reduce the incidence of SCD and may be related to a decrease in the re-entrant mechanism because of a reduction of fibrosis.

Ranolazine is a very complex antianginal compound with complex antiarrhythmic activities. It can block not only the K^+ and Ca^{2+} currents but also the late Na^+ current, thereby decreasing proarrhythmia; it also has potential antiarrhythmic properties. At this time, no trials have been performed using this agent in patients with heart failure. However, ranolazine suppresses malignant ventricular arrhythmias, as shown in the Metabolic Efficiency with Ranolazine for Less Ischemia in Non–ST Segment Elevation Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction (MERLIN-TIMI) trial.[41]

Numerous trials have shown that "statins" suppress the incidence of AF. This is especially true in the postoperative period, as shown in the Atorvastatin for Reduction of Myocardial Dysrhythmia After Cardiac Surgery (ARMYDA-3) trial, in which atorvastatin was shown to be superior to placebo.[42] In retrospective analyses, statins also lower the recurrence of VT or VF in patients with ICDs.[43,44]

In the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico Prevenzione (GISSI) trial, n-3 polyunsaturated fatty acids (PUFAs) have been shown to reduce SCD in patients with recent MI.[45] In the recently published GISSI-HF trial, PUFA reduced all-cause mortality and cardiovascular admissions.[46] Of note, PUFAs attenuate heart failure–associated atrial structural remodeling and AF promotion without changing atrial refractory periods and electrical remodeling.[47]

In patients at high risk for AF, warfarin is the drug of choice since the risk of embolization in these patients is unacceptably high. For patients not suitable for warfarin therapy, the combination of clopidogrel and aspirin has been shown to be superior to aspirin alone, in the recent publication of the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE) trial.[48]

Nonpharmacologic Therapy

Revascularization with coronary artery bypass grafting (CABG) has been shown to reduce SCD.[49] It is unclear whether this is related to suppression of arrhythmia. Data on revascularization in patients with heart failure and arrhythmia suppression are not available. The ongoing Surgical Treatment of Ischemic Heart Failure (STICH) trial may provide some answers. In the CABG PATCH trial, patients with prior MI and left ventricular dysfunction were randomized to CABG or to CABG with ICD.[50] The survival rates were the same in both groups, which suggests that revascularization possibly provides protection from arrhythmic death. Data on the effects of percutaneous coronary intervention on arrhythmias in patients with heart failure are not available.

ICD therapy has consistently shown survival benefits in patients with heart failure and left ventricular dysfunction. This is related to a reduction in SCD, as a result of tachyarrhythmias.[51,52] Of interest, SCD-HeFT did not show clear benefit in New York Heart Association class III heart failure but only in class II. In MADIT II, benefit was seen in patients with prior infarction and left ventricular dysfunction. A disconnect may exist between the degree of heart failure and benefit from ICD therapy. The SCD-HeFT substudy of AF did not show any survival benefit with ICD therapy. Moreover, in those with sinus rhythm at baseline, the ICD increased AF incidence.[10]

Cardiac resynchronization therapy (CRT) has been shown to reduce hospitalization and mortality in patients with heart failure.[53,54] Responders to CRT have shown a significant reduction

in ventricular arrhythmias and ICD shocks compared with non-responders.[55] The reduction in arrhythmia density is possibly related to reverse remodeling. A recent study on patients with predominantly class 2 congestive heart failure showed mortality reduction with CRT and ICD compared with ICD alone.[56]

Frequent PVCs may contribute to left ventricular dysfunction. Ablation of these isolated foci can abolish these PVCs with resolution of the cardiomyopathy.[57] Sustained monomorphic VT that recurs despite antiarrhythmic therapy can be successfully ablated. However, the 1-year mortality rate is still around 18%.[58,59]

Pulmonary vein isolation has been shown to have superior beneficial effects over AV node ablation in selected patients with AF and heart failure. Improvements were seen in the quality of life, 6-minute walk, and EF.[60]

Conclusion

Cardiac arrhythmias are common in patients with heart failure and include AF, PVCs, NSVT, VT, and VF. The mechanisms are multi-factorial and include re-entry, abnormal automaticity, triggered activity, and activation of stretch receptors. Therapies may include classic antiarrhythmic drugs, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone receptor blockers, warfarin, statins and PUFAs, ICDs, biventricular pacing, and ablation.

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CHAPTER 57

Arrhythmias in Coronary Artery Disease

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Other than hypertensive heart disease, coronary artery disease (CAD) is the most common cause of structural heart disease in the United States. Most patients who experience life-threatening arrhythmias have underlying structural heart disease, and the majority of patients presenting with sustained ventricular arrhythmias have underlying CAD.[1] Patients with coronary disease may also have various less severe forms of arrhythmias, including bradyarrhythmias and supraventricular and ventricular arrhythmias.

Arrhythmias Associated with Acute Ischemia and Myocardial Infarction

Acute myocardial ischemia (AMI) usually results from partial or total coronary occlusion with a subsequent imbalance between myocardial oxygen supply and demand. Acute coronary syndromes (ACS) include myocardial infarction (MI) (ST-segment elevation and depression, Q wave and non–Q wave) as well as unstable angina.[2,3] ACS may result in arrhythmias during acute coronary occlusion, reperfusion, myocardial infarct evolution, or the healing phase after infarction. Ischemia-induced changes in ions, metabolites, ion channels, gap junctions, and cellular and tissue architecture result in profound changes in the electrophysiological properties of the affected myocardium, which interact with modulating factors (autonomic nervous system, electrolytes, ischemic preconditioning, changes in heart rate) and the presence of concurrent structural heart disease (scar, hypertrophy, depressed ejection fraction), leading to generation of cardiac arrhythmia.

Mechanisms

Acute ischemia following coronary artery occlusion results in local tissue hypoxia and a loss of function of the adenosine triphosphate (ATP)-dependent sodium-potassium (Na^+-K^+) pump. Cellular membrane permeability is altered, pH falls, and a net K^+ leakage from the myocyte and a rise in extracellular K^+ occur. The normal cardiac resting membrane potential decreases from –80 mV to around –50 mV.[4,5] The action potential (AP) amplitude falls, and maximal upstroke velocity (dV/dt max) decreases.[6] Within the first 2 minutes, the fall in resting membrane potential results in an increase in conduction velocity.[7] As the AP upstroke velocity falls over the next 10 minutes, conduction velocities decrease by up to 50%.[8] Importantly, the effects of ischemia on the electrophysiological properties of myocardial cells are heterogeneous. AP duration and upstroke velocity are more reduced in subepicardial cells than in subendocardial cells.[9] Within the central zone of ischemia, refractory periods are prolonged, and conduction velocity is decreased.[10] In the surrounding nonischemic tissue, the refractory period may become shortened, and the conduction velocity may increase—possibly as a result of local catecholamines, circulating catecholamines, or both. Intermediate or mixed changes occur in the border zone between ischemic and nonischemic tissues, which results in a marked heterogeneity of electrophysiological properties. Changes in the degree of cell-to-cell coupling and tissue architecture also cause slowing and then failure of electrical propagation. The extracellular compartment shrinks, and extracellular resistance increases.[11] Gap junction disruption results in cellular uncoupling. Heterogeneities in the changes in intracellular and extracellular resistance are particularly pronounced in the border zone.

The myocardial substrate for re-entry is provided early by the infarcted area or by a pre-existing scar, and it becomes permanent once the scar has formed. This is a dynamic process, and remodeling of the scar and the distant, normal myocardium occurs over weeks to months. The characteristics of the scar, including size, location, transmurality, and the presence of channels of viable myocardium, are important.

Autonomic nervous system changes occur during MI. While infarcted areas show sympathetic denervation, surrounding and distant areas develop hyperinnervation.[12] In addition, subepicardial sympathetic fibers traveling from base to apex may be damaged by transmural infarctions, which results in denervation of areas located more apically; these areas may show denervation hypersensitivity to catecholamines.[13-18] Autonomic and neurohumoral influences can thus modify the electrophysiological properties of the substrate and can also result in arrhythmic triggers (premature ventricular contractions) via enhanced automaticity or after-depolarizations.

If the acute ischemia resolves, further myocardial injury occurs during reperfusion; this includes vascular damage, myocardial stunning, and further necrosis, mediated by intracellular calcium overload and oxygen free radicals. Calcium-dependent arrhythmias resulting from triggered activity, such as delayed afterdepolarizations, may develop. Premature ventricular contractions (PVCs) and accelerated idioventricular rhythms are the most common rhythms associated with this phase, and they do not portend an adverse prognosis.[19,20]

Recurrent ischemia may result in alterations of the cellular metabolism and local biochemical environment and thus modulate arrhythmogenicity. Short, repetitive coronary occlusions have

been shown experimentally to result in decreased incidence of ventricular fibrillation (VF) during reperfusion—a phenomenon termed *ischemic preconditioning*.[21]

Electrolyte abnormalities, particularly hypokalemia and hypomagnesemia, can alter myocardial electrophysiological properties and can also generate arrhythmia triggers. Circulating fatty acid levels have also been associated with an increased risk of sudden death as a manifestation of coronary disease.[22,23]

Genetic factors may play a significant role. In two retrospective studies, MI patients who experienced VF or sudden death were more likely to have a family history of sudden cardiac death (SCD).[24,25] Candidate genes include genes that predispose to the development of the underlying substrate (coronary disease as well as acute plaque rupture, thrombosis, or both) and genes that directly influence the electrical properties of the myocardium and its vulnerability to ventricular fibrillation. A number of monogenic arrhythmic disorders have been well characterized (long QT syndromes, short QT syndromes, Brugada syndrome, catecholaminergic polymorphic VT syndromes).[26] In addition, several genetic variants (polymorphisms) have been associated with sudden death or arrhythmia in general populations (*SCN5A* gene, β_2-adrenergic receptor gene[27,28]). These genetic abnormalities and variants, and others still undiscovered, clinically apparent or subclinical, are likely to influence an individual's susceptibility to develop arrhythmias during both acute and chronic coronary ischemia.

Stages of Ventricular Arrhythmogenesis Following Coronary Artery Occlusion

Arrhythmia mechanisms and prognostic implications vary, depending on the time of occurrence after the onset of coronary occlusion. The timeline has been divided into an acute phase (first 30 minutes) and a delayed phase (or subacute phase, 6 to 48 to 72 hours).

Two distinct phases of arrhythmogenesis (Table 57-1) occur during the initial 30 minutes ("acute phase") of ischemia after experimental coronary artery ligation.[8] Phase 1a arrhythmias occur 2 to 10 minutes following coronary artery occlusion (peak 5 to 6 minutes) and are caused by re-entry within the ischemic myocardium resulting from the inhomogeneity of refractory periods in normal and ischemic tissue. Mapping studies have revealed the presence of low-amplitude fractionated electrograms.[7,8]

Phase 1b arrhythmias occur 10 to 30 minutes following coronary artery occlusion (peak 15 to 20 minutes). The precise mechanism of type 1b ventricular arrhythmias is unclear. By this stage, the inhomogeneities in subepicardial refractoriness and conduction have improved to near-normal values.[8] Because of the important role of catecholamines in arrhythmogenesis, it has been postulated that abnormal automaticity is the underlying mechanism.[29] Myocardial stretch mechanisms have also been implicated in the generation of abnormal automaticity.[30] Studies in canine hearts during the first 30 minutes following coronary artery occlusion have suggested that up to 60% of ventricular tachycardias (VT) are focal in origin, arising from Purkinje fibers.[31] Generally, during these two phases, spanning the first 30 minutes following occlusion, no permanent structural damage occurs. On reperfusion, ischemic cells survive and generally recover function. However, toward the end of phase 1b, changes in the internal axial resistance of cardiac tissue are first noted, indicating the onset of irreversible cellular and gap junction damage.[32]

The subacute or delayed phase occurs 6 to 72 hours following coronary artery occlusion (peak 12 to 24 hours).[33] It coincides with the onset of cell death; reperfusion at this stage does not reduce the amount of cell damage. Although substantial myocardial cell death occurs in the infarcted region, subendocardial Purkinje fibers survive with altered electrophysiological properties predisposing to arrhythmia generation.[34] A reduced resting membrane potential and spontaneous membrane depolarizations lead to abnormal automaticity. Delayed after-depolarizations resulting in triggered activity have also been demonstrated.[35] In addition, heterogeneity of conduction and refractoriness at the border zone, which is the interface between the dead myocardium and the still-viable myocardium, may lead to re-entrant arrhythmias.

Reperfusion Arrhythmias

Reperfusion arrhythmias are more common after short ischemic episodes than after long ischemic periods.[36] In the canine model, reperfusion arrhythmias have been shown to occur in two stages. Immediately following restoration of perfusion after coronary artery occlusion, VF may occur due to multiple wavelet re-entry. This occurs as a result of a rapid but inhomogeneous return of APs to previously unexcitable cells within the ischemic zone and a shortening of refractory periods in the border zone brought about by the washout of K^+ and metabolites from the extracellular space.[37] In addition, premature depolarizations may be induced by triggered activity. Although overall electrical function can return

Table 57-1 Phases of Arrhythmogenesis

	STAGE 1A	STAGE 1B	REPERFUSION	SUBACUTE	CHRONIC
TIMING	**2–10 MINUTES**	**10–30 MINUTES**	**UP TO 6–12 HOURS**	**6–72 HOURS**	**LONG TERM**
Arrhythmia	VT = VF	VT > VF	VF > VT, AIVR	VT > VF, AIVR	VT > VF
Mechanism	Re-entry, triggered activity	Abnormal automaticity	Abnormal automaticity Triggered activity and re-entry	Abnormal automaticity Triggered activity and re-entry	Re-entry
Substrate	Local hypoxia, acidosis, and increased K^+ Increased sympathetic tone Increase in extracellular resistance, uncoupling		Endothelial damage, catecholamines, electrolyte shift with washout	Onset of cell death	Chronic scar ± aneurysm Acute-on-chronic ischemia

to normal at this stage, gap junction injury may persist with a corresponding inhomogeneous delay in conduction properties.

Accelerated idioventricular rhythms are commonly seen following reperfusion in the canine model. This arrhythmia may be due to the increased adrenergic stimulation of Purkinje fibers near the ischemic region causing enhanced automaticity or triggered activity.[38] As accumulation of catecholamines is required, these arrhythmias typically occur after 20 to 30 minutes of occlusion. Compared with the canine model, the incidence of early reperfusion arrhythmias in the human population is significantly lower. This probably reflects the longer occlusion times and less rapid or incomplete reperfusion typically seen in patients presenting with AMI.

Clinical Characteristics of Ventricular Arrhythmias in Acute Coronary Syndromes

Ventricular arrhythmias are present in 64.1% of patients following acute ST-segment elevation myocardial infarction (STEMI).[20] More than 10 PVCs per hour may be seen in 19.7% and nonsustained VT (NSVT) in 6.8% of patients. Sustained VT or VF occurs in 10.2% of admissions, with an incidence of 1.9% within the first 24 hours and 3.7% to 4.4% in the first 48 hours.[39-42] Older age, systemic hypertension, previous MI, Killip class, anterior infarct, and depressed ejection fraction are associated with a higher risk of sustained VT and VF.[39] Ventricular arrhythmias are more common in patients with signs of extensive left ventricular damage. However, early mortality is increased in patients who develop VT and fibrillation, even in the absence of congestive heart failure and hypotension. The incidence of VF in AMI seems to have declined over the last 20 years, whereas the incidence of VT has not changed much.[43]

Ventricular arrhythmias also occur in the setting of unstable angina (UA) or non–ST-elevation MI (NSTEMI), both during episodes of pain and when patients are pain free.[44] In a pooled analysis of over 25,000 patients with UA or NSTEMI from four trials, the incidence of sustained VT or VF was 2.1%.[45]

Premature Ventricular Contractions

PVCs are seen in the majority of cases of acute MI. Early PVCs (within the first 48 hours) do not appear to affect the prognosis, but frequent or complex PVCs occurring beyond 48 hours after AMI may be associated with increased arrhythmic risk. In the human heart, R-on-T PVCs are rarely observed, accounting for only 1.8% of PVCs during the first 24 hours of admission, and most PVCs do not trigger severe ventricular tachyarrhythmias.[46-48] However, in a canine model, 24% of PVCs occurring between 12 and 30 minutes (phase 1b) resulted in R-on-T and were responsible for the initiation of 34% of spontaneous episodes of VT and fibrillation.

Several studies from the prethrombolytic era have suggested that frequent PVCs (>10 PVCs per hour), complex PVCs (ventricular bigeminy, couplets, or multiform ventricular premature beats), or both are a risk factor independent of the degree of myocardial damage and left ventricular systolic dysfunction,[20,49] but in another trial, PVC frequency had no independent predictive value in multivariate analysis.[50] Antiarrhythmic suppressive therapy (lidocaine) has not been shown to improve outcomes, and class Ic antiarrhythmics may increase mortality. Electrophysiology study for risk stratification is currently not recommended for either early or late post-MI PVCs.

Accelerated Idioventricular Rhythm

Accelerated idioventricular rhythm (AIVR) is commonly witnessed in the first 12 hours after admission for AMI. Although more common in patients with successful reperfusion therapy, it is not a specific marker, with 63% of patients with occluded arteries still demonstrating the arrhythmia.[51] The presence of AIVR does not affect the prognosis.

Nonsustained Ventricular Tachycardia

The presence of NSVT identifies patients at risk of in-hospital cardiac arrest. NSVT that occurs within the first 2 to 3 hours does not carry an adverse prognosis, whereas NSVT that occurs beyond several hours after admission does, particularly in patients with prior MI. NSVT in the setting of AMI occurs in 1% to 7% and possibly in as many as 75% of patients (Figure 57-1).[52] NSVT occurring 24 hours after AMI carries a worse prognosis than NSVT occurring within the first 24 hours following AMI (Figure 57-2). This is contrary to the commonly held belief that arrhythmias occurring within the first 48 hours following MI do not carry an adverse long-term prognosis. NSVT in the setting of healing MI (7 to 10 days following MI) is also associated with a poorer prognosis. Aside from β-blockers, antiarrhythmic therapy is not currently recommended for either early or late post-MI asymptomatic NSVT. Electrophysiology testing is not currently recommended for risk stratification of NSVT in the first several weeks after AMI but is considered "reasonable" for risk stratification in patients with remote MI, NSVT, and left ventricular ejection fraction (LVEF) 40% or less.[53]

Ventricular Tachycardia, Polymorphic Ventricular Tachycardia, and Ventricular Fibrillation

The incidence of documented "early" sustained monomorphic VT (SMVT) within the first 48 hours of AMI is in the range of 2% to 3% in STEMI and less than 0.9% in NSTEMI.[39,45,54] It may indicate extensive myocardial damage and serve as an

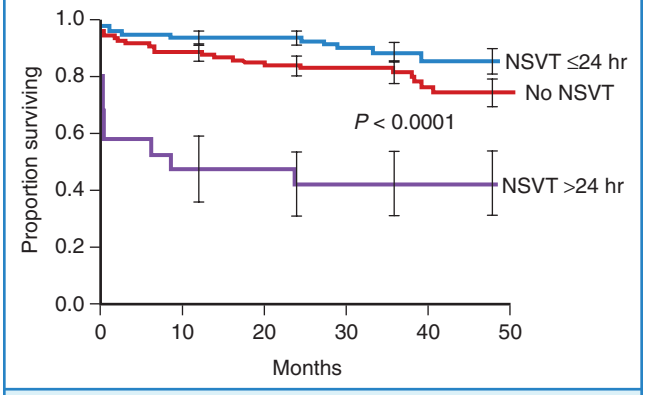

FIGURE 57-1 Kaplan-Meier survival curves for control and case patients stratified by time to occurrence of nonsustained ventricular tachycardia (*NSVT*) ≤24 hours from presentation (from time of admission). Patients with NSVT >24 hours after presentation had poorer survival rates ($P < .0001$) than the other two groups. *(From Cheema A, Sheu K, Parker M, et al: Nonsustained ventricular tachycardia in the setting of acute myocardial infarction: Tachycardia characteristics and their prognostic implications,* Circulation *98[19]:2030–2036, 1998.)*

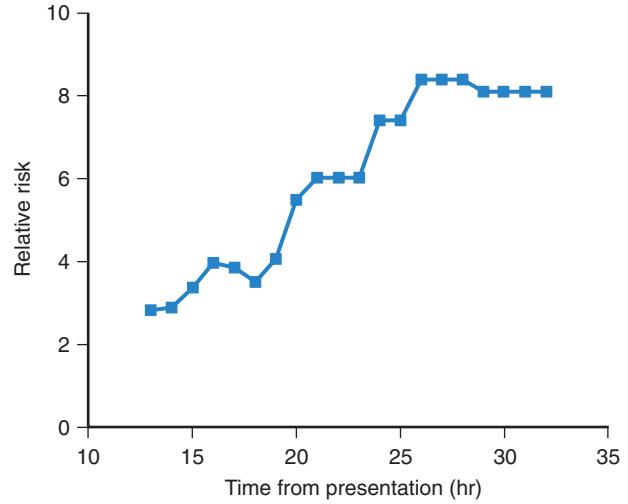

FIGURE 57-2 Plot of relative risk of nonsustained ventricular tachycardia using various time cutoffs from presentation. All time cutoffs <13 hours were significant. *(From Cheema A, Sheu K, Parker M, et al: Nonsustained ventricular tachycardia in the setting of acute myocardial infarction: Tachycardia characteristics and their prognostic implications,* Circulation *98[19]:2030–2036, 1998.)*

independent predictor of mortality.[54,55] As discussed above, arrhythmia mechanisms undergo dynamic changes in the early minutes and hours after onset of ischemia and may involve both re-entry (within ischemic areas of slowed conduction and increased refractoriness) or non–re-entrant mechanisms (triggered activity or increased automaticity). SMVT, however, implies stability of the ventricular depolarization pattern, which is most readily provided by a stable re-entry circuit. Thus, it is likely that SMVT, even in the early hours following MI, occurs in the presence of an already established permanent substrate (developing necrosis or pre-existing scar). Electrolyte abnormalities or ischemia that can cause the events that initiate re-entry (PVCs, NSVT) should be corrected; however, SMVT should be addressed as it would be even in the absence of these factors. From the currently available data, it is unclear that SMVT can be lumped together with other early post-MI arrhythmias in terms of its effect on the long-term prognosis—as most studies have not analyzed it separately from VF, polymorphic VT, or NSVT. In the GUSTO-I (Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries) study, patients with early (<48 hours) sustained VT had a 7.1% 1-year mortality among 30-day survivors, compared with 6.1% in patients with "late" (>48 hours) VF, and 2.6% in patients without any early or late VT or VF.[39] Therefore, SMVT, occurring even "early" after MI, is generally considered by many experts to be an indicator of high risk for future arrhythmia and SCD, warranting further investigation and intervention.[53,56]

Polymorphic VT, which occurs in 0.3% to 2% of patients, may be a marker of ongoing ischemia; therefore, it can often be effectively managed by anti-ischemic interventions. It is more often seen in patients who also develop VF.[57] In general, efforts are made to correct potential triggering factors such as hypokalemia, hypomagnesemia, abnormal serum calcium, or bradycardia (in those with bradycardia or pause-dependent onset).[53] In a case series of 11 patients with polymorphic VT, none had sinus bradycardia, but 3 of 11 had a sinus pause preceding the onset.[58] None had prolonged Q-T interval, hypokalemia, or abnormal serum magnesium or calcium. Nine of eleven had signs of recurrent ischemia immediately before arrhythmia onset. VF occurs in 3.7% of all acute STEMIs in the first 48 hours, and this is likely an underestimation, as prehospital events are not included.[39,41] Of these, most VF episodes occur within the first 4 hours (3.1%).[41] When all VF events, before and after 48 hours, were included, VF was found to occur in 6.7% of STEMI patients and in 1.3% of NSTEMI patients.[39,45] In the first 4 hours of admission, VF was more likely to occur in the setting of hypokalemia, low blood pressure, larger infarct size, current smoking, and a younger age. VF was more common in inferoposterior infarcts, possibly because of greater autonomic upset. The association of initial bradycardia with early fibrillatory risk fits with the observation that vagal overactivity may precede VF. VF at all stages of infarct evolution is more common in patients with larger infarcts as determined by serial cardiac enzyme measurements.[59]

Traditionally, *primary VF* has referred to VF that occurs during the first 48 hours of an uncomplicated MI (without recurrent ischemia or heart failure), and in the GISSI (Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico)-2 trial, it was associated with increased in-hospital mortality; however, no statistically significant association with post-discharge mortality (1-year mortality of those who survived to hospital discharge) was observed. These effects of early ventricular arrhythmias on early mortality were confirmed in the percutaneous coronary intervention era.[60,61] In contrast, *nonprimary VF* (VF occurring in the setting of recurrent ischemia or heart failure or beyond the first 48 hours following MI) was associated with marked increases in both 30-day mortality and 6-month mortality.[41] In the GUSTO trial, all "late" (>48 hours following MI) sustained VT, VF episodes, or both were associated with markedly increased long-term mortality at 1 year among 30-day survivors.[39] More recently published data from the GUSTO-V trial found that "early" VT or VF (<48 hours) was associated with increased in-hospital mortality but not with 1-year mortality among 30-day survivors[42]; however, all arrhythmias (VF, all VT) were pooled in this analysis. The temporal cutoff between "early" and "late" arrhythmias at 48 hours following MI is arbitrary to some extent; data to suggest that this should be at 24 hours or even earlier exist[52]; clearly, decisions should be individualized and based on expert evaluation and judgment. Moreover, additional tools for risk stratification are needed, and this is an area of active investigation; in the future, these may include a combination of electrophysiological testing, genetic evaluation, scar imaging, autonomic evaluation, and so on.

Preliminary data from a post hoc analysis suggest that ranolazine, an antianginal that inhibits the late inward Na^+ current, may decrease the incidence of VT or VF (as well as SVT or AF), but this requires further study.[62] A large pooled analysis has suggested that early administration of intravenous β-blockers in acute myocardial infarction may decrease the mortality and incidence rates of VF, but the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) performed on 46,000 patients with AMI did not show the mortality benefit of this intervention.[63,64]

In summary, the available data on the outcomes of ventricular arrhythmias in AMI have limitations. These data come mostly

from thrombolytic trials, retrospective analyses, limited numbers of events, and analyses of multiple types of arrhythmia, rather than specific arrhythmias, pooled together. Mainly on the basis of large thrombolytic trials, "early" sustained VF or polymorphic VT occurring within the first 24 to 48 hours of an uncomplicated AMI is associated with increased in-hospital and 30-day mortality but appears to have little effect on long-term mortality in patients surviving hospital discharge; however, this may be because high-risk patients die during their initial hospital stay. Conversely, all sustained ventricular arrhythmias that are "late" (>24 to 48 hours following MI) or in the context of complicated MI and any sustained monomorphic VT are considered indicators of high risk of arrhythmia and SCD, and patients are considered survivors of cardiac arrest. The temporal cutoff between "early" and "late" arrhythmias is unclear and may be close to 24 hours or even earlier. Occasionally, complete revascularization may be achievable with sufficient treatment—in the absence of prior MI, residual scar, SMVT, or systolic dysfunction—but most of these patients should be considered for defibrillator implantation, and expert, individualized decisions should be made. Detailed acute and chronic management guidelines for ventricular arrhythmias associated with AMI have been published.[2,3,53,56]

Supraventricular Arrhythmias in the Setting of Acute Ischemia

Incidence

Holter monitoring has revealed that 15% of patients recovering from MI have supraventricular tachycardia, ranging from single atrial premature beats (APBs) to sustained AF during their hospital stay.[65] The prevalence of SVT increases during the first month after MI. Overall, the incidence of AF in AMI in the modern era is 7.8% to 28%.[66-71]

Mechanism of Atrial Fibrillation During Acute Myocardial Ischemia

The pathophysiology of AF that occurs in the course of AMI has many components. Inflammation (pericarditis), changes in hemodynamics (atrial stretch and dilation), and atrial ischemia may all play a role.[72-75] Following significant ventricular damage, end-diastolic volume and pressure rise, causing an increase in atrial pressure and wall tension. This predisposes to AF and also explains the close relationship between heart failure and AF in the setting of MI. In an angiographic study, AF that occurred during inferior MI was shown to more likely occur in the setting of an occluded proximal left circumflex artery, with or without right CAD, if it was combined with impaired perfusion of the AV nodal artery.[76] AF did not occur in patients with right coronary artery occlusions if the circumflex artery was unobstructed. In a series of 266 patients, all 12 who developed atrial arrhythmias had inferior infarction. In the vast majority of these patients, the sinus node artery was distal to the site of right coronary occlusion, which suggests that sinus node ischemia may also play a role.[77] Evidence of atrial infarction in the 12-lead electrocardiogram (ECG; manifesting as PR-segment displacement) may also predict the onset of AF during AMI.[78] Other risk factors include advanced age, the presence of congestive heart failure, three-vessel coronary disease, right coronary artery (RCA) occlusion, female gender, anterior Q-wave MI, previous MI, and previous coronary artery bypass graft (CABG).[66,79]

Consequences of Atrial Fibrillation During Acute Myocardial Infarction

The development of AF results in the loss of atrial contraction and rapid, irregular heart rates, which, in turn, will cause impaired diastolic filling and increased myocardial oxygen demand. Atrial contraction is an important component of ventricular filling, particularly in failing hearts. In the ischemic canine heart, induced AF was shown to cause a reduction in cardiac output, a fall in mean aortic pressure, and a fall in mean myocardial blood flow.[80] This may precipitate a vicious downward spiral, with AF exacerbating heart failure, which, in turn, promotes AF. Both will increase the ischemic burden and the likelihood of ventricular arrhythmias.

In patients who sustain an AMI, hospital mortality is significantly higher in those with AF than in those without it (Figure 57-3).[66,68,69,71,72] It has been suggested that AF may be a risk factor for VF.[81] AF occurs in patients with signs of heart failure and larger infarctions. In large-scale trials, the negative impact of AF has been shown to be independent of other variables.[70,79] However, it is possible that the increase in in-hospital mortality is restricted to those patients with new-onset AF (after admission) rather than pre-existing AF (see Figure 57-3).[70,82]

Bradyarrhythmias in the Setting of Acute Ischemia

High-degree atrioventricular (AV) block is seen in a significant proportion of patients presenting with acute inferior MI. The incidence of advanced (second-degree and third-degree) AV block in the thrombolytic era ranges from 5.6% to 3.7% of all AMI patients.[83] In inferior wall MI, the reported incidence ranges from 7.3% to 9.8% of patients developing advanced AV block to 13% of patients having complete heart block, compared with 3.2% advanced AV block in patients with acute anterior wall infarction.[84-86]

All studies examining patients with heart block after infarction have found an association with a greater degree of myocardial damage, whether measured by cardiac enzymes, echocardiography, or nuclear scintigraphy.[85,87-90] As it has long been recognized that heart block is most prevalent in patients with inferior wall MI (two- to threefold increase compared with anterior AMI patients), the majority of studies were done in this population of patients.[84,86] Within this group, right ventricular involvement also appears to be associated with the development of advanced AV block.[88]

Patients with inferior MI and coexisting left anterior descending coronary artery obstruction have a sixfold greater chance of developing heart block in the acute phase of infarction than do patients with inferior infarction without such obstruction.[91] The site of left anterior descending artery occlusion is usually proximal to the origin of the first septal perforator. These findings suggest that the proximal AV conduction system has a dual arterial blood supply from both the right and left anterior descending coronary arteries and may explain the transient behavior of heart block and lack of necrosis of the AV node seen in many patients with inferior MI. A histopathologic study of hearts with posteroinferior MI has shown a strong correlation with atrial infarction in the region of the inputs to the AV node but a lack of correlation with infarction of the specialized conducting system.[92]

Patients with inferior MI with second-degree AV block generally have block of the Wenckebach type (Mobitz type I), whereas Mobitz type II second-degree AV block is typically associated

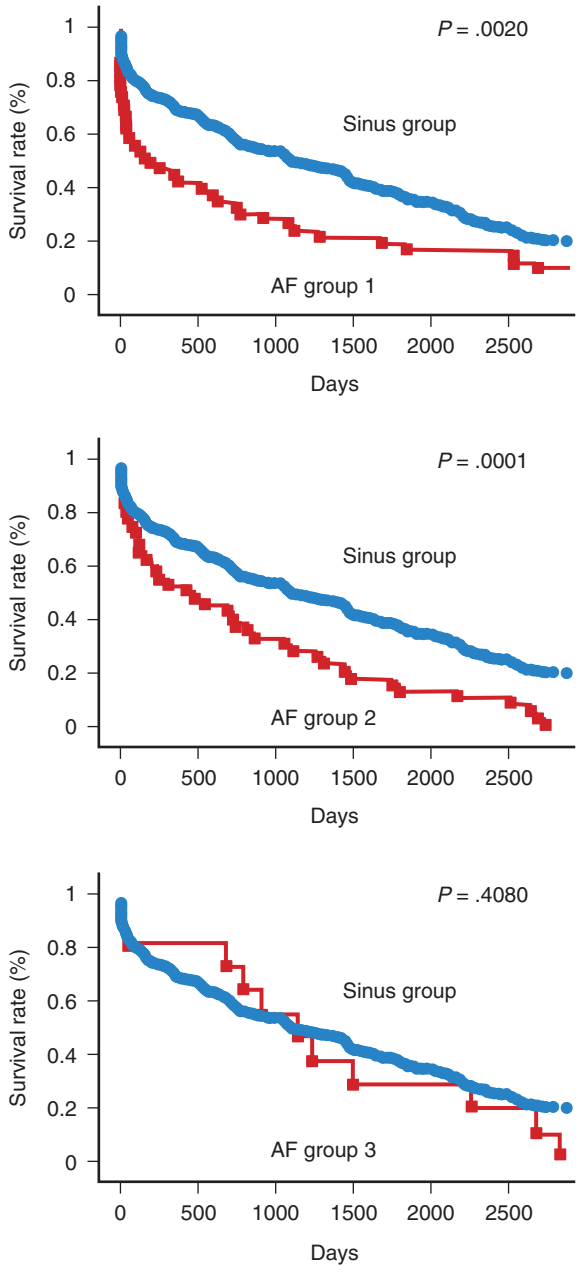

FIGURE 57-3 Kaplan-Meier analysis of cumulative survival rates for patients with myocardial infarction during 8-year follow-up. Survival rates are stratified by presence or absence of atrial fibrillation (AF). These patients were divided into AF group 1 (45 patients who developed AF within 24 hours of onset of acute myocardial ischemia [AMI]; 5 ± 2 hours, range 1 to 15), AF group 2 (41 patients who developed AF 24 hours after onset of AMI; 6 ± 4 days, range 2 to 14), and AF group 3 (14 who developed AF before the onset of AMI). The remaining 939 patients were classified as sinus patients. *(From Sakata K, Kurihara H, Iwamori K, et al: Clinical and prognostic significance of atrial fibrillation in acute myocardial infarction,* Am J Cardiol *80:1522–1527, 1997.)*

with anterior wall MI. Occasionally, complete heart block (CHB) may occur with acute inferior MI caused by RCA occlusion and concurrent left coronary disease resulting in poor collateral flow but is generally transient. As it is caused by AV nodal ischemia, it typically presents with a narrow junctional escape rhythm and asymptomatic bradycardia. In contrast, second-degree and complete AV block during anterior AMI are generally infranodal. The onset of CHB can be abrupt, without warning, frequently in the first 24 hours, and the escape rhythm has wide QRS and is unstable. CHB in this setting is associated with very high mortality (up to 80%), likely caused by extensive MI.

In the setting of inferior infarction, patients with CHB have higher mortality; more episodes of VF or tachycardia; and sustained hypotension, pulmonary edema, pericarditis, and atrial fibrillation than do patients without heart block.[71,84,85,89,90] In contrast, in those with inferior MI who survive to hospital discharge, the presence of heart block has no effect on long-term mortality.[84,85,89]

Differences between patients who develop heart block early and those who develop it late in the course of their AMI do exist. Different studies, however, reveal conflicting data. Sclarovsky et al reported that patients who develop early advanced block—defined as that occurring with continuing hyperacute changes of AMI on the ECG—had CHB that was of short duration, was unresponsive to atropine, and often required pacemaker therapy.[93] Symptoms of syncope, heart failure, and cardiogenic shock were frequently present. Patients with late block typically had second-degree heart block of longer duration, had a positive response to atropine, and rarely required pacemaker therapy. The mortality rate was high in the early group (23%) compared with that of the late group (7%). In another study, using a 6-hour cutoff time limit from admission, patients with inferior MI were divided into those who developed second- or third-degree block early and late.[94] In the early group, all patients had transient AV block that appeared suddenly, disappeared by 24 hours, and displayed a positive response to atropine. In the late group, heart block was often preceded by first-degree block, lasted longer, had a relatively fast ventricular escape rhythm, and had little response to atropine. A third study, dividing patients on the basis of AV block appearing before or after 24 hours from admission, found no significant difference in hospital mortality.[95]

The mechanisms responsible for AV block during acute inferior MI would, therefore, appear to be multiple and related to the time course. Along with acute necrosis of the perinodal atrial myocardium or specialized conduction tissue, increased parasympathetic tone is a factor that is usually postulated; however, persistence of AV block after atropine administration is frequently observed. It has been demonstrated that endogenously released adenosine in the oxygen-deprived myocardium can cause AV block.[96] Thus, not surprisingly, it has been reported that aminophylline may be successful in restoring sinus rhythm in atropine-resistant patients with inferior infarction.[97-99]

Arrhythmias in Chronic Coronary Artery Disease

Patients with chronic CAD may develop ventricular arrhythmias during episodes of AMI. In addition, prior MI may provide a nidus for the development of tachyarrhythmias in the setting of chronic CAD. It is often challenging for the clinician to determine the extent to which chronic infarction or acute ischemia contributes to a particular arrhythmic event. However, a determination as to whether ischemia, chronic scarring, or a combination is responsible for arrhythmia in patients with CAD can help direct therapy.[100]

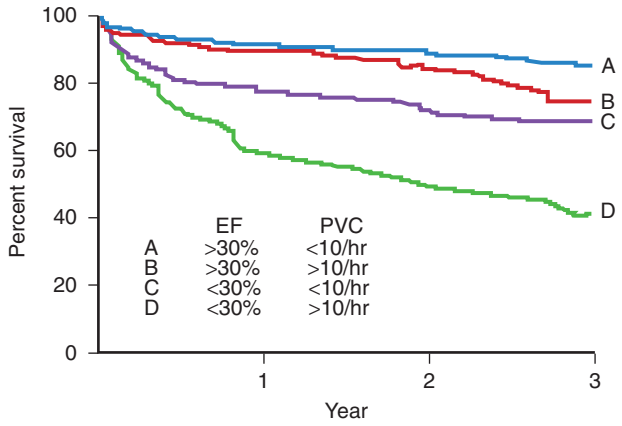

FIGURE 57-4 Influences of ejection fraction (*EF*) and premature ventricular contraction (*PVC*) frequency on mortality in patients after myocardial infarction. *(From Bigger J, Fleis J, Kleiger R, et al: The relationships among ventricular arrhythmias, left ventricular dysfunction, and mortality in the two years after myocardial infarction,* Circulation *69:250–258, 1984.)*

Patients with chronic CAD may present with PVCs and NSVT that are either asymptomatic or associated with mild palpitations.[101] However, more serious forms of arrhythmia include nonsustained polymorphic VT, nonsustained or sustained monomorphic VT, and VF (Figure 57-4).

Mechanisms

The mechanisms of ventricular arrhythmias in patients with chronic coronary disease are diverse. The contribution of ischemia to arrhythmogenesis were discussed earlier. The development of myocardial fibrosis can lead to VT through a number of mechanisms. In both experimental models and human tissue, activation in healed infarction takes a slow, "zigzag" course, in which fibrous septa separate bundles of muscle and the gap junction number is decreased to produce slow conduction, creating the substrate for re-entry.[102-106] This phenomenon is associated with the recording of fractionated electrograms. The poor coupling among surviving myocardial cells may also allow the development of unidirectional block.

The mechanism of beats initiating ventricular tachyarrhythmias in patients with CAD remains unclear. In experimental models, triggered activity, abnormal automaticity, and re-entry due to functional block in sinus rhythm all have occurred in healed MI.[7] One clinical study of monomorphic VT has demonstrated that the QRS configuration of the beat that initiates sustained VT is similar to that occurring in sustained tachycardia. This suggests the possibility that the initiating beat is, indeed, re-entrant. One careful intraoperative three-dimensional mapping study of NSVT has been performed. Ten patients with NSVT in the setting of CAD were studied, and in one half of these patients, a re-entrant circuit was identified, and in the other half, a focal origin to the tachycardia appeared to be present.[107,108] However, even with advanced mapping techniques, the mechanisms of isolated PVCs, short episodes of NSVT, and the beats that initiate VT or VF have not been established with certainty in humans because of the difficulty in mapping isolated premature beats and because of the inferential nature of the evidence required to determine the mechanism of isolated premature beats.

More is known about the mechanism of sustained VT. Mapping studies in the electrophysiology laboratory and in the operating room and inferential studies using pacing techniques suggest that most cases of myocardial sustained VT in patients or experimental animals with healed MI are caused by re-entry.[5,102,109,110] Both fixed and functional blocks may contribute to sustained VT in patients with coronary disease.[33,106,111] A number of experimental studies have suggested that VF, at least shortly after its origin, is caused by re-entry.[112-115] The mechanism of initiating beats is unclear and likely not uniform, but VF in most experimental models appears to be maintained by re-entry. Further study of human VF is required to better clarify these mechanisms.

Ventricular Arrhythmias in Chronic Coronary Artery Disease

Premature Ventricular Contractions and Nonsustained Ventricular Tachycardia

Brief episodes of ventricular arrhythmia (PVCs or episodes of NSVT lasting 15 beats or less) in patients with chronic CAD may be important for two reasons: (1) They may indicate an adverse prognosis, or (2) they may cause intolerable symptoms.

PVCs are common in patients with healed MI.[116] The prevalence of PVCs varies in different studies and is weakly related to the extent of left ventricular dysfunction. In the GISSI-2 study, over 64% of patients had some PVCs, as seen on Holter monitors, and obtained a mean of 17 days following MI.[20] Twenty percent had more than 10 PVCs per hour, and 6.8% had NSVT. In this and other studies, frequent PVCs (>10 premature beats per hour) and complex ventricular arrhythmias were shown to increase the risk of sudden cardiac death.[20,117-119] By multivariate analysis, the presence of more than 10 PVCs per hour in a week was associated with an odds ratio of 1.62 for total mortality and an odds ratio of 2.22 for sudden mortality.[20] In this study, NSVT (defined as three beats to 30 seconds of VT) was associated with an increased mortality during follow-up by univariate analysis but not multivariate analysis. In contrast, only a small fraction of post-infarction patients (<10%) with tachyarrhythmias during Holter monitoring die suddenly, which gives a low positive predictive value. However, the European Infarct Study Group showed that fewer than 1% of patients in whom Holter monitor readings were normal died suddenly during the first year after MI.[120] Thus, the absence of arrhythmia in the healing phase of infarction predicts a good prognosis.

The anatomic and electrophysiological characteristics of MI evolve in the first several months after infarction.[121] Thus, findings on the prognostic significance of spontaneous arrhythmia shortly after infarction may not apply to healed infarction. Data on patients with PVCs or NSVT after the subacute phase of MI are based on studies of smaller numbers of patients and are inconsistent.[101] Nonetheless, several studies have used NSVT in association with left ventricular dysfunction and inducible sustained VT at electrophysiological testing to risk stratify patients with chronic CAD.[122,123]

The symptomatology associated with PVCs and NSVT may vary dramatically from patient to patient. However, no data have suggested that the extent of cardiac awareness has any prognostic significance. Because of these observations, symptoms are an imperfect guide to the treatment of PVCs in NSVT.

In general, the primary goal of treatment of PVCs and NSVT is suppression of symptoms. Unless patients are experiencing palpitations, dizziness, or heart failure (the latter two being uncommon but real symptoms of frequent PVCs), specific antiarrhythmic therapy for the suppression of PVCs is not indicated. In patients whose symptoms are significant enough to warrant therapy, a trial of β-blockers or calcium channel blockers is an appropriate first approach. Therapy for PVCs is discussed in a later section.

Monomorphic Ventricular Tachycardia

The clinical presentation of monomorphic VT is also variable. Some patients, especially those with large MIs, may have stable monomorphic VT at slow rates that is hemodynamically reasonably well tolerated. This is particularly true if patients are treated with antiarrhythmic drugs. In other patients, sustained VT is associated with presyncope, syncope, or cardiac arrest.[124] A variety of factors may affect the hemodynamic tolerance of sustained VT. These include the rate of the tachycardia, atrial synchrony, and left ventricular function.[125]

Data on the prognostic significance of patients with sustained, hemodynamically well-tolerated VT are conflicting.[126] It is most likely that while presentation with sustained, hemodynamically well-tolerated VT does indicate a substantial increase in the risk of sudden cardiac death, this risk may not be as high as in patients who present with a cardiac arrest. However, in an AVID (Antiarrhythmics Versus Implantable Defibrillators) substudy, patients who presented with sustained, well-tolerated VT had at least as poor a prognosis as patients presenting with cardiac arrest.[127] This subanalysis of a large, prospective study strongly suggests that patients who present with stable VT are also at risk for life-threatening tachyarrhythmias.

Cardiac Arrest and Ventricular Fibrillation

Despite a decline in the incidence of cardiovascular disease, 300,000 to 350,000 sudden deaths still occur every year in the United States.[53,128] The precise arrhythmia initiating sudden death in patients with chronic CAD (and in patients with other types of structural heart disease) is not completely known. Data from the Seattle Heart Watch Project and from several Holter monitoring studies from the late 1970s and 1980s have demonstrated that VT, VF, or both may be responsible for 40% to 50% of cardiac arrests and that Q-wave infarction is only present in 20% of these.[129,130] It has been postulated that in many of the 40% of patients with cardiac arrests who present with asystole, this actually represents a terminal rhythm following prior VT or VF.[131,132] Holter monitoring data support this contention.[133] One study by Luu and colleagues in patients with advanced heart failure demonstrated that bradycardia, electromechanical dissociation, or both may be responsible for 50% or more of cardiac arrests, but it is likely that these data do not apply to the majority of patients having a cardiac arrest.[134] Thus, most patients with chronic CAD who suffer cardiac arrest have VT or VF as the mechanism of death. Even in the absence of infarction, ischemia may be a frequent contributing factor.[135]

Polymorphic Ventricular Tachycardia

Polymorphic VT is defined as VT in which QRS configuration varies from beat to beat but a clearly defined QRS complex (as opposed to ventricular flutter or fibrillation) can be detected. Polymorphic VT is often associated with a congenital or acquired long QT syndrome, which is rarely caused by CAD.[136] However, isolated case reports have described long QT syndrome and associated polymorphic VT in patients with coronary disease. AMI can also classically cause polymorphic VT. However, some patients with healed MI may also present with nonsustained polymorphic VT or episodes of polymorphic VT degenerating to VF.[133,137]

Electrical Storm

Implantable cardioverter-defibrillators (ICDs) have led to the recognition of a subset of patients who develop multiple recurrent episodes of VT or VF leading to cardiac arrest, multiple ICD shocks, or both in a short period. *Electrical storm* has been defined as two or more VT or VF episodes occurring in less than 24 hours, but some patients develop numerous arrhythmic episodes. The etiology of such temporal clustering of VT or VF episodes is not completely clear. Arrhythmic substrate (scar) is almost always present in patients with CAD, but other types of arrhythmia susceptibility may play a role, as VF storms also develop in patients without apparent structural heart disease ("idiopathic") or with channelopathies. An arrhythmic storm in a patient with CAD should prompt a search for and treatment of AMI, particularly with polymorphic VT storm. Other possible precipitating factors include electrolyte abnormalities, drug toxicity, biventricular pacing, bradycardia or pauses (pause-dependent VT initiation), and decompensated heart failure (though it is frequently difficult to discern cause from effect in these situations).[138,139] The autonomic nervous system appears to play a prominent role, and this is illustrated by the observed effectiveness of autonomic modulation (β-blockers, sedation, sympathetic nervous block, or stellate ganglion resection) and by the transient nature of the storm.[53,140] It is likely that arrhythmia, hemodynamic instability, ICD shocks, or all result in sympatho-adrenergic activation, which, in turn, sets up a vicious spiral. On the basis of anecdotal reports and case series, the treatment of VT or VF storm, includes correcting the precipitating factors, intravenous β-blockers and other antiarrhythmic drugs, overdrive pacing (for pause-dependent VT), autonomic modulation, and ablation.[53] When monomorphic PVC triggers of VF are observed, these are frequently mapped to infarct border zones and are preceded by Purkinje-like potentials, which suggests that they are caused by locally enhanced automaticity of the Purkinje fibers.[141] Ablation of these PVCs by targeting the Purkinje-like potentials has been reported to be effective.[141] While the short-term prognosis can be improved with treatment, the longer-term prognosis is unclear and is generally guarded.[142-144]

Exercise-Induced Arrhythmias

Exercise-induced arrhythmias represent a potentially life-threatening problem in patients with CAD. While physical training in general decreases total mortality from heart disease, the relative risk of sudden death during exercise is increased.[145] Data on the prognostic significance of PVCs or NSVT during exercise are controversial.[146] PVCs and NSVT that occur during exercise are likely multifactorial, including myocardial ischemia, the presence of scar substrate, and catecholamine and other autonomic effects. The extent to which exertional ventricular arrhythmias indicate myocardial ischemia in patients with

CAD and their prognostic significance are still not completely clear.

Treatment

Detailed guidelines and reviews of the available literature on management of ventricular arrhythmias in CAD have been published, and they provide an excellent source.[53,56]

Although the treatment of serious ventricular arrhythmias is also discussed elsewhere in this text, a few principles regarding the approach to less serious arrhythmias in patients with chronic CAD may be useful. The two potential indications for treatment of patients with premature beats and NSVT are (1) improvement of symptoms and (2) prolongation of life. Most patients with isolated premature beats or NSVT are asymptomatic or have mild symptoms that are not clinically or hemodynamically significant. Holter monitoring studies have shown that up to 10% of older patients, even in the absence of structural heart disease, may have ventricular premature beats and that ventricular premature beats are extremely common after MI. This confirms that most patients with ventricular ectopy do not need treatment. However, a subset of patients with PVCs or NSVT have highly symptomatic palpitations or impairment in left ventricular function because of extremely frequent ventricular ectopy.[147,148] In these patients, suppression of ventricular premature beats to control symptoms may be appropriate. In addition, ablation is an excellent option for patients who have significant symptoms, frequent PVCs resulting in cardiomyopathy, or PVCs that act as triggers for VF, as it offers the potential for long-term cure of arrhythmia.[141]

The therapy for arrhythmias is discussed in detail in a separate chapter. β-Blockers should be the therapy of first choice for the suppression of symptoms related to PVCs or NSVT in patients with CAD. Studies cited above have suggested that spontaneous ventricular arrhythmias may represent an independent risk factor for the prediction of sudden death in patients who have coronary disease and healed MI. Suppression of PVCs with antiarrhythmic drugs has failed to result in a decrease in mortality rates; encainide and flecainide have been, in fact, shown to increase mortality in the Cardiac Arrhythmia Suppression Trial (CAST).[149] Amiodarone probably has a neutral effect on mortality in patients with CAD, although a meta-analysis suggested that amiodarone may decrease mortality by approximately 10% when administered prophylactically.[150-152]

Dofetilide, a K^+ channel–blocking drug, has also been studied extensively in patients with prior MI and heart failure. Although the prognosis is not improved, dofetilide does not cause increased mortality in patients with CAD.[153] However, dofetilide may have adverse effects in patients with baseline prolonged Q-T intervals.[154] The available data do not support the routine use of antiarrhythmic drugs for the prevention of sudden death in patients with coronary disease and spontaneous arrhythmias. However, if drug therapy is required to suppress symptoms in patients with CAD, β-blockers, dofetilide, or amiodarone are all drugs that have been shown to have a beneficial or neutral effect on survival.

Atrial Fibrillation and Chronic Coronary Artery Disease

CAD is commonly cited as one of the principal causes of atrial fibrillation (AF). Although the role of AMI in the development of AF is undisputed (see earlier), the role of chronic CAD is much more controversial. It is likely that CHF, which is one of the potential consequences of CAD, predisposes to AF, but CAD itself does not.[155-157]

Advanced Atrioventricular Block and Chronic Coronary Artery Disease

Chronic CAD can be a cause of AV block, although it is a much less common cause than idiopathic fibrosis of the conduction system. AV block in coronary disease is usually related to extensive infarction and necrosis of the distal conduction system rather than ischemia. In 30 patients aged 45 to 65 years with CHB who were referred for pacing and had no symptoms of coronary disease, coronary angiography disclosed the presence of severe CAD in 13 patients (43%). Myocardial revascularization was undertaken in 6 patients but did not result in any sustained improvement in AV conduction.[158] In contrast, multiple case reports in the literature have suggested that ischemia of the AV node may have a role in patients with paroxysmal or exercise-induced heart block having complete resolution of their symptoms after angioplasty of a lesion in the RCA.[159-162] However, most patients with AV block and coronary disease require pacemaker therapy.

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CHAPTER 58

Nonischemic Dilated Cardiomyopathy: Diagnosis and Management

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Introduction and Classification

Nonischemic dilated cardiomyopathy (DCM) is the most common form of cardiomyopathy. The hallmarks of DCM are left or often biventricular enlargement with mostly global systolic hypokinesis, although some regionally more pronounced contraction abnormality may be present.[1] Several specific diseases of the heart muscle (e.g., infectious agents, chemotherapeutic agents, metabolic disorders, genetic mutations) present as clinical manifestations of DCM, which presumably represents a final common pathway of myocardial damage.[1] Therefore, DCM is defined as a primary cardiomyopathy with a mixed etiologic background. Nevertheless, a considerable overlap between the different groups must be taken into account (e.g., myocarditis and DCM caused by an infectious agent). The definitions of DCM and ischemic cardiomyopathy, with the latter defined as a "dilated cardiomyopathy with impaired contractile performance not explained by the extent of the coronary artery disease or ischemic damage," have been controversial in the past.[2] The recent definitions and the classification of cardiomyopathies by the American Heart Association do not include pathologic myocardial processes and dysfunction caused directly by other cardiovascular diseases; hence the term *ischemic cardiomyopathy* is not supported any more.[1] Therefore, although this term continues to be used, it is not directly linked to the previous definition but is meant to reflect any type of left ventricular dysfunction caused by coronary artery disease.[2] In this context, one should concede that without coronary angiography, the diagnosis of significant coronary artery disease solely based on clinical findings in patients with heart failure often fails to identify this cause.[3]

Epidemiology and Survival

The incidence of DCM varies from 5 to 8 cases per 100,000 per year, and the prevalence is estimated to be 1:2500, with approximately 10,000 deaths and 46,000 hospitalizations in the United States.[1] Heart failure caused by DCM represents a major health issue and is the primary indication for heart transplantation.[4] Usually, DCM presents for the first time in patients between 18 and 50 years of age; however, children and older adults may also be affected.[5] Furthermore, it develops almost three times more often in blacks and males than in whites and females, with apparently lower survival rates in blacks than in whites for unknown reasons.

Mortality and Causes of Death in Dilated Cardiomyopathy

The natural history of DCM is diverse. Some patients have minimal or no symptoms, whereas symptomatic patients usually experience a progressive deterioration; however, a minority improves with a reduction in cardiac size and longer survival. In some patients, clinical and functional improvements may occur years after the initial manifestation of symptoms. Recently, better survival rates have been achieved with improvement in medical (angiotensin-converting enzyme [ACE] inhibitors, β-blockers, aldosterone inhibitors) and device therapy (implantable cardioverter-defibrillator [ICD] and cardiac resynchronization therapy).[6] A difference between nonfamilial and familial cases of DCM could not be demonstrated.[7] Yet, the prognosis of some secondary cardiomyopathies, for example, the human immunodeficiency virus (HIV)–related form, is particularly bad. Irrespective of the underlying cause, patients with DCM are prone to ventricular arrhythmias and sudden cardiac death (SCD), with DCM representing the substrate for approximately 10% of all SCDs in adults.[8] Approximately 20% of patients with DCM will die within 1 year after diagnosis; in most of them, the cause is SCD.[9]

Genetics and Other Causes of Dilated Cardiomyopathy

DCM presumably represents a final common or toxic pathway that is the end result of myocardial damage caused by different mechanisms.[1] In about 50% of cases, patients are described as having "idiopathic" DCM because an etiologic cause or secondary reason cannot be identified.[10] Several specific diseases of the heart muscle or metabolism can lead to the clinical manifestations of DCM. Evidence that many idiopathic cases still result from inherited abnormalities is increasing, since 20% to 50% of these may be familial on further evaluation.[11] Genetically determined familial DCM, which refers to the presence of two or more family members with DCM, can be subdivided into at least four phenotypes[12]: isolated DCM, DCM with involvement of the cardiac conduction system, DCM with concomitant skeletal myopathy (with or without conduction disease), and DCM with sensorineural deafness.[13] The most common mode of inheritance is autosomal dominant (56%), and in 5% to 10%, it is linked to the X chromosome.[14-16] Autosomal recessive or mitochondrial forms of DCM are uncommon.[17-19] Molecular analysis has revealed a great

number of genes and chromosomal loci leading to DCM. The pathophysiological effects are a malfunction of force generation (because of mutations in sarcomeric protein genes) and of force transmission (due to mutations in cytoskeletal protein genes).[20,21] Other causes of DCM as a secondary cardiomyopathy may be infectious disease, a tachycardiomyopathy, inflammatory cardiomyopathy, deposition diseases, medications, toxins, endocrinologic disorders, neuromuscular diseases, rheumatologic diseases, postpartum cardiomyopathy, uremia, and others.[1] These causes have to be taken into account whenever a genetic cause is considered.

Pathophysiology of Arrhythmias in Dilated Cardiomyopathy

Multiple mechanisms contribute to the development of ventricular arrhythmias in patients with dilated cardiomyopathy.[22] Autopsy studies have shown substantial left ventricular subendocardial scarring in 33% of patients and patchy areas of replacement fibrosis in 57%, accompanied by increased perivascular fibrous tissue and perimyocytic fibrosis in the left ventricle.[23] This may be the substrate for re-entry. Other factors such as hypokalemia, hypomagnesemia, and ischemia caused by the occlusion of small intramyocardial arteries by thrombosis or emboli may serve as triggers for ventricular arrhythmias.[24] An elevated sympathetic tone and increased circulating catecholamines may also favor ventricular re-entrant arrhythmias.[25,26] Stretch-induced shortening of the ventricular refractory period may support the development of re-entry.[27]

A distinct form of ventricular arrhythmia in DCM is bundle branch re-entrant ventricular tachycardia (BBRVT). A macro–re-entry, which usually employs the right bundle branch as the antegrade limb and the left bundle branch as the retrograde limb, leads to a rapid ventricular tachycardia (VT). Apart from BBRVT, macro–re-entrant VTs involving myocardial scars at the mitral annulus are frequently observed.[28,29]

Ventricular arrhythmias in patients with chronic heart failure caused by DCM may be provoked by non–re-entrant mechanisms such as abnormal automaticity and triggered activity.[30,31] The occurrence of triggered activity and the causative early after-depolarizations is promoted by prolonged repolarization and prolonged action potential predominately induced by the downregulation of repolarizing potassium channels.[32,33] Focal ventricular arrhythmias originating from the distal Purkinje system are often nonsustained.[30,31] Although frequently occurring in patients with DCM, VT is not the only cause of SCD in these patients. At end-stage heart failure, bradycardia and electromechanical dissociation are very common causes of SCD.[34]

Risk Stratification for Arrhythmic Death in Dilated Cardiomyopathy

Left Ventricular Function

In patients with nonischemic DCM, overall mortality is associated with left ventricular dysfunction, but only a few studies have investigated the relationship between left ventricular function and SCD directly.[35] The combination of severely reduced left ventricular function (left ventricular ejection fraction [LVEF] <30%) and nonsustained VT was used to identify the highest-risk subgroup.[36] Since reduced LVEF was an inclusion criterion in all ICD prophylaxis trials, it is a prominent feature of guidelines for ICD therapy and a cornerstone in daily clinical practice.[37,38] Nevertheless, the majority of SCDs occur in patients with less severely reduced left ventricular function, which highlights the limited sensitivity of this parameter.[39]

Electrocardiography

In patients with nonischemic DCM, the presence of left bundle branch block (LBBB) has been associated with a worse outcome. The Vesnarinone Trial (VEST) and other studies confirmed a significant association between the degree of QRS duration and mortality.[40-42] However, other studies were not able to demonstrate a significant association between intraventricular conduction delay and SCD.[36,43,44] The Defibrillators in Nonischemic Cardiomyopathy (DEFINITE) trial was not able to show an association between QRS duration and all-cause mortality.[45] The Sudden Cardiac Death–Heart Failure Trial (SCD-HeFT), which enrolled patients with ischemic cardiomyopathy and those with nonischemic cardiomyopathy, reported that ICD therapy yielded a greater mortality reduction in patients with QRS duration ≥0.12 seconds, but specific information on the relationship between QRS duration and mortality reduction in patients with nonischemic cardiomyopathy has not been presented.[46] In a retrospective analysis of the Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy (CHF-STAT) database, Iuliano et al identified a prolonged QRS duration of ≥0.12 seconds as an independent predictor of total mortality and SCD in patients with heart failure.[47] The role of atrial fibrillation remains controversial, too. Survival rates may be reduced by increased thromboembolic events or ventricular arrhythmias, which may be evoked by an increased dispersion of refractoriness caused by long-short cycle lengths.[48]

Spontaneous Ventricular Arrhythmias

The prevalence of spontaneous ventricular arrhythmias in patients with DCM is very high.[49] Polymorphic premature ventricular contractions, ventricular pairs, and nonsustained VT are very common, with increasing prevalence of nonsustained VT and increasing severity of heart failure symptoms. The positive predictive value of these arrhythmias is relatively low, ranging from 20% to 50%, yet the negative predictive value has been cited as high as 95.5%.[50,51] In the absence of a treatment modality with proven efficacy, specific treatment for nonsustained VT is not indicated, except in the rare circumstances of symptomatic, frequent, or very rapid episodes leading to hemodynamic instability.

Heart Rate Variability, Baroreflex Sensitivity, and Heart Rate Turbulence

Heart rate variability (HRV) and baroreflex sensitivity (BRS) provide indirect (i.e., through their effects on the sinus node) measures for the autonomic effects in the ventricle that may be important in the pathophysiology of VT and SCD. Most studies using HRV, BRS, and heart rate turbulence (HRT) as predictors of adverse arrhythmic events have been conducted in patients after the occurrence of myocardial infarction (MI). One of the few

studies in DCM was conducted by Rashba et al.[52] They reported a significant difference in mortality rates in a substudy of the Defibrillators in Nonischemic Cardiomyopathy (DEFINITE) trial. With decreasing standard deviation of normal R-R intervals (SDNN) as a measurement of HRV, an increase in total mortality was noted: Among 70 patients with SDNN longer than 113 ms, no deaths occurred. However, in 69 patients with SDNN between 81 and 113 ms, the mortality rates was 7%; in 72 patients with SDNN less than 81 ms, the mortality rate was 10%. Similar results were seen when the predictive value of SDNN was examined for the composite endpoint of SCD and appropriate ICD shock. On the basis of this study, the authors suggested that patients with nonischemic DCM and preserved HRV have a good prognosis and may not benefit from ICD prophylaxis and that lower levels of SDNN were associated with a progressively increased mortality risk.

HRT describes the short-term fluctuation in sinus cycle length that follows a ventricular premature beat.[53,54] It has been postulated that it measures vagal responsiveness similar to BRS. It is a potentially attractive risk factor, as it can be performed with a relative small number of premature beats from 24-hour Holter electrocardiogram (ECG). In the Marburg Cardiomyopathy Study (MACAS), low HRT was a multivariate predictor of transplant-free survival, but not of arrhythmic events.[55] In the same study, blunted BRS, which identified patients with a higher cardiac mortality after a recent MI in the Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) study, was not a predictor of arrhythmic events.[56]

Microvolt T-Wave Alternans

The term *microvolt T wave alternans* (MTWA) refers to the presence of beat-to-beat changes in T-wave amplitude that are not detectable on the surface ECG. Bloomfield et al showed that in patients with left ventricular dysfunction (EF ≤40%), the negative predictive accuracy of MTWA was very high (≥98% at a follow-up of 2 to 3 years) regardless of the etiology of the cardiomyopathy, with significantly lower event rates in patients with normal MTWA test results.[57] In contrast, a prospective substudy of the SCD-HeFT trial, which tested the predictive value of MTWA in 490 (n = 250 nonischemic heart failure) of the 2521 patients with an EF 35% or less and New York Heart Association (NYHA) class II or III heart failure randomized to ICD therapy, amiodarone, or placebo, did not show any significant differences in the composite primary end point of the first occurrence of any of the following: SCD, sustained VT or ventricular fibrillation (VF), or appropriate ICD discharge.[58] In conclusion, further evidence is needed in the specific setting of nonischemic DCM.

Cardiac Magnetic Resonance Imaging

Wu et al recently observed that late gadolinium enhancement detected by cardiac magnetic resonance imaging (MRI) strongly predicts adverse cardiac outcomes, including adverse arrhythmic events in patients with nonischemic DCM, supporting earlier reports by Assomull et al.[59,60] In the latter study, midwall fibrosis was detected in 35% of patients with nonischemic DCM by late gadolinium enhancement. This finding was associated with a higher rate of the predefined combined primary endpoint of all-cause death and hospitalization for a cardiovascular event and also predicted secondary outcome measures of SCD or VT.

Electrophysiological Testing

The role of electrophysiological testing (i.e., programmed ventricular stimulation) in risk stratification in patients with nonischemic cardiomyopathy and no history of sustained ventricular arrhythmias has been addressed in nine studies.[61-69] The small numbers of patients in each study, the low rate of arrhythmia induction and reproducibility, and the low subsequent arrhythmia event rates have made it difficult to draw consistent conclusions. Therefore, programmed ventricular stimulation is not recommended for risk stratification in patients with nonischemic cardiomyopathy. However, Rolf et al showed that in a relatively large cohort of 160 patients with DCM who received ICDs for secondary prophylaxis, the induction of polymorphic VT or VF in contrast to the induction of monomorphic VT was associated with a high risk of subsequent fast ventricular arrhythmias during a mean follow-up of 53 months (Table 58-1). Nevertheless, a subgroup of patients with secondary prevention and sufficiently low risk that would render ICD therapy unnecessary could not be identified. A prospective study in a DCM population with primary prevention, possibly in combination with other risk factors, might be helpful in refining the indications for ICD therapy.

Management

Vasodilator Therapy

Treatment with ACE inhibitors improves ventricular function, patient well-being and reduces hospital admissions for worsening heart failure. Moreover, a reduction of total mortality and SCD by ACE inhibitor therapy has been demonstrated. Detailed information on the treatment of acute and chronic heart failure, which is beyond the scope of this chapter, is provided in current guidelines.[85,86]

Antiadrenergic Therapy

The pathophysiological rationale for antiadrenergic therapy in patients with DCM is to antagonize the heightened sympathetic tone and circulating catecholamines, thereby reducing the various adverse effects of these regulatory mechanisms. Several studies have shown symptomatic improvement in patients with DCM treated with β-blockers. To date, no specific studies have demonstrated the benefit of β-blockers for the prevention of SCD in DCM. However, several studies have shown that the reduction in mortality is similar in patients with ischemic heart failure or nonischemic heart failure. The Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) randomized 3991 patients with an LVEF 40% or less and NYHA class II to IV to metoprolol or placebo in addition to conventional therapy. It showed a reduction in overall mortality by 34% at 21 months (30% in patients without coronary artery disease).[87] Of note, a 41% reduction in SCD was observed. Similarly, the CIBIS II study showed in 1327 patients (160 patients with nonischemic DCM) in NYHA class III and IV randomized to bisoprolol, a significant 34% reduction in total mortality at 1.3 years because of a 44% reduction in SCD mortality rates.[88] Taking these studies and the results of the Carvedilol Heart Failure Study Group (HFSG) trial into account, all patients with congestive heart failure should receive β-blockers and ACE inhibitors unless contraindicated.[89]

Table 58-1 Programmed Ventricular Stimulation in Idiopathic Dilated Cardiomyopathy with a History of Ventricular Arrhythmia

AUTHOR	YEAR	PATIENTS (n)	INDICATION	LVEF (%)	ICD (%)	INDUCIBLE ARRHYTHMIAS		FOLLOW-UP (MONTHS)	AAD	AIT/VT (%)	SCD (%)	ARRHYTHMIC EVENTS DURING FOLLOW-UP		
						SMVT (%)	PVT/VF (%)					SMVT (%)	PVT/VF (%)	NON (%)
Naccarelli[71]	1982	39	VT	NA	—	33	NA	12–16	Yes*	28	5	25†	NA	NA
Poll[72]	1984	11	SMVT	30	—	82	NA	21	Yes*	18	36	56	NA	50
Poll[63]	1986	27	CA, VT	30	30	52	15	18	Yes*	15	30	57	—	44
Rae[73]	1987	38	CA, VT, syncope, NSVT	35	—	47	18	21	Yes*	NA	NA	NA	NA	NA
Liem[74]	1988	64	VT, VF	30	20	64	3	15	Yes*	NA	19	NA	NA	NA
Milner[75]	1988	19	VT, VF, syncope†	26	—	63	11	17	Yes*	21	32	50	100	50
Constantin[76]	1989	31	VT, VF, syncope	29	19	61	NA	13	Yes*	23	6	37	NA	17
Brembilla-Perrot[66]	1991	11	SMVT	33	—	73	NA	24	Yes*	9	36	50	NA	33
Chen[77]	1994	102	VT, VF	37	31	40	16	32	Yes*	63	14	6†	NA	29
Fazio[78]	1991	40	CA, syncope	33	100	53	NA	30	Yes*	62	13	82†	NA	29
Grimm[79]	1995	49	CA, VT, syncope	27	100	26	35	28	Yes*	51	4	NA	NA	NA
Bänsch[80]	2000	106	VT, VF, syncope, NSVT†	26	100	39	54	33	Yes	69	NA	NA	NA	NA
Russo[81]	2001	46	Syncope	25	100	21	16	17	Yes	33	2	44	43	22
Rankovic[82]	2002	54	VT, VF, misc	24	100	31	14	27	Yes	42	NA	62	33	41
Rinaldi[83]	2003	10	VT, VF	31	100	25	NA	28	Yes	60	NA	NA	NA	NA
Rinaldi[83]	2003	49	VT, VF	60	100	57	NA	28	Yes	27	NA	NA	NA	NA
Cuesta[84]	2003	40	CA, VT, syncope	29	93	53	25	≤30	Yes	63	3	95	30	22
Rolf[70]	2007	160	CA/VF, VT	34	100	19	31	53	No	34	6	27	66	28

AAD, *Antiarrhythmic drugs;* AIT, *adequate ICD therapy;* CA, *cardiac arrest;* ICD, *implantable cardioverter-defibrillator;* LVEF, *left ventricular ejection fraction;* NON, *noninducible;* PVT/VF, *polymorphic ventricular tachycardia/ventricular flutter/fibrillation;* SCD, *sudden cardiac death;* SMVT, *sustained monomorphic ventricular tachycardia;* VT, *ventricular tachycardia;* VF, *ventricular fibrillation;* NA, *not applicable.*

**Serial drug testing.*

†Studies did not clearly distinguish between SMVT and PVT/VF.

Modified from Rolf S, Haverkamp W, Borggrefe M, et al: Induction of ventricular fibrillation rather than ventricular tachycardia predicts tachyarrhythmia recurrences in patients with idiopathic dilated cardiomyopathy and implantable cardioverter-defibrillator for secondary prophylaxis, Europace *11:289–296, 2009.*

Antiarrhythmic Drugs

Since patients with DCM are prone to atrial and ventricular arrhythmias, antiarrhythmic drugs may be considered for treatment. However, most antiarrhythmic drugs may exhibit proarrhythmic effects and exacerbate the left ventricular dysfunction; the mortality rate may be increased when some class I or III antiarrhythmic drugs are used. Data from the Cardiac Arrhythmia Suppression Trial (CAST) on patients who have had MIs have been extrapolated to others with reduced left ventricular function and to those with structural heart disease in general.[90] Therefore, despite the fact that patients with DCM frequently have symptomatic as well as asymptomatic supraventricular and ventricular arrhythmias, treating them with class Ia and Ic drugs is not advised. This also applies to D-sotalol.[91-93] Proarrhythmia rarely occurs with amiodarone therapy, even in patients with depressed left ventricular function. Therefore, amiodarone is the most frequently used antiarrhythmic agent in patients with DCM. Of note, patients with nonischemic cardiomyopathy were underrepresented in most studies, except for the relatively small Amiodarone Versus Implantable Cardioverter-Defibrillator: Randomized Trial in Patients with Nonischemic Dilated Cardiomyopathy and Asymptomatic Nonsustained Ventricular Tachycardia (AMIOVIRT) and SCD-HeFT (Sudden Cardiac Death-Heart Failure Trial).[46,94] Since no placebo group was included in AMIOVIRT, the role of nonsustained VT for risk stratification in nonischemic DCM and the superior effectiveness of amiodarone compared with placebo remain unclear.

In the CHF-STAT (Congestive Heart Failure-Survival Trial of Antiarrhythmic Therapy), amiodarone proved to be more effective in patients with nonischemic cardiomyopathy versus those with ischemic cardiomyopathy with regard to survival without SCD or hospitalization.[95] However, a reduction in overall mortality or in mortality from SCD could not be demonstrated in the entire study cohort. The outcomes of patients as a function of NYHA class were not reported.

In contrast to this, in the Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA) trial, which was a randomized but open trial, all-cause mortality was reduced by 28% ($P < .03$), and mortality from SCD was reduced by 27% ($P = .056$) in the amiodarone treatment group.[96] Moreover, a higher percentage of patients improved by NYHA functional class. In comparison to the CHF-STAT, the GESICA trial included fewer patients with ischemic cardiomyopathy (39% vs. 72%) but a significant number of patients with Chagas disease. Hence, the positive results of the CHF-STAT in the case of patients with nonischemic DCM might be confirmed by GESICA. Nevertheless, these two trials present conflicting data on amiodarone treatment for patients with heart failure.

In the larger SCD-HeFT trial, which randomized patients with ischemic or nonischemic cardiomyopathy, an LVEF less than 36%, and a history of congestive heart failure to placebo, amiodarone, or an ICD, no significant difference was seen in all-cause mortality in the placebo group and the amiodarone group, but the ICD significantly reduced overall mortality. Of note, in SCD-HeFT, a relative 44% increase was seen in the risk of death in the amiodarone group compared with the placebo or ICD group among patients with NYHA III heart failure. Thus, although survival in the amiodarone and placebo arms of class II patients was identical, amiodarone was worse than placebo in class III patients (Figure 58-1).

Consistent with these findings from post hoc analyses, the Antiarrhythmic Trial with Dronedarone in Moderate to Severe CHF Evaluating Morbidity Decrease (ANDROMEDA) trial reported an increased early mortality related to the worsening of heart failure in patients with recent-onset heart failure or with aggravation of pre-existing heart failure.[97] After randomization of 310 patients with new or worsening heart failure to the multiple-channel blocker dronedarone (25.5% with nonischemic DCM) and 317 matched patients to placebo (32.5% with nonischemic DCM), the trial was prematurely terminated after a median follow-up of 2 months because of excessive mortality in the dronedarone group (8.1% vs. 3.8% in the placebo group). Post hoc subgroup analyses revealed that patients with more severely reduced left ventricular function were at higher risk of death associated with dronedarone treatment. These data are difficult to extrapolate to patients in stable heart failure.

In conclusion, antiarrhythmic drugs are not primarily indicated to improve the prognosis of patients with nonischemic cardiomyopathy. Mostly, they may be used in addition to ICD therapy to reduce ICD shock frequency and in the treatment of symptomatic atrial fibrillation.[38,98]

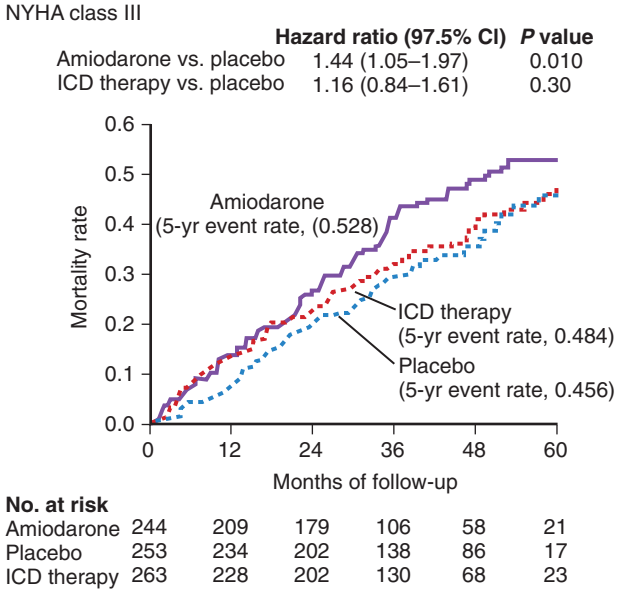


FIGURE 58-1 Kaplan-Meier estimates of death from any cause for the prespecified subgroup of New York Heart Association *(NYHA)* class III in the Sudden Cardiac Death–Heart Failure Trial. *CI*, Confidence interval; *ICD,* implantable cardioverter-defibrillator. *(Modified from Bardy GH, Lee KL, Mark DB, et al: Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure,* N Engl J Med *352:225–237, 2005.)*

Implantable Cardioverter-Defibrillator Therapy

The Amiodarone versus Implantable Cardioverter-Defibrillator Trial (AMIOVIRT) compared ICD therapy with amiodarone therapy in patients with nonischemic left ventricular dysfunction with a mean duration of 3 years and asymptomatic nonsustained VT.[94] According to calculations, 219 patients were required in each group for an 80% power to identify a reduction in total mortality from 20% to 10%. A difference in the primary endpoint of total mortality could not be demonstrated after enrollment of 103 patients and an average follow-up of 2 years (6 deaths in the

ICD group vs. 7 in the amiodarone group; $P = .8$). Thus, AMIOVIRT neither supported nor disproved the value of ICD therapy in this population. In contrast to AMIOVIRT, the Cardiomyopathy Trial (CAT) evaluated the significance of ICD therapy in patients with nonischemic left ventricular dysfunction after exclusion of significant coronary artery disease by angiography and recent onset of heart failure symptoms within 9 months or less before inclusion.[99] The primary endpoint of CAT was all-cause mortality. However, the observed mortality rate in the non-ICD group was markedly lower than the expected mortality rate (3.7% and 30%, respectively). Over a mean follow-up of 5.5 years, 30 deaths were observed (13 deaths in the ICD group, 17 in the control group; $P = .6$). The trial was terminated early owing to futility. Like AMIOVIRT, CAT was underpowered, so no consistent conclusions regarding the efficacy of ICD therapy in patients with nonischemic DCM could be drawn from this trial.

The Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial evaluated the efficacy of ICD therapy in comparison with no ICD therapy in 458 patients with nonischemic left ventricular dysfunction (LVEF ≤35%) with a history of heart failure NYHA functional class I to III.[45] Additionally, patients were required to have frequent premature ventricular beats (>10/hour) or nonsustained VTs. The absence of clinically significant coronary artery disease as the cause of the cardiomyopathy was confirmed by coronary angiography or by a negative stress imaging study. The mean ejection fraction (21%) was lower than that seen in CAT (24%) and SCD-HeFT (25%), and the average duration of heart failure was 2.8 years longer than that seen in CAT. During a mean follow-up of 29 months, 28 deaths occurred in the ICD group compared with 40 deaths in the control group, leading to a 35% relative reduction in mortality in the ICD group (95% confidence interval [CI] = 1.06 to 0.4; $P = .08$). In contrast, a significant reduction in SCD (80%; 95% CI = 0.06 to 0.71; $P = .006$) was observed.[45]

The SCD-HeFT compared the efficacies of ICD therapy, amiodarone, and placebo in 2521 patients with heart failure. The rate of heart failure medication use was higher in the SCD-HeFT than in other ICD studies. Patients with ischemic cardiomyopathy (52%) as well as those with nonischemic cardiomyopathy (48%) were enrolled. Patients randomly assigned to ICD therapy had a significantly lower risk of death compared with those assigned to amiodarone and placebo (28.9%) over 60 months with a relative risk reduction of 23% (95% CI = 0.62 to 0.96; $P = .007$). Moreover, the relative benefit of ICD therapy and the absolute reduction in mortality were similar in the ischemic cardiomyopathy group and the nonischemic cardiomyopathy group (21% vs. 27%, and 7.3% vs. 6.5%, respectively). However, statistical significance was not reached for the use of ICDs in patients with nonischemic DCM. In contrast to the DEFINITE trial, in which patients in NYHA functional class III derived the largest survival benefit from ICD therapy, this group of patients had no apparent reduction in the risk of death with ICD therapy (Figure 58-2).

It is not entirely clear whether a history of syncope in patients with nonischemic DCM is a prognostic indicator because these patients were excluded from the large randomized controlled ICD trials. Phang et al retrospectively compared 108 consecutive non-ICD patients with DCM and a mean LVEF of 27% presenting with syncope with 71 consecutive patients with DCM who presented with sustained ventricular arrhythmias, with regard to freedom from any ventricular arrhythmias or life-threatening arrhythmias and all-cause mortality.[100] They were not able to show any significant differences between the groups in the three

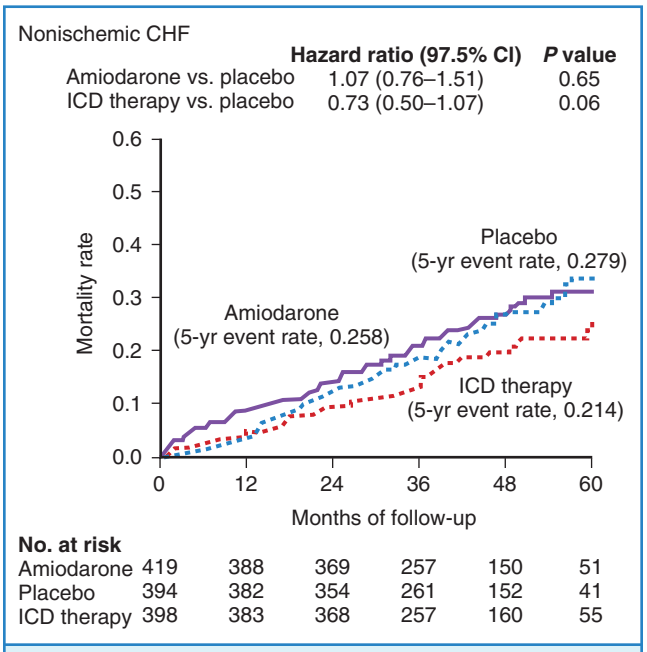


FIGURE 58-2 Kaplan-Meier estimates of death from any cause for the prespecified subgroup of nonischemic CHF in the Sudden Cardiac Death–Heart Failure Trial. *CHF,* Congestive heart failure; *CI,* confidence interval; *ICD,* implantable cardioverter-defibrillator. *(Modified from Bardy GH, Lee KL, Mark DB, et al: Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure,* N Engl J Med *352:225–237, 2005.)*

outcome parameters during the mean follow-up of 44 months. This supports the results of Knight et al, who found no differences in the rates of appropriate ICD shocks in 14 patients with DCM, unexplained syncope, and a negative electrophysiological study compared with 19 patients with DCM and previous cardiac arrest.[101] Therefore, patients with DCM presenting with syncope are probably a high-risk group, with event rates similar to those of patients with DCM presenting with sustained arrhythmias, and should be considered for ICD therapy.

Biventricular Pacing

The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial randomized 1520 patients in NYHA class II and III and a QRS duration of 0.12 seconds or greater to cardiac resynchronization therapy (CRT) plus ICD (CRT-D, 595 patients), to CRT alone (617 patients), or to optimal medical treatment (308 patients).[102] In 45% of these patients, nonischemic cardiomyopathy was present. The primary endpoint was a composite of death from or hospitalization for any cause. Secondary endpoints were all-cause mortality and cardiac morbidity. The risk of the combined primary endpoint was reduced by 34% in the CRT group ($P < .002$) and by 40% in the CRT-D group ($P < .001$ for comparison with optimal medical therapy alone). CRT reduced the risk of the secondary endpoint of death from any cause by 24% ($P = .059$), and CRT-D reduced the risk by 36% ($P = .003$). The absolute risk reduction of 7% in the CRT-D group indicates that 15 patients need to be treated with a CRT-D device in order to prevent 1 death over 12 months. Of note,

patients with nonischemic cardiomyopathy received a greater benefit from biventricular pacemaker–defibrillator therapy than did patients with ischemic cardiomyopathy when comparing the secondary endpoint of all-cause mortality. Most of the baseline parameters of patients in the COMPANION trial were similar to other trials of ICD in heart failure. However, the annual mortality rate in the control group in the COMPANION trial was higher than in other trials. The 12-month mortality rate in the medical therapy group in the CARE-HF trial was 12.6% versus 19% in the COMPANION trial.[102,103]

Recently, the Multicenter Automatic Defibrillator Implantation Trial–CRT (MADIT-CRT) trial randomized 1820 patients in NYHA functional class I or II (85% in class II), with an EF 30% or less and a QRS duration 0.13 seconds or longer to CRT-D or ICD therapy in a 3:2 fashion (1089 and 731 patients, respectively). A significant reduction in the primary endpoint death from any cause or a nonfatal heart failure event (whichever came first) was shown in patients with ischemic cardiomyopathy as well as in those with nonischemic cardiomyopathy, strengthening the earlier results of the smaller Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) study, which was not significant with regard to its primary endpoint of patients' conditions worsening because of the smaller sample size and shorter follow-up.[104-106] However, a longer follow-up of the European subgroup of the REVERSE trial showed a significant improvement in the clinical status of patients in the CRT-ON group and a significantly reduced risk of first hospital stay or death and reversed left ventricular remodeling.[107] The observed significant reduction of the primary endpoint in the MADIT-CRT trial was driven by a reduction of heart failure events primarily in a prespecified subgroup of patients with a QRS duration of 0.15 seconds or longer, whereas no effect on mortality was seen in this early heart failure cohort, which can be considered as a low-risk group (3% annual mortality rate) (Figure 58-3).

The Resynchronization Therapy In Narrow QRS (RETHINQ) study addressed the question whether CRT will increase peak oxygen consumption during exercise in patients with NYHA class III heart failure, an EF of 35% or less, a QRS interval of less than 0.13 seconds, and evidence of mechanical dyssynchrony on echocardiography. The trial failed to reach this primary endpoint.[108]

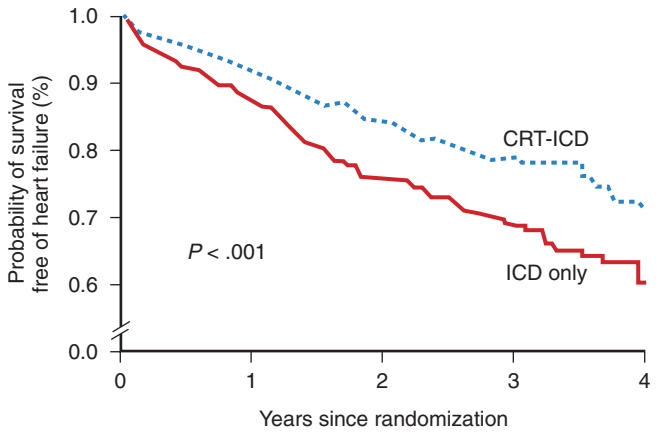
Catheter Ablation

Catheter ablation of ventricular arrhythmias in patients with nonischemic DCM has been used after the authors' initial case report with increasing frequency.[109,110] The authors' initial experience had demonstrated that monomorphic VT in nonischemic DCM may be caused by a fixed reentry circuit, similar to what occurs after myocardial infarction. Modern modalities such as electroanatomic mapping systems, irrigated tip catheters, and the integration of three-dimensional computed tomography or MRI may facilitate ablation. However, entrainment and pace mapping are still important cornerstones in the ablation procedure. Apart from the three-dimensional information, MRI with late enhancement may also provide information about the localization and extent of myocardial scars, which might be involved in the VT circuit. Integration of this additional information into modern mapping systems might add to the procedural success rate. The percutaneous epicardial approach is increasingly used also in patients with nonischemic cardiomyopathy because approximately one third of VTs in this setting can only be ablated successfully epicardially (Figure 58-4).[28]

As mentioned above, bundle branch re-entry (BBR) is a distinct arrhythmia in DCM, which may lead to syncope and even SCD because of degeneration into ventricular fibrillation by destabilizing the dysfunctional left ventricle. Baseline examination often shows LBBB and a prolonged His-ventricular interval. In case of BBR VT, ablation of the right bundle branch is curative, but in some patients, an implantation of a permanent dual-chamber pacemaker or defibrillator is subsequently necessary, since abolition of BBR VT does not prevent SCD caused by VF. Depending on the degree of left ventricular dysfunction and the NYHA functional class, a placement of a biventricular ICD should be considered.

Conclusion

Patients with nonischemic DCM are prone to recurrent ventricular arrhythmias and are at risk of SCD. Identification of subgroups of patients who are at high risk or low risk has proven difficult, partly because of an under-representation of these patients in



No. at risk (probability of survival)

ICD only	731	621 (0.89)	379 (0.78)	173 (0.71)	43 (0.63)
CRT-ICD	1089	985 (0.92)	651 (0.86)	279 (0.80)	58 (0.73)

FIGURE 58-3 Kaplan-Meier estimates of the probability of survival free of heart failure in the Multicenter Automatic Defibrillator Implantation Trial–CRT trial. *CRT,* Cardiac resynchronization therapy; *ICD,* implantable cardioverter-defibrillator. *(Modified from Moss A, Hall W, Cannom D, et al: Cardiac-resynchronization therapy for the prevention of heart-failure events,* N Engl J Med *361[14]:1329–1338, 2009.)*

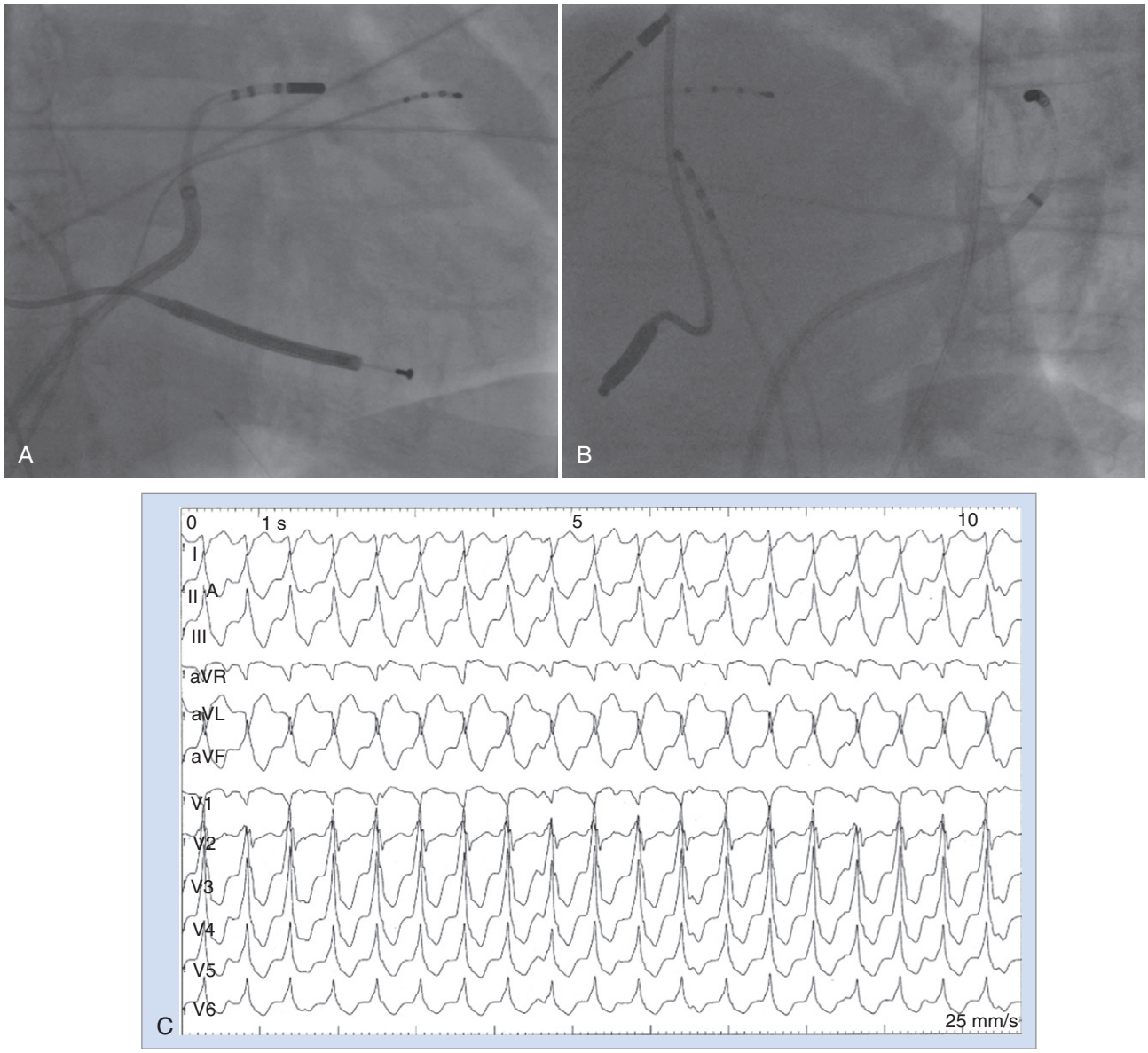


FIGURE 58-4 Epicardial catheter ablation in a patient with nonischemic dilated cardiomyopathy and recurrent monomorphic ventricular tachycardia. **A** and **B,** Posteroanterior and left anterior oblique views, respectively. **C,** Surface electrocardiogram showing monomorphic ventricular tachycardia.

large randomized clinical trials. Nevertheless, the increasing use of β-blockers, ACE inhibitors, angiotensin blockers, and device therapy (ICD; CRT) has led to an improvement in overall survival of patients in clinical trials. Owing to this, the increased prevalence of DCM and long-term consequences such as recurrent VT and frequent ICD shocks pose a growing problem. Refinement in medical therapy and adjunctive therapy such as catheter ablation is therefore necessary. Apart from this, risk stratification in nonischemic DCM needs to be improved so that a more individualized therapy can be developed and the sparse medical resources can be distributed more efficiently.

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CHAPTER 59

Arrhythmogenic Right Ventricular Cardiomyopathy

Alison R. Muir and Perry M. Elliott

Arrhythmogenic right ventricular cardiomyopathy (ARVC), also known as *arrhythmogenic right ventricular dysplasia* (ARVD), is a genetically determined disease of the heart muscle, which is characterized histologically by cardiomyocyte loss and replacement with fibrous or fibro-fatty tissue and clinically by arrhythmia, sudden death, and heart failure. In many individuals, the disease is caused by mutations in genes that encode components of the intercalated disc of cardiomyocytes. Clinically, ARVC is difficult to diagnose, requiring integration of data from family members, electrocardiography, and a range of imaging techniques. The major management issues in ARVC are prevention of sudden cardiac death (SCD) and treatment of symptomatic arrhythmia and heart failure.

Historical Summary

In 1977, Fontaine et al reported six cases of sustained ventricular tachycardia (VT) in patients with enlarged right ventricles and hypothesized that this was a specific cardiomyopathy limited to the right ventricle.[1] In 1982, Marcus et al coined the term *arrhythmogenic right ventricular dysplasia* (ARVD) in a report of 24 cases characterized by left bundle branch block (LBBB) pattern VT, wall motion abnormalities of the right ventricle (RV), and replacement of the RV myocardium by adipose and fibrous tissue.[2] In 1994, the first diagnostic criteria were proposed. These were based on the identification of structural abnormalities, fibro-fatty replacement of the RV myocardium, particular electrocardiographic changes, arrhythmias of RV origin, and familial disease.[3] This led to ARVC being recognized as a separate entity in the reclassification of cardiomyopathies by the World Health Organization/International Society and Federation of Cardiology Task Force on the definition and classification of cardiomyopathies.[4-6] Over the following decade, various groups mapped familial forms of ARVC to a number of genetic loci.[7-14] Molecular studies in a recessive, syndromic variant of ARVC, known as *Naxos disease*, led to identification of the first disease-causing mutation in the gene encoding plakoglobin, a major constituent of cell-to-cell junctions.[15] This paved the way for the discovery of disease-causing mutations in other genes encoding desmosomal proteins in the more common autosomal dominant forms of ARVC.

Epidemiology

The prevalence of ARVC in the general population is difficult to determine because of the challenging nature of the diagnosis.[16] Various studies in Europe reported a prevalence of between 0.6 and 4.4 per 1000, but it is unclear whether these represent local interest and expertise in the disease. ARVC is reported as a cause of SCD in 11% to 27% of individuals 35 years old and younger.[17-19] The prevalence in one Italian cohort was found to be higher in athletes (22.4%) compared with nonathletes (8.2%).[17]

Pathology

In the original descriptions of ARVC, the RV cavity was described as typically dilated, and the RV wall was characterized by dome-shaped aneurysms, occurring particularly on the anterior surface of the pulmonary infundibulum, at the RV apex, and on the inferior wall of the RV (subsequently called the *triangle of dysplasia*). These macroscopic changes were accompanied by abundant subepicardial fat and endocardial thickening (Figure 59-1). Microscopically, a marked decrease was seen in myocardial fibers, with replacement of the myocardium with fatty tissue and fibrosis (Figure 59-2).[2] Later, pathologic descriptions divided ARVC into two morphologic patterns: the fatty and the fibro-fatty forms, but fatty infiltration alone can be a normal phenomenon, particularly in older women.[20]

In a small series of studies on deaths due to ARVC, apoptosis was reported in 75% of patients.[21] These apoptotic myocardial cells were frequently found in the myocardium not affected by fibro-fatty replacement, which suggests that this could account for the progressive loss of myocardial cells in the disease.[22] Endomyocardial biopsy in 20 patients with ARVC revealed apoptosis in 35%. This was significantly associated with acute symptoms and signs and with a shorter (<6 months) clinical history, indicating that apoptosis is present in an early symptomatic stage of the disease.[23]

A number of postmortem reports described inflammatory infiltrates, and endomyocardial biopsies from some ARVC cases have been found to contain enteroviral ribonucleic acid (RNA) with homology to Coxsackie virus type B.[21,24-26] In one study, the frequency of viral deoxyribonucleic acid (DNA) was similar to that observed in patients with myocarditis or dilated cardiomyopathy (DCM), but subsequent reports have failed to confirm these findings, perhaps reflecting patient selection and differences among inherited, sporadic, and nonfamilial forms of ARVC.[27]

Left Ventricular Involvement

By definition, the right ventricle must be affected to make a clinical diagnosis of ARVC, but it is well recognized that left

ventricular involvement is common in patients fulfilling current diagnostic criteria. Pathologic examination of heart specimens at autopsy or cardiac transplantation revealed macroscopic and microscopic evidence of left ventricular involvement in up to 76% of cases.[28] More recently, a study of 200 patients with ARVC undergoing cardiac magnetic resonance imaging (MRI) reported biventricular involvement in 56% of cases and predominant left-sided disease in 5%.[29]

Genetics

Systematic family studies have shown that ARVC is inherited in up to 50% of cases. Numerous genetic loci have been identified in linkage studies (Table 59-1). The mode of transmission is usually autosomal dominant, with a male predominance of 3:1 and variable penetrance, but autosomal recessive forms are well recognized and have provided the first insights into the genetic basis of ARVC.[16]

The first disease causing mutation was identified in an autosomal recessive syndromic form of ARVC, characterized by diffuse palmo-plantar keratoderma, woolly hair, and cardiomyopathy (Naxos disease).[30] A homozygous mutation was identified in the gene encoding plakoglobin, a member of the armadillo protein family found in the adherens and desmosomal junctions between cardiac myocytes.[15] Mutations in another desmosomal protein,

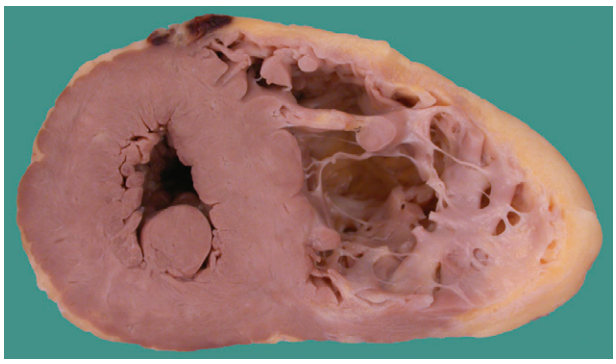

FIGURE 59-1 Dilated right ventricle with partial replacement of free wall by a mixture of fat and white fibrous tissue. The patient, aged 31 years, died suddenly while exercising. *(Courtesy Dr. Margaret Burke, Consultant Pathologist, Royal Brompton and Harefield Trust, UK.)*

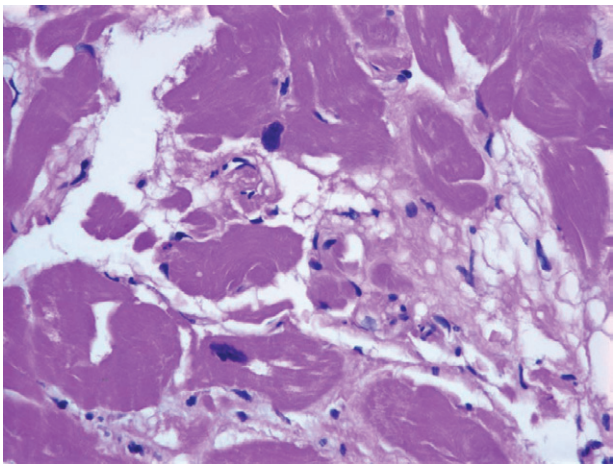

FIGURE 59-2 Histologic specimen of the right ventricle showing fatty infiltration and fibrosis within the myocardium. *(Courtesy Dr. Antonis Pantazis, Consultant Cardiologist, University College London Hospitals, UK.)*

Table 59-1 Chromosomal Location, Involved Genes, and Mutations in Arrhythmogenic Right Ventricular Cardiomyopathy

LOCUS	CHROMOSOMAL LOCATION	MODE OF INHERITANCE	PHENOTYPE	GENE	NUMBER OF MUTATIONS
ARVD1	14q23–q24	Autosomal dominant		*TGFβ3*	2
ARVD2	1q42–q43	Autosomal dominant	CPVT	*hRYR2*	<10
ARVD3	14q12–q23	Autosomal dominant			
ARVD4	2q32.1–q32.3	Autosomal dominant			
ARVD5	3p23	Autosomal dominant			
ARVD6	10p12–p14	Autosomal dominant			
ARVD7	10q22	Autosomal dominant	Myofibrillar myopathy		
ARVD8	6p24	Autosomal dominant Autosomal recessive Autosomal recessive	DCM, keratoderma, and woolly hair (Carvajal syndrome) Pemphigous-like skin disorder, woolly hair	Desmoplakin	<15 1 1
ARVD9	12p11	Autosomal dominant Autosomal recessive		Plakophilin-2	>50 1
Naxos disease	17q21 18q12 18q12 17q21	Autosomal recessive Autosomal dominant Autosomal dominant Autosomal dominant	Non-epidermolytic palmoplantar keratoderma and woolly hair	Plakoglobin Desmoglein-2 Desmocollin-2 Plakoglobin	1 <25 <5 1

CPVT, *Catecholaminergic polymorphic ventricular tachycardia;* TGFβ3, *transforming growth factor β3;* hRYR2, *human ryanodine receptor;* DCM, *dilated cardiomyopathy.*

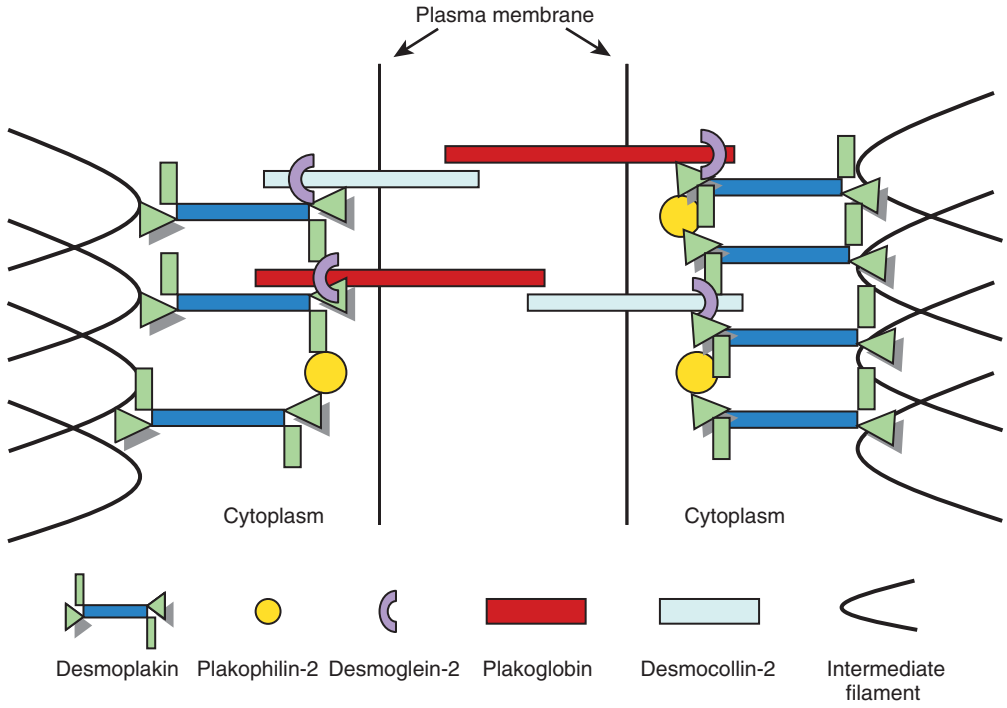

FIGURE 59-3 A schematic representation of the molecular desmosome. *(Data adapted from Green KJ, Gaudry CA: Are desmosomes more than tethers for intermediate filaments?* Nat Rev Mol Cell Biol *1:208–216, 2000.)*

desmoplakin, were subsequently identified in similar autosomal recessive syndromic forms of ARVC in South American and Arab families.[31,32] Since then, heterozygous mutations in genes encoding these and other desmosomal proteins have been identified in patients with nonsyndromic autosomal dominant forms of ARVC.

The Intercellular Junction

Intercalated discs are specialized structures that provide mechanical and electrical coupling between adjacent cardiomyocytes. The intercalated disc is made up of three distinct structures: (1) gap junctions, (2) adherens junctions, and (3) desmosomes. The *gap junction* mediates the transfer of ions between cells, whereas the *adherens junction* (composed of cadherins, β-catenin, and γ-catenin [plakoglobin]) mediates the transmission of force between cells. The *desmosome* also mediates mechanical attachment between cells by linking the desmosomal cadherins, desmocollin, and desmoglein with the intermediate filament cytoskeleton.[33,34] The intracellular components of the desmosomal cadherins interact with plakoglobin and plakophilin, which, in turn, bind to the N-terminal domain of desmoplakin, a plakin protein. The C-terminal of desmoplakin anchors desmin intermediate filaments to the cell surface.[35] Another protein of the plakin family, plectin, is also present in desmosomes and contributes to the mechanical strength of cells.[36,37] As well as providing cells with mechanical strength, the desmosome also plays an important role in tissue morphogenesis and differentiation.[38] A simplified schematic representation of the organization of the cardiac desmosome is shown in Figure 59-3.

In 2002, the first mutation in the autosomal dominant form of ARVC was reported. This was found in the plakoglobin-binding domain of desmoplakin, and mutations in this gene have been reported in 6% to 16% of probands.[14,39,40] Since then, heterozygous mutations have also been reported in plakoglobin, plakophilin-2 (PKP2), desmocollin-2 (DSC2), and desmoglein-2 (DSG2). PKP2 mutations are the most frequently found in patients with ARVC, with a reported prevalence between 27% and 43% of patents fulfilling diagnostic criteria.[41] Over 50 individual mutations have been identified to date, but studies have not as yet revealed consistent genotype-phenotype correlations. The mechanism by which mutations result in disease is also unclear. It is suggested that mutations increase the susceptibility of the myocardium to the damaging effects of mechanical stress, thereby predisposing to cardiomyocyte detachment, death, and eventual replacement by fibro-fatty tissue.[42] The predilection for the right ventricle has been explained by its thin wall and greater distensibility, but this is unlikely to be the sole explanation for disease in either ventricle.[43] As desmosomal proteins interact with many other proteins, including key components of the cellular cytoskeleton and intermediate filaments, it is possible that ventricular dysfunction occurs as the result of reduced cytoskeletal integrity and impaired force transduction.[37] Some desmosomal proteins (in particular plakoglobin) are also important signaling molecules that regulate the transcription of many other genes.[44] Finally, a reduction in the number and size of gap junctions may result in an electrical coupling defect, thus increasing the propensity to arrhythmia, and could explain the occurrence of sudden death in patients without significant morphologic changes Figure 59-4.[42]

Nondesmosomal ARVC

Two nondesmosomal genes have been linked to ARVC: (1) the cardiac ryanodine receptor (*hRYR2*) and (2) transforming growth factor β3 (*TGFβ3*). Mutations in *hRYR2* are more

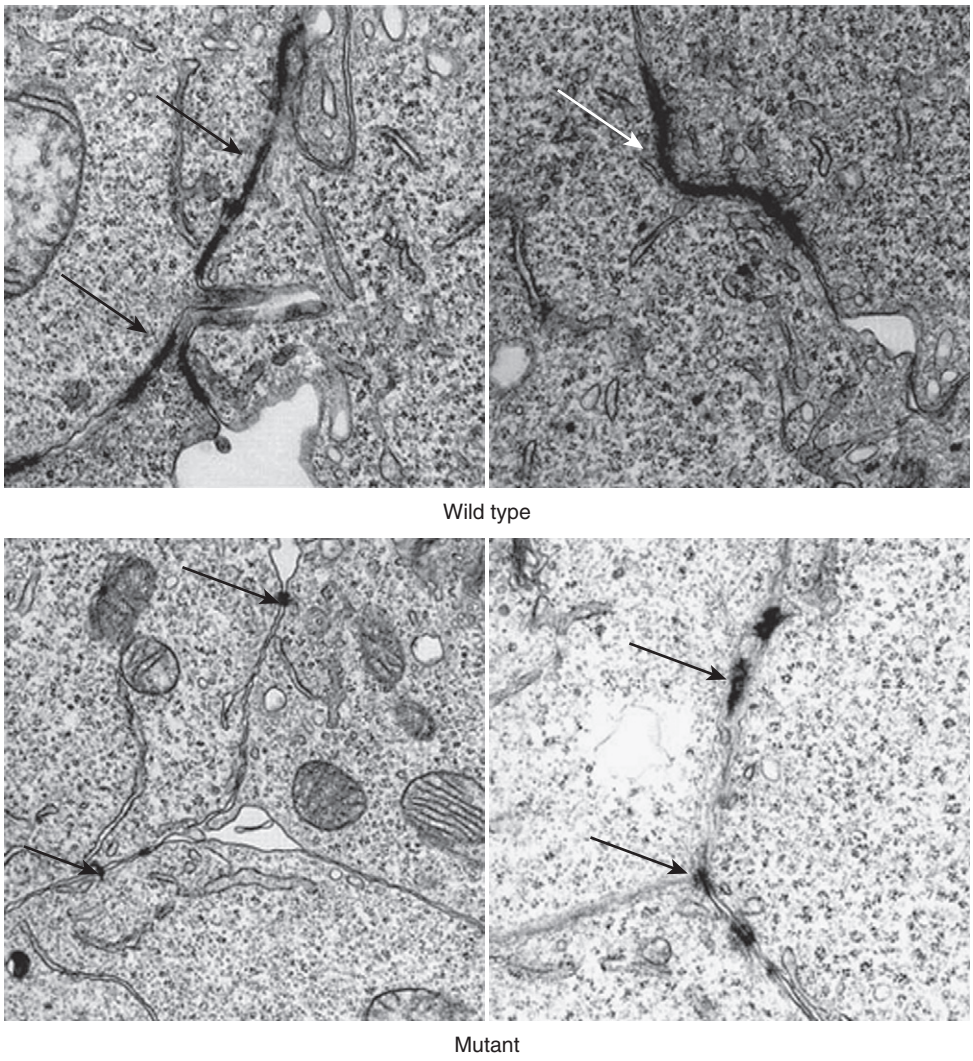

FIGURE 59-4 Electron micrographs of cardiac cells expressing wild-type and mutant plakoglobin. The *arrows* indicate adhesive junctions between cells (desmosomes). Mutant forms show fewer desmosomes per micrograph. *(From Asimaki A, Syrris P, Wichter T, et al: A novel dominant mutation in plakoglobin causes arrhythmogenic right ventricular cardiomyopathy,* Am J Hum Genet *81:964–973, 2007.)*

typically associated with effort-induced polymorphic VT and juvenile sudden cardiac death, without resting electrocardiogram (ECG) abnormalities or structural abnormalities, and mutations in this gene are no longer classified as a subtype of ARVC.[45,46] Mutations in the intronic region of *TGFβ3*, which stimulates the production of extracellular matrix components, have been found to promoting myocardial fibrosis in vivo.[47-49] Two ARVD1 kindred, however, lacked mutations in *TGFβ3*, which raises a question about its involvement in the pathogenesis of ARVC.[50] Recently, a mutation in the transmembrane protein 43 (TNEM43) has been described (ARVD5). TNEM43 is predicted to be a cytoplasmic membrane protein without a cadherin domain, and the *TNEM43* gene contains a response element for an adipogenic transcription factor.[51]

Phenocopies

When the left ventricle is involved and severe biventricular dysfunction is present, the differentiation from DCM can be difficult.[52] Cardiac sarcoidosis can also mimic some of the clinical and structural abnormalities of ARVC but can be differentiated on endomyocardial biopsy.[53] Right ventricular outflow tract VT can be difficult to distinguish from ARVC but generally has a good prognosis and can be successfully treated with catheter ablation therapy.[54] Right ventricular myocarditis can mimic ARVC, and significant overlap between these two conditions exists, as inflammatory infiltrates are a feature of both.[55,56] The histopathologic features of the heart in X-linked Emery-Dreifuss muscular dystrophy (EDMD) can mirror those of ARVC, but the two can be distinguished by family history and the presence of skeletal muscle involvement in EDMD.[57]

Clinical Features

The natural history of ARVC has been divided into four phases. In the earliest ("concealed") phase, patients are asymptomatic and have few if any morphologic abnormalities in the right ventricle.

In the second ("electrical") phase, symptoms of arrhythmia occur, and structural and functional abnormalities are easier to identify. The third phase is typified by the classic right ventricular functional abnormalities that can progress to right ventricular failure with relatively preserved left ventricular function. The final or end stage is characterized by the development of biventricular systolic impairment. It is not inevitable that affected persons will progress through all these phases, but this can be a useful disease paradigm. Moreover, it is likely that many other genetic and environmental factors (e.g., exercise) influence the clinical manifestations and natural history of the condition in individual patients.

Symptoms and Physical Signs

Patients can present at any age with syncope, presyncope, or palpitations, In one case series, approximately one third of live probands gave a history of syncope, with over half reporting palpitations and presyncope.[58] Other symptoms include chest pain or dyspnea often precipitated by exercise.[59] In approximately 50% of cases, the first manifestation of ARVC is SCD, but in living patients, aborted SCD is the first manifestation in less than 10% of cases.[28,60] Heart failure as a first presentation is probably uncommon; it accounted for less than 10% of cases in one series.[58] Increasingly, patients are identified through family screening and are often asymptomatic. Cardiac examination in symptomatic and asymptomatic individuals is usually unremarkable.

Diagnosis

Because of the nonspecific nature of the clinical findings and the absence of a single diagnostic test, the diagnosis of ARVC is challenging. Recognition of these difficulties resulted in the formation of an International Task Force, which proposed standardized criteria for the diagnosis of ARVC in 1994.[3] These criteria are based on the identification of structural, histologic, ECG, arrhythmic, and familial features, which are subdivided into major and minor criteria according to specificity. The presence of two major criteria, one major criterion plus two minor criteria, or four minor criteria from different categories is considered diagnostic (Table 59-2).[3]

The main goal of these guidelines was to establish a definitive diagnosis in probands, but tertiary referral center experience suggests that while the criteria are highly specific, they lack sensitivity for early disease.[59] This led to the proposal of modified familial criteria for the diagnosis of ARVC in relatives of index cases. According to these criteria, the presence of a single disease feature (right precordial T-wave inversion, late potentials on signal averaged ECG, VT with LBBB morphology, or minor functional or structural abnormalities of the RV on imaging) in a relative of an index case should be considered diagnostic of ARVC (Table 59-3).[58]

Electrocardiographic Features of Arrhythmogenic Right Ventricular Cardiomyopathy

A wide range of ECG changes are seen in ARVC.[59] ECG changes also change with disease progression and may be dynamic.[61] The most common abnormality is T-wave inversion in the right precordial leads (V1-V3) in the absence of right bundle branch block (RBBB), which has been reported in 54% to 85% of probands.[62,63] This constitutes a minor diagnostic criterion for ARVC but is more common in cases with severe RV dysfunction and overt right ventricular dilation.[64] Complete and incomplete RBBB are commonly observed but are also common among normal subjects and are therefore not included in the diagnostic criteria.[59]

Table 59-2 Task Force Criteria for the Diagnosis of Right Ventricular Dysplasia/Cardiomyopathy

	MAJOR CRITERIA	MINOR
Global and/or regional dysfunction and structural alterations	Severe dilation and reduction of RV ejection fraction Localized RV aneurysms (akinetic or dyskinetic areas with diastolic bulging) Severe segmental dilation of the RV	Mild global RV dilation and/or ejection fraction reduction with normal LV Mild segmental dilation of the RV Regional RV hypokinesia
Tissue characterization of wall	Fibro-fatty replacement of myocardium on endomyocardial biopsy	
Repolarization abnormalities		Inverted T waves in right precordial leads (V2 and V3) in people aged >12 years, in absence of RBBB
Depolarization/conduction abnormalities	Epsilon waves or localized prolongation (>110 ms) of QRS complex in right precordial leads (V1–V3)	Late potentials (SAECG)
Arrhythmias		LBBB-type ventricular tachycardia (sustained and non-sustained) by ECG, Holter, or exercise testing Frequent ventricular extrasystoles (>1000/24 hours on Holter)
Family history	Familial disease confirmed at necropsy or surgery	Family history of premature sudden death (<35 years) from suspected RV dysplasia Familial history (clinical diagnosis based on present criteria)

RV, *Right ventricle;* LV, *left ventricle;* RBBB, *right bundle branch block;* SAECG, *signal-averaged electrocardiogram.*
From McKenna WJ, Thiene G, Nava A, et al: Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy, Br Heart J *71:215–218, 1994.*

The presence of a post-excitation epsilon wave, reflecting delayed right ventricular activation, is a major diagnostic criterion.[3,65] This has been reported in around 30% of cases, but its sensitivity can be increased by using a highly amplified, modified recording technique (Figure 59-5).[63,64] Another major ECG criterion is localized prolongation (>110 ms) of the QRS complex in the right precordial leads (V1-V3).[3] In some series, this has been reported in 70% to 75% of patients.[62,64] A more recently proposed criterion of prolonged (≥55 ms) S-wave upstroke in V1-V3 has been reported in 84% to 95% of ARVC patients without RBBB.[63,64] This parameter has been correlated with disease severity, and in one study, it was an independent marker for VT induction at electrophysiology study.

Table 59-3 Familial Criteria for the Diagnosis of Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy

Meet the familial criteria for a diagnosis of ARVC if ARVC is present in a first-degree relative plus one of the following:	
ECG	T-wave inversion in right precordial leads (V2 and V3)
SAECG	Late potentials seen on signal-averaged ECG
Arrhythmia	LBBB-type VT on ECG, Holter or during exercise testing Extrasystoles >200 over 24-hour period
Structural or functional abnormalities of the RV	Mild global RV dilation or EF reduction with normal LV Mild segmental dilation of the RV Regional RV hypokinesia

ARVC, Arrhythmogenic right ventricular cardiomyopathy; ECG, *electrocardiogram;* SAECG, *signal-averaged electrocardiogram;* LBBB, *left bundle branch block;* VT, *ventricular tachycardia;* RV, *right ventricle;* EF, *ejection fraction.*
Modified from Hamid MS, Norman M, Quraishi A, et al: Prospective evaluation of relatives for familial arrhythmogenic right ventricular dysplasia/cardiomyopathy reveals a need to broaden diagnostic criteria, J Am Coll Cardiol *40(8):1445–1450, 2002.*

The signal-averaged ECG (SAECG) detects late potentials, a sign of delayed after-depolarizations. It is considered abnormal when two or more of the following parameters are met[66]:

- QS duration >114 ms
- Low-amplitude signal duration ([LAS] <40 μV) is >38 ms
- Root mean square voltage in the last 40 ms of the QRS (RMS40) <20 μV

An abnormal SAECG has been reported in 58% of probands and 45% of affected relatives.[58,63]

Arrhythmia

Ventricular arrhythmias with LBBB morphology are reported in 42% to 64% of patients on ECG, ambulatory ECG monitoring, or exercise testing.[29,58,60] The presence of more than 1000 extrasystoles in a 24-hour period is a minor diagnostic criterion and has been reported in 22% to 42%.[58,63] However, the cutoff 1000 extrasystoles is arbitrary; Hamid et al proposed a lower burden of ventricular ectopy (>200 per 24 hours) as a manifestation of the disease in relatives of affected individuals.[58]

Electroanatomic Mapping

Electroanatomic mapping combines electrophysiological and spatial information to allow real-time three-dimensional anatomic reconstruction of the cardiac chamber in sinus rhythm, with electrophysiological information color-coded and superimposed on the reconstruction (electroanatomic map). In a small study, Baulos et al demonstrated that patients with ARVC could be differentiated from controls by the presence of discrete areas of low-amplitude electrograms.[67] In a larger study of 31 patients who fulfilled diagnostic criteria, three-dimensional electroanatomic voltage mapping of the RV increased accuracy in the diagnosis of ARVC.[54] Mapping may help differentiate RVOT VT from

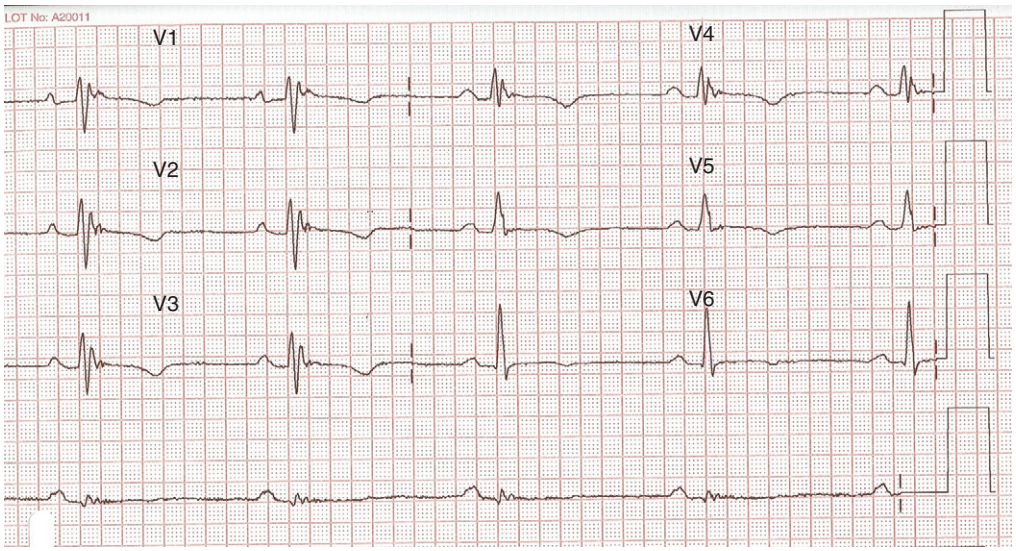

FIGURE 59-5 Highly amplified electrocardiogram showing epsilon wave in V1-V4. *(Courtesy Dr. Antonis Pantazis, Consultant Cardiologist, University College London Hospitals, UK.)*

early ARVC by detecting electroanatomic scars, which correlate with fibro-fatty replacement on endomyocardial biopsy.[68]

Imaging

Morphologic abnormalities of the right ventricle are challenging to identify in vivo. At the time of publication of the Task Force Criteria, cine-angiography of the RV was considered the gold standard, but the technique is associated with considerable interobserver variability and is invasive. For these reasons, it has been largely superseded by noninvasive imaging techniques. In addition to detecting ARVC, imaging has a major role in the exclusion of congenital heart diseases that cause RV abnormalities.

Echocardiography

The greatest challenge when using echocardiography to assess the RV is the chamber's complex three-dimensional structure. Considering the segmental nature of the disease, this also means that structure and function must be assessed using multiple (standardized) views. Initial reports described echocardiographic abnormalities in 100% of affected patients (64% mild, 30% moderate, and 6% severe), but contemporary studies in individuals with disease-causing genetic mutations have shown that echocardiography results are often normal.[60] Major echocardiographic criteria for ARVC include severe dilation and reduced RV function, RV aneurysms, and severe segmental dilation of the RV (Figure 59-6). Minor criteria include mild RV dilation and regional RV hypokinesis. Other features of uncertain significance include increased echogenicity of the moderator band and RV apical hypertrabeculation.[69]

Magnetic Resonance Imaging

Three-dimensional imaging and the ability to characterize tissue give cardiac magnetic resonance (CMR) an important advantage over echocardiography in the assessment of ARVC.[69,70] However, both these techniques have in common a high level of interobserver variability and subjectivity with regard to interpretation of wall thinning, localized functional abnormalities, and fatty replacement.[71] Early studies had suggested that high intramyocardial T1 signals indicative of fat replacement were present in 75% of ARVC patients meeting Task Force criteria, but these studies failed to account for normal epicardial fat that is seen in older adults, in obese patients, and in conditions other than ARVC.[72-75] Intramyocardial fibrosis can be assessed by late gadolinium enhancement (LGE) techniques but can be difficult to detect in the thin RV wall. The presence of LGE in the LV is more readily apparent and is common in patients fulfilling diagnostic criteria. It is not, however, included in the current diagnostic criteria (Figure 59-7).[76]

Endomyocardial Biopsy

A definitive or gold standard for the diagnosis of ARVC is histologic demonstration of transmural fibro-fatty replacement of the RV myocardium at autopsy or surgery.[3] These alterations can also be demonstrated on RV endomyocardial biopsy (EMB), which, however, lacks sensitivity because of the segmental nature of the disease and because tissue is usually obtained from the septum, which is rarely involved in the disease process. Some studies show

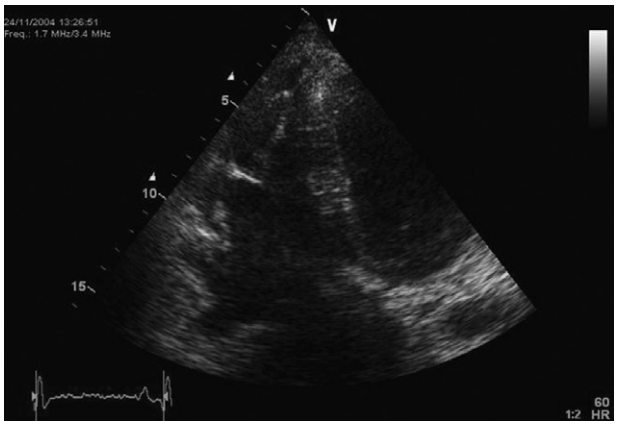

FIGURE 59-6 Modified apical view showing right ventricular free wall aneurysms. *(Courtesy Dr. Antonis Pantazis, Consultant Cardiologist, University College London Hospitals, UK.)*

that biopsy guided by electroanatomic voltage mapping to areas of low voltage increases the diagnostic accuracy of biopsy.[77]

Quantitative diagnostic histomorphometric parameters have been proposed to increase the specificity of the histopathologic diagnosis of ARVC at biopsy. A fat percentage greater than 3%, fibrous tissue greater than 40%, and residual myocytes less than 45% has a sensitivity and specificity of 67% and 92%, respectively.[78] Nither septal nor LV EMB has diagnostic value, as the dystrophic process in the LV is usually segmental and restricted to the subepicardial or midmural layers of the thick free wall, which are not accessible with the EMB approach.[79] Endomyocardial biopsy with immunohistochemical staining has been proposed as a diagnostic test for ARVC to identify patients before the development of extensive fibro-fatty infiltration or structural abnormalities of the RV. Diffuse reduction in the plakoglobin signal has been observed not only in areas of the RV showing typical pathologic features of ARVC but also in the LV and interventricular septum, which otherwise appear structurally normal; this suggests that a conventional EMB of the right side of the septum may reliably show this diagnostic change. This has been shown to be a consistent feature of ARVC but not other forms of severe heart disease and suggests that a shift in plakoglobin from junctional pools to intracellular or intranuclear pools may play a role in disease pathogenesis through signaling changes that could contribute to myocyte injury. This diagnostic approach requires further validation in larger cohorts.[80]

Disease Management

The main treatment goal in patients with ARVC and their relatives is the prevention of sudden arrhythmic death and heart failure. The recommended workup for patients with suspected ARVC and for their family members includes annual review of personal and family histories, 12-lead ECG, SAECG, exercise testing, ambulatory ECG monitoring, and echocardiography. CMR can be performed to aid in the assessment of cardiac morphology; invasive, intracardiac electrophysiological studies should be reserved for patients with symptomatic VT, ventricular fibrillation (VF), or syncope with negative noninvasive investigations.[59,70]

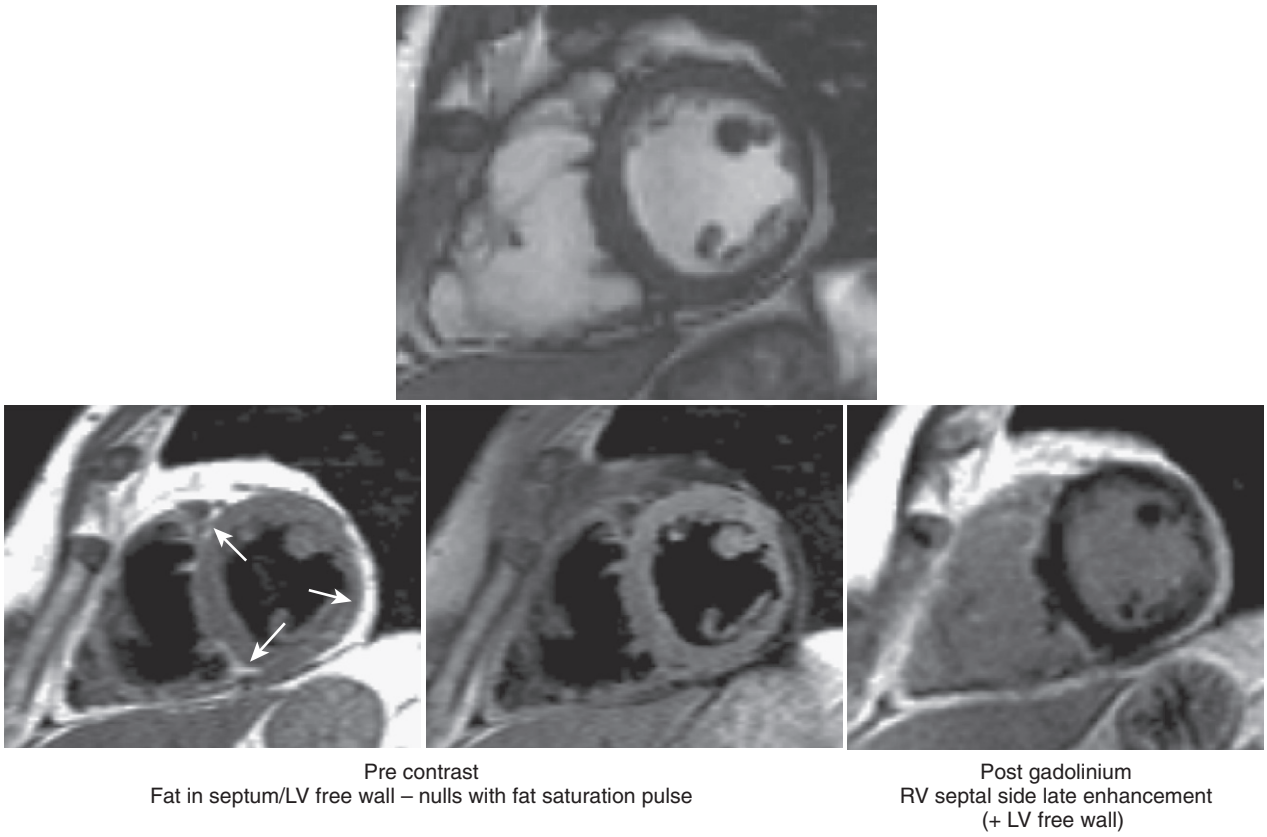

FIGURE 59-7 Cardiac magnetic resonance images showing right ventricular aneurysms and intramyocardial fatty deposition. *(Courtesy Dr. James Moon, Consultant Cardiologist, University College London Hospitals, UK.)*

Prevention of Sudden Cardiac Death

The overall mortality of ARVC has been estimated in one study at 18.5% over 8.1 ± 7.8 years, with an annual mortality rate of 2.3%.[81] In another study, the incidence of sudden death declined after the fourth decade of life. Evidence from prospective controlled trials assessing clinical markers that can predict SCD is lacking. Retrospective analyses of clinical and pathologic series have identified a number of possible predictors of adverse outcome in probands. These include an onset of symptoms at an early age, involvement in competitive sports, a significant family history of SCD, severe RV dilation, LV involvement, syncope, episodes of complex ventricular arrhythmias or VT, and increased QRS dispersion on 12-lead ECG.[30,59,82,83]

The AHA/ACC/ESC 2006 guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD state that implantable cardioverter-defibrillator (ICD) implantation is recommended for the prevention of SCD in patients with ARVC with documented sustained VT or VF, who are receiving optimal medical therapy and have reasonable expectation of survival with a good functional status for more than 1 year (class I recommendation). It can also be effective in the prevention of SCD in patients with extensive disease, including those with LV involvement, one or more affected family members with SCD, or undiagnosed syncope when VT/VF has not been excluded as the cause of syncope (class IIa recommendation).[84]

Management of Arrhythmia

Evidence for the efficacy of antiarrhythmic drugs in ARVC is largely anecdotal, and the impact of medical therapy on mortality is unknown.[84-86] Pharmacologic treatment is the first-choice therapy for patients with well tolerated, non–life-threatening ventricular arrhythmias such as frequent ventricular extrasystoles. As arrhythmias are often precipitated by an increase in heart rate, a reasonable first-line agent is a β-blocker; a number of studies have suggested that sotalol may be the most effective.[85,87]

Catheter ablation is not routinely carried out in ARVC patients unless drug-refractory, incessant ventricular arrhythmia is present or VT recurs frequently after ICD implantation. This is caused by the low efficacy of the therapy and the recurrence of further arrhythmia with disease progression.[88] In one study of 32 patients, acute success was achieved in 75%, with the remainder having only partial acute success. After a successful primary procedure, 21% experienced recurrent VT within the first 3 months, and 63% of those with only partial success from the primary procedure had recurrent arrhythmia. None of the patients, however, experienced syncope or sudden death during a mean follow-up of 28 months.[89]

Management of Heart Failure

Studies have reported an incidence of heart failure in up to 20% of patients.[74,86] In one study, death from heart failure occurred

twice as frequently as from SCD, whereas in a large American cohort, only 6% of patients developed right-sided failure, and of these, only one progressed to biventricular failure and death while awaiting cardiac transplantation.[81,90] Standard therapy for heart failure is indicated in patients in whom ARVC has progressed to severe heart failure or biventricular systolic dysfunction, including diuretics, angiotensin-converting enzyme inhibitors, and β-blockers. Anticoagulation should be considered in the presence of atrial fibrillation, marked ventricular dilation, or ventricular aneurysms. In patients in whom congestive heart failure is refractory, cardiac transplantation should be considered.[59,70]

Genetic Testing

The discovery of gene mutations involved in the pathogenesis of ARVC has introduced the possibility of molecular genetic diagnosis in clinical care. The aim of molecular genetic screening is to identify family members at risk. As the first presentation of ARVC can be with SCD, genetic screening has the potential to identify at-risk individuals at an early stage and thus save lives.[16] However, the value of genetic testing in predicting outcomes is limited by the fact that many sequence variants are private (i.e., confined to single families), which makes it difficult to determine the pathogenicity of these variants. Even when mutations have been described previously, either an absence of data on genotype-phenotype relations or variations in disease expression is an issue.[16] Finally, more than 10% of patients are homozygous, double-heterozygotes, or compound-heterozygotes, which underscores the need to screen every coding region of all known disease-causing genes, even after the identification of a first mutation.[50]

Advice on Lifestyle Changes

Patients in whom a diagnosis of ARVC is confirmed or strongly suspected should be discouraged from participating in competitive sports and endurance training. This advice is based on animal models and on reports suggesting that individuals who perform intensive, regular sports activities have more symptoms at an earlier age and a greater risk of SCD.[91,92]

Future Directions

Since its first description in the 1970s, concepts of pathogenesis in ARVC have evolved from a developmental abnormality confined to the RV to a complex genetic disorder that affects both ventricles, characterized by incomplete penetrance and variable expressivity. Together with the inherent difficulties in assessing the RV in vivo, this had made ARVC one of the hardest cardiomyopathies to diagnose and treat. Fortunately, advances in molecular genetics, cardiovascular imaging, and electrical mapping technologies have provided cardiologists with powerful tools that can detect subtle but clinically important structural and functional abnormalities in patients and affected relatives. However, the most important determinant of diagnosis remains a high index of suspicion when young patients present with unexplained arrhythmia, cardiovascular symptoms, or a family history of unexplained SCD.

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CHAPTER 60

Postoperative Arrhythmias After Cardiac Surgery

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Arrhythmias occur frequently after cardiac surgery. This chapter discusses postoperative atrial and ventricular tachyarrhythmias as well as bradyarrhythmias. The incidence, prognosis, potential mechanisms of pathogenesis, and management of these arrhythmias are described. Postoperative atrial arrhythmias are associated with increased morbidity, lengthy hospitalization, and medical costs, whereas prophylactic therapy is frequently given in an attempt to avoid these problems and be cost effective. The chapter discusses whether these goals are being met in clinical practice. Treatments with pharmacologic and nonpharmacologic modalities; management strategies for postoperative atrial arrhythmias; the incidence, risk factors, and potential etiologies of ventricular arrhythmias and bradyarrhythmias that occur following cardiac surgery; and the risk stratification techniques and treatments for ventricular arrhythmias and bradyarrhythmias are all discussed as well.

Atrial Arrhythmias

Incidence and Predictors

Atrial arrhythmias occur frequently after most types of cardiac surgery, with a prevalence as high as 40% following coronary artery bypass grafting (CABG).[1-4] Atrial fibrillation (AF) and flutter are the most common arrhythmias; atrial tachycardias (ATs), including multifocal AT, are also observed. Clinical variables that convey higher risk for the development of postoperative AF are described in Box 60-1.[5-15]

Passman and colleagues have proposed a series of nomograms to assess the degree of risk for postoperative AF based on multiple preoperative clinical and electrocardiogram (ECG) variables.[11] These investigators performed a chart review of 229 consecutive patients who underwent CABG and found that independent predictors for postoperative AF included advanced age; left main or proximal right coronary artery stenoses; history of AF or heart failure; or preoperative ECG findings of a P-R interval 185 milliseconds (ms) or longer or a P-wave duration in lead V1 of 110 ms or longer. Univariate analysis indicated that in this cohort, chronic obstructive pulmonary disease (COPD), left main or proximal right coronary artery stenoses, frequent premature atrial contractions, and left atrial abnormality on ECG were not significant predictors for postoperative AF. Initial reports indicated that a minimally invasive approach to CABG (vs. a conventional sternotomy) does not lessen the incidence of postoperative AF, when corrected for disease severity.[15,16] However, more recent investigations indicate that the incidence of postoperative AF is lessened with minimally invasive techniques for CABG and valvular surgery.[17-19]

CABG without the use of cardiopulmonary bypass (CPB) has been associated with a decreased incidence of postprocedural AF in situations of minimally invasive techniques, reoperative ("redo") single-vessel revascularization, and octogenarian patients.[20-22] Ascione and colleagues investigated, in a prospective, randomized trial, whether the use of CPB and cardioplegic arrest influenced the incidence of postoperative AF.[10] Two hundred patients were randomized to CPB (with normothermic CPB vs. cardioplegic arrest CPB) and off-pump "beating heart" surgery. In this study, a risk factor for postoperative AF was observed to be CPB with cardioplegic arrest, not CPB in general. Other risk factors for postoperative AF described by this study included postoperative inotropic support, intubation time, chest infection, and length of hospital stay. In summary, similar to patients with postoperative AF observed after conventional CABG, patients with AF after minimally invasive techniques have a higher in-hospital morbidity rate, length of stay, and mortality rate compared with patients without AF; however, AF can occur with a lower frequency following minimally invasive cardiac surgery or after cardiac surgery without CPB or cardioplegia.

Risk stratification for postoperative atrial arrhythmias can be performed using clinical characteristics (see Box 60-1) or by laboratory methods. One example of a stratification method is based on P-wave duration, as calculated directly from the surface ECG or from signal-averaged data.[23] An investigation by Buxton and Josephson assessed P-wave duration from standard electrocardiographic leads in 99 cardiac surgical patients and found that the mean total P-wave duration in patients who developed AF or atrial flutter was significantly longer than in patients who remained in sinus rhythm (mean total P-wave duration of 160 ms and 126 ms [$P = .001$], respectively).[23] A significantly prolonged P-wave duration was observed to be a sensitive (83%) but not specific (43%) predictor of postoperative atrial arrhythmias. Prolonged P-wave duration in patients who develop postoperative atrial arrhythmias may be a reflection of underlying preoperative atrial disease.

Prognosis

Postoperative AF usually arises 1 to 5 days following surgery, with a peak incidence on day 2, and usually has a self-limited course.[24-26] More than 90% of patients with AF following cardiac surgery who have no history of atrial arrhythmias are in sinus rhythm 6 to 8 weeks following their operation. Rubin and associates followed up postcardiac surgical patients for an average of 26 months and

Box 60-1 Predictors of the Development of Post–Cardiac Surgery Atrial Arrhythmias

- Advanced age
- Valvular heart disease (particularly mitral valvular disease and stenosis)
- Increased left atrial size
- Sinus electrocardiogram showing pulse rate ≥185 ms, P-wave duration in lead V1 ≥110 ms, atrial premature depolarizations, or left atrial abnormality
- Radiographic cardiomegaly
- History of congestive heart failure
- Previous atrial arrhythmias
- Previous cardiac surgery
- Long bypass times
- Method of cardioprotection, hypothermia, and cardiac venting via right superior pulmonary vein during bypass
- Right coronary artery grafting
- Left main coronary stenosis grafting
- Postoperative inotropic support and endotracheal intubation time
- Elevated postoperative adrenergic tone
- Postoperative chest infection
- Absence of β-blocker treatment (or withdrawal of previous treatment)
- Chronic obstructive pulmonary disease
- Chronic renal failure
- Electrolyte disturbances: hypokalemia, hypomagnesemia
- Pericarditis
- Long hospital stay

Box 60-2 Potential Factors Implicated in the Pathogenesis of Post–Cardiac Surgery Atrial Arrhythmias

- Pericarditis
- Atrial injury from surgical handling or from cannulation
- Acute atrial enlargement from pressure or volume overload
- Inadequate cardioprotection during bypass
- Atrial infarction or ischemia
- Hyperadrenergic state
- Pulmonary issues (e.g., infection, atelectasis, pleural effusion, hypoxia)

observed no differences in cardiovascular or cerebrovascular morbidity or mortality between patients with postoperative AF and patients without AF.[27] However, other studies have shown an increased rate of early and late postoperative stroke in association with AF (see later section on postarrhythmia therapy).[14,20,28,29] Postoperative atrial arrhythmias are usually considered to increase morbidity, length of stay in the intensive care unit (ICU), length of hospitalization, and medical costs. Almassi and coworkers, in a series of 3855 cardiac surgical patients, found that postoperative AF was associated with a longer ICU stay (3.6 vs. 2 days for patients without AF, $P = .001$), an increased rate of ICU re-admission (13% vs. 4%), a greater incidence of perioperative myocardial infarction (7.4% vs. 3.4%), more persistent congestive heart failure (4.6% vs. 1.4%), and a higher rate of re-intubation (10.6% vs. 2.5%).[14] An investigation by Abreu and colleagues reported a longer hospital stay of 4.9 days because of postcardiac surgical AF, and it was calculated to increase medical costs by $10,000.[17] It should be noted that, in slight distinction, a study by Kim and associates observed a shorter hospital stay (1 to 1.5 days in this study) attributed to postoperative AF.[30] Villereal and colleagues found that the occurrence of AF after CABG identifies a subset of patients at an increased risk for both early and long-term cardiovascular events.[31]

Etiology

Many perioperative factors have been described in the pathogenesis of postoperative AF (Box 60-2), but no definitive data are available. The pathophysiology of postoperative AF is probably related to pre-existing age-related degenerative cardiac changes in many patients, coupled with perioperative abnormalities in several electrophysiological parameters such as dispersion of atrial refractoriness, atrial conduction velocity, and atrial transmembrane potential. Nonuniform atrial conduction is greatest on postoperative days 2 and 3, and the longest atrial conduction time is greatest on day 3.[32] These abnormalities coincide with the time of greatest risk for AF, which has a peak incidence on days 2 and 3.[33] AF after CABG has been associated with increased expression and heterogeneity in distribution of connexin40, an intercellular gap junction protein, unlike in patients who do not develop AF.[34] These changes could result in differences in resistive properties and conduction velocity among spatially adjacent regions of the atrial myocardium. Postoperative pericarditis is generally felt to be an etiology, or at least a potentiating factor, for AF. Perioperative hypokalemia has been shown to be associated with atrial arrhythmias with an odds ratio of 1.7 (even after adjusting for confounding factors) in a multicenter trial that followed up over 2400 patients through cardiac surgery.[35] Potential mechanisms whereby hypokalemia might alter atrial electrophysiology include increased phase 3 depolarization, increased automaticity, and decreased conduction velocity.

Prophylactic Therapy with Pharmacologic Agents

Given the high incidence of postoperative AF, it is strongly recommended that prophylactic treatment be considered, especially in the presence of the risk factors described in Box 60-1. The magnitude of benefit from β-blockers, sotalol, amiodarone, and pacing was evaluated in a 2004 meta-analysis of 58 randomized trials that included over 8500 patients and in which placebo or routine therapy was given to controls.[36] Despite the significant reduction in AF, prophylactic drug therapy was associated with a nonsignificant reduction in stroke (odds ratio [OR], 0.76; 95% confidence interval [CI], 0.43 to 1.31), which may be attributed to a low rate of events (1.2% vs. 1.4%).[36] The use of β-blockers, in the presence or absence of digitalis, has been demonstrated to decrease AF from 40% for CABG patients and 60% for valvular surgery patients to 20% and 30%, respectively.[25,26,37] The effect of β-blockade in reducing postoperative AF, both alone or with digoxin, has been demonstrated in multiple meta-analyses.[37,38] Even though a preventive strategy of β-blocker administration might save both medical resources and decrease the length of hospital stay, such benefits have not yet been demonstrated. Specifically, in the β-Blocker Length of Stay Study (BLOSS) trial, 1000 patients undergoing cardiac surgery were randomized in a double-blinded fashion to receive either metoprolol (possibly in an up-titrated dose) or placebo.[12] In this trial, patients treated with β-blockers had a decreased incidence of atrial arrhythmias, but this did not translate into decreased length of hospital stay. Although investigators have found an association between postoperative AF and cardiovascular and other morbidities, broadly accepted therapies that reduce the incidence of AF have not yet been demonstrated to have long-term benefit or cost effectiveness.[31]

Digitalis given preoperatively or postoperatively has been shown only to be *possibly* helpful and not to the same extent or with the same reliability as β-blockers.[38] Postoperative verapamil given to patients in sinus rhythm has been observed to slow the rate of AF if it occurs but not to alter the prevalence.[39] Other antiarrhythmic agents such as procainamide have been studied in a prophylactic role but have been associated with varying benefits in different reports.[40] No comprehensive data on the effectiveness of propafenone or flecainide are available.

DL-Sotalol has β-blocker and class III activities and may have a role in the prophylactic treatment of postoperative AF. Preliminary data indicate that oral sotalol may reduce the incidence of AF following cardiac surgery.[41,42] Sotalol may be more effective than metoprolol, speaking to a potential incremental benefit of the activity of sotalol class III.[43] Conversely, a relatively large study of 429 consecutive patients by Suttorp and associates demonstrated no dramatic difference in the benefit of low-dose sotalol versus high-dose sotalol compared with low-dose β-blockers versus high-dose β-blockers, which suggests that the potential benefit of DL-sotalol arises from its β-blocker effect.[44]

The potential prophylactic role of sotalol was further examined in a recent prospective, randomized, double-blinded, placebo-controlled study of 85 post–cardiac-surgery patients by Gomes and coworkers.[45] In this group of patients, a significant reduction in postoperative AF was observed with sotalol treatment compared with either placebo or β-blocker treatment. Also, no increase in ventricular arrhythmias was detected, which suggests that the membrane effect of sotalol class III, when given in this study's setting, was not a liability. However, this study excluded patients with heart failure or marked left ventricular dysfunction (characteristics that might predict a high risk for postoperative AF or for ventricular proarrhythmia), which suggests that although sotalol may be useful, it cannot be broadly applied.[46]

Amiodarone—both oral and parenteral formulations—have been evaluated for prophylaxis against perioperative atrial arrhythmias. Daoud and colleagues, in a placebo-controlled trial, assessed the potential benefit of preoperatively administered amiodarone in 124 patients undergoing cardiac surgery.[47] Patients who received amiodarone, which had been initiated at least 7 days preoperatively, had a lower incidence of AF (25%) compared with patients who had received placebo (53%). Amiodarone administration was also associated with shorter duration of hospitalization and resultant decreased hospital costs. These data suggest a possible benefit of outpatient preoperative medication with oral amiodarone in decreasing the incidence of AF. However, despite a high rate of use of β-blockers—an approach shown to prevent at least 50% of AF in almost every trial in which it has been studied—a high incidence of atrial arrhythmias was observed in the control group, which suggests that these observations may not be broadly applicable. A more complete assessment of the effects of prophylactic amiodarone was provided by a 2005 meta-analysis of 10 trials.[2,38,48] Amiodarone therapy was associated with a significant reduction in the rate of AF or atrial flutter (22% vs. 35%; relative risk [RR], 0.64; 95% CI, 0.55 to 0.75). Also, significant reductions in the much less frequent complications of ventricular tachycardia (VT) or ventricular fibrillation (3.6% vs. 9.6%; RR, 0.42; 95% CI, 0.28 to 0.63) and stroke (1.5% vs. 4.%; RR, 0.39; 95% CI, 0.21 to 0.76) were seen. Only 61% of patients in these trials were treated with β-blockers. A similar magnitude of benefit was seen in the largest randomized trial of amiodarone in relation to cardiac surgery (PAPABEAR).[49] In this trial, which was published after the above-mentioned meta-analysis, 601 patients undergoing elective CABG or valve surgery were randomly assigned to oral amiodarone (10 mg/kg daily starting 6 days prior to surgery and continued until 6 days after surgery) or placebo. In the entire population, a 48% reduction was seen in perioperative atrial tachyarrhythmias. This benefit was consistent across a number of predefined subgroups, including patients 65 years of age or younger, those undergoing CABG or valve surgery, and those who were taking preoperative β-blockers, and those not taking β-blockers. Patients assigned to amiodarone who had an atrial tachyarrhythmia had a significantly lower average ventricular rate (105 vs. 131 beats/min with placebo). Patients randomly assigned to amiodarone had more adverse cardiac events compared with those taking placebo, including bradycardia requiring temporary pacing (5.7% vs. 2%) and QT prolongation (1.3% vs. 0%). Preoperative amiodarone treatment does have distinct disadvantages: the need to identify patients well in advance of their procedure, potential bradyarrhythmic hazards (especially in an outpatient setting and in older adults), and, although rare, a risk of perioperative pulmonary toxicity.[50] The latter may be caused by a potentiated risk, from amiodarone, of CPB-associated adult respiratory distress syndrome (ARDS), which has a poor prognosis.

The Amiodarone Reduction in Coronary Heart (ARCH) trial investigated, in a placebo-controlled, double-blind study of 300 patients, whether postoperative administration of intravenous (IV) amiodarone reduced the incidence of AF.[51] Results showed a significant decrease in the incidence of AF in patients given amiodarone (35%) compared with those given placebo (47%), without significant risk from the active agent. However, the size of the benefit did not result in shorter hospital stay in this study. The relatively modest benefit of IV amiodarone in this report would probably have been even smaller had a greater number of patients received β-blockers.[51]

In any clinical situation, potential benefits have to be balanced against risks. Antiarrhythmic medications have possible proarrhythmic effects, particularly classes I and III agents in the context of structural heart disease, myocardial ischemia, and metabolic dysfunction. Caution is urged, especially with these agents and in these circumstances.

β-Blockers have been shown to be the most effective prophylactic agents and carry a lower risk relative to other antiarrhythmic agents.[2,38] On the basis of these data, the authors of this chapter believe that β-blocker prophylaxis should be widely applied. Use of other drugs for prophylaxis needs to be further investigated.

Prophylactic Therapy with Pacing

The potential role of nonpharmacologic therapy in the prevention of postoperative AF has been examined in several studies. Single-site and multiple-site atrial pacing has been shown to be helpful in some cases of non-perioperative paroxysmal AF.[52] Investigations into the potential role of single-site and multiple-site atrial pacing in the prevention of postoperative AF have shown varying benefits.

Initial reports indicated that atrial pacing might not be beneficial for postoperative AF. An investigation of 86 post-CABG patients found that atrial pacing via single-site atrial epicardial wires, at a rate of at least 80 beats/min and always above the intrinsic sinus rate ("overdrive pacing"), was not associated with a different incidence of postoperative atrial arrhythmias when

compared with the absence of pacing. A recent study of 100 post-CABG patients, randomized to no atrial pacing versus atrial pacing at 10 beats/min or more above the resting heart rate, indicated that atrial pacing significantly increased atrial ectopy and did not attenuate the rate of AF occurrence.[53] The potential role of bi-atrial overdrive pacing in the prevention of postoperative AF has also been investigated in several studies. One prospective, randomized trial by Kurz and colleagues examined the effect of bi-atrial pacing in a group of post-CABG patients, assessing the incidence of AF and the possible proarrhythmic effects of pacing.[54] Unfortunately, after only 21 of the planned 200 patients were randomized, the study was terminated because this study's pacing protocol was observed to promote AF, a possible consequence of undersensing of atrial signals by the epicardial pacing system leading to asynchronous atrial pacing. An investigation by Gerstenfeld and coworkers studied 61 post-CABG patients who were randomized to right atrial pacing, left and right atrial pacing, or no pacing, using epicardial wires.[55] No significant difference in the incidence of AF was observed among groups, although a trend toward less atrial arrhythmia in paced patients also receiving a β-blocker was seen.

Some studies, however, have shown a potential benefit from atrial pacing in the prevention of postoperative AF. Greenberg and associates performed an investigation of 154 patients following CABG or CABG plus aortic valve replacement.[56] Patients were randomized to no pacing, right atrial pacing, left atrial pacing, or bi-atrial pacing for 72 hours postoperatively, and efforts were made to administer β-blocker medications. Any pacing modality reduced the incidence of AF from 37.5% to 17% and the length of hospitalization from 7.8 to 6.1 days. In this study, multivariate analysis indicated that the most effective sites of pacing were the right atrial, left atrial, and bi-atrial sites, in that order. Of note, patients in this study did not have significant left ventricular dysfunction (average ejection fraction 53 ± 10%). In contrast, an investigation by Blommaert and colleagues examined the course of 96 postoperative patients who had a wide range of left ventricular function.[57] Patients were randomized to no pacing versus 24 hours of atrial pacing using a dynamic overdrive algorithm.[57] Attention was paid to the use of β-blocker medication. Pacing was associated with a lower incidence of AF (10%) compared with no pacing (27%). Multivariate analyses showed that the beneficial effect of atrial pacing was observed particularly in patients with preserved left ventricular function and older patients.

Findings regarding the potential benefit of bi-atrial pacing in the prevention of postoperative AF have been varied. In contrast to the findings of Greenberg and coworkers, Fan and colleagues observed a greater benefit with bi-atrial versus single-site atrial pacing.[56,58] Fan and associates studied 132 postoperative patients without a history of AF and randomized them to no pacing, bi-atrial pacing, left atrial pacing, or right atrial pacing. After overdrive atrial pacing for 5 days, the incidence of AF was 41.9%, 12.5%, 36.4%, and 33.3%, respectively. Reductions in the rates of postoperative AF translated into shorter hospital stays in this study. Also, patients who remained in sinus rhythm had significant reductions in P-wave duration and variability in P-wave duration following pacing therapy.

One component of the potential benefit of postoperative pacing in the prevention of AF might be its allowance for more thorough dosing with β-blockers. Clearly, additional studies are necessary to investigate the potential role of overdrive pacing in the prevention of postoperative AF.

Other Prophylactic Agents

Angiotensin Inhibition

Although angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) have not previously been considered a specific therapy in patients with AF, a number of observations suggest their benefit in nonsurgical settings. A reduction in the incidence of postoperative AF with ACE inhibitors was also seen in a multicenter analysis of 4657 patients undergoing CABG.[59] Postoperative AF occurred significantly less often in patients who were treated preoperatively and postoperatively with ACE inhibitors compared with those who were not (20% vs. 34%; OR, 0.62). Patients who had previously been taking ACE inhibitors and were withdrawn from therapy had an increase in risk (46%; OR, 1.69).

Statins

Statins may reduce the incidence of perioperative AF. This was illustrated in the ARMYDA-3 (Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty Study–3) trial with 200 patients who underwent CABG without a prior history of statin treatment.[60] Patients were randomly assigned to 40 mg of atorvastatin or placebo daily, starting 7 days prior to surgery. Atorvastatin significantly lowered the incidence of AF (35% vs. 57% with placebo). On the basis of the established benefits of statin therapy in patients with coronary heart disease, patients should be on a statin prior to elective CABG. The possible suppression of perioperative AF may be an added benefit, but the validity of this finding does not impact the recommendation for statin use in this setting.

Glucocorticoids

On the basis of the hypothesis that perioperative inflammation may contribute to the development of AF, glucocorticoids have been suggested as prophylactic therapy. In a multicenter trial, 241 patients undergoing CABG, valve surgery, or both were randomly assigned to 100 mg of hydrocortisone every 8 hours for 3 days after surgery or to placebo.[61] During a follow-up period of 84 hours after surgery, the incidence of AF was significantly reduced with hydrocortisone therapy (30% vs. 48% with placebo). No difference in adverse events, including infections, was observed between the groups. Because of the wide range of the physiological effects of glucocorticoids, additional data on both the efficacy and safety of this approach are necessary before it can be considered for routine use.

Fish Oil

Consumption of fish that induce high plasma levels of n-3 polyunsaturated fatty acids (PUFAs) may be associated with a moderate reduction in the risk of AF.[62] A randomized controlled trial of 160 patients assessed whether the administration of PUFAs (2 g per day), compared with placebo, would reduce the incidence of postoperative AF after CABG.[63] The development of AF was significantly reduced in patients receiving PUFAs (15.2% vs. 33.3%).

Postarrhythmia Therapy

Rate Control Treatment for Postoperative Atrial Fibrillation

Given the self-limited course of postoperative AF in the vast majority of patients with no history of preoperative atrial arrhythmias, treatment to control the ventricular response rate in

postoperative AF is a useful strategy. Rate control therapy with β-blockers should be the first-line choice, with the relative benefit partly attributable to treatment of the hyperadrenergic postoperative state and prevention of the well-demonstrated phenomenon of β-blocker withdrawal. Rapid administration of IV digoxin is occasionally mentioned as being helpful in restoring sinus rhythm, although the data are not supportive.[64] AV-nodal blocking agents such as calcium channel blockers and digoxin have roles in the control of the ventricular rate in AF but are not more effective than β-blockers; calcium channel blockers or digoxin may be useful when β-blockers cannot be given (for instance, in the presence of bronchospasm). A randomized, double-blind investigation by Tisdale and associates, comparing parenteral diltiazem and digoxin in post-CABG patients with AF, indicated that this calcium channel blocker results in rate control of AF more rapidly than does digoxin; however, after 12 and 24 hours, no significant difference in effect or in length of hospital stay was observed.[65]

Administration of IV β-blocking agents with short half-lives (e.g., esmolol) can be particularly useful if potential for bronchospasm, bradyarrhythmias, or hypotension exists, as the IV administration can be discontinued with a resultant rapid disappearance of the pharmacologic effect.

An investigation by Clemo and colleagues assessed the potential benefits of IV amiodarone in critically ill patients with atrial arrhythmias with rapid ventricular response rates, in some cases following cardiac surgery.[66] The data were retrospectively obtained from 38 patients with atrial arrhythmias in an ICU setting who had AF with resultant hemodynamic destabilization despite previous use of conventional AV-nodal blocking agents for rate control. IV amiodarone administration was associated with improved rate control, peripheral blood pressure, cardiac filling pressures, and cardiac output. However, no significantly increased rate of spontaneous reversion to sinus rhythm after IV amiodarone treatment was observed. In summary, this investigation showed that IV amiodarone has a beneficial role in slowing ventricular rate in AF in critically ill patients, possibly including groups of post-CABG patients, particularly when previous AV-nodal blocking drugs have not been fully effective. Although sole treatment with IV amiodarone cannot be relied on for conversion from AF, it is likely to be quite helpful in maintaining sinus rhythm, and it (or some anti-arrhythmic agent) should be considered before electrical cardioversion.[67]

Electrical Cardioversion for Postoperative Atrial Fibrillation

Conversion from well-tolerated postoperative AF is generally not actively pursued because of the high recurrence rate as well as the self-limited course. For patients with symptoms, however, therapies are similar to those employed in non-postoperative circumstances; however, a greater emphasis should be placed on postconversion pharmacologic therapy because causative factors inevitably persist to cause a recurrence. If conversion is necessary, atrial defibrillation or, if atrial flutter or tachycardia is present, pace termination can be employed.[68] In a case of AF that is difficult to convert by using the usual external techniques, consideration should be given to (1) internal defibrillation using transvenous coils if available; (2) a "double defibrillator" technique in which two pairs of orthogonally placed transthoracic, external patch electrodes are discharged simultaneously; or (3) pretreatment with IV ibutilide.[69-71] Information is emerging on low-energy atrial defibrillation via operatively implanted temporary epicardial coils in animal models and in clinical studies; this may ultimately be an effective strategy for high-risk patients (see Box 60-1) who are unable to tolerate pharmacologic therapy or as an adjunct to prophylactic therapy.[72,73]

Pharmacologic Cardioversion for Postoperative Atrial Fibrillation

Pharmacologic measures for the conversion of AF should be considered, especially if the patient's respiratory status makes anesthesia for an electrical conversion potentially hazardous or some other contraindication to general anesthesia exists. Medications that have been shown to be potentially useful include newer class III agents (such as ibutilide) and investigational agents such as tedisamil and tercetilide. A recent study by the Ibutilide Investigators compared the use of increasing doses of IV ibutilide with placebo in the treatment of postoperative atrial arrhythmias.[74] Ibutilide was significantly more effective than placebo in a dose-responsive fashion. This IV type III agent was also observed to be more efficacious in atrial flutter than in AF, as is often the case with class III agents. Ibutilide carries a risk of ventricular proarrhythmia (which occurs most often as sustained or nonsustained torsades de pointes) in about 2% to 4% of patients; this is particularly associated with bradyarrhythmia, hypokalemia, hypomagnesemia, and female gender.[74] However, when this medication is used carefully (with attention to the above risk factors and with telemetry observation during and following its administration), the risk of proarrhythmia can be mitigated. Indeed, the Ibutilide Investigators group observed that ibutilide-treated patients with higher heart rates had a lower incidence of ventricular arrhythmias than did rate-controlled patients, a likely consequence of bradyarrhythmia-induced torsades de pointes in the latter group.[74]

Anticoagulation for Postoperative Atrial Fibrillation

Although one might expect a relatively low risk for thromboembolic events in association with a limited course of postoperative AF, several studies have shown, with both prospective case series and case-controlled retrospective analyses, an increased rate of post-CABG stroke in association with postoperative AF, even after correction for comorbid risk factors.[14,28,29] Given the potentially devastating consequences of a thromboembolic event, anticoagulation with warfarin (Coumadin) should be considered for postoperative AF, particularly for patients with mitral valvular disease or prosthesis, left atrial enlargement, marked left ventricular dysfunction, previous thromboembolic events, and age 65 years or older (Table 60-1). Because of the risk of bleeding in postoperative patients, anticoagulation must be performed carefully, and IV heparin is often not employed. If cardioversion is performed for postoperative AF, conventional recommendations for anticoagulation should be followed. A summary of therapeutic measures for post-CABG atrial arrhythmias, including treatments for prophylaxis and treatments for postoperatively occurring AF, are summarized in Box 60-3.

For the prevention of postoperative AF, guidelines were published in 2006 by the American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) and in 2004 by the ACC/AHA.[75,76] This is summarized in Box 60-4. β-Blockers are the most widely used and, if not contraindicated, should be given as soon as possible after cardiac surgery.[36,48,75,76]

Although nonselective β-blockers can cause bronchospasm in patients with COPD, β1 selective β-blockers (e.g., atenolol or

Table 60-1 CHADS2 Score, Thromboembolic Risk, and Effect of Warfarin in 11,526 Patients with Nonvalvular Atrial Fibrillation and No Contraindications to Warfarin Therapy

CLINICAL PARAMETER	POINTS
Congestive heart failure (any history)	1
Hypertension (prior history)	1
Age ≥75 years	1
Diabetes mellitus	1
Secondary prevention in patients with a prior ischemic stroke or a transient ischemic attack; most experts also include patients with a systemic embolic event	2

CHADS2 SCORE	EVENTS PER 100 PERSON-YEARS*		
	WARFARIN	NO WARFARIN	NNT
0	0.25	0.49	417
1	0.72	1.52	125
2	1.27	2.50	81
3	2.20	5.27	33
4	2.35	6.02	27
5 or 6	4.60	6.88	44

NNT, *Number needed to treat to prevent one stroke per year with warfarin.*
Note: *The CHADS2 score estimates the risk of stroke, which is defined as focal neurologic signs or symptoms that persist for more than 24 hours and that cannot be explained by hemorrhage, trauma, or other factors or by peripheral embolization, which is much less common. Transient ischemic attacks are not included. All differences between the warfarin and no-warfarin groups are statistically significant except for a trend with a CHADS2 score of 0. Patients are considered to be at low risk with a score of 0, at intermediate risk with a score of 1 or 2, and at high risk with a score ≥3. One exception is that most experts would consider patients with a prior ischemic stroke, transient ischemic attack, or systemic embolic event to be at high risk, even if they had no other risk factors and therefore a score of 2. However, the great majority of these patients have some other risk factor and a score of at least 3. Data from Go AS, Hylek EM, Chang Y, et al: Anticoagulation therapy for stroke prevention in atrial fibrillation: How well do randomized trials translate into clinical practice?* JAMA *290:2685, 2003; CHADS2 score, from Gage BF, Waterman AD, Shannon W: Validation of clinical classification schemes for predicting stroke: Results from the National Registry of Atrial Fibrillation,* JAMA *285:2864, 2001.*

Box 60-3 Summary of Therapeutic Measures for Postcardiac Surgical Atrial Arrhythmias

PROPHYLAXIS (PREOPERATIVE ADMINISTRATION, POSTOPERATIVE ADMINISTRATION, OR BOTH)
Proved benefit: β-Blockers
Possible benefit: sotalol, amiodarone, digitalis, procainamide
To date, no benefit proved: propafenone, flecainide, atrial pacing
Ineffective: calcium channel blockers

TREATMENT (FOR POSTOPERATIVE ATRIAL ARRHYTHMIA)
Ventricular rate control with β-blocker, calcium channel blocker, digitalis, or amiodarone
Anticoagulation
Electrical or pharmacologic conversion if marked symptoms or hemodynamic problems, preferably after drug loading; administration of the agent that is used for maintenance of sinus rhythm following conversion will probably be needed for at least 1–2 months
Example of medication for pharmacologic conversion: Ibutilide
Examples of medications for maintenance of sinus rhythm following conversion: Amiodarone, sotalol

Box 60-4 ACC/AHA/ESC Guideline Summary: Management of Postoperative Atrial Fibrillation

Class I: There is evidence, general agreement, or both that the following approaches are effective for the management of postoperative atrial fibrillation (AF):

- Unless contraindicated, an oral β-blocker for prevention of postoperative AF in patients undergoing cardiac surgery
- Atrioventricular nodal blockers for rate control

Class IIa: The weight of evidence or opinion is in favor of the usefulness of the following approaches for the management of postoperative AF:

- In patients undergoing cardiac surgery, preoperative amiodarone for prevention in patients at high risk for postoperative AF
- Restoration of sinus rhythm with ibutilide or direct-current cardioversion in patients who develop postoperative AF using the same indications as recommended for nonsurgical patients with AF
- Antiarrhythmic drugs to maintain sinus rhythm in patients with recurrent or refractory postoperative AF using the same indications as recommended for nonsurgical patients with AF
- Antithrombotic therapy using the same indications as recommended for nonsurgical patients with AF

Class IIb: The weight of evidence or opinion is less well established for the usefulness of the following approaches for the management of postoperative AF:

- In patients undergoing cardiac surgery, preoperative sotalol for prevention in patients at risk for postoperative AF

Data from Fuster, V, Ryden, LE, Cannom, DS, et al: ACC/AHA/ESC guidelines 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 European Society of Cardiology Committee for Practice Guidelines (writing committee to revise the 2001 guidelines for the management of patients with atrial fibrillation), J Am Coll Cardiol *48:e149, 2006.*

metoprolol) appear to be safe even when a bronchospastic component is present.[77] The optimal duration of therapy for the prevention of postoperative atrial arrhythmias is uncertain, but β-blockers are often continued until the first postoperative visit. However, many patients who undergo cardiac surgery have a clear indication for the continued use of β-blocker therapy (e.g., previous myocardial infarction [MI], heart failure, or hypertension).

Amiodarone and sotalol are also effective in the postoperative setting.[36,48] With respect to amiodarone, the cost, the need for monitoring, and the transient nature of postoperative AF have limited its use. The authors of this chapter and the 2004 ACC/AHA guidelines suggest use of preoperative amiodarone in patients who have a contraindication to β-blockers and are at high risk for postoperative AF.[48,75] High-risk features include previous AF and mitral valve surgery.[33]

Ventricular Arrhythmias

Incidence and Prognosis

Sustained and unsustained ventricular arrhythmias—both monomorphic VT and ventricular fibrillation (VF)—are observed after

cardiac surgery. The reported incidence of de novo sustained and nonsustained ventricular arrhythmias is 0.7% to 3% and 36%, respectively.[78,83] Much earlier observations have shown an incidence of postoperative sustained ventricular arrhythmias of up to 6%, consistent with the known development of cardiac surgical techniques and postoperative care since the 1960s.[84] Nonetheless, the occurrence of ventricular arrhythmias predicts significant mortality. For example, Tam and colleagues observed de novo, sustained ventricular arrhythmias in only 16 of 2364 patients in the first week following cardiac surgery (most notably in patients with marked left ventricular dysfunction preoperatively).[79] However, of those patients with ventricular arrhythmias, 75% had recurrences of sustained VT or VF, with a 19% mortality rate. Kron and coworkers, in studying 1251 postoperative patients, observed an in-hospital mortality rate of 44% in patients with unprecedented and sustained ventricular arrhythmias. Recurrences of VT beyond the immediate postoperative period have been observed in 40% of patients with early postoperative VT who are also inducible to VT at electrophysiological study (EPS).[85]

Etiologies

Etiologies of postoperative ventricular arrhythmias include structural heart disease, such as previous infarction, fibrosis and dilation, and hypertrophy. Potential acute precipitants of postoperative ventricular arrhythmias are also described in Box 60-5.[78-82,86-88] Several electrolyte and metabolic abnormalities are associated with postoperative ventricular arrhythmias, most notably hypokalemia (but not low potassium levels intracellularly).[89]

Diagnostic Issues

In the postcardiac surgical patient with a wide-complex tachycardia, the diagnosis of VT is most often favored because of the high frequency of structural heart disease. In situations where the surface ECG recordings are ambiguous, a diagnosis of VT versus supraventricular tachycardia or rapidly conducted AF with aberrancy can often be made with the use of epicardial atrial wire recordings.[90,91]

Sustained Monomorphic Ventricular Tachycardia

A study by Steinberg and associates prospectively enrolled consecutive patients undergoing CABG and found that 3.1% of patients had at least one episode of sustained VT at a mean of 4.1 days following the operation; these patients had a 25% in-hospital mortality rate.[78] Predictors of postoperative VT included previous MI, marked heart failure, significant left ventricular dysfunction (defined as an ejection fraction <0.40), and revascularized myocardium previously supplied by a noncollateralized native vessel. When the first three of these predictive factors were present, the incidence of VT increased to 30%.

Box 60-5 Potential Acute Precipitants of Post–Cardiac Surgery Ventricular Arrhythmias

- Cardiac ischemia
- Acute myocardial infarction
- Reperfusion injury
- Electrolyte or metabolic abnormalities
- Acidemia
- Extreme hemodynamic instability
- Hypoxia
- Pharmacologic toxicity (particularly with drugs prolonging the Q-T interval)
- High levels of catecholamines (endogenous or administered sympathomimetics)
- Asynchronous ventricular pacing

Ventricular Fibrillation or Polymorphic Ventricular Tachycardia

An underlying arrhythmogenic substrate for monomorphic VT (e.g., myocardial scarring) is almost always present, whereas polymorphic VT is more likely related to transient perioperative abnormalities.[81,82,92] Kron and colleagues observed that acute cardiac ischemia following heart surgery was more highly associated with primary VF than with VT.[80] The perioperative factors that may contribute to polymorphic ventricular arrhythmias are described earlier and in Box 60-3. Whether polymorphic VT or VF events occurring immediately after CPB, in the absence of additional risk factors for ventricular arrhythmia, predict an increased risk for ventricular arrhythmic events in the long term is not supported by clear data.

Acute Management

No comprehensive or controlled studies of the acute treatment for postoperative VT have been conducted so far. However, commonly accepted and consensus treatments include ACLS-based algorithms, including synchronized DC cardioversion and pace termination (facilitated by the presence of epicardial pacing wires). Prevention of additional episodes can be aided by attention to abnormalities such as ischemia, fluid overload, electrolyte disturbances, and polypharmacy with potentially proarrhythmic cardiac or other agents.[93] Effective acute treatment can also be achieved with antiarrhythmic agents such as parenteral amiodarone, β-blockers, sotalol, magnesium sulfate (specifically for torsades de pointes), and procainamide.[40,94-98] Recurrent VT can also be prevented or treated with the use of overdrive ventricular pacing or burst ventricular pacing, respectively.[99] Mechanical supportive measures such as intra-aortic balloon counterpulsation, intrathoracic ventricular-assist devices, or external cardiopulmonary support have been used.[100-104] A case of simultaneous intra-aortic balloon and external cardiopulmonary therapy allowing for high-dose β-blocker infusion in a patient with refractory postoperative VT has been reported, although this technique is not widely applied.[105]

Postoperative Risk Stratification and Treatment

Longer-term treatment for patients who have manifested monomorphic VT postoperatively may involve risk stratification with an assessment of left ventricular function, EPS, or both.[81,85] Post–hospital discharge recurrences of VT have been noted in 40% of patients with postoperative VT who were also inducible to VT at postoperative EPS, which suggests the value of long-term treatment (e.g., with an implantable cardioverter-defibrillator [ICD]), although data showing a direct benefit in terms of mortality rates or other measures are lacking.[85] Of note, a discordance has been observed at EPS in inducibility of VT by programmed electrical stimulation (PES) performed via single-site epicardial pacing and that performed via dual-site endocardial pacing. Sheppard and colleagues performed EPS on 26 post-CABG patients using both

Box 60-6 Risk Factors for the Need for Permanent Pacemaker Implantation Following Cardiac Surgery

- Pre-existing left bundle branch block or other signs of atrioventricular conduction disease
- Valvular surgery (procedures in descending order of risk: multiple valvular, tricuspid, aortic, mitral)
- Coronary artery bypass grafting with concomitant valvular surgery
- Left ventricle aneurysmectomy or arrhythmia ablative surgery
- Repeat cardiac operation
- Advanced age
- Type of cardioplegia solution, if hypothermia was used
- Prolonged cardiopulmonary bypass and cross-clamp duration
- Number of bypass grafts (perhaps related to operative times)
- Presence of active endocarditis
- Female gender

operatively implanted epicardial pacing wires and endocardial electrophysiological catheters.[106] Despite similar effective and functional refractory periods that were epicardially and endocardially measured, concordant results of inducibility to VT between the techniques were obtained in only 70% of patients; 40% of patients inducible with dual-site endocardial PES had been uninducible via single-site epicardial PES, which suggests that single-site PES from epicardial wires may not fully assess the postoperative risk for VT.

The presence of late potentials on postoperative signal-averaged ECG has been reported as an independent predictor for VT early after CABG, but no comprehensive data on longer-term VT occurrences or outcomes in patients with an abnormal signal-averaged ECG are available.[107] The modality of exercise testing is also employed, although no direct evidence has shown its utility in predicting the risk of postoperative VT. The timing of postoperative risk stratification is important, with some investigators suggesting a waiting period of at least 1 week to allow for both healing and equilibration of substrate to occur.[83,108]

Lifelong treatment with antiarrhythmic medication, ICD placement, or both is likely useful for patients who are found to be at high risk for ventricular arrhythmia, such as those who have manifested postoperative ventricular arrhythmias and who also have significant left ventricular dysfunction, inducible monomorphic ventricular arrhythmias at EPS, or both. The significant rate of subsequent clinical ventricular arrhythmic events in patients with postoperative VT who are also inducible to VT at postoperative EPS indicates the value of long-term treatment, although direct data showing a benefit in mortality or other measures for patients with VT that emerges postoperatively are lacking.[85]

Bradyarrhythmias

Incidence and Prognosis

Cardiac conduction abnormalities and sinus bradyarrhythmias are reported in 17% to 34% of postoperative patients, depending on a multitude of factors (Box 60-6); however, a significant rate of reversibility does exist.[109,110] Persistent bradyarrhythmias requiring permanent pacing occur in 0.8% to 4% of postcardiac surgical patients.[111-116] The need for permanent pacemaker implantation following cardiac surgery is significant following valvular surgery, in the presence of pre-existing conduction system disease, and in several other situations, as described in Box 60-4.[111-114,117-120] Bradyarrhythmias necessitating permanent pacing have been associated with longer postoperative courses in the ICU and in the hospital, as well as with inevitably increased postoperative economic costs, although no direct data on cost exist.[16]

It is likely that recovery from postoperative bradyarrhythmias occurs in a significant proportion of patients. An investigation by Glikson and colleagues on long-term pacemaker dependency in a group of 120 patients who had received a permanent pacemaker following cardiac surgery indicated that 41% of patients eventually became pacemaker nondependent.[117] Patients with postoperative complete heart block (CHB) as the indication for pacemaker implantation were more likely to remain pacemaker dependent in this study. In contrast, in a smaller study of 93 consecutive post-CABG patients by Baerman and Morady, all three patients who underwent pacemaker implantation because of third-degree heart block were no longer in heart block after 2 months.[112] The issue of eventual use of a permanent pacemaker implanted after cardiac surgery was further explored in a study by Gordon and coworkers.[114] This investigation, which involved prospective data collection from 10,421 consecutive patients who had cardiac operations, included a logistic regression analysis of independent and multivariate predictors of permanent pacing following cardiac surgery (with predictors including the risk factors listed in Box 60-4). The investigators also found that their predictive model had a high correlation with eventual pacemaker use, which suggests that the presence of a greater number of risk factors for pacemaker implantation following cardiac surgery predicts a higher rate of actual pacemaker use.

Risk Stratification and Management Strategies

The decision to implant a permanent pacemaker in a post-CABG patient with high-grade atrioventricular (AV) block and a poor escape rhythm who is otherwise ready for hospital discharge is relatively straightforward. However, no clear data on the optimal waiting time in more equivocal situations exist. For complete AV block, some authors have recommended that a decision regarding permanent pacemaker implantation be made no later than day 6 and day 9 following surgery for wide-complex and narrow-complex escape rhythms, respectively.[117] In a study of pediatric patients with CHB following operation for congenital heart disease (with most cases involving the closure of a ventricular septal defect), Bonatti and associates recommend permanent pacing after at least a 2-week observation period with temporary pacing in that population.[115]

Any decision regarding timing of implantation of a permanent pacemaker will be impacted by the stability of the temporary pacing system. Epicardial electrode temporary pacing systems frequently display increasing pacing thresholds with time, and endocardial pacing catheters can have similar problems plus infective and vascular complications. A prospective study of 30 post-CABG patients by Kosmas and colleagues found that effective atrial, ventricular, and dual-chamber pacing via epicardial wires could not be performed by the fifth postoperative day in 39%, 38%, and 61% of patients, respectively.[121]

In cases of resolved or resolving heart block, the assessment of persistent risk of bradyarrhythmias and the need for permanent pacemaker implantation can be influenced by several factors. First, consideration should be given to determining the need for concomitant antiarrhythmic medication (which would be

expected to exacerbate even borderline bradyarrhythmias). Second, consideration should be given to performing an EPS (an abbreviated but effective form of which can be performed at the bedside with atrial pacing via operatively placed epicardial wires) to help detect significant AV conduction, sinus node, or both. EPS results suggesting that permanent pacing is needed are similar to generally applied criteria, including an H-V interval greater than 75 ms, infra-Hisian block occurring spontaneously or at an atrial paced cycle length of 400 ms or less (300 ms in a pediatric population), or a corrected sinus node recovery time of 550 ms or longer.[115] Third, an exercise study can be performed to assess chronotropic competence and AV conduction at elevated heart rates.

ACKNOWLEDGMENT

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CHAPTER 61

Arrhythmias and Electrolyte Disorders

Nabil El-Sherif, Gioia Turitto, and Dionyssios Robotis

Cardiac arrhythmias are an expression of the same fundamental electrophysiological principles that underlie the normal electrical behavior of the heart. The electrical activity of the heart depends on transmembrane ionic gradients and the time-dependent and voltage-dependent alterations of their conductance. The resting membrane potential (V_m) is calculated by the Goldman constant field equation[1]:

$$V_m = \frac{RT}{zF} \ln \frac{P_K a_{Ko} + P_{Na} a_{Nao} + P_{CL} a_{Cli}}{P_K a_{Ki} + P_{Na} a_{Nai} + P_{CL} a_{Clo}},$$

which incorporates the permeability (*P*) and activity (*a*) of all ionic species that contribute to it.

Electrolyte abnormalities may generate or facilitate clinical arrhythmias, even in the setting of normal cardiac tissue. Furthermore, electrolyte aberrations are more likely to interact with abnormal myocardial tissue to generate their own cadre of cardiac arrhythmias. Antiarrhythmics exert their actions by modulating the conduction of ions across specific membrane channels; hence, abnormal ionic gradients across the membrane will augment or mitigate their antiarrhythmic effects and potentiate or alleviate their proarrhythmic sequelae.

Potassium

Potassium is the most abundant intracellular cation and the most important determinant of the resting membrane potential (RMP). The electrophysiological effects of potassium depend not only on its extracellular concentration, but also on the direction (hypokalemia versus hyperkalemia) and rate of change. Hoffman and Suckling have noted that the effect of potassium on the RMP is modulated by the simultaneous calcium concentration.[2] The interrelationship is such that an elevated calcium level decreases the depolarizing effect of an elevated potassium level, and low calcium levels diminish the depolarization produced by hypokalemia. When extracellular potassium levels are higher than normal, the cell membrane behaves as a potassium electrode, as described by the Nernst equation:

$$V_m = -61.5 \log [K^+]_I / [K^+]_o$$

At levels of less than ~3 mmol/L, the transmembrane potential (Vm) is less than that predicted by the Nernst equation, because hypokalemia reduces membrane permeability to potassium (P_k).[3]

Indeed, potassium currents are modulated by the potassium gradient itself and other electrolytes as well (Table 61-1). The conductance of the inward rectifier current (i_{K1}) is proportional to the square root of the extracellular potassium concentration $[K^+]_o$.[4,5] The dependence of the activation of the delayed rectifier current (I_{Kr}) on the extracellular potassium concentration $[K^+]_o$ helps explain why the action potential duration (APD) is shorter at higher $[K^+]_o$ and longer at low $[K^+]_o$ concentrations (see Table 61-1).[6] As important as the time factor may be on the electrophysiological impact of different potassium levels, it is equally important to note that rapid fluctuations in extracellular potassium levels do occur, especially through transcellular shifts (Table 61-2). Insulin, β-adrenergic agonists, aldosterone, and changes in blood pH may independently affect serum potassium levels.[6]

Hypokalemia

Hypokalemia is the most common electrolyte abnormality encountered in clinical practice. Potassium values of <3.6 mmol/L are seen in over 20% of hospitalized patients.[8] As many as 10% to 40% of patients on thiazide diuretics and almost 50% of patients resuscitated from out-of-hospital ventricular fibrillation have low potassium levels. Hypokalemia results from decreased potassium intake, transcellular shift, and, most commonly, increased renal or extra-renal losses (Table 61-3).[9,10]

Electrophysiological Effects of Hypokalemia

Hypokalemia leads to a higher (more negative) RMP and, at least during electrical diastole, a decrease in membrane excitability as a result of widening of the RMP and the threshold potential (TP) difference. Low extracellular potassium decreases the delayed rectifier current (I_{Kr}), resulting in an increase in the APD and a delay in repolarization. It has been suggested that extracellular K^+ ions are required to open the delayed rectifier channel.[7]

Most importantly, hypokalemia alters the configuration of the action potential (AP), with the duration of phase 2 first increasing and subsequently decreasing, whereas the slope of phase 3 decelerates. The latter effect leads to an AP with a long "tail," resulting in an increase in the relative refractory period (RRP) and a decrease in the difference of the RMP from the TP during the terminal phase of the AP. Thus, cardiac tissue demonstrates increased excitability with associated ectopy for a considerable portion of the AP. Conduction slows because depolarization begins in incompletely repolarized fibers. Furthermore, hypokalemia prolongs the plateau in the Purkinje fibers but shortens it in the ventricular fibers.[11] The AP tail of the conducting system

Table 61-1 Modulation of Potassium Currents by Electrolyte Concentration

I_{K1}, Inward rectifier	Its conductance is proportional to the square root of $[K^+]_o$. The instantaneous inward rectification on depolarization is caused by the Mg^{2+} block at physiological $[Mg^{2+}]_i$.*
I_{Kr}, Delayed rectifier	Low $[K^+]_o$ decreases the delayed rectifier current (I_{Kr}).
I_{to}, Transient outward	One type is voltage activated and modulated by neurotransmitters. The other type is activated by intracellular calcium.
$IK_{(Ca)}$	Opens in the presence of high levels of intracellular calcium.
$IK_{(Na)}$	Opens in the presence of high levels of intracellular sodium.

**From Ishihara K, Mitsuiye T, Noma A, Takano M: The Mg^{2+} block and intrinsic gating underlying inward rectification of the K^+ current in guinea-pig cardiac myocytes, J Physiol (Lond) 419:297–320, 1989.*

Table 61-2 Factors That Affect the Transcellular Shift of Potassium

FROM INSIDE TO OUTSIDE	FROM OUTSIDE TO INSIDE
Acidosis	Alkalosis
β-Adrenergic receptor stimulation	β_2-Adrenergic receptor stimulation
Digitalis	Insulin
Solvent drag	

prolongs more than that of the ventricles, increasing the dispersion of repolarization. Hypokalemia increases diastolic depolarization in Purkinje fibers, thereby increasing automaticity.

In summary, the electrophysiological effects of hypokalemia are (1) a decrease in conduction velocity; (2) shortening of the effective refractory period (ERP); (3) prolongation of the RRP; (4) increased automaticity; and (5) early after-depolarizations (EADs) (Box 61-1).

Electrocardiographic Manifestations of Hypokalemia

The electrocardiographic manifestations of hypokalemia can be conceptualized as those caused by its effects on repolarization and those emanating from its effects on conduction (Box 61-2).[12] The electrocardiogram (ECG) changes resulting from its effects on repolarization include (1) decreased amplitude and broadening of the T waves; (2) prominent U waves; (3) ST-segment depression; and (4) T and U wave fusions, all of which is seen in severe hypokalemia (Figure 61-1). When the U wave exceeds the T wave in amplitude, the serum potassium is less than 3 mmol/L. Electrocardiographic changes caused by conduction abnormalities are seen in the more advanced stages of hypokalemia and include (1) increase in QRS duration without a concomitant change in the QRS configuration; (2) atrioventricular (AV) block; (3) cardiac arrest; (4) increase in P-wave amplitude and duration; and (5) slight prolongation of the P-R interval.

Table 61-3 Causes of Hypokalemia

Decreased intake	
Potassium shift into the cell (see Table 61-2)	
RENAL POTASSIUM LOSS	
Increased mineralocorticoid effects	Increased flow to distal nephron
Primary or secondary aldosteronism	Diuretics
Ectopic adrenocorticotropic hormone–producing tumor or Cushing syndrome	Salt-losing nephropathy
	Hypomagnesemia
Bartter syndrome	Nonresorbable anion
Licorice	Carbenicillin, penicillin
Renovascular or malignant hypertension	Renal tubular acidosis (type I or II)
Congenital abnormality of steroid metabolism	Congenital defect of distal nephron
Renin-producing tumor	Liddle syndrome
EXTRARENAL POTASSIUM LOSS	
Vomiting, diarrhea, laxative abuse, villous adenoma, Zollinger-Ellison syndrome	

Box 61-1 Electrophysiological Effects of Hypokalemia

Decrease in conduction velocity
Shortening of the effective refractory period
Prolongation of the relative refractory period
Increased automaticity
Early after-depolarizations

Box 61-2 Electrocardiogram Manifestations of Hypokalemia

REPOLARIZATION CHANGES
Decreased amplitude and broadening of T waves
Prominent U waves
ST segment depression
Fusion of T and U waves (in severe hypokalemia)

CONDUCTION ABNORMALITIES
Increase in QRS duration
Atrioventricular block
Cardiac arrest
Increase in P-wave amplitude and duration
Slight prolongation of the P-R interval

Arrhythmogenic Potential and Clinical Implications of Hypokalemia

Hypokalemia-induced hyperexcitability is clinically manifested by an increase in supraventricular and ventricular ectopy. In the Framingham Offspring Study, potassium and magnesium levels were inversely related to the occurrence of complex or frequent

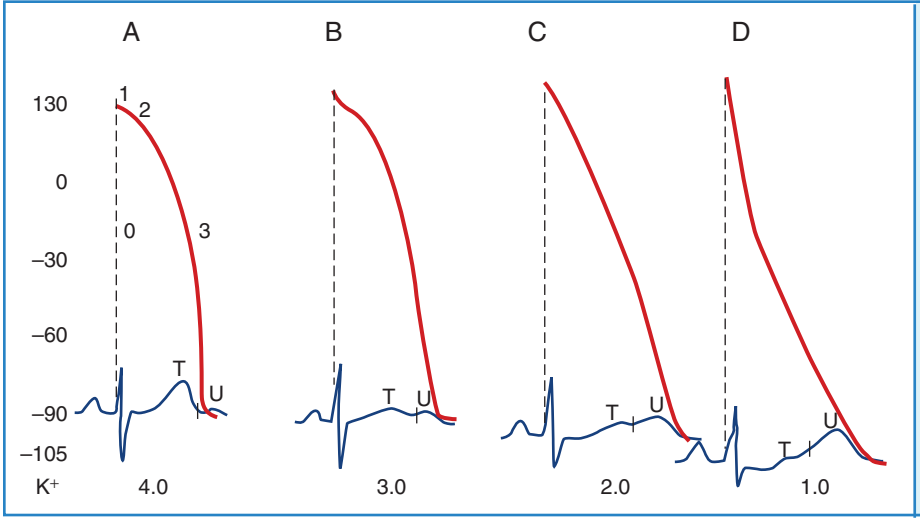

FIGURE 61-1 Diagram of the ventricular action potential superimposed on the electrocardiogram at different extracellular potassium concentrations (4.0, 3.0, 2.0 mEq/L). The numbers on the left designate the transmembrane potential in millivolts. *(From Surawicz B: Relation between electrocardiogram and electrolytes,* Am Heart J *73:814–834, 1967.)*

ventricular premature complexes (VPCs) after adjustment for covariates.[13]

Hypokalemia facilitates re-entry by slowing conduction during the prolonged RRP and by causing an increase in the dispersion of refractoriness. Its suppressant effect on the sodium-potassium (Na-K) pump leads to intracellular Ca^{2+} overload and this facilitates the development of delayed after-depolarizations (DADs) via a transient inward current (I_{ti}). Hypokalemia enhances the propensity for ventricular fibrillation in the normal as well as the ischemic canine heart.[14] An association between hypokalemia and ventricular fibrillation in patients with acute myocardial infarction has been well established.[15-17]

Dofetilide and quinidine were found to exert increased block of I_{kr} in the setting of low $[K^+]_o$ providing a mechanism that explains the link between hypokalemia and torsades de pointes (Figures 61-2 and 61-3).

Hyperkalemia

Although less common than hypokalemia, hyperkalemia may affect approximately 8% of hospitalized patients in the United States. Hyperkalemia is seen mainly in the setting of compromised renal function, particularly in association with the administration of a variety of nephrotoxic medications. Hyperkalemia may result from either decreased excretion or a shift of potassium from within the cell (Box 61-3).

Electrophysiological Effects of Hyperkalemia

The disproportional effects of varying levels of hyperkalemia on the RMP and the TP explain the initial increase in excitability and conduction velocity and then their decrease as the potassium level increases further (Table 61-4). Mild-to-moderate levels of hyperkalemia decrease the RMP (less negative) more than the TP, thereby diminishing the difference between the two and increasing excitability. The decrease in the slope of the upstroke of the AP (dV/dT), one of the major determinants of conduction velocity, is counterbalanced by a decrease in the difference between the RMP and the TP, resulting in an ultimate increase in conduction velocity. Severe hyperkalemia is associated with an increase in the difference between the RMP and the TP, leading to a decrease in excitability. Further decrement in the AP upstroke overwhelms the positive effect of the TP decrease on conduction velocity, resulting in a definitive decrease of the latter.

Hyperkalemia is associated with increased membrane permeability to potassium, a consequence of an increase of the inward-going rectifier current [i_{k1}] and the delayed rectifier current (I_{Kr}).[4-6]

Box 61-3 Causes of Hyperkalemia

DECREASED EXCRETION
Renal failure
Renal secretory defects
Hyporeninemic hypoaldosteronism
Heparin
Drugs (angiotensin-converting enzyme inhibitors, spironolactone, triamterene, nonsteroidal anti-inflammatory drugs, trimethoprim)

SHIFT OF POTASSIUM FROM WITHIN THE CELL (SEE TABLE 61-2)
Massive release of intracellular potassium
Hypertonicity
Insulin deficiency
Hyperkalemic periodic paralysis

Table 61-4 Effect of $[K^+]_o$ on RMP, TP, and V_{max} in Ventricular Muscle Fibers of Guinea Pigs

$[K^+]_o$ (mmol/L)	RMP (mV)	TP (mV)	RMP–TP (mV)	V_{MAX} (V/S)
2.0	99.4	72.7	26.7	236
5.4	83.0	65.1	17.9	219
10.0	65.8	51.4	14.4	178
11.5	62.8	45.6	17.2	154
13.0	60.7	41.9	18.8	103
16.2	55.4	34.7	20.7	45

RMP, *Resting membrane potential;* TP, *threshold potential;* $[K+]_o$, *extracellular potassium concentration.*
From Kishida H, Surawicz B, Fu LT: Effects of K^+ and K^+-induced polarization on $(dV/dt)_{max}$, threshold potential and membrane input resistance in guinea pig and cat ventricular myocardium, Circ Res *44:800–814, 1979.*

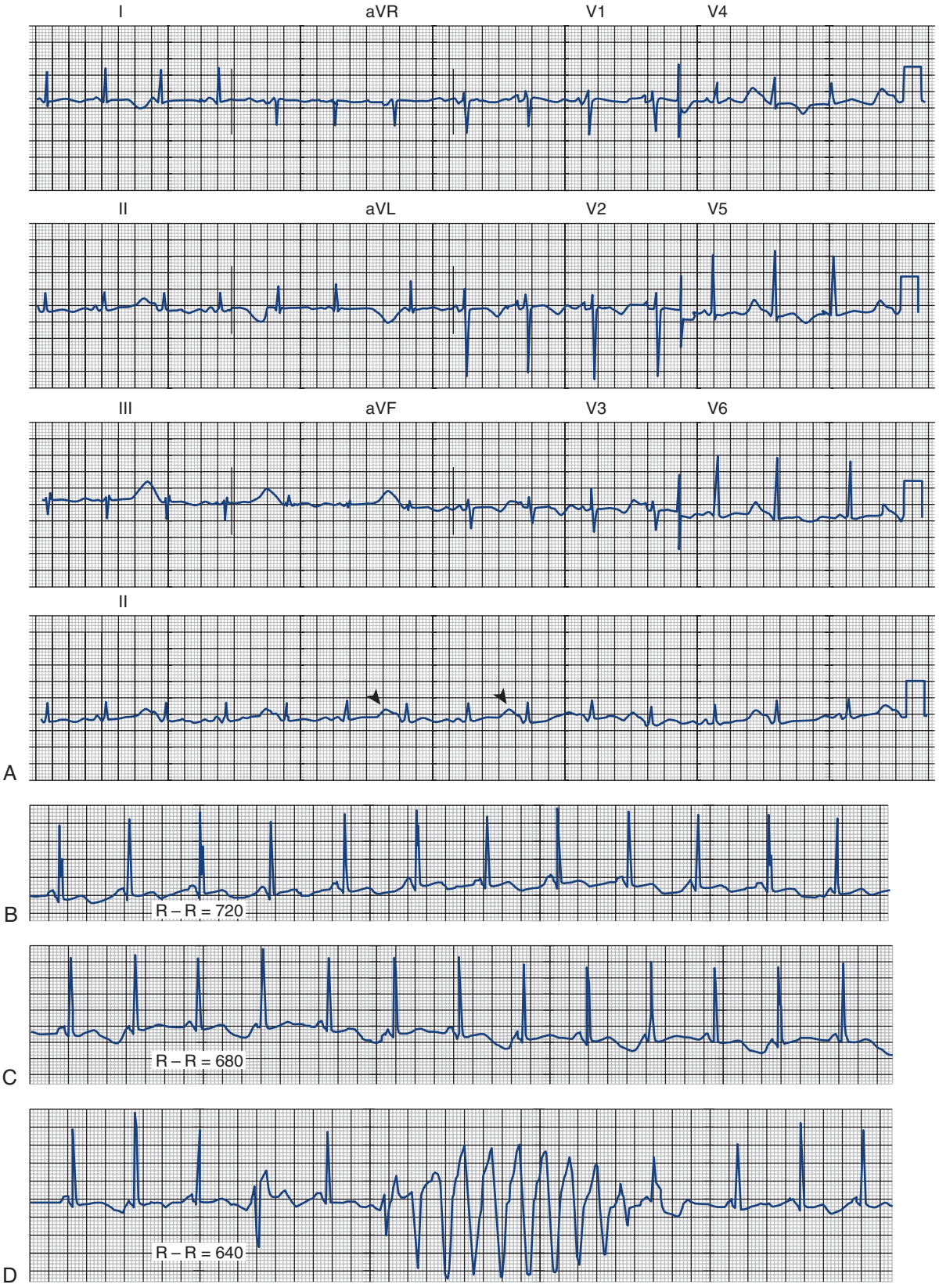

FIGURE 61-2 **A,** Twelve-lead electrocardiogram from a patient with hypokalemia and hypomagnesemia showing marked QTU prolongation and QTU alternans (*arrowheads*). **B** to **D,** Representative rhythm strips from the same patient as in **A,** showing tachycardia-dependent QTU alternans and torsades de pointes. *(From Habbab MA, El-Sherif N: TU Alternans, long QTU, and torsades de pointes,* PACE *15:916–931, 1992.)*

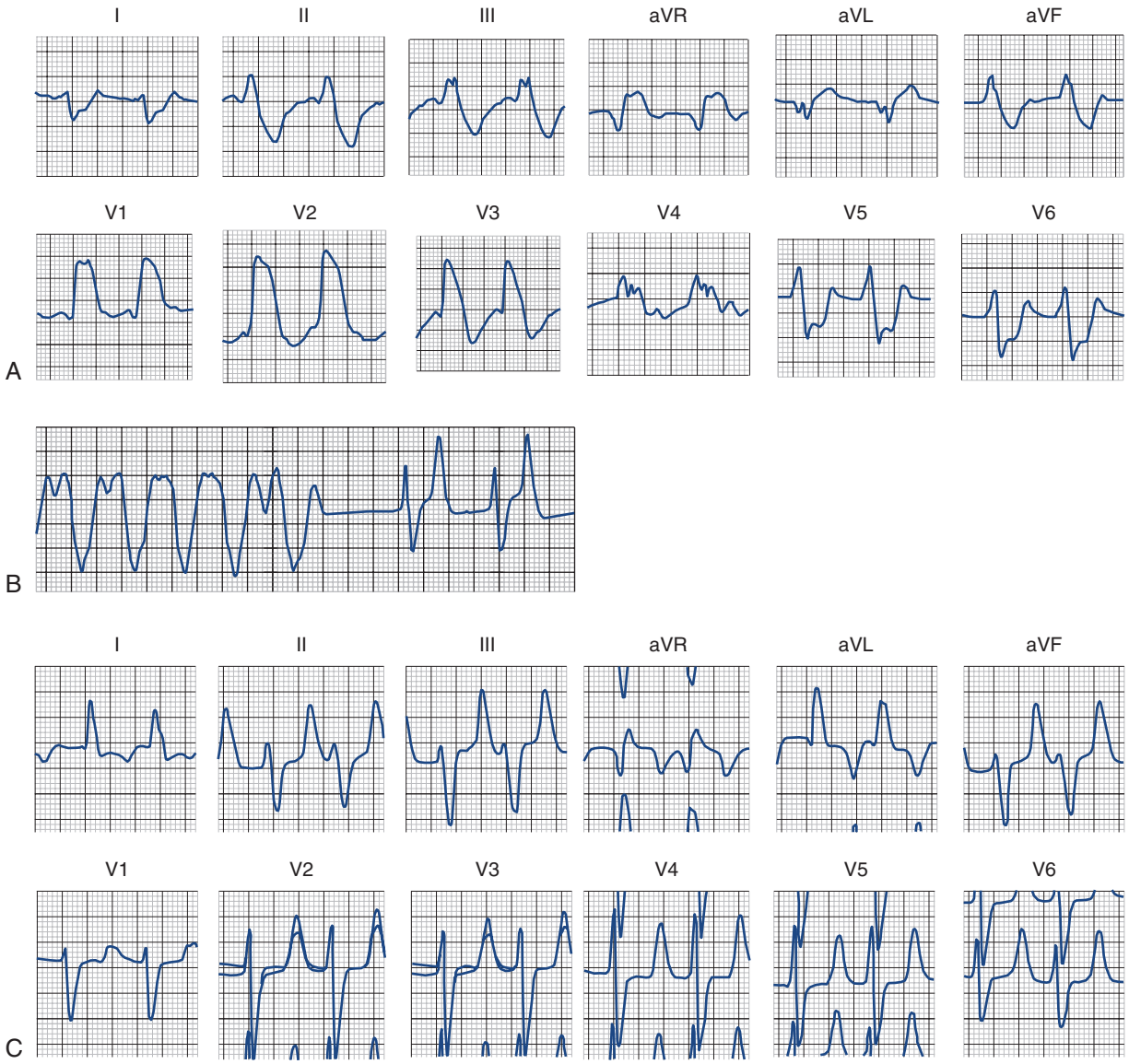

FIGURE 61-3 Tracings from a 39-year-old patient with end-stage renal disease who was on dialysis. The patient presented with weakness and palpitations; chemistry showed a serum potassium level of 10 mEq/L. **A,** Atypical bundle branch block; the QRS is wide and is merging with the T wave. **B,** Ventricular tachycardia that failed to respond to adenosine and procainamide given by paramedics. **C,** Gradual resolution of above electrocardiogram changes with dialysis and normalization of serum potassium level.

This accelerates the rate of repolarization and shortens the AP duration. Hyperkalemia preferentially shortens the plateau of the Purkinje fibers, thereby decreasing the dispersion of repolarization in the ventricle.[11] Furthermore, it slows the diastolic depolarization of the Purkinje fibers.

The effects of hyperkalemia depend on the tissue involved, with the atrial myocardium being the most sensitive, the ventricular myocardium less sensitive, and the specialized tissue (sinoatrial node and His bundle) the least sensitive. In other words, the depression of excitability and conduction in the atrium occur at lower extracellular potassium levels than in other types of myocardial tissue, as exemplified by the occasional pacemaker case of atrial noncapture and ventricular capture.[18] The sympathetic nervous system seems to contribute to the sinus node resistance to hyperkalemia.[19]

Many investigators have observed regional differences in repolarization time in the nonischemic myocardium in response to hyperkalemia. Sutton and colleagues have recorded monophasic action potentials (MAPs) from the endocardium and the epicardium in open-chest canine studies during graded intravenous infusion of potassium to a plasma level of 9 mmol/L. Their results suggested that the regional differences in repolarization times are mainly a result of local changes in activation times rather than a direct effect on the APD.[20]

An interesting phenomenon, the Zwaardemaker-Libbrecht effect, is the result of a change from a low extracellular potassium level to a high level and manifests itself by a transient arrest of pacemaker cells, abbreviation of APD, and hyperpolarization.[21-23] This phenomenon underscores the fact that the rate of intravenous administration of potassium is more important—from a

proarrhythmic standpoint—than the absolute amount of potassium administered and the final level of extracellular potassium.

Electrocardiographic Manifestations of Hyperkalemia

The ECG is not a sensitive indicator of hyperkalemia; 50% of patients with potassium levels >6.5 mmol/L will not manifest any electrocardiographic changes (Box 61-4).[24] The ECG changes caused by mild potassium elevations (K = 5.5 to 7.0 mmol/L) include tall, peaked, narrow-based T waves and fascicular blocks (left anterior fascicular block and left posterior fascicular block). Moderate hyperkalemia (K = 7.5 to 10.0 mmol/L) is associated with first-degree AV block and diminished P-wave amplitude. As the potassium level increases further, the P-wave disappears, and sinus arrest as well as ST-segment depression may develop. Atypical bundle branch blocks (left bundle branch block [LBBB] and right bundle branch block [RBBB]), intraventricular conduction delays (IVCDs), ventricular tachycardia (see Figure 61-3), ventricular fibrillation, and idioventricular rhythm are more commonly seen in cases of severe hyperkalemia (K^+ >10.0 mmol/L). The bundle branch blocks associated with hyperkalemia are atypical, that is, they involve the initial and terminal forces of the QRS complex. Shifts in the QRS axis indicate disproportionate conduction delays in the left bundle fascicles. These manifestations of intraventricular conduction delay correlate with a prolonged intracardiac H-V interval.[25] As hyperkalemia progresses, depolarization merges with repolarization, expressed on the ECG with QT shortening and apparent ST segment elevation simulating acute injury. The latter disappears with hemodialysis—*dialyzable current* of injury.[26] The effect of hyperkalemia on QRS morphology of ventricular paced beats have also been studied.[27] Hyperkalemia is the most common electrolyte abnormality to cause loss of capture. In patients with pacemakers, hyperkalemia causes two important clinical abnormalities: (1) widening of the paced QRS complex (and paced P wave) on the basis of delayed myocardial conduction. When the K level exceeds 7 mEq/L, the intraventricular conduction velocity is usually decreased and the paced QRS complex widens (Figure 61-4); (2) increased atrial and ventricular pacing thresholds with or without increased latency.[27]

The parallel changes in the AP and ECG can be appreciated better by reviewing Figure 61-5.[24]

Box 61-4 Electrocardiogram Manifestations of Hyperkalemia

MILD HYPERKALEMIA (K = 5.5–7.5 mEq)
Tall, peaked, narrow-based T waves

FASCICULAR BLOCKS (LAFB, LPFB)
Moderate hyperkalemia (K = 7.5–10.0 meq)
First-degree atrioventricular block
Decreased P-wave amplitude followed by disappearance of the P waves and sinus arrest
ST-segment depression

SEVERE HYPERKALEMIA (K >10.0 mEq)
Atypical bundle branch block (LBBB, RBBB), IVCD
Ventricular tachycardia, ventricular fibrillation, idioventricular rhythm

LAFB, *Left anterior fascicular block;* LPFB, *left posterior fascicular block;* LBBB, *left bundle branch block;* RBBB, *right bundle branch block;* IVCD, *intraventricular conduction delay.*

Arrhythmogenic Potential and Clinical Implications of Hyperkalemia

Potassium and Myocardial Ischemia

In the early phases of an ischemic insult, the cardiac membrane becomes increasingly permeable to potassium. After coronary ligation in dogs and pigs, the rise in extracellular potassium concentration was seen to result in currents of injury, refractory period shortening, conduction slowing, and ventricular fibrillation.[28,29] During ischemia, APD shortening is more pronounced and the conduction velocity is slower in failing than in the control myocardium. Extracellular potassium $[K^+]_o$ reaches higher values

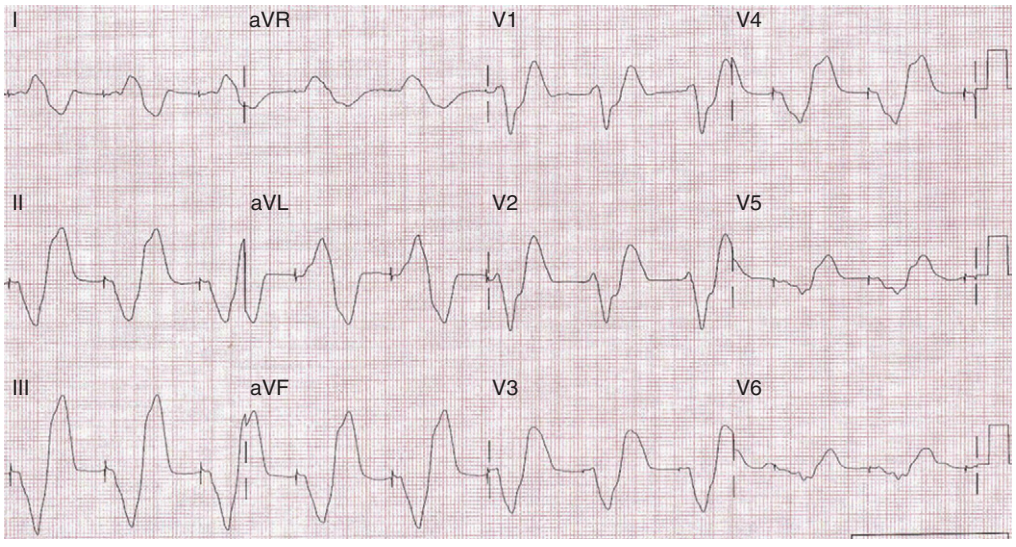

FIGURE 61-4 Twelve-lead electrocardiogram is from a 74-year-old patient with a history of pacemaker implantation for sick sinus syndrome who presented to the emergency department with "weakness." He went into asystole shortly thereafter. His serum potassium level at the time of the cardiac arrest was 10 mEq/L.

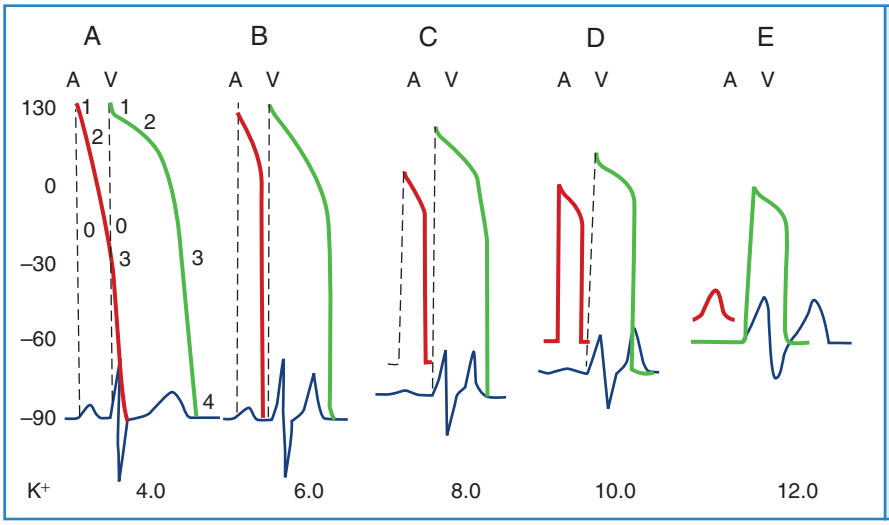

FIGURE 61-5 Diagram of an atrioventricular action potential superimposed on the electrocardiogram for extracellular potassium at 4.0, 6.0, 8.0, 10.0, and 12.0 mEq/L. The numbers on the left designate the transmembrane potential in millivolts, and the numbers at the bottom designate extracellular potassium concentration (mEq/L). *(From Surawicz B: Relation between electrocardiogram and electrolytes,* Am Heart J *73:814–834, 1967.)*

during acute ischemia in failing versus normal myocardium. Increased spatial dispersion in electrophysiological parameters and $[K^+]_o$ over the ischemic border in failing hearts may explain the higher propensity for re-entrant arrhythmias during acute regional ischemia.[30]

Potassium and Calcium Abnormalities

The combination of hyperkalemia and hypocalcemia has a cumulative effect on AV and intraventricular conduction delay and facilitates the development of ventricular fibrillation. Hypercalcemia, through its membrane-stabilizing effect, counteracts the effects of hyperkalemia on AV and intraventricular conduction and averts the development of ventricular fibrillation. This protective effect of calcium is immediate and its intravenous administration should be the first therapeutic measure in cases of hyperkalemia.

Potassium, Digitalis, and Quinidine

Hyperkalemia inhibits glycoside binding to Na^+-K^+-adenosine triphosphatase (ATPase), decreases the inotropic effect of digitalis and suppresses digitalis-induced ectopic rhythms. Alternatively, hypokalemia increases glycoside binding to Na^+-K^+-ATPase, decreases the rate of digoxin elimination, and potentiates the toxic effects of digitalis. Finally, hyperkalemia and hypokalemia augment quinidine toxicity.

Calcium

Isolated abnormalities of calcium concentration produce clinically significant electrophysiological effects only when they are extreme in either direction. As expected by reviewing the Goldman equation, extracellular calcium concentrations in the physiological range have no appreciable effect on the RMP. Hypocalcemia and hypercalcemia have opposing effects on the APD and ERP by affecting intracellular calcium concentration and modulating potassium currents.[2]

Hypocalcemia

Hypocalcemia is most frequently seen in the setting of chronic renal insufficiency and is usually associated with other electrolyte abnormalities. Generally, hypocalcemia may result from decreased intake or absorption or an increase in calcium loss (Box 61-5).

Box 61-5 Causes of Hypocalcemia

DECREASED INTAKE OR ABSORPTION
Malabsorption
Decreased absorptive area (small-bowel bypass, short bowel)
Vitamin D deficit (decreased absorption, decreased 25-hydroxy-D or 1,25-dihydroxy-D production)

INCREASED LOSS
Alcoholism
Chronic renal insufficiency
Diuretic therapy (furosemide, bumetanide)

ENDOCRINE DISEASE
Hypoparathyroidism or pseudohypoparathyroidism
Medullary carcinoma of the thyroid (calcitonin secretion)
Familial hypocalcemia

PHYSIOLOGICAL CAUSES
Associated with decreased serum albumin (normal calcium ion concentration)
Decreased end-organ response to vitamin D
Sepsis; hyperphosphatemia; induced by aminoglycoside antibiotics, plicamycin, loop diuretics, foscarnet

Electrophysiological Effects of Hypocalcemia

Low extracellular calcium decreases the slow inward current and intracellular calcium concentration during the AP plateau. The latter decreases outward current, possibly via $I_{k(Ca)}$, prolonging phase 2 of the AP, the total APD, and the duration of the ERP. As a consequence of low intracellular calcium, contractility decreases. Moreover, hypocalcemia slightly decreases the rate of diastolic depolarization in the Purkinje fibers and increases excitability through a direct interaction with the sarcolemma.

Electrocardiographic Manifestations of Hypocalcemia

ECG changes of hypocalcemia involve a prolongation of the ST segment and QTc interval and T-wave alterations, including

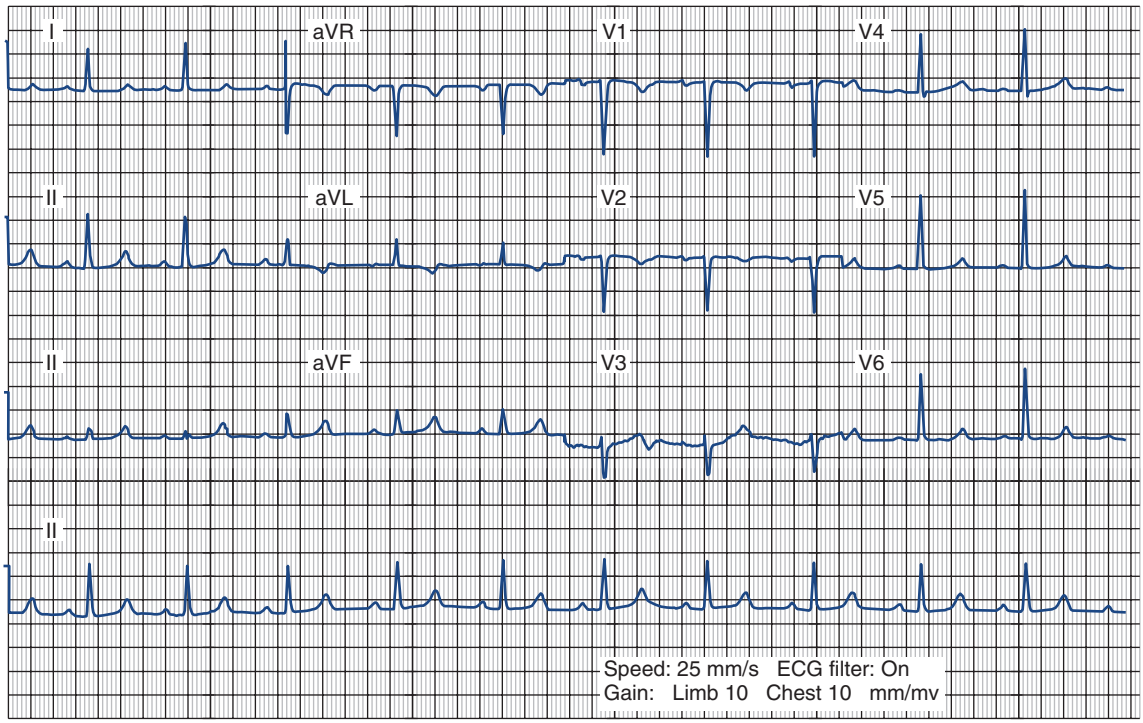

FIGURE 61-6 Twelve-lead electrocardiogram (ECG) is from a 24-year-old female black patient with sickle cell disease, end-stage renal disease, and hyperparathyroidism. The patient's serum calcium level was 7 mg/dL, and the potassium level was 6.5 mEq/L. This ECG demonstrates a prolongation of the ST segment and QTc interval (leads V5 and V6).

Box 61-6 Causes of Hypercalcemia

INCREASED INTAKE OR ABSORPTION
Vitamin D or vitamin A excess

ENDOCRINE DISORDERS
Primary hyperparathyroidism or secondary hyperparathyroidism (renal insufficiency, malabsorption)
Acromegaly
Adrenal insufficiency

NEOPLASTIC DISEASES
Tumors producing parathyroid hormone–related protein (ovary, kidney, lung)
Multiple myeloma (osteoclast-activating factor)

MISCELLANEOUS CAUSES
Thiazides
Sarcoidosis
Paget disease of the bone
Hypophosphatasia
Familial hypocalciuric hypercalcemia
Iatrogenic

upright, low, flat, or sharply inverted T waves in leads with an upright QRS complex.

Hypercalcemia

Hypercalcemia occurs most commonly in the setting of hyperparathyroidism or as a consequence of several malignancies. A plethora of other causes account for the remaining clinically encountered cases (Box 61-6).

Electrophysiological Effects and Electrocardiographic Manifestations of Hypercalcemia

High extracellular calcium levels shorten the AP plateau, the total APD, and, consequently, the duration of the ERP. A study of the effect of hypercalcemia on the guinea pig ventricular AP suggested that a decrease in the inward Na^+/Ca^{2+} exchange current might be largely responsible for the shortening of the AP.[31] Elevated extracellular Ca^{2+} concentration has a stabilizing effect on the membrane, increasing the extent of depolarization needed to initiate an AP. In addition, hypercalcemia has a positive inotropic effect, decreases excitability, and slightly increases the rate of diastolic depolarization in the Purkinje fibers.[32] The electrocardiographic changes as a result of hypercalcemia are limited to shortening or elimination of the ST segment and decreased QTc interval.

Magnesium

Magnesium is the second most abundant intracellular cation after potassium. The significance of magnesium disorders has been debated because of difficulties in accurate measurement and their frequent association with other electrolyte abnormalities.[33,34] It is an important cofactor in several enzymatic reactions that contribute to normal cardiovascular physiology. Magnesium deficiency is common, but its electrophysiological sequelae have escaped even the closest scrutiny. Magnesium therapy in pharmacologic doses has been beneficial in treating torsades de pointes. Magnesium toxicity rarely occurs except in patients with renal dysfunction.

Electrophysiological Effects and Electrocardiographic Manifestations of Hypomagnesemia and Hypermagnesemia

In the presence of extremely low extracellular calcium concentrations, magnesium exerts an effect on the current or currents that modulate the duration of the ventricular AP plateau. Hoffman and Suckling found that in the presence of normal calcium concentrations, magnesium deficiency had little effect on the AP of the canine papillary muscle.[2] However, when the calcium concentration was lowered to one tenth of the normal, complete omission of magnesium in the superfusate prolonged the AP plateau, which was already increased in duration by low calcium, from a normal value of 100 to 150 ms to 1000 ms or more.

Magnesium blocks the calcium channel, shifts the steady-state inactivation curve of the fast sodium channel in the hyperpolarizing direction, modifies the effect of hyperkalemia, and exerts modulating effects on several potassium currents. Hypermagnesemia depresses AV and intraventricular conduction. DiCarlo and coworkers observed the following electrocardiographic effects of intravenous administration of magnesium in patients with normal baseline serum magnesium and other electrolyte levels[35]: (1) prolongation of sinus node recovery time (SNRT) and corrected sinus node recovery time (CSNRT); (2) prolongation of the AV nodal functional, relative, and effective refractory periods; (3) a small increase in QRS duration during ventricular pacing at cycle lengths of 250 and 500 ms; and (4) a significant increase in the atrium–His interval and the atrial paced cycle length causing AV node Wenckebach conduction.

Kulick and associates, in studying healthier hearts, noted the following ECG effects of intravenous magnesium administration[36]: (1) significant prolongation of the P-R interval from 145 to 155 ms after magnesium infusion; (2) prolongation of the atrium–His interval; (3) prolongation of the sinoatrial conduction time (SACT); (4) prolongation of the AV nodal effective refractory periods; and (5) no significant increase in SNRT in the atrial paced cycle length which causes AV node Wenckebach conduction or in QRS duration. Hypermagnesemia and hypomagnesemia do not produce specific ECG changes.

Magnesium and Torsades de Pointes

The administration of intravenous magnesium sulfate to patients with prolonged Q-T interval and torsades de pointes, whether the initial magnesium level is normal or low, may suppress ventricular tachycardia. Takanaka and colleagues studied the effects of magnesium and lidocaine on the APD and on barium-induced EADs in canine Purkinje fibers. Their data suggested that hypomagnesemia may be arrhythmogenic when combined with hypokalemia and bradycardia, and that magnesium administration may suppress triggered activity, mainly by directly preventing the development of triggered APs.[37] In conclusion, magnesium sulfate is a very effective and safe treatment for torsades de pointes.[38]

Magnesium and Heart Failure

In a sample of ambulatory patients with heart failure, magnesium depletion in serum and tissue did not appear to occur more commonly in those with serious ventricular arrhythmias than in those without serious ventricular arrhythmias.[39] In patients with moderate to severe heart failure, serum magnesium does not appear to be an independent risk factor for either sudden cardiac death or all-cause mortality.[40] Hypomagnesemia was found to be associated with an increase in frequency of ventricular couplets, but it did not lead to a higher incidence of clinical events.[40]

Magnesium and Myocardial Infarction

Magnesium administration has been found to have a positive effect on the consequences of myocardial infarction in experimental models. Its effect in the clinical setting of myocardial infarction has been controversial. In the LIMIT-2 (Leicester Intravenous Magnesium Intervention Trial–2) study, magnesium administration was noted to have a positive effect on mortality rate, a finding that has not been reproduced in the ISIS-4 (International Study of Infarct Survival–4) trial.[41-46]

Relationship Among Potassium, Magnesium, and Cardiac Arrhythmias

No specific electrophysiological effects or arrhythmias have been linked to isolated magnesium deficiency. Nonetheless, magnesium may influence the incidence of cardiac arrhythmias through a direct effect by modulating the effects of potassium or through its action as a calcium channel blocker. Magnesium deficiency is thought to interfere with the normal functioning of membrane ATPase and, thus, the pumping of sodium out of the cell and potassium into the cell. This affects the transmembrane equilibrium of potassium, which may result in changes in the RMP, changes in potassium conductance across the cell membrane, and disturbances in the repolarization phase.[47]

Sodium

Sodium is the most abundant extracellular cation, and the sodium current determines the phase 0 and amplitude of the AP. Its conductance increases precipitously with the initiation of the AP, allowing its transmembrane gradient to determine the first phase of the AP, and, consequently, its ultimate configuration. Hence, hypernatremia increases and hyponatremia decreases phase 0 of the AP by altering the transmembrane sodium gradient. The upstroke of the AP is determined by the sodium gradient and the TP. Therefore, hypernatremia, by increasing the sodium gradient, negates many of the effects of hyperkalemia, which decreases the TP. By increasing the amplitude of the AP, high sodium levels prolong the APD. In vitro, an increased sodium concentration restores the normal configuration of AP that is altered by previous treatment with sodium channel blockers. Despite the frequency of sodium abnormalities, particularly hyponatremia, its electrophysiological effects are rarely of clinical significance.

Lithium

Although lithium is not a naturally occurring electrolyte, it is frequently encountered clinically in the treatment of manic-depressive disorders, and, as such, its potential adverse effects on the sinoatrial node should not be overlooked. Lithium is associated with sinoatrial node dysfunction (sinus bradycardia, sinoatrial arrest, or exit block, either type I or type II) and reversible T-wave changes.[48-50]

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CHAPTER 62

Genetic Diseases: The Long QT Syndrome

Peter J. Schwartz

Congenital long QT syndrome (LQTS) is a relatively uncommon but important clinical disorder. Since 1975, under the unifying name of the "long QT syndrome," it has been considered to include two hereditary variants.[1] Jervell and Lange-Nielsen syndrome (J-LN) is associated with deafness, and Romano-Ward syndrome (R-W) is not.[2-5]

Interest in LQTS has grown almost exponentially in the past 15 years for several reasons. One such reason is the dramatic manifestations of the disease, namely, syncopal episodes that often result in cardiac arrest (CA) and sudden death and usually occur in conditions of either physical or emotional stress in otherwise healthy young individuals, mostly children and teenagers. Another is that even though LQTS is a disease with a very high mortality rate among untreated patients, very effective therapies are available; this makes it unacceptable and inexcusable that symptomatic patients still remain undiagnosed or misdiagnosed. Last, but most certainly not the least, the identification of several genes responsible for LQTS as well as the realization, so far, that most of them encode ion channels has provided a new stimulus for clinical cardiologists and basic scientists. The impressive correlation between specific mutations and critical alterations in the ionic control of ventricular repolarization makes this syndrome a unique paradigm, which allows the correlation of genotype and phenotype, thus providing a direct bridge between molecular biology and clinical cardiology in the area of sudden cardiac death. In this chapter, the focus will be primarily on aspects related to clinical management, including some recent developments.

Molecular Genetics of Long QT Syndrome

The list of LQTS genes continues to grow. At the latest count, 12 of them had been identified, and the number is certain to increase. For practical purposes, however, the first three genes identified continue to remain the most important. This chapter will review only essential concepts; for additional details, interested readers are referred to more extensive reviews.[6]

KCNQ1 (LQT1) and *KCNE1* (LQT5)

The delayed rectifier current (I_K) is a major determinant of phase 3 of the cardiac action potential. It comprises two independent components: one rapid (I_{Kr}) and one slow, (I_{Ks}). The *KCNQ1* and *KCNE1* genes encode the α (KvLQT1) subunit and the β (MinK)-subunit, respectively, of the potassium channel conducting the I_{Ks} current. *KCNQ1* mutations are found in the LQT1 variant of LQTS, which is also the most prevalent.

Homozygous or compound heterozygous mutations of *KCNQ1* and *KCNE1* have been associated with the recessive J-LN form of LQTS (JLN1). LQT5 is an uncommon (2% to 3%) variant caused by mutations in the *KCNE1* gene. These mutations cause both R-W (LQT5) and J-LN (JLN2) syndromes.

Expression studies of mutated proteins have suggested multiple mechanisms of functional failure. Defective proteins may coassemble with wild-type proteins and exert a dominant negative effect. Other mutations lead to defective proteins that do not assemble with wild-type peptides, which results in a loss of function that reduces the I_{Ks} current by 50% or less (haplo-insufficiency). Finally, defective peptides may not even reach the membrane of the cardiac cell because the mutations interfere with intracellular protein trafficking.[7]

The I_{Ks} current is increased by sympathetic activation and by heart rate increases and is essential for QT adaptation. If I_{Ks} is defective, the Q-T interval will fail to shorten appropriately during tachycardia, and this creates a highly arrhythmogenic condition.

KCNH2 (LQT2) and *KCNE2* (LQT6)

The *KCNH2* and the *KCNE2* gene encode the α (HERG)-subunit and the β (MIRP)-subunit, respectively, of the potassium channel conducting the I_{Kr} current. This is the second most common variant of LQTS accounting for 35% to 40% of mutations in patients with the LQTS genotype. Mutations in *KCNH2* cause a reduction of I_{Kr} current. Defective proteins may cause a dominant negative effect on the wild-type subunits, or they may not interfere with the function of the normal subunits, thus causing haplo-insufficiency. Trafficking abnormalities are another consequence of *KCNH2* mutations.[7]

Mutations in the *KCNE2* gene are found in the LQT6 variant of LQTS. This gene encodes MiRP1 (MinK-Related Peptide 1), a small peptide that coassembles with the HERG protein to form the I_{Kr} channel. Few examples of *KCNE2* mutations associated with LQTS exist.

SCN5A (LQT3)

The *SCN5A* gene encodes the protein of the cardiac sodium channel. In vitro expression studies have shown that LQTS-*SCN5A* mutations produce the LQTS phenotype by inducing a "gain of function" leading to increase in the Na^+ inward current, which prolongs the action potential duration. The prevalence of LQT3 among LQTS patients is around 10%.[8]

CACNA1c (LQT8): Timothy Syndrome

LQT8 is a rare variant characterized by marked Q-T interval prolongation, often presenting with 2:1 functional atrioventricular (AV) block, macroscopic T-wave alternans, and syndactyly. LQT8 is highly malignant and 10 (59%) of 17 of the children reported by Splawski et al died at a mean age of 2.5 years. Additional abnormalities may be present in Timothy syndrome.[9]

This variant has been associated, so far, with one specific missense mutation (G406R) in the voltage-gated calcium channel gene (*CACNA1c*).[9] G406R produces sustained inward Ca^{2+} currents by causing nearly complete loss of voltage-dependent inactivation.[9] In the heart, prolonged Ca^{2+} current delays cardiomyocyte repolarization and increases the risk of arrhythmia.

Prevalence

In 1975, it was already suggested that LQTS "could be more unrecognized than rare."[1] However, until now the prevalence was assumed to be anywhere between 1 in 5000 and 1 in 20,000. None of these estimates was based on actual data.

The first data-based assessment of the prevalence of LQTS comes from the largest prospective study of neonatal electrocardiography ever performed, which involved 44,596 infants of 3 to 4 weeks of age in 18 Italian maternity hospitals.[10] An electrocardiogram (ECG) was performed in 44,596 infants 15 to 25 days old (43,080 whites). In infants with a QTc greater than 450 ms, the ECG was repeated within 1 to 2 weeks. Genetic analysis, by screening seven LQTS genes, was performed in 28 (90%) of 31 and in 14 (50%) of 28 infants with a QTc greater than 470 ms or between 461 and 470 ms, respectively, regarded as markedly prolonged by the European Task Force on Neonatal Electrocardiography.[11] QTc readings of 451 to 460 ms, 461 to 470 ms, and greater than 470 ms were observed in 184 (0.41%), 28 (0.06%), and 31 (0.07%) infants, respectively (Figure 62-1). Among genotyped infants, disease-causing mutations were found in 12 (43%) of 28 with a QTc greater than 470 ms and in 4 (29%) of 14 with a QTc of 461 to 470 ms. One genotype-negative infant (QTc of 482 ms) was diagnosed to be affected by LQTS on clinical grounds. Among family members of genotype-positive infants, 51% were found to carry disease-causing mutations. In total, 17 of 43,080 white infants were affected by LQTS, which demonstrated a prevalence of at least 1 per 2534 apparently healthy live births (95% confidence interval [CI] 1:1 to 583 to 1:4 to 350). Among them, 1.4% had a QTc between 440 ms and 469 ms and 0.7 of 1000 had a QTc of 470 ms or greater. As 43% of the infants with QTc 470 ms or greater (0.7 per 1000) and 29% of the infants with a QTc between 460 ms and 469 ms have disease-causing mutations and as at least some of the infants with a QTc between 450 ms and 459 ms are also likely to be mutation carriers, it follows that the prevalence of LQTS must be close to 1 per 2000. This does not include the silent mutation carriers (QTc < 440 ms), a group ranging between 10% and 36% according to genotype.[6] This is the first time that the prevalence of a cardiac disease of genetic origin has been quantified on the basis of actual data.

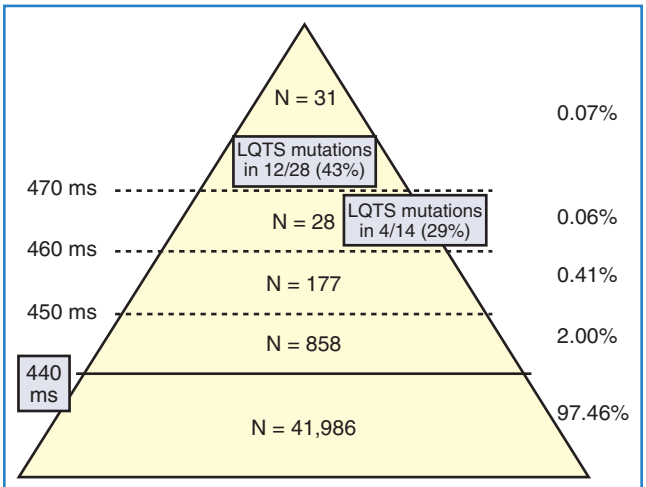

FIGURE 62-1 Distribution of the 43,080 white neonates among five subgroups (absolute numbers and percentage) according to QTc duration on the screening electrocardiogram. Neonates positive at the genetic analysis are also reported. *(From Schwartz PJ, Stramba-Badiale M, Crotti L, et al: Prevalence of the congenital long-QT syndrome,* Circulation *120:1761–1767, 2009.)*

Clinical Presentation

The large increase in the number of patients diagnosed as affected has significantly modified the perception of the natural clinical history of the disease. Since the early 1970s, when the first consistent series of patients were reported, the typical clinical presentation of LQTS was considered to be the occurrence of syncope or CA, precipitated by emotional or physical stress, in a young individual with a prolonged Q-T interval on the surface ECG.[1] If these symptomatic patients were left untreated, the syncopal episodes would recur and eventually prove fatal in the majority of cases. This concept was largely based on the fact that the patients initially diagnosed were those most severely affected. It has become progressively evident that this traditional picture represents an oversimplification, and it now appears that even though some patients have the severe manifestations described above, numerous patients have a very benign course as well. Unfortunately, the occasional occurrence of sudden death cannot yet be predicted. Evidence that modifier genes, some of them associated with the release of autonomic mediators, contribute to the highly different severity of the clinical manifestations of LQTS is growing.[12-15]

When family screening is performed, prolongation of the Q-T interval can be often detected, and a family history of fainting episodes or of sudden unexpected deaths in an early age is often present. Nonetheless, numerous sporadic cases (approximately 30%), that is, patients with syncope and a prolonged Q-T interval but without clinical evidence of familial involvement, do exist.[6]

The clinical history of repeated episodes of loss of consciousness under emotional or physical stress is typical and unique and is therefore unmistakable; however, the physician must be aware of the existence of LQTS to make the correct diagnosis. However, the clinical presentation is not always clear, so sometimes the diagnosis may be uncertain. The highly malignant J-LN syndrome will not be discussed here[2]; it must, however, be noted that its clinical course is very severe and that the patients become symptomatic at a very early age (Figure 62-2). Interested readers are referred to a comprehensive report on this variant.[3]

The two cardinal manifestations of LQTS are syncopal episodes and electrocardiographic abnormalities. The latter have

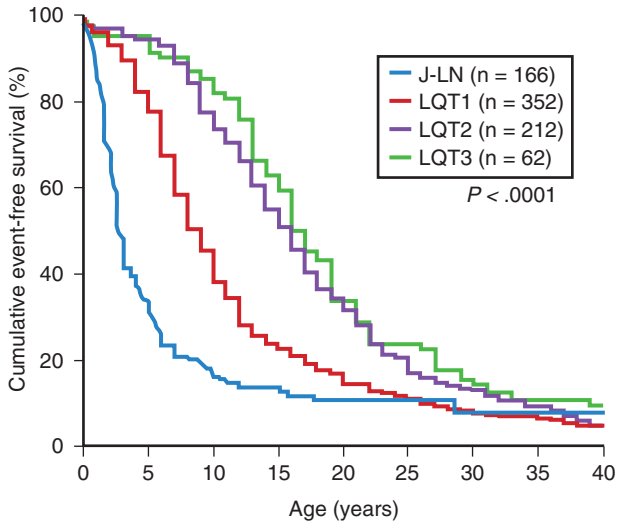

FIGURE 62-2 Kaplan-Meier curves of event-free survival. **A,** all patients with Jervell and Lange-Nielsen (*J-LN*) syndrome. **B,** All patients with J-LN, with a magnified view of the events occurring in the first 15 years of life. **C,** Patients with J-LN versus symptomatic patients with Romano-Ward syndrome of known genotype.[10] **D,** Patients with J-LN versus symptomatic patients with LQT1 and an unselected LQT1 population.[10,12] *(From Schwartz PJ, Spazzolini C, Crotti L, et al: The Jervell and Lange-Nielsen syndrome. Natural history, molecular basis, and clinical outcome,* Circulation *113:783–790, 2006.)*

been repeatedly described. Interested readers are referred to previous reviews.[5] Here we will mention only T wave alternans and a specific echocardiographic pattern.

T-Wave Alternans

In 1975, Schwartz proposed that T-wave alternans represents a characteristic ECG feature of LQTS.[16] Beat-to-beat alternation of the T wave, in polarity or amplitude, may be present at rest for brief moments but usually appears during emotional or physical stress and may precede torsades de pointes (TdP) (Figure 62-3). T-wave alternans is a marker of major electrical instability, and it identifies patients at particularly high risk. Its transient nature limits the possibility of its observation. This is a rather gross phenomenon that should not go unnoticed, when present. The observation of T-wave alternans in a patient with LQTS who is already on therapy strongly suggests the presence of a persisting high degree of cardiac electrical instability, which should prompt reassessment of therapy.

Echocardiographic Abnormalities

LQTS is still regarded by many as a purely electrical disease that does not involve any mechanical alterations. However, a case-control study demonstrated the frequent presence of highly unusual echocardiographic abnormalities among the patients.[17] These abnormalities included an increased rate of thickening in the early phase of contraction and the presence of a slow movement in the late thickening phase with a plateau morphology

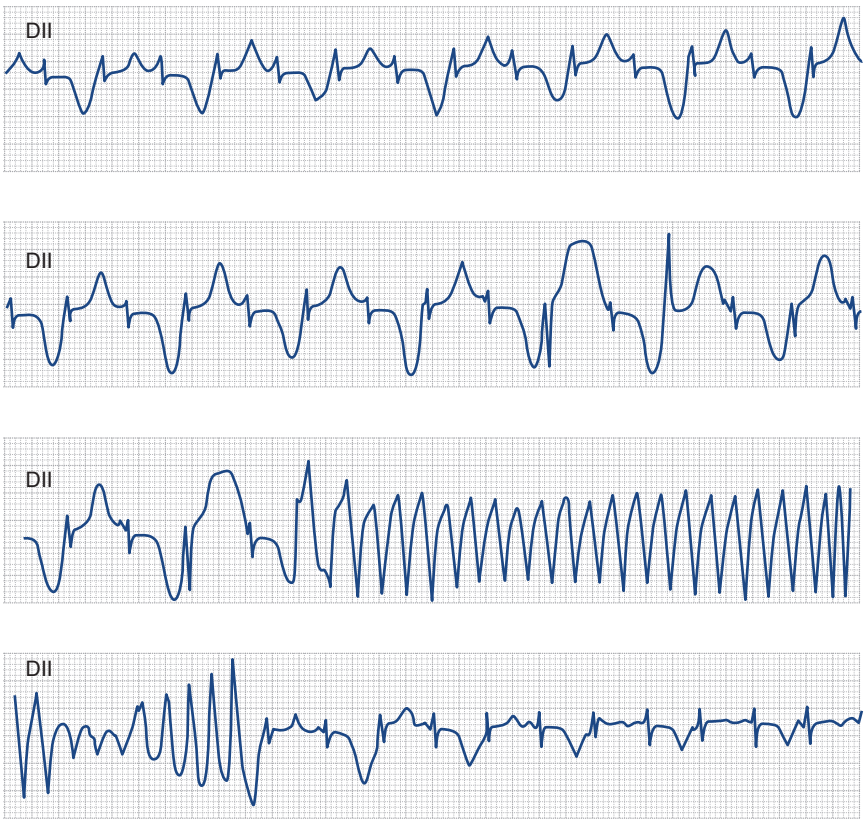

FIGURE 62-3 Five-year-old patient with Jervell and Lange-Nielsen syndrome. Tracing recorded during a syncopal episode. T-wave alternans precedes the onset of torsades de pointes (TdP). TdP is not preceded by a pause. *(From Pernot C: Le syndrome cardio-auditif de Jervell et Lange-Nielsen. Aspects electrocardiographiques,* Proc Ass Eur Paediat Cardiol *8:28–36, 1972.)*

sometimes accompanied by a second peak. Recently, these findings have been fully confirmed by a Norwegian study.[18,19] LQTS is, therefore, not a purely electrical disease. These abnormalities were more frequent in symptomatic patients than in asymptomatic patients, which suggests that these abnormalities may reflect the presence of an arrhythmogenic mechanism. The evidence that the calcium-entry blocker verapamil completely normalizes the contraction pattern suggests that symptomatic LQTS patients may have an abnormal increase in the intracellular calcium concentration before relaxation is completed and that this may be related to an early after-depolarization (EAD): The contraction abnormality would be the mechanical equivalent of an EAD.[20] The inward flux of calcium linked to the EAD may cause a small but rapid increase in intracellular calcium, which may be sufficient to trigger the calcium-induced release of calcium from the sarcoplasmic reticulum, causing a much greater increase in cytosolic calcium and the occurrence of a second contraction or the prolongation of the contraction itself.

Cardiac Events and Their Relationship to Genotype

The syncopal episodes are caused by TdP often degenerating into ventricular fibrillation. Long pauses facilitate the onset of TdP.[21] Although most LQTS patients develop their symptoms under stress, sometimes these life-threatening cardiac events occur at rest. The reason(s) for these different patterns remained obscure until molecular biology was able to distinguish among different genotypes. In 1995, an unexpected observation was made that among a tiny group of genotyped individuals, LQT2 patients appeared to be at higher risk during emotional stress, whereas LQT3 patients had their events mostly at rest or during sleep; this fostered a large and targeted study that shed light on this issue of major clinical relevance.[22,23]

In 670 LQTS patients of known genotype and who all had symptoms (syncope, CA, or sudden death), Schwartz et al examined possible relationships between genotype and the conditions ("triggers") associated with the events.[23] As predicted by their impairment on the I_{Ks} current (essential for QT shortening during increases in heart rate), most of the events in LQT1 patients occurred during exercise or stress. Swimming is especially dangerous for them, and 99% of the events which occurred while swimming did involve LQT1 patients. Conversely, most of the events (including the lethal ones) in LQT2 patients occurred during emotional stress such as auditory stimuli (e.g., sudden noises and telephone ringing, especially occurring while at rest), and most of the events of LQT3 patients occurred while they were asleep or at rest (Figure 62-4).

Patients with LQT2 and LQT3 are at low risk during exercise because they have a well-preserved I_{Ks} current and are therefore able to shorten their Q-T interval whenever the heart rate increases. The practical implication is that young individuals with LQT2 and LQT3 should be allowed to play (no competitive sports, however) rather freely, which would give them significant psychological benefits.

In women, even during the postpartum period, genotype is important because the risk is higher for patients with LQT2 than for those with LQT1.[24,25] The higher risk for women with LQT2 is probably partly related to sleep disruption; accordingly, it is recommended that the spouses or other caregivers take on some of the night-time feeding of the infants, thus allowing a fair amount of uninterrupted sleep for the women with LQT2.

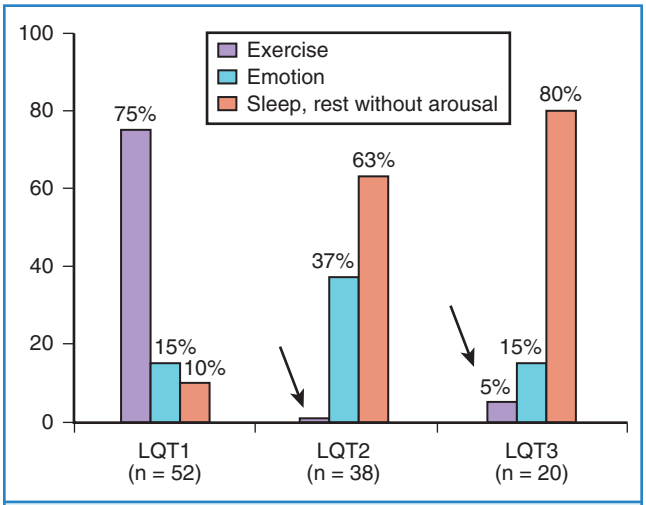

FIGURE 62-4 Lethal cardiac events according to triggers and genotype. Numbers in parentheses are triggers, not patients. *(Modified from Schwartz PJ, Priori SG, Spazzolini C, et al: Genotype-phenotype correlation in the long QT syndrome. Gene-specific triggers for life-threatening arrhythmias,* Circulation *103:89–95, 2001.)*

These significant genotype-phenotype correlations have an impact on management.

Molecular Diagnosis in Long QT Syndrome

Who Should Be Screened for Long QT Syndrome and Medico-legal Implications

Molecular diagnosis should always be attempted whenever LQTS has either been diagnosed or is suspected on sound clinical grounds. When successful (80% to 85% of cases in the author's laboratory), it allows the rapid screening of all the family members and the identification of all the "silent mutation carriers" (individuals with a disease-causing mutation and a QTc less than 440-ms interval) whose prevalence increases from 10% for LQT3 to 37% for LQT1 patients.[26]

This has major clinical and medico-legal implications. For example, suppose that in a family with a boy and a girl, the boy and one parent are clearly affected (syncope and prolonged QTc). If the girl has a normal Q-T interval and is incorrectly assumed to be unaffected, she might later be treated with one of the many drugs that block the I_{Kr} current; she could develop TdP and die. This would not be bad luck; it would be the direct responsibility of the physician who had not had molecular screening done for the boy who was clearly affected: Identification of the disease-causing mutation would have allowed rapid determination of whether the girl was a mutation carrier, which would have saved her life. Physicians who do not attempt to genotype their LQTS probands are deliberately choosing to ignore the possibility that other family members might be mutation carriers at risk for sudden death.

Molecular Genetics and Risk Stratification

Molecular genetics contribute importantly to risk stratification. In 2003, data on 647 patients of known genotype from 193

families indicated that the incidence of life-threatening events was lower among LQT1 patients, but this was partly because of the high prevalence of silent mutation carriers (QTc < 440 ms); the risk was higher among females with LQT2 compared with males with LQT2 and among males with LQT3 compared with females with LQT3. Independent of genotype, the risk of becoming symptomatic was strongly correlated with QTc and was markedly greater with QTc greater than 500 ms. Most of the patients with LQT1 go through life without ever having cardiac events; also, among patients with LQT2 and LQT3, almost half of them remain asymptomatic. The fact that this is often forgotten is shown by the growing preference for implantable cardioverter-defibrillator (ICD) implantations in asymptomatic individuals just because they have been diagnosed with LQTS.[27]

In 2002, Moss et al indicated that patients with LQT2 with mutations in the pore region were at higher risk compared with patients with LQT2 with mutations in different regions of the same gene.[28] In 2007, Moss et al demonstrated in 600 patients with LQT1 that both the transmembrane location of the mutations and their dominant-negative effect are independent risk factors for cardiac events.[29] Shortly thereafter, Crotti et al focused on the hot spot *KCNQ1*-A341V, a common mutation found responsible for a founder effect in 25 South African families, and demonstrated that the unusually high clinical severity already reported by Brink et al in the South African families is present also among patients with LQT1 from different ethnic backgrounds but carrying the same A341V mutation.[30,31] Moreover, as *KCNQ1*-A341V has a mild dominant-negative effect (the current loss barely exceeds 50%), its striking clinically severe phenotype is explained neither by the location (transmembrane) nor by the functional consequence of the mutation (dominant-negative). This implies that the current biophysical assessments of the electrophysiological effects of LQTS-causing mutations do not provide all the information necessary to make a complete genotype-phenotype correlation. In this regard, the study by Crotti et al paves the way for a mutation-specific risk stratification.[30]

The risk stratification process is complicated by the presence of additional genetic variants that may modify clinical severity, as demonstrated in a family with LQT2 with C-terminal A1116V mutation, where the risk for life-threatening events was increased by the presence of the very common *KCNH2*-K897T polymorphism. Electrophysiological evidence did show that K897T produces an accentuation of the mutation-dependent I_{Kr} current loss resulting in the unmasking of a clinically latent C-terminal LQT2 mutation.[13] This finding has very recently confirmed by Antzelevitch's group in sudden infant deaths.[32]

Genetic variations in *NOS1AP*, which encodes a nitric oxide synthase adaptor protein, contribute to Q-T interval duration in the general population.[33] Accordingly, the author's group tested in their enlarged South African founder population (500 subjects, 205 mutation carriers) the hypothesis that *NOS1AP* is a genetic modifier of LQTS. The main findings were that two *NOS1AP* variants (rs4657139 and rs16847548) were significantly associated with occurrence of symptoms, with clinical severity manifested by an almost double probability for CA and sudden death, and with a greater likelihood of having a Q-T interval in the top 40% of the values among all mutation carriers. This is the first evidence, demonstrated in subjects sharing the same mutation, that *NOS1AP* is a genetic modifier of LQTS and that some of its variants are associated with a greater risk for CA and sudden death.[15] One of the best evidences for the value of molecular biology in risk stratification comes from J-LN syndrome, in which a striking difference in prognosis is seen, according to the gene involved, *KCNQ1* or *KCNE1* (Figure 62-5).[3]

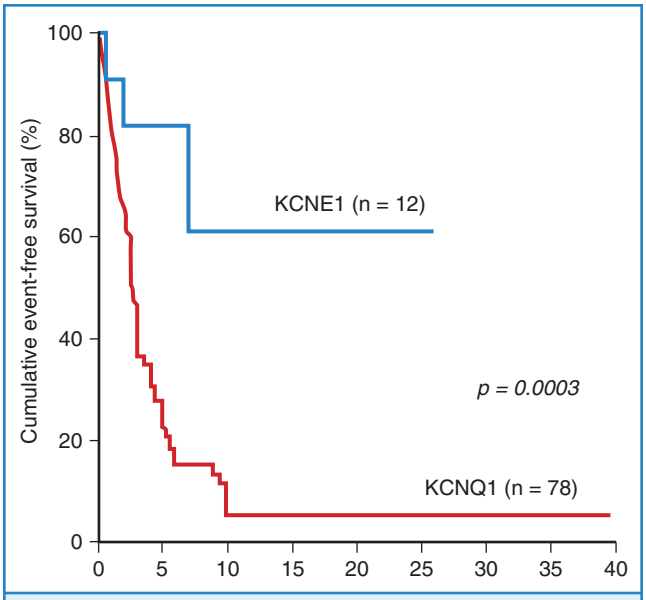

FIGURE 62-5 Kaplan-Meier curve of event-free survival in patients with Jervell and Lange-Nielsen syndrome, with mutations in *KCNQ1* or *KCNE1* genes. *(From Schwartz PJ, Spazzolini C, Crotti L, et al: The Jervell and Lange-Nielsen syndrome. Natural history, molecular basis, and clinical outcome,* Circulation *113:783–790, 2006.)*

Clinical Diagnosis

Given the characteristic features of LQTS, the typical cases present no diagnostic difficulty for the physicians who are aware of the disease. However, borderline cases are more complex and require the evaluation of multiple variables besides clinical history and ECG studies. Diagnostic criteria were proposed in 1985 and subsequently updated in 1993 and in 2006.[4,34-36]

The new diagnostic criteria are listed in Table 62-1. In the experience of the author of this chapter, the point score was arbitrarily divided into three probability categories: (1) ≤1 point = low probability of LQTS; (2) >1 to 3 points = intermediate probability of LQTS; and (3) ≥3.5 points = high probability of LQTS. Whenever a patient receives a score of 2 to 3 points, serial ECGs and especially several 24-hour Holter recordings should be obtained because the QTc value in patients with LQTS may vary from time to time and from day to night. In this group, with intermediate probability of LQTS, the presence of additional morphologic abnormalities may help in diagnostic decisions. Often, precordial leads are more informative.

The diagnostic criteria discussed above were conceived in the premolecular era and should be used with common sense. Obviously, they cannot be of value in identifying the so-called *silent mutation carriers,* who have a normal Q-T interval. For these individuals, molecular screening is essential. The main value of these clinical criteria is at the time of the first contact with a patient and in clinical studies when uniformity in diagnosis is essential.

Table 62-1 1993–2006 Long QT Syndrome (LQTS) Diagnostic Criteria

	POINTS
ELECTROCARDIOGRAPHIC FINDINGS*	
>480 ms	3
A. QTc†	
460–470 ms	2
450–459 (male) ms	1
B. Torsade de pointes‡	2
C. T-wave alternans	1
D. Notched T wave in three leads	1
E. Low heart rate for age§	0.5
CLINICAL HISTORY	
With stress	2
A. Syncope‡	
Without stress	2
B. Congenital deafness	0.5
FAMILY HISTORY¶	
A. Family members with definite LQTS	1
B. Unexplained sudden cardiac death before age 30 years among immediate family members	0.5

**In the absence of medications or disorders known to affect these electrocardiographic features.*
†QTc calculated by Bazett's formula, where $QTc = QT/\sqrt{RR}$.
‡Mutually exclusive.
§Resting heart rate below the second percentile for age.
¶The same family member cannot be counted in A and B.
Score: ≤1 point = low probability of LQTS; >1 to 3 points = intermediate probability of LQTS; ≥3.5 points = high probability of LQTS.

Therapy

Antiadrenergic Interventions

The most significant information on therapy still comes from a 1985 study, which included 233 symptomatic patients with detailed clinical information on the time of first syncope and with an adequate follow-up.[37] The mortality at 15 years after the first syncope was 9% in the group treated by antiadrenergic therapy (β-blockers, sympathectomy, or both) and more than 53% in the group not treated or treated by miscellaneous therapies not including β-blockers. These data conclusively demonstrated that pharmacologic antiadrenergic therapy, surgical antiadrenergic therapy, or both radically modify the prognosis for symptomatic patients with LQTS. In 2009, mortality among patients treated with β-blockers and left cardiac sympathetic denervation (LCSD) dropped to around 1%. The dramatic success of carefully executed therapies underscores the unacceptability of symptomatic patients with LQTS being either undiagnosed or incorrectly treated.

β-Blockers

β-Adrenergic blocking agents represent the first-choice therapy in symptomatic patients with LQTS, unless specific contraindications are present.

Propranolol and nadolol are the two most effective drugs. Their dosages are 3 mg/kg (sometimes increased to 4 mg/kg) and 1 mg/kg, respectively. The main advantages of propranolol are its lipophilicity, which allows it to cross the blood-brain barrier, and its well-known tolerability for chronic therapy; its main disadvantages are the need of multiple daily administrations and its contraindications for patients with asthma and diabetes. Nadolol is used more and more often, as its longer half-life allows twice-daily administration at a daily dose slightly lower than that of propranolol. This increases compliance, particularly in teenagers who may easily forget to take their medication in the afternoon. Unfortunately, β-blockers are not identical, and many of them are unquestionably less effective; this group includes bisoprolol, metoprolol, atenolol, and carvedilol.

In a large number of patients of unknown genotype, mortality on β-blocker therapy was 2%, and it was 1.6% when limited to patients with syncope (no cardiac arrest) and without events in the first year of life.[38] Clear evidence that β-blockers are extremely effective in LQT1 patients does exist. Data from two large studies reported mortality around 0.5% and sudden death combined with CA up to 1%.[23,39] The impairment in the I_{Ks} current makes these patients particularly sensitive to catecholamines and quite responsive to β-blockade. These patients seldom need more than antiadrenergic therapy.

Particularly, important information has come from a study published in 2009.[40] Vincent et al performed a retrospective study of the details surrounding cardiac events in 216 patients with genotyped LQT1, who were treated with β-blockers and were followed up for 10 years. Before β-blocker therapy, cardiac events occurred in 157 patients (73%) at a median age of 9 years, with CA in 26 (12%). After β-blockers, 75% were asymptomatic, and the risk for life-threatening cardiac events was reduced by 97% ($P < .001$). Twelve patients (5.5%) had a CA or sudden death, but 11 (92%) of 12 were noncompliant (n = 8), were on a QT-prolonging drug (n = 2), or both (n = 1) at the time of the event. The risk for CA or sudden death in compliant patients not taking QT-prolonging drugs was dramatically less compared with noncompliant patients on QT-prolonging drugs (odds ratio, 0.03; 95% CI, 0.003 to 0.22; $P < .001$). None of the 26 patients with CA before β-blocker had CA or sudden death on β-blockers. The conclusion was that β-blockers are extremely effective in treating LQT1. Noncompliance with β-blocker therapy and use of QT-prolonging drugs are responsible for almost all life-threatening β-blocker "failures."

Partly because of the small numbers available (which affect percentages), a concept unsupported by firm evidence has rapidly spread—that LQT3 patients are not protected at all by β-blockers or by antiadrenergic therapy. In fact, actual data point to a profound difference seen among these patients on the basis of the age of the first manifestation. On the one hand, if cardiac events occur during the first year of life, then β-blockers are insufficient and the disease has a highly malignant course. On the other hand, with a mean follow-up of 9 years, patients without cardiac events in the first year of life have done extremely well with β-blockers, LCSD, or both.[41] Larger studies will have to be performed, but available evidence indicates that a molecular diagnosis of LQT3 in an asymptomatic patient should never lead to an automatic decision for ICD implantation.

Left Cardiac Sympathetic Denervation

A thorough description of LCSD has recently been published.[42] Following a small incision in the left subclavicular region, LCSD is performed using an extrapleural approach, which makes thoracotomy unnecessary. The average time for surgery is 35 to 40 minutes. LCSD requires the removal of the first four thoracic ganglia. The cephalic portion of the left stellate ganglion is left intact to avoid Horner's syndrome. In almost 30% of patients, a very modest (1 to 2 mm) ptosis, which can be noted only by close examination but fully escapes notice in normal social interactions, results.

The latest data published in 2004 include 147 patients with LQTS who underwent LCSD during the past 35 years.[43] They represented a very high-risk group, as 99% were symptomatic, their mean QTc being very long (563 ± 65 ms), 48% had a CA, and especially 75% continued to have syncope despite full-dose β-blockers. The data most relevant to current clinical decisions are those regarding patients without cardiac arrest (who almost always should receive an ICD) who have syncope despite being treated with a full dose of β-blockers. During a mean follow-up of 8 years, a 91% reduction in cardiac events was observed. LCSD produced a mean QTc shortening of 39 ms, which indicates an action on the substrate as well as on the trigger. Mortality was 3% in this high-risk group. A postsurgery QTc less than 500 ms predicted a highly favorable outcome. Importantly, this series included five patients who underwent LCSD because they had experienced multiple ICD shocks and electrical storms: in this group, over a 4-year follow-up, a 95% decrease in the number of shocks (from an average of 29 shocks per year), with a dramatic improvement in the quality of life of the patients and of their families, was observed.

The major antifibrillatory efficacy of LCSD has been previously demonstrated in high-risk patients with post–myocardial infarction; and recently, it was demonstrated in patients with catecholaminergic polymorphic ventricular tachycardia (CPVT), who were not protected by β-blockers and were receiving multiple appropriate shocks from the ICD.[44,45] The Boston Children Hospital and the Mayo Clinic have recently published their highly successful experience with LCSD in both LQTS and CPVT.[46-48]

Whenever syncopal episodes recur despite full-dose β-blocking therapy, LCSD should be considered and implemented whenever possible. It is unfortunate that despite its relative simplicity, LCSD is not performed in many high-risk patients because cardiovascular surgeons are no longer familiar with the procedure. The consequence is that too often the choice goes to the easiest approach, namely, ICD implantation, even when this choice is not the best for the patient. Before making a decision on therapy for a young patient who experiences syncope despite β-blockers, the patient and the family have the right to be informed about the long-term benefits and limitations of both LCSD and ICD implantation.

Implantable Cardioverter-Defibrillators

A major, largely unjustified, increase has been seen in the number of ICDs implanted in patients with LQTS. A consensus seems to exist for immediately implanting an ICD in case of a documented CA, either on or off therapy, unless the event occurs because of a transient and reversible cause. By contrast, opinions differ strongly regarding the use of ICDs in patients who have not had a cardiac arrest.

The U.S. and the European ICD-LQTS Registries provide the disquieting information that the majority of implanted patients had not had a CA and that many had not even failed β-blocker therapy.[49,50] A recent multicenter study went so far as to indicate that the mere presence of an *SCN5A* mutation, even in a totally asymptomatic individual, is sufficient for immediate ICD implantation.[27]

It should not be forgotten that ICDs do not prevent occurrence of malignant arrhythmias and that TdP is frequently self-terminating in LQTS. The recurrence of electrical storms has led to suicide attempts by teenagers; the high incidence (>10%) of electrical storms in children has been considered "devastating" by a large group of experienced pediatric cardiologists.[51] The massive release of catecholamines—triggered by pain and fear that follow an ICD discharge in a conscious patient, especially a young one—leads to further arrhythmias and to further discharges, all of which produce a dramatic vicious circle.

Special caution is necessary before choosing to implant an ICD in a child with LQTS. Such a decision is seldom justified before a proper trial with combined antiadrenergic therapy, that is, full-dose β-blockade and LCSD, which prevents sudden death in 97% to 98% of symptomatic and high-risk patients and which still allow an ICD implant in case of a new syncope or CA. However, the nature of the disease is such that CAs may recur and have lethal consequences. Thus, concerns for the life of the patients and the interference of medico-legal considerations are the reality. The risk-benefit ratio of an ICD should be clearly explained to the patient or to his or her parents, and information on the pros and cons of LCSD should be provided, to allow them to make an informed choice.

The European data on 233 patients with LQTS who had an ICD indicate that 9% of these patients were asymptomatic and that 41% received an ICD without having been first on LQTS therapy.[50] Within 5 years 31% of the patients had adverse events. Appropriate ICD discharges (in 28% of patients) were predicted by age younger than 20 years at implantation, prior CA, and cardiac events despite therapy. Among patients without these factors, no one received appropriate shocks within 7 years, in contrast to 70% of those with all four factors.

The current policy of the author's group is to implant an ICD after a CA has occurred, with the exception of reversible or transient triggers; always when firmly requested by the patient; when syncope recurs despite β-blockade and LCSD; and whenever clinical sense detects imminent danger despite therapy.

Gene-Specific Therapy and Management

Patients with LQT1 are at higher risk during sympathetic activation, such as during exercise and emotions. They should not participate in competitive sports. Swimming is particularly dangerous, as 99% of the arrhythmic episodes in patients with LQT1 were associated with swimming.[23]

In patients with LQT2, some of whom have a tendency to lose potassium (K^+), it is essential to preserve adequate K^+ levels. Oral K^+ supplements in combination with K^+-sparing agents are a reasonable approach. As these patients are at higher risk, especially when aroused from sleep or rest by a sudden noise, it is recommended that telephones and alarm clocks be removed from their bedrooms; especially in the case of children, whenever they have to be wakened in the morning, it should be done gently and without yelling.[23]

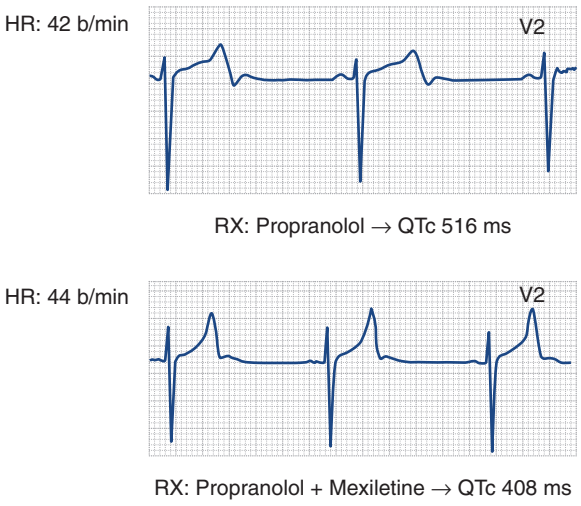

FIGURE 62-6 LQT3 patient aged 17 years, major QTc prolongation (QTc 516 ms) not modified by β-blocker therapy. The addition of oral chronic therapy with mexiletine (200 mg twice daily) produced a major shortening of QTc by over 100 ms and persisted over time. *HR,* Heart rate. *(From Schwartz PJ, Crotti L: Long QT and short QT syndromes. In Zipes DP, Jalife J, editors:* Cardiac electrophysiology: From cell to bedside*, ed 5, Philadelphia, 2009, Saunders.)*

The realization that *SCN5A* mutations producing LQT3 have a "gain-of-function" effect has lent support to the early suggestion by the author's group to try sodium channel blockers, especially mexiletine, as possible adjuvants in the management of patients with LQT3.[8,22,36] The author's group tests the effectiveness of mexiletine in all patients with LQT3 by using the acute oral drug test technique (half the daily dose during continuous ECG monitoring). Within 90 minutes, the peak plasma concentration is reached; if the QTc is shortened by more than 40 ms, then mexiletine is added to β-blocker therapy. In fact, in most patients with LQT3, QTc is shortened by more than 70 to 80 ms with mexiletine (Figure 62-6). Even though no conclusive evidence for a beneficial effect exists and definite failures have occurred, evidence of significant benefit in a number of individual cases is growing. The highly malignant forms manifest in infancy because of mutations that cause extremely severe electrophysiological dysfunction, which is corrected by the combination of mexiletine and propranolol.[52]

During heart rate increases, QTc shortens more in patients with LQT3 than among healthy controls; indeed, normal physical activity may not have to be restricted in patients with LQT3.[22] They are at higher risk of death at rest, especially at night-time. When these patients sleep and are in a horizontal position, the onset of TdP produces a progressive but slow fall in blood pressure, which facilitates noisy gasping preceding death. Patients with LQT2 (also at risk while resting) as well as those with LQT3 have, on occasion, been saved by family members, for example, the spouse sleeping next to the patient. Therefore, it is recommended that patients with LQT2 and LQT3 keep an intercom system in their bedrooms and, if young, in the parents' or other caregivers' bedrooms.

Asymptomatic Patients with LQTS and Patients with a Normal QTc

As the first manifestation of LQTS in approximately 12% of cases is sudden death, β-blocker treatment should be initiated in all patients, including those still asymptomatic. Among these, reasonable exceptions appear to be males above age 20 to 25 years with LQT1—because very seldom does the first event occur later than this age—and adults with a QTc less than 500 ms. Women with LQT2 seem to remain at risk throughout life, and it is recommended that they receive treatment throughout their lives. Patients with a normal QTc (<440 ms) appear to be at very low risk for life-threatening arrhythmias. In the absence of any clear follow-up data, treatment is optional for them; the characterization of the mutation could influence this choice. Cardiac and noncardiac drugs that block the I_{Kr} current and thereby prolong the Q-T interval should always be avoided by patients with LQTS. A drug list is available at www.torsades.org. Such a list, updated every year, should be given to all patients with LQTS because their physicians may not be aware of these electrophysiological actions.

Overview on Therapy

The clear data available and decades of clinical experience dictate the therapeutic approach for the patient affected by LQTS who already has had a syncopal episode. Treatment should always begin with β-blockers, unless valid contraindications are present. If the patient has one more syncope despite full dose β-blockade, LCSD should be performed without hesitation, and ICD implantation should be considered and the final decision based on individual patient characteristics (age; sex; previous history; genetic subgroup, sometimes including mutation-specific features; presence of ECG signs, including 24-hour Holter recordings, that indicate high electrical instability). In the final analysis, careful clinical judgment, accompanied by a thorough knowledge of the several variants of this unique life-threatening cardiac disorder has no substitute, as the goal is to not only protect patients but also ensure their quality of life.

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CHAPTER 63

Genetic Diseases: Brugada Syndrome

Begoña Benito, Pedro Brugada, Josep Brugada, and Ramon Brugada

Sudden cardiac death (SCD) is a major cause of mortality in the Western world, with an approximate incidence of 1 per 1000 per year. Coronary artery disease is the most common cause of SCD. In the absence of coronary disease, SCD is commonly caused by a ventricular arrhythmia in patients with some form of structural heart disease. However, in 10% to 20% of cases, no cardiac structural abnormalities are found at autopsy or after extensive medical investigation of the survivors. In 1992, Brugada and Brugada described a new syndrome causing SCD in individuals with normal hearts.[1] Today, generally known as *Brugada syndrome,* this new entity is thought to be responsible for up to 20% of SCDs that occur in individuals with structurally normal hearts.[2]

Brugada syndrome was initially described as a clinical syndrome characterized by (1) an electrocardiogram (ECG) resembling a right bundle branch block with a particular morphology of ST-segment elevation in right precordial leads (Figure 63-1, *A*) and (2) a susceptibility to developing polymorphic ventricular arrhythmias that cause syncope when self-terminating and SCD when long lasting and not terminated by cardiopulmonary resuscitation.[1] After the initial description of the first eight patients, numerous works appeared either focusing on clinical characteristics of larger populations or defining the genetic, molecular, and cellular aspects of the disease.[3-12] In recent years, major advances in clinical and mechanistic knowledge have provided very valuable information about the disease, but questions still remain, propelling large research activity on the subject. This chapter reviews the current knowledge on clinical, genetic, and molecular features of Brugada syndrome and provides updated information supplied by recent clinical and basic studies.

Definition and Epidemiology

The diagnosis of Brugada syndrome is obvious when the ECG has a certain appearance, as in Figure 63-1, *A*. However, certain ambiguities appeared in the years following the initial description of the syndrome. Three repolarization patterns were soon identified (Figure 63-1, *B*)[13]: (1) type 1 ECG pattern, as described in the initial report in 1992, in which a coved ST-segment elevation 2 mm or greater is followed by a negative T wave, with little or no isoelectric separation, this feature being present in more than one right precordial lead (from V1 to V3); (2) type 2 ECG pattern, also characterized by an ST-segment elevation but followed by a positive or biphasic T wave, which results in a saddle-back configuration; (3) type 3 ECG pattern, a right precordial ST-segment elevation 1 mm or less either with a coved-type or a saddle-back morphology. Although all three patterns can be present in Brugada syndrome patients (see section on Electrocardiography and Modulating Factors), only the type 1 ECG is diagnostic of the syndrome, as it was stated in the first consensus report of the Arrhythmia Working Group of the European Society of Cardiology and subsequently confirmed in the II Consensus Conference published in 2005.[2,13] Both documents also held that in order to establish the definite diagnosis of Brugada syndrome, the type 1 ECG pattern should be documented in combination with one of the following clinical criteria: (1) documented ventricular fibrillation (VF), (2) polymorphic ventricular tachycardia (VT), (3) a family history of sudden death (SD) at an age younger than 45 years, (4) the presence of coved-type ECG in family members, (5) inducibility of ventricular arrhythmias with programmed electrical stimulation, (6) syncope, or (7) nocturnal agonal respiration.[2,13] However, this definition should be applied with caution, especially when causative mutations have been identified and the disorder can be understood as a disease rather than a syndrome.[14,15] In this regard, data from the authors of this chapter confirm that only the presence of the characteristic type 1 ECG pattern, even with no further clinical criteria, may be associated with SD in the follow-up.[15] This confirms the need for monitoring all patients, even when an isolated type 1 ECG pattern is found.

The prevalence of Brugada syndrome has been estimated as 5 in 10,000, although this rate may be an underestimation of the real prevalence, as many patients have concealed forms of the disease and remain underdiagnosed. Importantly, significant ethnic and geographic differences have been described.[2] For example, the type 1 ECG pattern was observed in 12 of 10,000 in Japan, whereas the few available data on North American and European populations point to a much lower prevalence.[16-18] In fact, the syndrome is considered endemic in certain Southeast Asian countries, where it has long been known as sudden unexplained death syndrome (SUDS), also called *bangungot* (in the Philippines), *pokkuri* (in Japan), or *lai tai* (in Thailand); all of these are phenotypically, genetically, and functionally identical to Brugada syndrome.[19]

Genetics of Brugada Syndrome

Inheritance in Brugada syndrome occurs via an autosomal dominant mode of transmission, although in some cases, the disease can be sporadic, that is, absent in parents and other relatives.[2] Thus far, all the mutations that have been linked to Brugada syndrome affect (directly or indirectly) the normal function of specific ion channels participating in the action potential (AP). Therefore, Brugada syndrome is included among the so-called

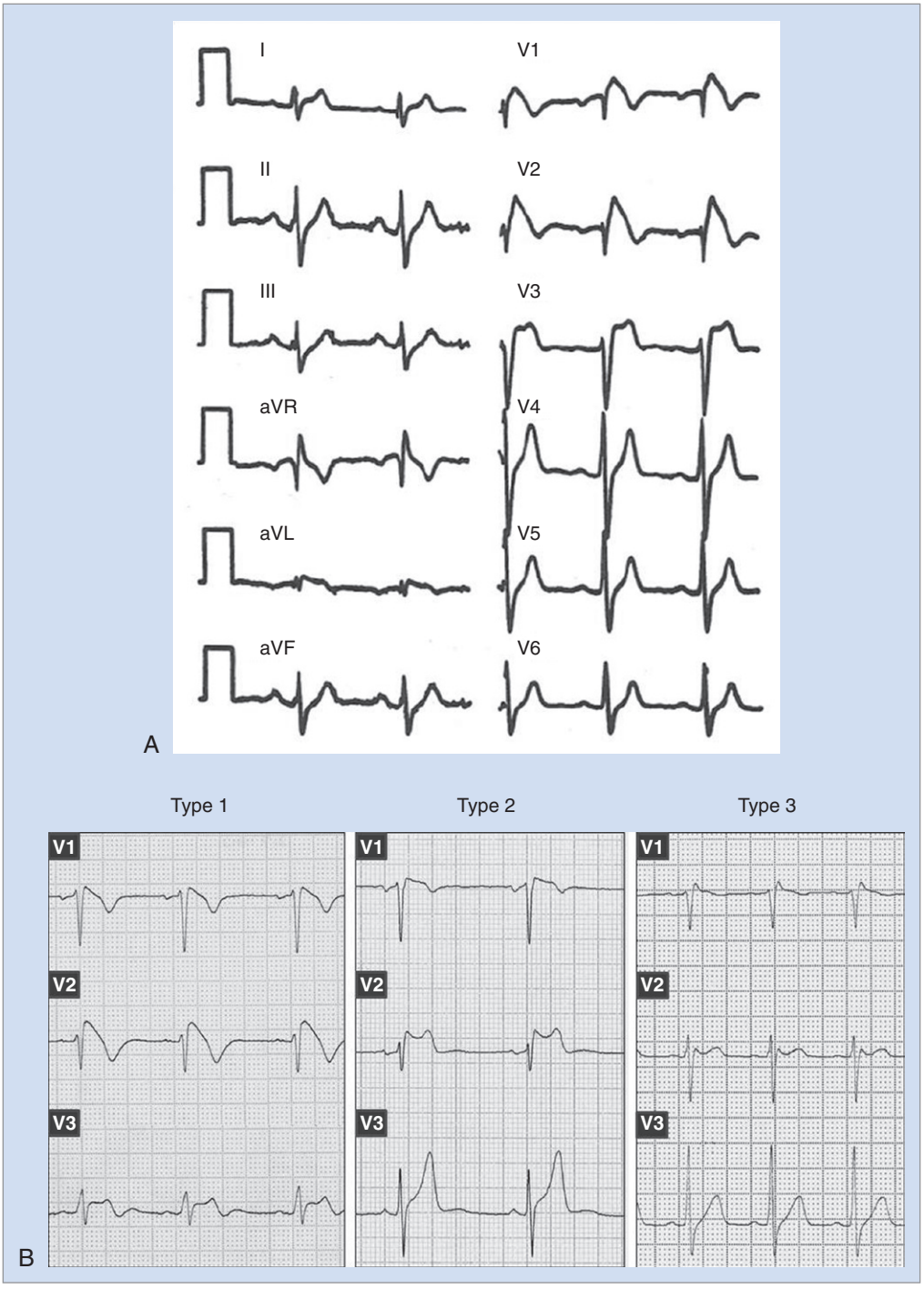


FIGURE 63-1 A, Typical electrocardiogram (ECG) of Brugada syndrome. Note the ST-segment elevation in leads V1 to V3 with a terminal negative T wave. **B,** Three different ECG patterns in right precordial leads frequently observed in patients with Brugada syndrome: type 1, also called *coved-type*, ECG pattern, in which a descendent ST-segment elevation is followed by negative T waves; this is the characteristic ECG in Brugada syndrome [*see also* ***A***] and the one required to establish the definite diagnosis of the disease; type 2, or saddle-back pattern, an ST-segment elevation followed by positive or biphasic T waves; type 3, either a coved-type or a saddle-back morphology with ST-segment elevation <1 mm.

channelopathies, together with other primary electrical disorders such as long QT syndrome (LQTS).

The first mutations related to Brugada syndrome were described in 1998 by Chen and coworkers and were identified in *SCN5A*, the gene encoding the α-subunit of the cardiac sodium channel (locus 3p21, 28 exons).[8] To date, more than 100 other different mutations associated with the syndrome have been found in the same gene.[9,12,19-23] For the majority of them, functional studies performed with expression systems have demonstrated a loss of function of the sodium channel that translates into a decrease in sodium

current (I_{Na}), which is achieved either through a quantitative decrease (failure in their expression) or through a qualitative dysfunction (impaired kinetics) of the channels.[9,12,19-23]

Although for almost a decade *SCN5A* has been the only gene linked to Brugada syndrome, mutations in *SCN5A* are generally found in only 18% to 30% of patients, which suggests a genetic heterogeneity of the disease.[2] Accordingly, in the past 2 years, four other genes have been found to be linked to Brugada syndrome. The first of them, glycerol-3-phosphate dehydrogenase 1–like (*GPD1-L*), was described in 2007 after previous identification of the locus on chromosome 3 (3p22-p24) in 2002.[24,25] The A280V mutation in *GPD1-L* was shown to induce a sodium loss-of-function effect by affecting the trafficking of the cardiac sodium channel to the cell surface.[24] Very interestingly, two recent reports demonstrated that mutations in genes other than those involved in the sodium channel function can be responsible for some cases of Brugada syndrome. In 2007, Antzelevitch et al linked loss-of-function mutations in the genes encoding the cardiac calcium channel Cav1.2 (*CACNA1c*) and its β-subunit *CACNB2b* to a syndrome overlapping short QT and the Brugada ECG pattern.[26] More recently, the same group of investigators described the first family with Brugada syndrome identified to be carrying a mutation (R99H) in the *KCNE3* gene, which encodes a β-subunit that is thought to modulate Kv4.3 channels and to be responsible for an increase in transient potassium I_{to} currents.[27] Together, these findings open up new lines of research, where the concept of Brugada syndrome as a pure sodium channelopathy has given way to the concept of the syndrome as an ionic imbalance between inward and outward currents during phase 1 of the AP.

Cellular and Ionic Mechanisms

Experimental studies have elucidated cellular and molecular bases for the two main characteristic features of Brugada syndrome: (1) the specific ECG morphology (ST-segment elevation in right precordial leads) and (2) the susceptibility for VF and SD. Figure 63-2, *A*, represents the normal ventricular myocyte AP and the major ionic currents involved in each one of the phases. Sodium loss-of-function conditions, the most encountered disorder in *SCN5A* mutations related to Brugada syndrome, create an imbalance between outward and inward positive currents during phase 1, favoring repolarization and the appearance of a particular notch in the AP (*dashed line*) that is mediated by the outward transient potassium currents (I_{to}).[9,12,19-23] Comparable imbalances can appear either by decrease in I_{CaL} (in calcium channel loss-of-function mutations) or relative increase in I_{to} (in the recently described *KCNE3* mutation).[26,27]

The accentuated notch present in patients with Brugada syndrome, especially in the epicardium, gives rise to a transmural voltage gradient between the epicardium and the endocardium, producing the characteristic ST-segment elevation on ECG (Figure 63-2, *B*).[28] The imbalance between outward and inward positive currents during phase 1 also establishes the basis for the development of ventricular arrhythmias in Brugada syndrome. The proposed mechanism would be a phase 2 re-entry (Figure 63-2, *C*). When the notch is such that phase 1 reaches approximately –30 mV, all-or-none repolarization can lead to a complete loss of the AP dome. The heterogeneity of the loss of the dome among different sites within the epicardium and between the epicardium and the endocardium results in epicardial and transmural dispersions of repolarization, respectively. This substrate may facilitate the development of premature beats by means of conduction of the AP dome from the sites where it is maintained to the sites where it is lost.[11,28]

The understanding that the imbalance between inward and outward ionic currents at phase 1 defines the pathologic substrate for Brugada syndrome has multiple implications. First, it has helped in the development of experimental models of the disease, which have been successfully created by the administration of potassium openers (pinacidil), the combination of a sodium channel blocker (flecainide) and acetylcholine, or drugs with combined sodium channel blocker and calcium channel blocker effects.[11,29] These interventions create a relative predominance of outward positive currents at the end of phase 1, thus accentuating the notch. The ionic imbalance hypothesis also explains the effects of certain modulators and certain particularities of the syndrome, such as the enhanced phenotypic expression (accompanied by an increased risk of arrhythmias) during vagal situations (acetylcholine inhibits calcium currents, whereas β-adrenergic drugs increase them) or the worse prognosis in men than in women affected with the disease (men could have constitutionally greater I_{to} density than women).[11,30-34] Likewise, it appears that interventions that decrease inward positive currents (as do sodium channel blockers) could be potentially harmful to patients with Brugada syndrome, as they increase ST-segment elevation and the risk of arrhythmic events; however, they could be useful in unmasking concealed forms of the disease.[35] In contrast, I_{to} blockers such as quinidine could be a good therapeutic option, as they reduce the notch at the end of phase 1 (see section on Treatment).[36]

Clinical Manifestations of Brugada Syndrome

Patients with Brugada syndrome usually remain asymptomatic. However, syncope or cardiac arrest, a consequence of an arrhythmic complication such as polymorphic VT or VF, has been described in up to 17% to 42% of diagnosed individuals.[37-40] This rate is probably an overestimation of the real prevalence of symptoms among patients with Brugada syndrome, given that most asymptomatic patients remain underdiagnosed. The age of symptom occurrence (especially cardiac arrest) is consistently around the fourth decade of life in all the series (Figure 63-3), with no definite explanation for this observation thus far.[41] Previous syncope may be present in up to 23% of patients who present with cardiac arrest.[38] Brugada syndrome should therefore be considered during the workup of patients who have suffered an aborted SD or syncope suspected to be of cardiac origin, especially if no underlying structural heart disease is found (see section on Approach to Patients with Suspected Brugada Syndrome: Family Screening).

Up to 20% of patients with Brugada syndrome may present with supraventricular arrhythmias and thus complain of palpitations, dizziness, or both.[42] An increased atrial vulnerability to both spontaneous atrial fibrillation (AF) and induced AF has been reported in patients with Brugada syndrome.[43] Other symptoms, such as neurally mediated syncope, have been also recently associated with Brugada syndrome.[44,45]

As in the case of other sodium channel–related disorders such as type 3 LQTS, ventricular arrhythmias in Brugada syndrome typically occur at rest, especially during night-time or sleep. In a study by Matsuo et al, 26 of 30 episodes of VF documented in implantable cardioverter-defibrillator (ICD) recordings of Brugada syndrome patients appeared during sleep, which suggests that

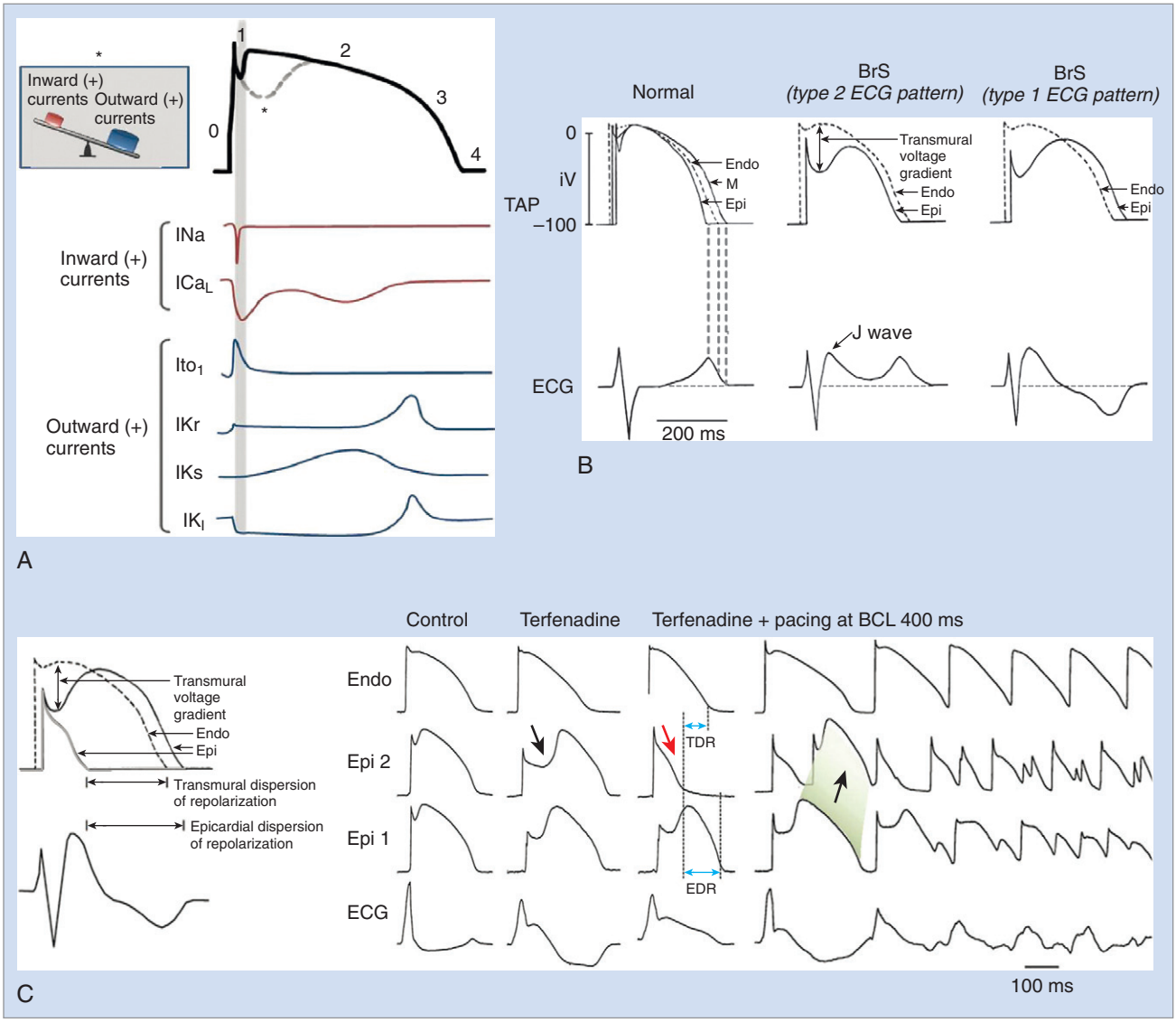


FIGURE 63-2 Cellular mechanisms that are thought to underlie the ST-segment elevation and the susceptibility to ventricular arrhythmias in patients with Brugada syndrome. **A,** Ventricular myocyte action potential and ionic currents involved in each one of the phases. The *shaded area* highlights phase 1, mostly determined by the balance among I_{Na}, I_{Ca}, and I_{to}. When positive inward currents are impaired with respect to positive outward currents (*asterisk*), the cell achieves greater degree of repolarization, and the normal dome of the action potential is lost, leading to the development of a particular notch at the end of phase 1 (*dashed line*). This phenomenon is the basis of Brugada syndrome produced by sodium channel loss-of-function mutations and also explains Brugada syndrome that is caused by mutation-causing calcium channel loss of function or a relative increase in I_{to}. **B,** The accentuated notch present in the epicardium but not in the endocardium gives rise to transmural voltage gradient and J-point elevation (Brugada saddle-back). Further accentuation of the notch may be accompanied by a prolongation of the action potential in the epicardium, which becomes longer than in the endocardium, thus leading to the development of negative T waves in addition to ST-segment elevation (Brugada coved-type). **C,** With a further shift in the balance of currents at the end of phase 1, all-or-none repolarization occurs and leads to a complete loss of the action potential dome (*inset at left* and *red arrow*). The arrhythmogenic substrate is thought to develop when the loss of dome appears at some epicardial sites but not at others, creating both transmural dispersion of repolarization and epicardial dispersion of repolarization (*blue arrows*). At this point, a premature impulse or extrasystole can develop by propagation of the dome from the sites where it is maintained (epicardial site 1) to the sites where it is lost (epicardial site 2, *green shaded area*), inducing polymorphic ventricular tachycardia by a phase 2 re-entry mechanism. (**B** *and* **C,** *Modified from Antzelevitch C: Brugada syndrome,* Pacing Clin Electrophysiol *29[10]:1130–1159, 2006.)*

vagal activity may play an important role in the arrhythmogenesis of Brugada syndrome.[30] This finding has been confirmed in more recent series.[31] As mentioned before, the increase in vagal tone is mediated by acetylcholine decreases in calcium currents, which could favor arrhythmogenesis through a phase 2 re-entry mechanism.[11]

Sex Differences

It is currently accepted that the clinical phenotype of Brugada syndrome is 8 to 10 times more prevalent in male patients than in female patients.[46] Consequently, the main clinical studies published thus far have included 71% to 77% of the male population,

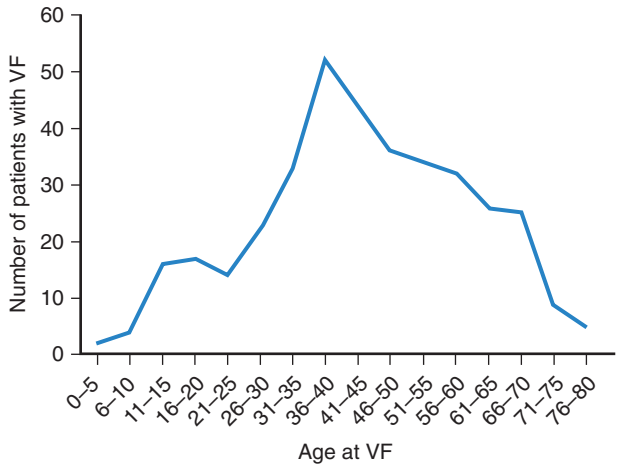


FIGURE 63-3 Incidence of spontaneous ventricular fibrillation (*VF*) or sudden death (SD) according to age in patients with Brugada syndrome. Data from 370 updated patients of the international registry. SD or VF occurred in 120 (32.4%) patients. *(From Benito B, Arzamendi D, Porres J, et al: Seguimiento a largo plazo de los pacientes con sindrome de Brugada. Estudio multicentrico de los factores de mal pronostico [abstract],* Rev Esp Cardiol *60[suppl 2]:116, 2007.)*

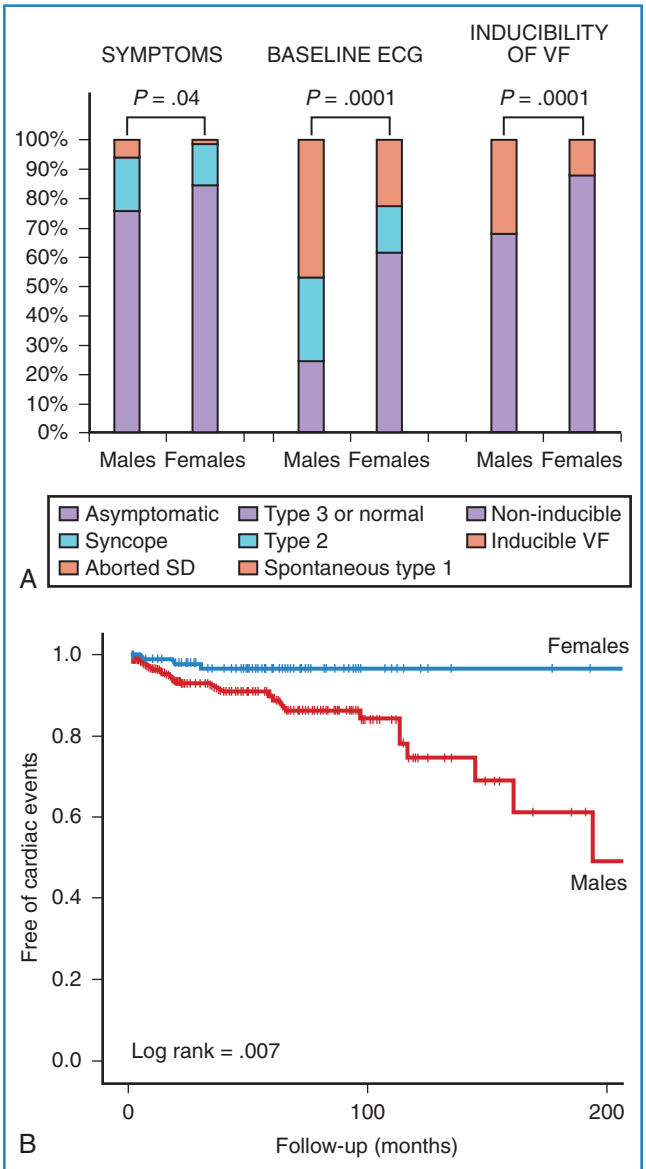


FIGURE 63-4 Gender differences in clinical manifestations of Brugada syndrome. **A,** Differences in clinical characteristics at the time of first evaluation. Men are more symptomatic, display more pathologic electrocardiogram (*ECG*) at baseline and present more inducibility of ventricular fibrillation (*VF*) than do women. **B,** Kaplan-Meier analysis of cardiac events defined as sudden death or documented VF during follow-up. A total of 31 (11.6%) of 272 men and 3 (2.8%) of 112 women experienced cardiac events during a mean follow-up period 58 ± 48 months (log-rank test = .007).

which generally appears to be more symptomatic compared with the female population.[37-40] The fact that in the case of SUDS, SD mainly occurs in young males during sleep has long been recognized in Southeast Asia, where men from certain small villages dress in women's bedclothes, as they believe that the syndrome is a female spirit searching for young men at night.

The authors of this chapter recently conducted a study aimed at analyzing gender differences in a large population of patients with Brugada syndrome.[33] The study population (n = 384) included 272 men (70.8%) and 112 women (29.2%). General demographic characteristics were similar between both groups (mean age, 45.8 years), but at diagnosis, men presented more frequently with symptoms (syncope in 18%, previous aborted SD in 6%) than did women (14% and 1%, respectively; $P = .04$). Men also had higher rates of spontaneous type 1 ECG (47% vs. 23%; $P = .0001$) and inducibility of VF during the electrophysiological study (32% vs. 12%; $P = .0001$) (Figure 63-4, *A*).[33] The prognosis also differed between men and women. Cardiac events (defined as SD or documented VF) appeared in 31 men (11.6%) and in 3 women (2.8%) during a mean follow-up period of 58 ± 48 months (log-rank test, $P = .007$). The Kaplan-Meier estimate of cardiac event–free survival according to gender is given in Figure 63-4, *B*. In accordance with these results, in a recent meta-analysis pooling data from 30 studies and including more than 1500 patients, male gender appeared as an independent predictor of cardiac events defined as SD, syncope, or internal defibrillator shock, with a relative risk (RR) of 3.47 (95% confidence interval [CI], 1.58 to 7.63) compared with women.[47]

Two main hypotheses have been proposed for the gender distinction, which perhaps interact with each other. First, according to some experimental models, it appears that men could have constitutionally greater I_{to} density in the right ventricular epicardium than do women, which enhances the ionic imbalance. Second, sex hormones could play a role. Regression of the typical ECG features has been reported in castrated men, and levels of testosterone seem to be higher in male patients with Brugada syndrome compared with those in controls.[48,49] Because of this hypothesis, the few data available thus far regarding Brugada syndrome in children have not shown a difference in phenotypic presentation between boys and girls before age 16.[50]

Children

Although 3 of the 8 patients reported in the first description of the disease were in the pediatric age group, little information has been

available on the behavior of Brugada syndrome during childhood.[1] Probst et al recently provided data from a multicenter study including 30 patients with Brugada syndrome aged younger than 16 years (mean age, 8 ± 5).[50] More than half (n = 17) had been diagnosed during family screening, but symptoms were present in 11 patients (1 aborted SD and 10 syncope). Interestingly, 10 of the 11 symptomatic patients displayed spontaneous type 1 ECG, and in 5 of them, symptoms were precipitated by fever. Five patients received an ICD, and 4 were treated with hydroquinidine.[50] During a mean follow-up period of 37 ± 23 months, 3 patients (10% of the population) experienced SD (n = 1) or an appropriate shock from an ICD (n = 2). Importantly, all the 3 patients had presented with syncope at the time of diagnosis and displayed spontaneous type 1 ECG. The 4 patients receiving quinidine remained asymptomatic during 28 ± 24 months of follow-up.[50]

The results of the chapter authors' study on 58 pediatric patients with Brugada syndrome are in line with the ones from Probst et al and provide further information on prognosis markers during childhood.[51] In the authors' population (mean age, 11.8 ± 4), up to 22 patients (38%) were symptomatic (11 with previous syncope and 11 with aborted SD), and 36 had been diagnosed during family screening. Spontaneous type 1 ECG was present in 18 patients (31%), and the electrophysiological study (EPS), which was performed in 31 patients, induced VF in 7 of them. An ICD was indicated for 14 patients. Cardiac events appeared in 6 patients (2 SD and 4 appropriate ICD shocks) during a mean follow-up of 48.8 ± 48 months, this rate of 2.5% per year being somewhat lower than the 3.2% per year reported by Probst et al.[50] Cardiac events occurred more frequently among patients with spontaneous type 1 ECG and among those with inducible VF at the EPS, but in the authors' series, symptoms at diagnosis was the strongest variable to predict events during follow-up.[51]

Though small, these studies clearly suggest the following:

- Brugada syndrome can manifest during childhood.
- Symptoms may appear particularly during febrile episodes.
- Symptomatic patients, especially if they have spontaneous type 1 ECG, may be at a high risk of cardiac events in a relatively short period of follow-up.
- Individuals at risk can be protected with an ICD, although quinidine could be an option in certain patients, particularly the youngest.

Electrocardiogram and Modulating Factors

As mentioned above, three types of repolarization have been described in patients with Brugada syndrome, but only the coved-type ST-segment elevation (type 1 ECG pattern) is diagnostic of the syndrome (see Figure 63-1). However, it must be stressed that the ECG pattern typically fluctuates over time in patients with Brugada syndrome, and thus can change from type 1 to type 2 or type 3 or even be transiently normal (Figure 63-5). A large variety of conditions influence the electrocardiographic aspect (see below). The prevalence of spontaneous ECG fluctuations was assessed in a work by Veltmann et al, which included 310 ECGs on 43 patients followed up for 17.7 months.[52] Among 15 patients with initial diagnostic ECGs, 14 revealed at least one nondiagnostic ECG in a median period of 12 days, while 8 of 28 patients with nondiagnostic ECGs developed a type 1 ECG pattern in a median period of 16 days. On the basis of these results, it appears that

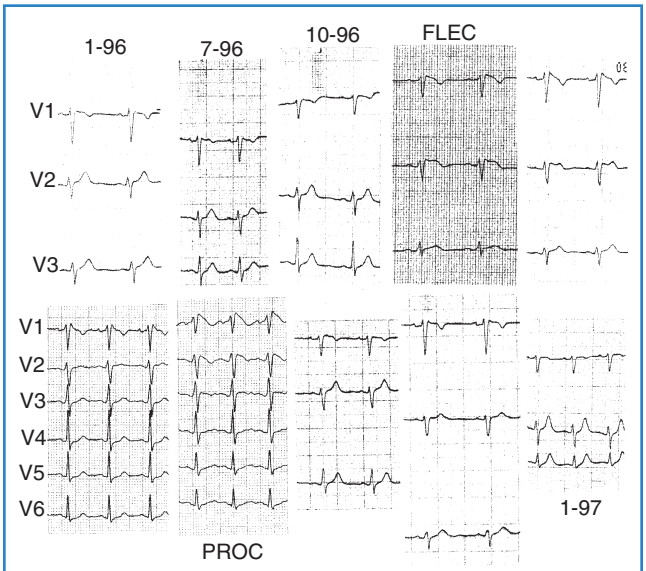


FIGURE 63-5 Spontaneous and drug-induced variations of the electrocardiogram in a patient with Brugada syndrome. Note the saddle-type (type 2) ST-segment elevation in 7-96 compared with the coved-type (type 1) ST-segment elevation after administration of flecainide (*FLEC*) or procainamide (*PROC*).

repetitive ECG recordings may be mandatory in patients with the syndrome; however, the role of the basal ECG as a risk marker should be understood with some caution (see section on Prognosis and Risk Stratification).[52,53]

It is worth noting that some factors can account for an ECG abnormality that can closely resemble the Brugada ECG (Table 63-1). Importantly, some of them are conditions different from the syndrome and should be carefully excluded during differential diagnosis, and some others may induce ST-segment elevation probably because an underlying genetic predisposition is present.[54]

Modulating factors play a major role in the dynamic nature of the ECG and also may be responsible for the ST-segment elevation in genetically predisposed patients (see Table 63-1). As mentioned before, sympathovagal balance, hormones, metabolic factors, and pharmacologic agents, by means of specific effects on transmembrane ionic currents, are thought to not only modulate the ECG morphology but also explain the development of ventricular arrhythmias under certain conditions (see section on Cellular and Ionic Mechanisms).[11,30,31,48,49,55,56] Temperature may be an important modulator in some patients with Brugada syndrome. Premature inactivation of the sodium channel has been shown to be accentuated at higher temperatures in some *SCN5A* mutations.[10] Accordingly, several case reports in which fever precipitates the syndrome or an arrhythmic complication have been published recently.[57,58] It seems that fever would be a particularly important trigger factor among pediatric patients.[50]

Numerous studies have analyzed the ECG of Brugada syndrome aiming to identify new electrocardiographic hallmarks or risk markers. Pitzalis and coworkers described a prolongation of the corrected Q-T interval (QTc) in right precordial leads, but not in left precordial leads, after administration of flecainide to patients with Brugada syndrome and nondiagnostic basal ECG.[59] Subsequently, other groups have correlated a QTc 460 ms or greater in V2 to the occurrence of life-threatening arrhythmias.[60]

Table 63-1 Electrocardiogram Abnormalities That Can Lead to ST-Segment Elevation in Leads V1 to V3

DIFFERENTIAL DIAGNOSIS	GENETIC PREDISPOSITION?
Atypical right bundle branch block	Hyperkalemia
Acute MI, especially of the RV	Hypercalcemia
Acute pericarditis/myopericarditis	Cocaine intoxication/alcohol intoxication
Hemopericardium	Treatment with:
Pulmonary embolism	I. Antiarrhythmic drugs:
Dissecting aortic aneurysm	Sodium channel blockers (class IC, class IA)
Central and autonomic nervous system disorders	Calcium channel blockers
Duchenne muscular dystrophy	β-blockers
Friedreich ataxia	II. Antianginal drugs:
LV hypertrophy	Calcium channel blockers
Arrhythmogenic RV cardiomyopathy	Nitrates
Mechanical compression of the RV outflow tract:	III. Psychotropic drugs:
Mediastinal tumor	Tricyclic antidepressants
Pectus excavatum	Tetracyclic antidepressants
After electrical cardioversion	Phenothiazines
Early repolarization, especially in athletes	Selective serotonin reuptake inhibitors
Hypothermia	Lithium

MI, *Myocardial infarction;* RV, *right ventricle;* LV, *left ventricle.*
From Benito B, Brugada R, Brugada J, Brugada P: Brugada syndrome, Prog Cardiovasc Dis *51(1):1–22, 2008.*

More recently, the aVR sign (an R wave ≥3 mm or an R/q ratio ≥0.75 in lead aVR; Figure 63-6, *A*) has also been defined as a risk marker of cardiac events in Brugada syndrome, the prominent R wave possibly reflecting some degree of right ventricular conduction delay and consequently more electrical heterogeneity.[61] In addition, T-wave alternans (Figure 63-6, *B*), an indicator of transmural dispersion of repolarization, has been reported after administration of sodium blockers to patients with Brugada syndrome and is thought to be associated with an increased risk for the development of VF.[62] Indeed, in a recent study conducted in 77 patients with Brugada syndrome, who were undergoing a pharmacologic test, the presence of T-wave alternans after administration of a sodium blocker identified a subgroup of patients with higher risk of spontaneous VF (52.9% vs. 8.3%, $P < .001$).[63]

Following the description of several sporadic cases, a recent study has confirmed that up to 11% of patients with Brugada syndrome have inferior-lateral spontaneous repolarization pattern, defined as 1 mm or greater J-wave elevation or slurring in leads other than V1 to V3 (usually inferior, lateral, or both leads; Figure 63-6, *C*).[64,65] Almost always, this pattern appears together with the typical coved-type ST-segment elevation in leads V1 to V3, which defines Brugada syndrome, either spontaneously or after administration of sodium channel blockers (see section on Diagnostic Tools: Drug Challenge). These patients present with the same clinical characteristics as those of patients with the typical form of Brugada syndrome, although they seem to develop more arrhythmic complications in their lifetime.[65] Interestingly, the early repolarization pattern in inferior and lateral leads—found isolated and in the absence of ECG features typical of Brugada syndrome—has been associated with an increased susceptibility to VF and cardiac death in population studies, which suggests that this could be an independent syndrome responsible for some cases of SD in individuals with a normal heart.[66,67]

Although some similarities between Brugada syndrome and the new early repolarization disorder (high rate of arrhythmic complications at night, relative effectiveness of quinidine and isoproterenol in the treatment of arrhythmias) have been described, recent data suggest that both entities have distinct particularities, at least with regard to the mode of initiation of arrhythmic complications.[66,68] On the basis of this, Brugada syndrome should always be carefully excluded in patients with inferior-lateral early repolarization pattern and idiopathic VF, even when the spontaneous ECG in leads V1 to V3 is normal. To date, the main difference between early repolarization disorder and Brugada syndrome seems to be the appearance of coved-type ST-segment elevation in response to sodium channel blockers in Brugada syndrome (see section on Diagnostic Tools: Drug Challenge). Therefore, it seems appropriate to recommend a pharmacologic test with sodium blockers for all individuals with early repolarization pattern and idiopathic VF in order to establish the definite diagnosis and unmask possible atypical forms of Brugada syndrome.[65]

Cardiac conduction disturbances may be present in patients with Brugada syndrome. Both phenotypes (Brugada syndrome and cardiac conduction disorders) can be explained by a reduction in the sodium current and have been described within the same family carrying a mutation on the *SCN5A* gene.[69] Consequently, conduction parameters (specifically P-Q interval, QRS duration, and H-V interval) seem to be longer among those patients with Brugada syndrome who are *SCN5A* gene carriers (and do have a mutation in the sodium channel) compared with non-*SCN5A* gene carriers, in whom the underlying mechanism or mutation is not identified.[70] These differences have been recently shown to become progressively accentuated during follow-up.[71] In a recent study by this chapter authors' group, it was observed that some conduction parameters such as QRS duration are increased among symptomatic patients. Indeed, in a population of 200 patients with Brugada syndrome, of whom 66 (33%) were symptomatic, the optimized cutoff point of QRS in lead V2 was 120 ms or greater, with an odds ratio (OR) of 2.5 (95% CI, 1.4 to 4.6; $P = .003$) for being symptomatic.[72]

Although sinus rhythm is the most common, supraventricular arrhythmias, especially AF, can be found in up to one third of patients with Brugada syndrome.[42,43] Recently, it has been shown that patients with Brugada syndrome who present with spontaneous AF have more severe clinical phenotype.[73] Other rhythm disorders such as bradycardia secondary to sick sinus syndrome or atrial standstill have also been reported in association with Brugada syndrome.[28]

Diagnostic Tools: Drug Challenge

The diagnosis of Brugada syndrome can be established when a type 1 (coved-type) ECG pattern is found in right precordial leads in the absence of confounding factors and other causes of ST-segment elevation (see Table 63-1). However, because the ECG in Brugada syndrome is dynamic in nature and can even be transiently normal in affected patients, pharmacologic provocative tests have been used in an attempt to unmask concealed forms of the disease. Sodium channel blockers, which increase the ionic imbalance at the end of phase 1 of the AP by decreasing sodium currents, appear as the most attractive option.[35] Ajmaline, flecainide, procainamide, pilsicainide, disopyramide, and propafenone have been used.[2] The recommended dose regimens for the most commonly used drugs are listed in Table 63-2. Brugada

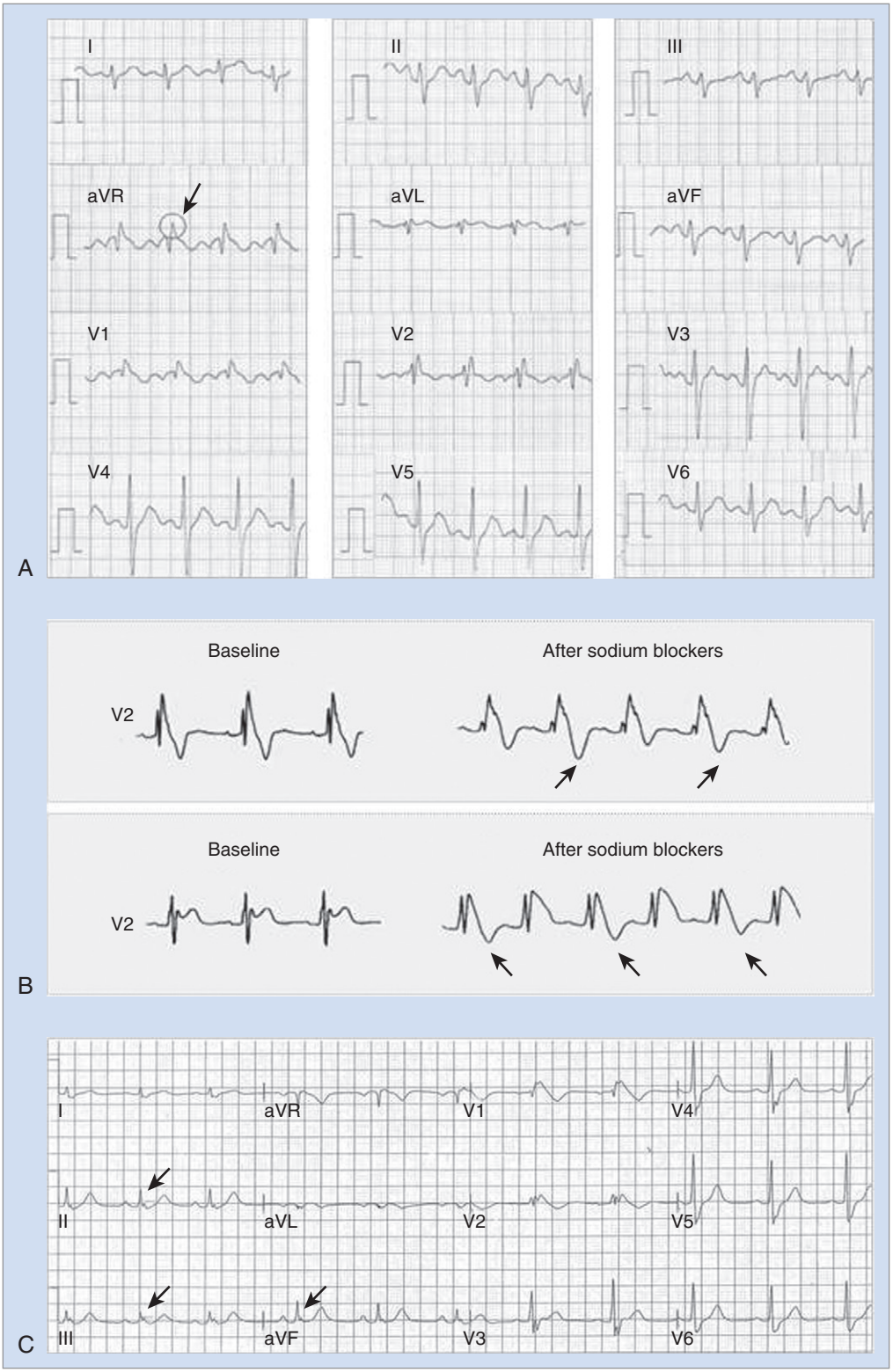


FIGURE 63-6 Additional electrocardiogram (ECG) findings that have been associated with an increased risk of ventricular arrhythmias in patients with Brugada syndrome. **A,** aVR sign. **B,** T-wave alternans appearing after administration of sodium channel blockers. **C,** Early repolarization pattern in inferior leads, lateral leads, or both; note the characteristic coved-type ECG in leads V1 to V3, which establishes the distinction with the recently described early repolarization disorder. *(**A,** From Babai Bigi MA, Aslani A, Shahrzad S: aVR sign as a risk factor for life-threatening arrhythmic events in patients with Brugada syndrome,* Heart Rhythm *4[8]:1009–1012, 2007. **B,** Modified from Tada T, Kusano KF, Nagase S, et al: The relationship between the magnitude of T wave alternans and amplitude of the corresponding T wave in patients with Brugada syndrome,* J Cardiovasc Electrophysiol *19[1]:56–61, 2008. **C,** From Sarkozy A, Chierchia GB, Paparella G, et al: Inferior and lateral electrocardiographic repolarization abnormalities in Brugada syndrome,* Circ Arrhythmia Electrophysiol *2[2]:154–161, 2009.)*

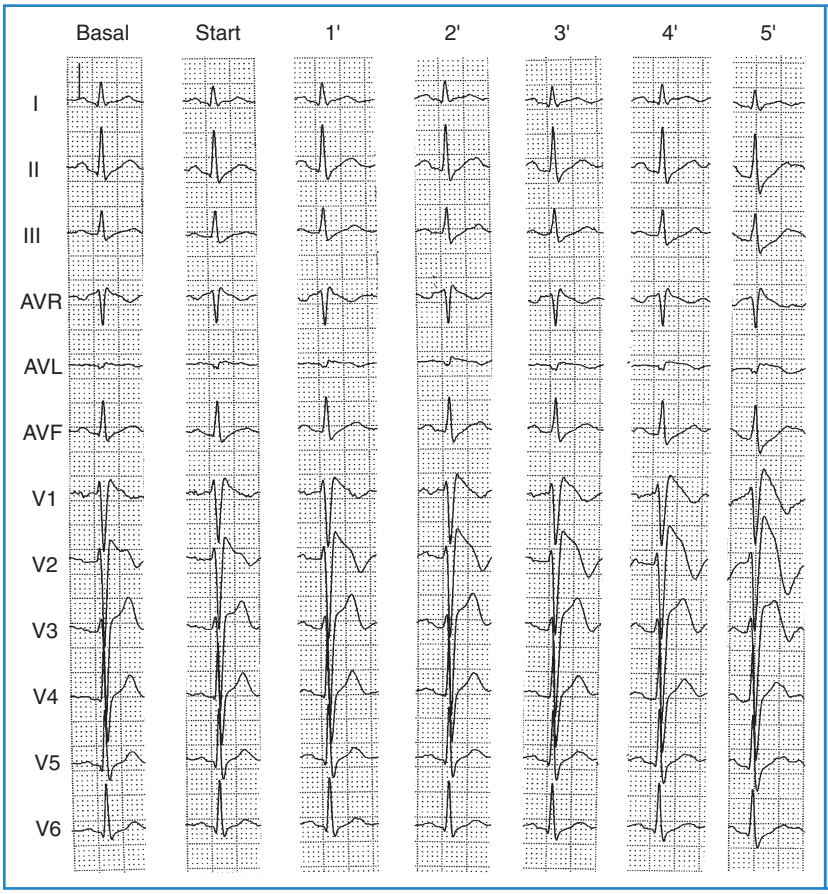


FIGURE 63-7 Effects of acute intravenous administration of 50 mg ajmaline in a patient with the concealed form of Brugada syndrome. Note the acute worsening of ST-segment elevation in leads V1 through V3.

Table 63-2 Drugs Used to Unmask Brugada Syndrome

DRUG	DOSAGE	ADMINISTRATION
Ajmaline	1 mg/kg over 5 min	IV
Flecainide	2 mg/kg over 10 min 400 mg	IV PO
Procainamide	10 mg/kg over 10 min	IV
Pilsicainide	1 mg/kg over 10 min	IV

IV, *Intravenous;* PO, *oral.*
From Antzelevitch C, Brugada P, Borggrefe M, et al: Brugada syndrome: Report of the Second Consensus Conference: Endorsed by the Heart Rhythm Society and the European Heart Rhythm Association, Circulation *111(5):659–670, 2005; and Benito B, Brugada R, Brugada J, Brugada P: Brugada syndrome,* Prog Cardiovasc Dis *51(1):1–22, 2008.*

syndrome is diagnosed if a coved-type (type 1 ECG) pattern appears after administration of a sodium channel blocker (Figure 63-7). According to the Second Consensus Committee, the pharmacologic test should be monitored under continuous ECG recording and should be terminated when (1) the diagnostic test is positive, (2) premature ventricular beats or other arrhythmias develop, or (3) QRS widens to 130% or more of baseline.[2] The last criterion has recently been questioned. In a retrospective study, Batchvarov et al evaluated QRS duration and the occurrence of ventricular arrhythmias in 148 patients during ajmaline challenge and found that QRS prolonged to 130% or more of baseline in more than 50% of cases.[74] The incidence of ventricular arrhythmias did not differ between patients with QRS prolongation and those without QRS prolongation, and no sustained arrhythmias were documented after drug administration. More importantly, in 40% of the positive tests, prolongation of QRS 130% or more occurred more than 1 minute earlier than the diagnostic Brugada ECG changes developed. Therefore, it seems that early termination of the test could possibly have resulted in false-negative results.[74] On the basis of these results, these authors have proposed that the criteria for test termination be redefined according to baseline QRS duration (>150% in patients with normal QRS duration and >125% in patients with major intraventricular conduction disturbances).[74]

Current data indicate that ajmaline is probably the best drug available to unmask Brugada syndrome, whereas procainamide, the only drug available in the United States, seems to be the weakest to uncover ECG abnormalities. In a study with 147 individuals from four large families with identified *SCN5A* mutations, ajmaline provided a sensitivity of 80%, a specificity of 94.4%, a positive predictive value of 93.3%, and a negative predictive value of 82.9% for the diagnosis of Brugada syndrome.[75] The penetrance of the disease phenotype increased from 32.7% to 78.6% with the use of a sodium channel blocker.[75] These results show values considerably higher than those obtained for flecainide in another study with 110 genotyped patients, in which the sensitivity, the specificity, and the positive and the negative predictive values for the diagnosis were 77%, 80%, 96%, and 36%, respectively.[76] It is important to note the low negative predictive value, which should be taken into account when using flecainide, especially during

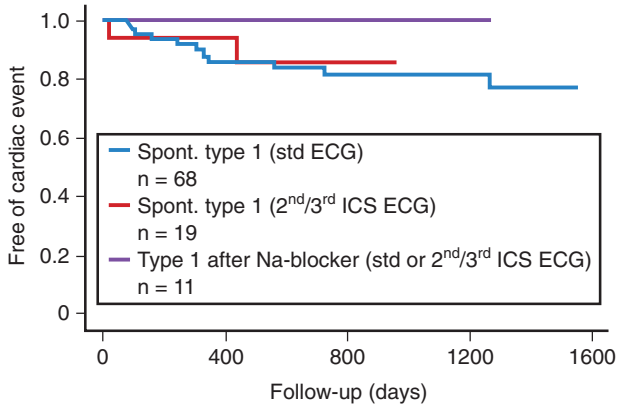


FIGURE 63-8 Kaplan-Meier analysis of cardiac events (documented VF or SD) during follow-up in patients with spontaneous type 1 ECG pattern at standard leads (*blue line*), patients with spontaneous type 1 ECG recorded only at a higher intercostal space (*red line*), and patients with type 1 ECG pattern at standard intercostal spaces, higher intercostal spaces, or both only after receiving a sodium channel blocker (*purple line*). No significant difference was observed in the frequency of cardiac events between the first two groups. *ECG*, Electrocardiogram; *std*, standard; *VF*, ventricular fibrillation; *ICS*, intercostal space. *(Modified from Miyamoto K, Yokokawa M, Tanaka K, et al: Diagnostic and prognostic value of a type 1 Brugada electrocardiogram at higher [third or second] V1 to V2 recording in men with Brugada syndrome,* Am J Cardiol *99[1]:53–57, 2007.)*

genetic screening. Ajmaline and flecainide were compared in a study with 22 patients with confirmed Brugada syndrome who were subjected to both pharmacologic tests. Although the test was positive in all 22 patients after ajmaline administration, only 15 patients showed a positive response to flecainide.[77] Experimental studies revealed that flecainide inhibits not only sodium currents but also I_{to} currents, which explains its lesser effectiveness in enhancing the ionic imbalance at phase 1.[77]

Given the limitations of drug tests and the restricted availability of genetic analysis, new strategies have been proposed to help in the clinical diagnosis of Brugada syndrome. Placement of the right precordial leads in an upper position (second or third intercostal spaces) can increase the sensitivity of the ECG to detect the Brugada phenotype, in the presence or absence of a drug challenge, although it is still uncertain whether the greater sensitivity is at the expense of a lower specificity.[78,79] Recent data demonstrate that the presence of a type 1 ECG pattern recorded at higher intercostal spaces, even when the standard ECG is normal, can identify a subgroup of patients with a prognosis similar to those with spontaneous type 1 ECG pattern at standard leads (Figure 63-8).[80] Therefore, this strategy seems to allow the identification of a subset of patients at risk who would otherwise be underdiagnosed.

Pharmacologic challenge with sodium channel blockers should be performed on patients with syncope, aborted SD of unknown origin, or both to unmask possible concealed forms of Brugada syndrome. Other indications of pharmacologic testing include asymptomatic patients with a suspicious ECG (spontaneous type 2 or type 3 ECG) and family members of a confirmed index case during family screening if they do not have a spontaneous type 1 ECG (see section on Approach to Patients with Suspected Brugada Syndrome: Family Screening).

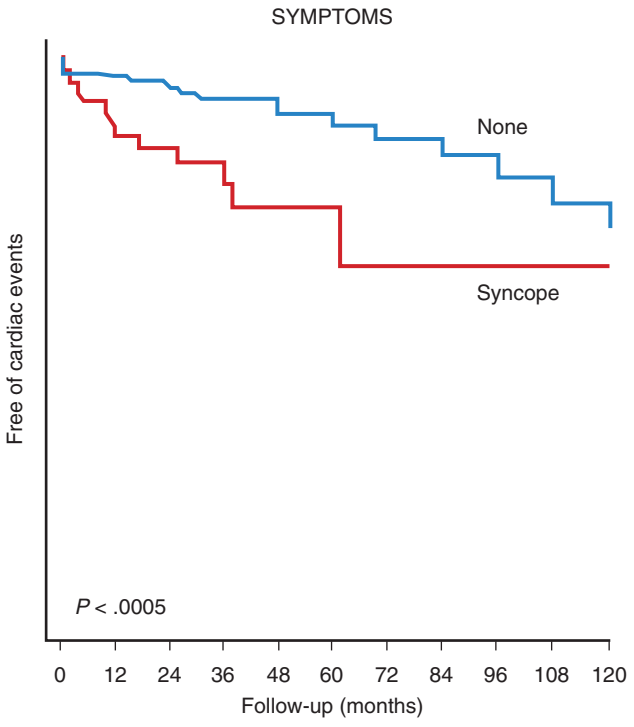
Prognosis and Risk Stratification

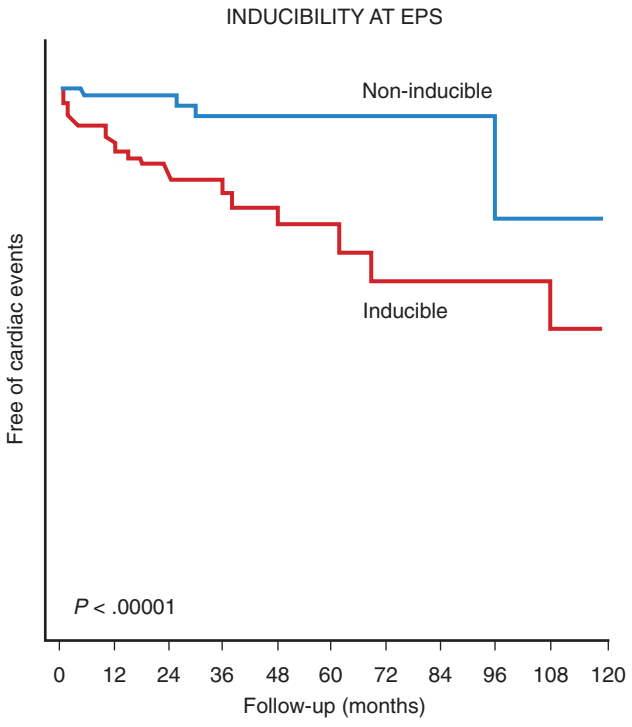
Prognosis and risk stratification are probably the most controversial issues in Brugada syndrome. The main clinical studies arising from the largest databases have different findings on the risk of SCD or VF in the population with Brugada syndrome, and particularly have different definitions of the specific risk markers with regard to prognosis.

In the authors' most recent study population with Brugada syndrome coming from the international registry, the percentage of patients who experienced SCD or VF throughout their lifetime was 25% (177 of 724 patients).[81] The mean age at cardiac events was 42 ± 15 years. Of course, such a high rate might have been influenced by a baseline high-risk population referred to the international registry and included in this analysis. In fact, the authors' reported annual rate of events has decreased from the first patients included in the registry to the most recent published series; the change probably reflects the inherent bias during the first years after the description of a novel disease, in which particularly severe forms of the disease are most likely to be diagnosed.[4,37,39,81] It is important to note that in the global series, the lifetime probability of having a cardiac event during varied widely (from 3% to 45%), depending on the baseline characteristics of the individuals. Thus, a careful risk stratification of every individual is mandatory.

Several clinical variables have been demonstrated to predict a poor outcome in patients with Brugada syndrome. In all the analyses of the authors' series over time, the presence of symptoms before diagnosis, a spontaneous type 1 ECG at baseline, the inducibility of ventricular arrhythmias at the EPS, and male gender have consistently been related to the occurrence of cardiac events during follow-up.[4,33,37,39,81]

Little controversy exists on the value of a previous cardiac arrest as a risk marker for future events. The authors' data show that up to 62% of patients recovered from an aborted SCD are at risk of a new arrhythmic event within the following 54 months.[37] Thus, these patients should be protected with an ICD irrespective of the presence of other risk factors (indication class I).[2,82] Because a general agreement on the best approach toward patients who have never developed VF is lacking, the authors conducted a prospective study including 547 individuals with Brugada syndrome and no previous cardiac arrest.[39] Of them (mean age 41 ± 45 years, 408 men), 124 had presented with syncope (22.7%) and 423 (77.3%) were asymptomatic and had been diagnosed during routine ECG or family screening. The baseline ECG showed a type 1 ECG pattern spontaneously in 391 patients (71.5%) and after sodium channel blocker challenge in 156 (28.5%). During a mean follow-up of 24 ± 32 months, 45 individuals (8.2%) developed a first major cardiac event (documented VF or SD).[39] By univariable analysis, a previous history of syncope (heart rate [HR], 2.79; 95% CI, 1.5 to 5.1; $P = .002$), a spontaneous type 1 ECG (HR, 7.69; 95% CI, 1.9 to 33.3; $P = .0001$), male gender (HR, 5.26; 95% CI, 1.6 to 16.6; $P = .001$), and inducibility of ventricular arrhythmias at the EPS (HR, 8.33; 95% CI, 2.8 to 25; $P = .0001$) were significantly related to VF or SCD in follow-up. Multivariable analysis identified previous syncope and inducibility of VF as the only independent risk factors for the occurrence of events during follow-up (Figure 63-9, *A*).[39] Logistic regression analysis allowed the definition of eight categories of risk, of which asymptomatic patients with normal ECG at baseline and non-inducible VF at the EPS would represent the population at lowest risk; and patients with syncope, spontaneous type 1 ECG, and inducibility

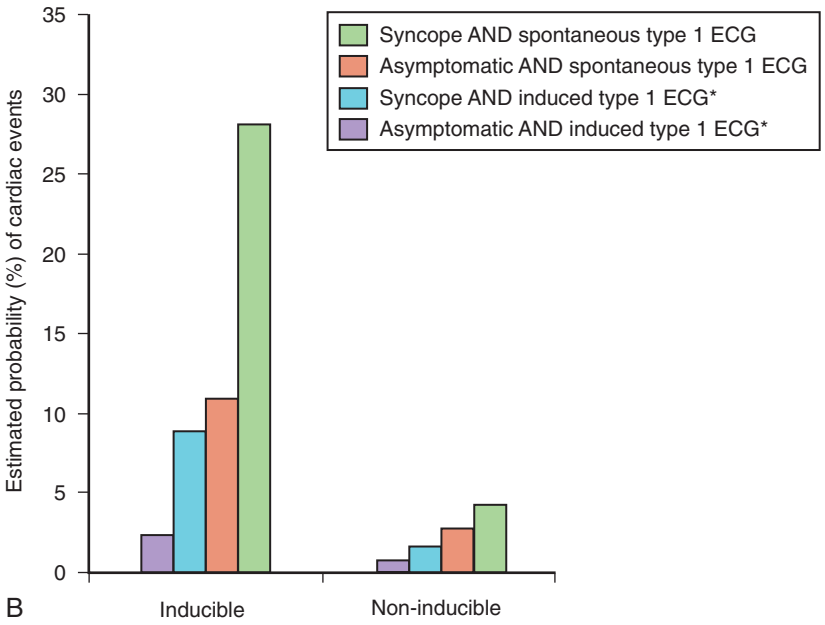




Multivariable	HR	95% CI	P
Syncope	2.51	1.2–5.3	.017

Multivariable	HR	95% CI	P
Inducibility of VF	5.88	2.0–16.7	.0001

A



B

FIGURE 63-9 Cardiac events (sudden death or documented ventricular fibrillation) during follow-up. **A,** Kaplan-Meier analysis according to previous symptoms and inducibility of ventricular fibrillation in the electrophysiological study (*EPS*), both independent predictors in the series by Brugada et al. **B,** Estimated probability of events in follow-up by logistic regression according to symptoms, inducibility of ventricular arrhythmias at the EPS and baseline electrocardiogram (*ECG*). *Asterisk,* Induced type 1 ECG after administration of sodium channel blockers. *HR,* Heart rate; *CI,* confidence interval; *VF,* ventricular fibrillation. *(Data from Brugada J, Brugada R, Brugada P: Determinants of sudden cardiac death in individuals with the electrocardiographic pattern of Brugada syndrome and no previous cardiac arrest,* Circulation *108[25]:3092–3096, 2003.)*

at EPS would have the worst outcome (Figure 63-9, *B*). Further analysis indicated that the EPS was particularly useful in predicting cardiac events among asymptomatic patients with no family history of SCD (named *fortuitous cases,* n = 167).[81] Indeed, 11 (6%) of 167 patients presented with VF during follow-up, and the only independent predictor was inducibility at the EPS. In contrast, not performing an EPS in this subgroup of patients with the aim of identifying those at risk was shown to be predictive of effective SD ($P = .002$).[81]

Other groups agree that previous symptoms and a spontaneous type 1 ECG are risk factors, although they have found a much lower incidence of arrhythmic events for the whole population (6.5% in 34 ± 44 months of follow-up in the work of Priori et al and 4.2% in 40 ± 50 months of follow-up in that of Eckardt et al).[38,40] The worse outcome in the authors' series may probably reflect a more severely ill baseline population.[40] The other large registries also agree that EPS inducibility is greatest among patients with previous SCD or syncope, but failed to demonstrate the value of the EPS in predicting outcome.[38,40] Several reasons could explain this discrepancy: (1) the use of multiple testing centers with nonstandardized stimulation protocols; (2) the inclusion of patients with type 2 and type 3 ST-segment elevation (and not type 1) in some series, which suggests that they may contain individuals who do not have the syndrome; and (3) the lack of events during follow-up in the other registries.[81] The latter might change when longer follow-ups are available because events can only increase in follow-up and so will the positive predictive value.[81]

Males have consistently shown a trend to experience more arrhythmic events in all the studies, and male sex even has been defined as an independent predictor for a worse outcome in a recent meta-analysis.[47] A very recent study by the authors' group indicates that men with Brugada syndrome display a higher risk profile than do women and thus have a worse prognosis during follow-up (see section on Sex Differences).[33] This study also suggests that although the classical risk markers (symptoms, spontaneous type 1 ECG, and inducibility of VF) are useful in identifying male patients at risk, the female population with worse outcome is usually characterized by more severe conduction disturbances.[33] Spontaneous AF, which can appear in 10% to 53% of cases, has been recently shown to have prognostic significance.[43,73] Kusano et al, in a series of 73 patients with Brugada syndrome, observed that spontaneous AF was associated with a higher incidence of syncopal episodes (60.0% vs. 22.2%; $P < .03$) and documented VF (40.0% vs. 14.3%; $P < .05$).[73] In the same line, the authors' results demonstrate that AF is more frequently observed in patients who experience SCD or VF during follow-up compared with asymptomatic patients, both in the male and female populations.[33] Multiple ECG parameters have been assessed in the search for new risk markers, of which a prolonged QTc in V2, the aVR sign, the presence of T-wave alternans, the early repolarization pattern in inferior or lateral leads, and probably a wide QRS complex seem to be the most important (see section on Electrocardiogram and Modulating Factors).[60-63,65,72] Interestingly, a positive family history of SD or the presence of an *SCN5A* mutation have not been proven to be risk markers in any of the large studies conducted thus far.[38,40,47]

However, recent data suggest that other genetic findings might have prognostic implications. In a recent study with 147 patients with Brugada syndrome or progressive cardiac conduction disease carrying 32 different mutations in the *SCN5A* gene, Meregalli et al found that those with a mutation leading to a premature stop codon (and thus a truncated protein) had a higher rate of syncope than did patients with other types of mutation (25.3% vs. 5.7%, respectively; $P = .03$).[83] Nevertheless, these authors could not find differences in the rate of major arrhythmic complications (SCD or VF) according to the type of mutation.[83] The chapter authors' data on 188 patients (all with Brugada syndrome) carrying 69 different mutations in *SCN5A* demonstrated that the presence of a mutation leading to a premature stop codon is related to a greater rate of major cardiac events defined as SCD or documented VF.[84] Moreover, in the authors' series, the presence of a mutation leading to a truncated protein was confirmed as an independent predictor of cardiac events (HR, 2.9; 95% CI, 1.2 to 7.2; $P = .02$), together with the classic clinical risk factors reported in previous series.[84] From these data, it can be concluded that genetic testing could be useful in the risk stratification of patients with Brugada syndrome who are carriers of an *SCN5A* mutation. This finding is particularly important because, in contrast to previously defined clinical variables, genetic information is constitutional and thus invariable over time within the same individual.

Treatment

Implantable Cardioverter Defibrillator

The implantable cardioverter defibrillator (ICD) has been the only proven effective treatment so far for Brugada syndrome. On the basis of available clinical and basic science data, a second Consensus Conference was held in September 2003, focusing on risk stratification schemes and approaches to therapy.[2] The recommendations for ICD implantation stated by this consensus are summarized in Figure 63-10, although not all of them have been endorsed in the most recent ACC/AHA/ESC 2006 Guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD (Table 63-3).[82] Symptomatic patients should always receive an ICD. The EPS could be performed in these patients to better assess the sensitivity and specificity of the test to predict the outcome and also for the study of supraventricular arrhythmias. Asymptomatic patients may benefit from the EPS for risk stratification, especially if they have a spontaneous type 1 ECG: An ICD should be implanted in those with inducible VF. Indications for the EPS and ICD implantation in asymptomatic patients with sodium channel blocker–induced ECG are, however, less established. Although the second Consensus Conference proposed performing an EPS for risk stratification in these patients and ICD implantation in those who had inducible arrhythmias (indication class IIb), this recommendation has not been included in the most updated guidelines.[2,82] According to the latter, asymptomatic patients who develop a type 1 ECG only after sodium channel blockade should probably be closely followed up, whether or not they have a family history of SCD (see Figure 63-10).[82]

Single- or dual-chamber ICDs can be implanted in patients with Brugada syndrome, and the decision usually depends on a history of supraventricular arrhythmias, concomitant pacing indication, or both. In the routine protocol employed by the authors of this chapter, a single VF zone is programmed, with a detection rate between 180 and 220 beats/min (individualized for all patients) and backup pacing at a rate of 35 to 50 beats/min.[85]

From the two main retrospective studies conducted on patients with Brugada syndrome who had received ICD, it can be concluded that ICD is an effective therapy for patients at risk, which can have an annual rate of appropriate shocks of up to 3.7%.[85,86]

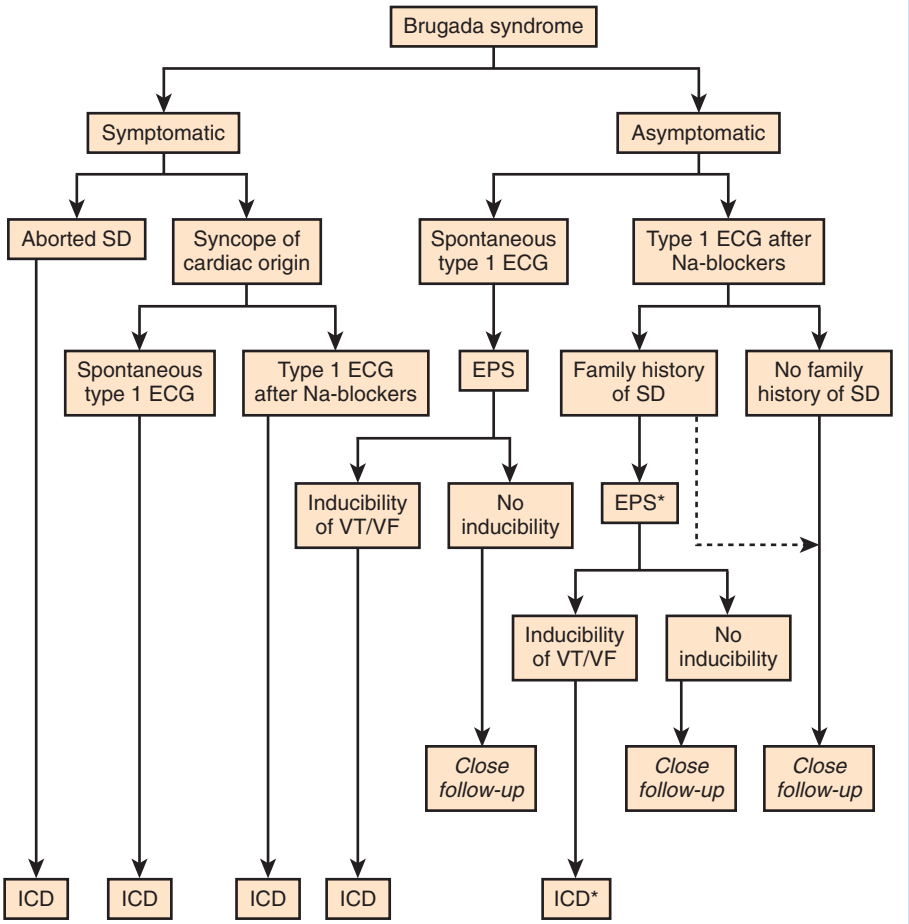


FIGURE 63-10 Indications for implantable cardioverter-defibrillator (*ICD*) implantation in patients with Brugada syndrome according to the Second Consensus Conference. *Asterisk,* Indications that have not been endorsed by the more updated *ACC/AHA/ESC 2006 Guidelines* for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Instead, the correspondent recommendation of the *ACC/AHA/ESC Guidelines* is represented by a *dashed line. SD,* Sudden death; *ECG,* electrocardiogram; *VT/VF,* ventricular tachycardia/ventricular fibrillation; *EPS,* electrophysiological study. *(From Zipes DP, Camm AJ, Borggrefe M, 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] developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society,* Europace *8[9]:746–837, 2006.)*

Table 63-3 Recommendations from the *ACC/AHA/ESC 2006 Guidelines* for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: Brugada Syndrome

Class I benefit > risk ("should be done")	An ICD is indicated for patients with Brugada syndrome who have had a previous cardiac arrest and who have reasonable expectation of survival with a good functional status for more than 1 year.
Class IIa benefit ≅ risk ("it is reasonable")	An ICD is reasonable for patients with Brugada syndrome who have spontaneous elevation in V1, V2, or V3, who have had syncope with or without causative mutations demonstrated, and who have reasonable expectation of survival with a good functional status for more than 1 year. An ICD is reasonable for patients with Brugada syndrome who have documented VT that has not resulted in cardiac arrest and who have reasonable expectation of survival with a good functional status for more than 1 year. Clinical monitoring for the development of a spontaneous ST-segment elevation pattern is reasonable for the management of patients with ST-segment elevation induced only with provocative pharmacologic challenge in the presence or absence of symptoms. Isoproterenol can be useful in treating an electrical storm in patients with Brugada syndrome.
Class IIb benefit ≥ risk ("may be considered")	EPS testing may be considered for risk stratification in asymptomatic patients with Brugada syndrome who have spontaneous ST-segment elevation with or without a mutation identified. Quinidine might be reasonable for the treatment of electrical storm in patients with Brugada syndrome.

ICD, *Inplantable cardioverter-defibrillator;* VT, *ventricular tachycardia.*
Modified from Zipes DP, Camm AJ, Borggrefe M, 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) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society, Europace *8(9):746–837, 2006.*

It is important to note that this rate is not only comparable with ICD trials dealing with other cardiac diseases, but it also affects young and otherwise healthy people, whose life expectancy could be more than 30 years.[87,88] Therefore, should this rate remain constant in time, most patients would be likely to receive appropriate ICD therapy in their lifetime. The rate of appropriate shocks is significantly higher among patients who were symptomatic prior to ICD implantation (22% in patients with previous resuscitated SCD and 10% in patients with previous syncope during a mean follow-up of 38 ± 27 months) than in previously asymptomatic patients (4% during comparable follow-up; $P = .025$), symptoms prior to ICD implantation being the only predictor of subsequent appropriate ICD therapies (Figure 63-11).[86] However, a noteworthy rate of inappropriate shocks from the device has also been reported (see Figure 63-11). In the study by Sacher et al, 45 (20%) of 220 patients had inappropriate shocks in a follow-up.[86] In the chapter authors' series, the rate was even higher (36%).[85] The reasons for inappropriate therapies were mainly sinus tachycardia, supraventricular arrhythmias, T-wave oversensing, and lead failure in both studies.[85,86] In fact, a previous history of supraventricular arrhythmias, the presence of T-wave oversensing, and a low R-wave amplitude (<5 mV) at the time of implantation have all been found to be predictors of inappropriate therapies in follow-up. On the basis of these results and because ICD is not affordable worldwide, efforts to find pharmacologic approaches to help treat the disease are growing.

Pharmacologic Options

With the aim of rebalancing the ion channel currents active during phase 1 of the AP, so as to reduce the magnitude of the notch (see Figure 63-2, *A*), two main pharmacologic approaches have been assessed (Table 63-4): (1) drugs that decrease outward positive currents, such as I_{to} inhibitors; and (2) drugs that increase inward positive currents (I_{Ca}, I_{Na}).

Quinidine, a drug with I_{to}-blocking and I_{Kr}-blocking properties, has been the most assayed drug in clinical studies. In a work by Belhassen et al, 25 patients with inducible VF were treated with quinidine (1483 ± 240 mg orally).[36] After treatment, 22 (88%) of 25 patients were no longer inducible at the EPS, and none of the 19 patients with ongoing medical therapy with oral quinidine developed arrhythmias during follow-up (56 ± 67 months).[36] However, 36% of the patients had transient side effects that led to drug discontinuation. Preliminary data have also proven quinidine as a good adjunctive therapy in patients with ICD and multiple shocks and as an effective treatment of electrical storms associated with Brugada syndrome.[89,90] More recently, quinidine has been proposed as a good alternative to ICD implantation in children with the syndrome and at high risk for malignant arrhythmias.[50]

β-Adrenergic agents, through an increase in I_{Ca} currents, have been shown to decrease transmural dispersion of repolarization and epicardial dispersion of repolarization in experimental models.[11] Clinically, they have proven effectiveness in the treatment of electrical storms associated with Brugada syndrome.[91] Recently, phosphodiesterase III inhibitors have appeared as a new appealing option because they would increase I_{Ca} and decrease I_{to}. Indeed, cilostazol was reported to be effective in preventing ICD shocks in a patient with recurrent episodes of VF.[92] However, a recent publication reports the failure of this drug in another patient with multiple ICD discharges despite sustained therapy.[93]

Table 63-4 Pharmacologic Approach to Therapy in Brugada Syndrome

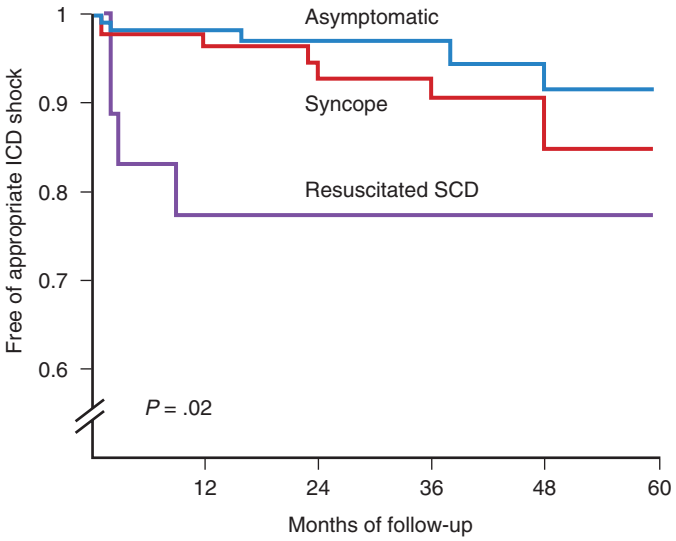
ACTION	PROVED ON
I_{to} BLOCKERS	
4-Aminopyridine	Effective in experimental models (suppression of phase 2 re-entry)[28] Probable neurotoxicity in humans
Quinidine	Effective in experimental models (suppression of phase 2 re-entry)[28] Initial results showing effectiveness in clinical practice: ↓ inducibility of VF[36] ↓ spontaneous VF in follow-up[36, 89] Adjunctive therapy in patients with ICD and multiple shocks[89] Effective in electrical storm[90] A possible option in children[50]
Tedisamil	Effective in experimental models (suppression of phase 2 re-entry)
AVE0118	Effective in experimental models (suppression of phase 2 re-entry)
I_{Ca} ACTIVATORS	
Isoproterenol	Effective in experimental models (suppression of phase 2 re-entry)[28] Effective in electrical storm[91]
Cilostazol	Controversial preliminary results in preventing VF[92,93]
I_{Na} OPENERS	
Dimethyl lithospermate B (dmLSB)	Effective in experimental models (suppression of phase 2 re-entry)*

See references 28, 36, 50, 89, and 90 to 93.
ICD, *Implantable cardioverter-defibrillator;* VF, *ventricular fibrillation.*
**Fish JM, Welchons DR, Kim YS, et al: Dimethyl lithospermate B, an extract of Danshen, suppresses arrhythmogenesis associated with the Brugada syndrome,* Circulation *113(11):1393–1400, 2006.*
From Benito B, Brugada R, Brugada J, Brugada P: Brugada syndrome, Prog Cardiovasc Dis *51(1):1–22, 2008.*

Approach to Patients with Suspected Brugada Syndrome: Family Screening

The diagnosis of Brugada syndrome strongly depends on the degree of suspicion on the part of the physician. Patients with syncope, aborted SD of unknown origin, or both and normal hearts should be recommended to have a standard ECG to rule out a spontaneous diagnostic type 1 ECG pattern. If the ECG is found to be normal, a modified ECG with recording from upper precordial leads and a pharmacologic challenge with a sodium channel blocker should be performed to detect possible concealed forms of Brugada syndrome. If a type 1 ECG is documented, the diagnosis of Brugada syndrome can be established (Figure 63-12).

The first step after identification of a proband with Brugada syndrome is to evaluate his or her individual risk of SD and recommend ICD if necessary (see section on Prognosis and Risk



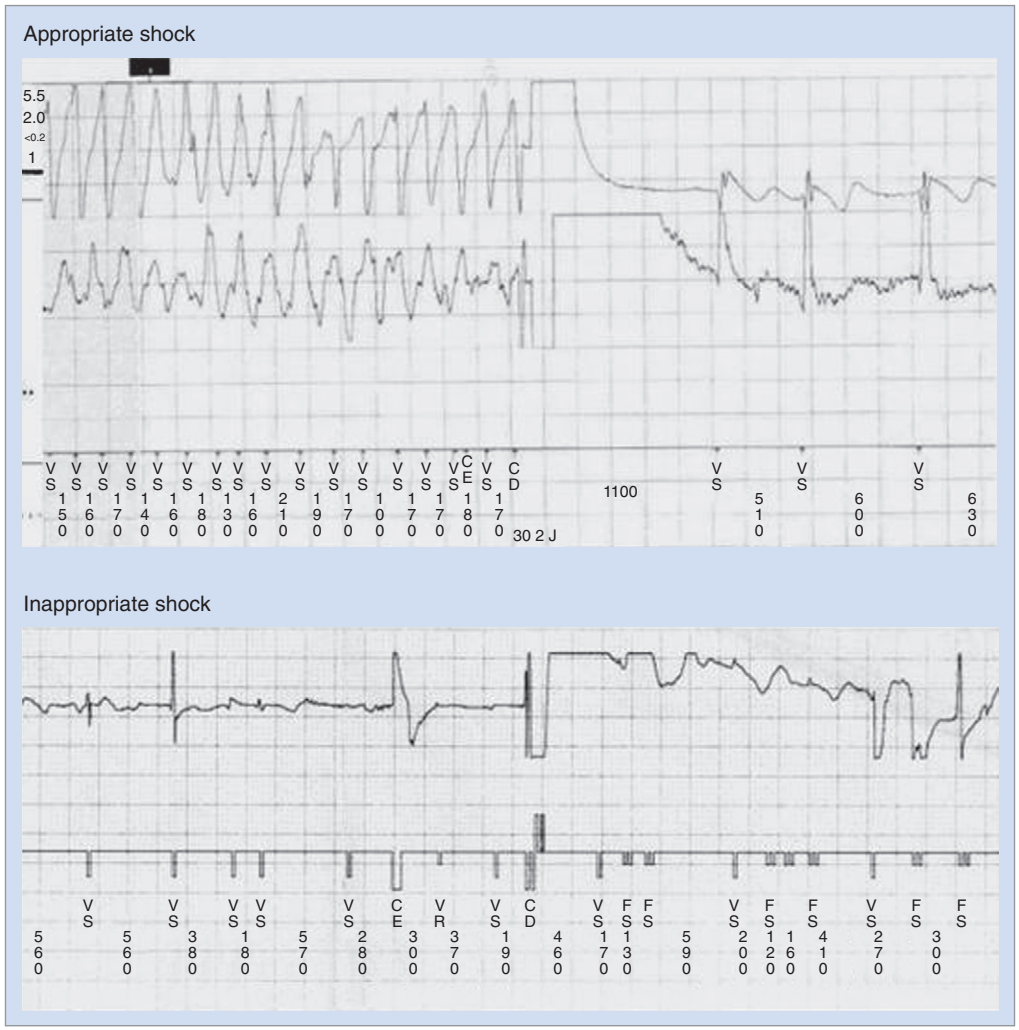


FIGURE 63-11 Kaplan-Meier curve of appropriate implantable cardioverter-defibrillator (*ICD*) therapies in patients with Brugada syndrome according to symptoms prior to implantation. An example of an appropriate therapy and an example of an inappropriate therapy following lead failure are shown. *SCD,* Sudden cardiac death. *(Modified from Sacher F, Probst V, Iesaka Y, et al: Outcome after implantation of a cardioverter-defibrillator in patients with Brugada syndrome: A multicenter study,* Circulation *114[22]:2317–2324, 2006.)*

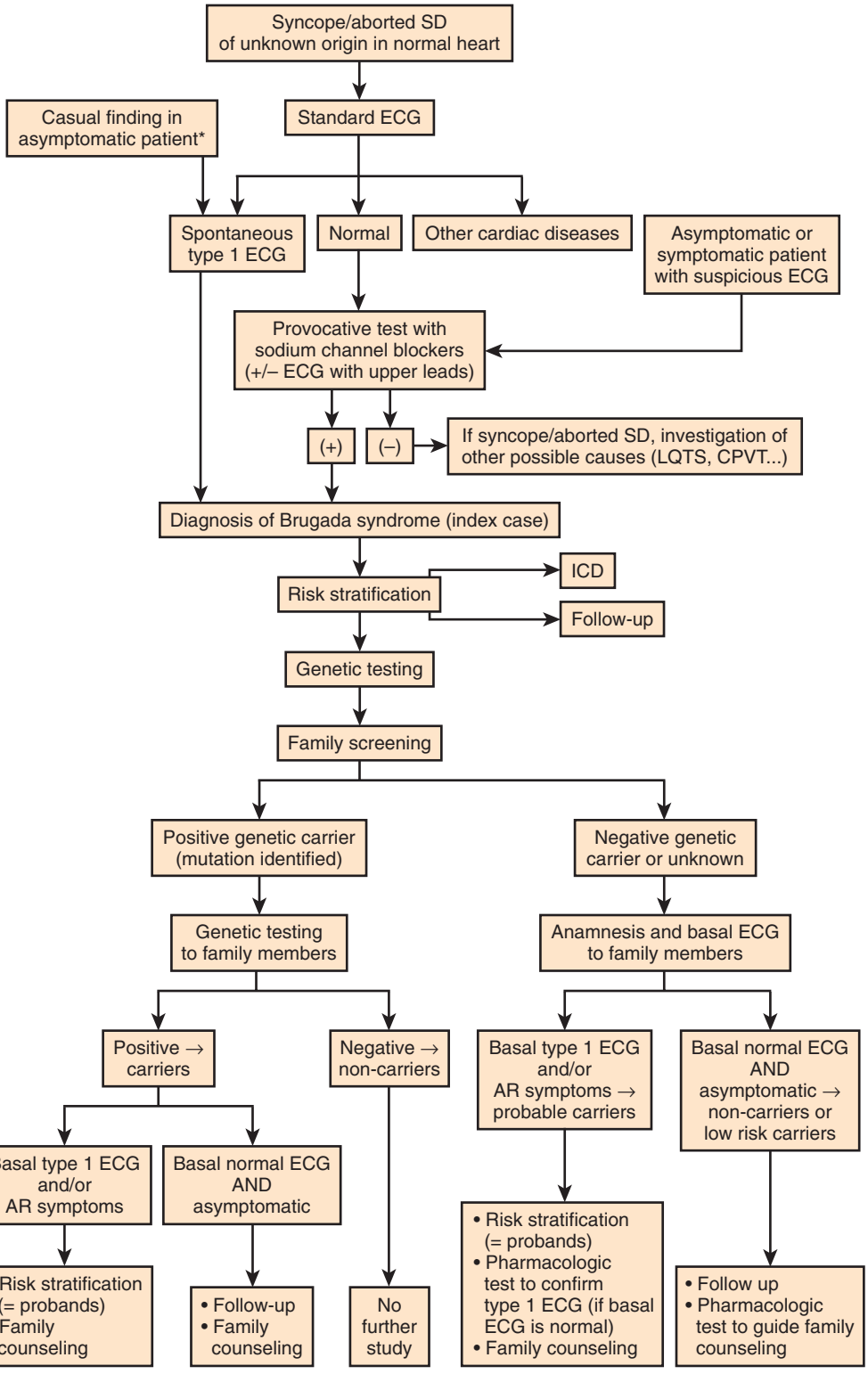


FIGURE 63-12 Proposed decision algorithm for diagnostic approach and family screening in Brugada syndrome. *Asterisk,* Even in the case of a type 1 electrocardiogram (*ECG*) found to be isolated (not associated with symptoms, documented arrhythmias, or family history), patients should be considered at risk of sudden cardiac death and should be assessed for usual risk stratification. *SD,* Sudden death; *LQTS,* long QT syndrome; *CPVT,* catacholaminergic polymorphic ventricular tachycardia; *ICD,* implantable cardioverter-defibrillator; *AR,* aortic regurgitation.

Stratification). Currently, genetic testing is recommended because it helps confirm the disease in patients with borderline phenotype, may provide information on arrhythmic risk during lifetime (see above), and can be helpful in family screening.

Given that Brugada syndrome is commonly an inherited disorder, family screening should always be performed to identify possible relatives who are unaware of the risk of SD (see Figure 65-12). It is important to remember that hereditary forms of Brugada syndrome are autosomal dominant and not linked to sex and that each affected patient has a 50% probability of transmitting the disease to his or her offspring.

If genetic testing is available and the mutation that is responsible has been identified in the proband, genetic testing of all other family members (starting with first-degree relatives) is the best approach in family screening because it helps establish as well as rule out the disease with the maximum sensitivity and specificity. If genetic testing is not available or the mutation that is responsible has not been identified, all direct relatives should be tested first with basic anamnesis and a basal ECG. For those with diagnostic type 1 ECG and thus carriers of the disease, conventional risk stratification should be performed to estimate their probability of suffering cardiac events during follow-up. Data from the chapter authors' group indicate that in those family members with normal ECG at baseline, as long as they are asymptomatic, the probability of cardiac events during follow-up is extremely low (1 per 131 at 100 months, unpublished data); that is, they are either not carriers of the disease or, if they are, have little expressivity and thus are at a very low risk of arrhythmias. Pharmacologic provocative tests could be performed in these patients to increase the penetrance and better identify possible disease carriers, which would be useful for planning and counseling for the family.

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CHAPTER 64

Genetic Diseases: Short QT Syndrome

N.A. Mark Estes III and Nathan Van Houzen

Short QT syndrome (SQTS) was recently recognized as a familial clinical electrocardiographic entity characterized by ion channel mutations, leading to sudden cardiac death (SCD), short refractory periods, and inducible ventricular fibrillation (VF). The genetic inheritance pattern is autosomal dominant with a positive family history of SCD. To date, three principal genetic mutations in potassium channels have been linked to SQTS. The electrocardiogram is characterized by a short Q-T interval of typically less than 320 ms, with tall, peaked, narrow, symmetrical T waves. Short refractory periods lead to a propensity to develop atrial fibrillation (AF) or VF at electrophysiology study (EPS). The following review addresses the genetics, pathophysiology, clinical presentation, and treatment of SQTS.

Historical Context

It has long been recognized that long QT syndrome (LQTS) is a clinical entity with a significant risk of SCD. When analyzing retrospective Holter monitor strips, Algra et al first recognized that short Q-T intervals had an increased risk of SCD. Gussak and associates were the first to propose SQTS as a unique clinical entity in a case series of three patients from one family with similar electrocardiogram (ECG) findings in the setting of atrial and ventricular arrhythmias.[1] In 2003, the definitive link was demonstrated between SQTS and SCD. Gaita et al studied several members of two families who exhibited Q-T intervals less than 280 ms and presented with syncope, palpitations, and a family history of SCD.[2]

EPS confirmed short atrial and ventricular refractory periods consistent with increased vulnerability to AF and VF.

Pathophysiology

Ion channels are essential in modulating the electrical gradient across myocardial cells in the process of depolarization and repolarization. Depolarization is modulated primarily through sodium and calcium channels, which allow an inward current into the cell.

Repolarization currents are mediated through potassium channels that allow ions to exit the cell and restore the negative transmembrane potential. The underlying basis of the SQTS is a gain of function abnormality of the potassium channel leading to a shortening of the action potential duration (APD), refractory period, and Q-T interval.

Furthermore, the shortening of the refractory period is heterogeneous within the myocardial cells, leading to nonuniform dispersion of refractoriness.[3] This, in turn, may lead to VF through the mechanism of wavebreak through re-entry initiation, wavelet formation and, ultimately, fibrillation.[3-5]

Molecular Genetics

SQTS is a genetically heterogeneous disease characterized by at least three different gene mutations of potassium channels involved in repolarization.

The *KCNH2* gene, or *HERG*, encodes a transmembrane protein responsible for the rapidly activating delayed rectifier potassium channel I_{Kr}. Two missense mutations have been described that lead to "gain in function" and shortening of the APD leading to SQT1.[6,7] This potassium channel is the most commonly implicated in LQTS as well.

The *KCNQ1* gene encodes the ion channel responsible for the slowly activating delayed rectifier potassium channel I_{Ks}. A missense mutation in the *KCNQ1* gene results in accelerated activation kinetics consistent with a gain of function in the outward current. This mutation also leads to shortening of the APD and is considered the sporadic form of SQTS, called SQT2.[8,9]

The *KCNJ2* gene encodes for a protein responsible for the inward potassium rectifier current (I_{K1}). A mutation in this gene generates electrical currents that do not decrease to the extent of normal potassium channels. This corresponds to the end of phase 3 of repolarization, leading to acceleration of late repolarization, thereby shortening the APD. This mutation leads to a unique ECG finding of asymmetric tall T waves with a rapid descending portion that is now called SQT3.[10]

The three different mutations identified to date are all linked to potassium channels that alter currents at different points in the cardiac action potential. Mutations leading to loss of function in the *KCNQ1*, *KCNH2*, and *KCNJ2* genes are also involved in LQT1, LQT2, and Andersen syndrome (LQT7), respectively. It has been difficult to classify the different forms of SQTS on the basis of genetic mutation because of the heterogeneity of the clinical syndrome and the inability to link clinical symptoms to a specific genotype.

Antzelevitch et al were the first to report loss-of-function mutations in genes encoding the cardiac L-type calcium channel to be associated with a familial SCD, in which a Brugada syndrome phenotype is combined with shorter than normal Q-T intervals. Among 82 probands with a clinically robust diagnosis

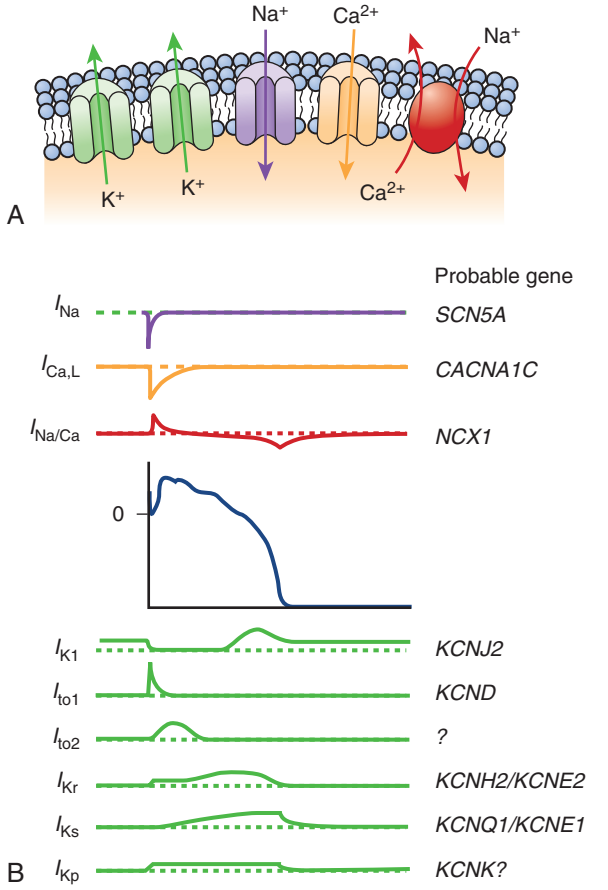

FIGURE 64-1 A, Ion channels are embedded in the membrane and allow the flux of ions in and out of the cells following voltage gradients. The sodium-calcium (Na^+/Ca^{2+}) exchanger (*red*) is electrogenic because it transports three sodium ions for each calcium ion across the surface membrane. **B,** Ionic currents and their corresponding genes. The generation of electrical activity by the different ionic currents will generate the cardiac action potential. *Top*, Three depolarizing currents. *Middle*, A ventricular action potential. *Bottom*, Repolarizing currents. Mutations in *KCNJ2*, which affects the I_{K1} current, result in the third form of short QT syndrome. Mutations in *KCNH2/KCNE2*, affecting the I_{Kr} current, result in the syndrome's first form. Mutations in *KCNQ1/KCNE1*, affecting the I_{Ks} current, result in the second form. *(From Brugada R, Hong K, Cordeiro JM, Dumaine R: Short QT syndrome,* CMAJ *173[11]:1349–1354, 2005.)*

of Brugada syndrome in the present registry, 6% (5 patients) presented with a shorter than normal Q-T interval, specifically mutations in *CACNA1C* and *CACNB2b*. Although the QTc intervals (330 to 360 ms) are longer than those encountered in *KCNH2* and *KCNQ1* mutations, they do overlap within the range found in patients with *KCNJ2* mutations (SQT3) (Figure 64-1).[11]

Clinical Manifestations

SQTS has been characterized by major and minor cardiac events or symptoms. Major events include SCD, syncope, and VF. Minor events include palpitations, lightheadedness or dizziness, and paroxysmal AF. SCD is the most frequent first symptom and first clinical presentation. Most patients have a significant family history of SCD, occurring in relatives with a variable age distribution, ranging from 3 months to 70 years. The mean age of diagnosis is 30 years.[12] It has been suggested that sudden infant death syndrome may, in some cases, be attributed to SQTS.[12,13] Paroxysmal AF was first reported in 2000 as being linked to SQTS in a young woman who developed rapid AF during surgery. She subsequently underwent cardioversion to sinus rhythm that uncovered a Q-T interval of 280 ms. It was found that she had multiple family members with paroxysmal AF in the setting of short Q-T intervals.[14] It is vital to exclude SQTS in a young patient with lone AF. SCD was definitively linked to SQTS in a case series in which five of six members were inducible for VF during EPS, and all six received an implantable cardioverter-defibrillator (ICD).[2]

The classic sign on ECG is a very short Q-T interval. A cutoff of 320 ms should raise suspicion for SQTS because the two families first identified by Gaita et al had Q-T intervals less than 280 ms.[2] The T waves are tall, peaked, and symmetrical except in patients with the form of SQTS involving a mutation in the *KCNJ2* gene (SQT3).[10] The T wave is upright, and the interval of the T wave is not usually prolonged. The ST segment is often noted to be very short or completely absent. An appearance of a U wave has been reported in a few cases. Occasionally, the PR segment may be depressed, consistent with abnormal atrial repolarization.[15] A slight reduction in the Q-T interval accompanies a physiological increase in the heart rate, although it can often be difficult to make a diagnosis of SQTS when the heart rate is above 100 beats/min. It is important to exclude other potential etiologies of acquired short Q-T interval, such as sinus tachycardia, hyperthermia, hypocalcemia, acidosis, hyperkalemia, and digoxin therapy.[16]

EPS uniformly reveals short atrial and ventricular refractory periods with easily inducible AF and VF by programmed stimulation. In a study by Giustetto et al, 18 patients with SQTS underwent EPS to determine effective refractory periods and inducibility of VT or VF. The effective refractory period (ERP), determined from the apex of the right ventricle at a drive cycle length of 500 to 600 ms, varied between 140 and 180 ms. The ERP from the high right atrium with drive cycle length of 600 ms varied between 120 and 180 ms. The significance of ventricular programmed stimulation as a risk stratifier in patients with inherited channelopathies is unclear. In the study by Giustetto et al, VF was induced in only 11 of 18 patients, of whom only three had a prior history of resuscitated cardiac arrest. Only three of six patients with prior documented VF could be induced by EPS.[12]

Prognosis

Patients with SQTS are at considerable risk for SCD. In the largest group of patients evaluated in a single study, 29 patients were diagnosed with SQTS. Of these, three patients died before clinical evaluation and six other patients had resuscitated cardiac arrest. In eight of the nine patients, sudden cardiac arrest was the initial presentation, and six other patients had documented syncope; 62% of patients reported symptoms at the time of diagnosis.[17] In a Kaplan-Meier estimate of cumulative survival free from cardiac arrest from birth to age 40 years, only 14 of 29 patients are expected to survive, free of cardiac arrest, to the age of 40 years.[12]

Therapy

The clinical syndrome is extremely heterogeneous, with variations in symptoms and risk of SCD within an individual genotype. It currently is difficult to link genotypes with definite phenotypic expression.[18] Given the high incidence of SCD, an ICD is recommended unless an absolute contraindication to implantation exists.[19] Implantation of an ICD in young children remains a technical challenge for a number of reasons: a body too small to accommodate the generator, a right ventricle too small to accommodate a lead, difficulty of vascular access, and the need to account for body growth.[19] Transvenous leads may need to be replaced multiple times in a child or adolescent throughout the person's lifetime, which further complicates the treatment process. The psychological impact of this in a young child cannot be understated, especially if the child experiences therapy from the device, which can lead to anxiety and depression. Research is being conducted on the role of pharmacologic therapy in in overcoming this difficulty until the minimum body size is attained.

Patients with SQTS are at an increased risk for inappropriate therapy caused by the detection of short coupled and prominent T waves. Schimpf et al observed inappropriate shocks in three of five patients who received an ICD for SQTS. This occurred soon after implantation and was caused by oversensing of the shortly coupled T waves.[20] This constitutes a significant proarrhythmic risk and the potential for psychological stress. Even with true bipolar sensing, inappropriate shocks still occurred during sinus rhythm in two of three patients with bipolar leads. Increased T-wave amplitude in SQTS, in combination with reduced R wave, accounts for the majority of inappropriate shocks. Device algorithms to allow for decreased sensitivity and linear or programmable decay after the R wave to avoid oversensing of the T wave may address this particular dilemma. However, to avoid detection problems with ventricular arrhythmias, it is important to be careful with programming.

Pharmacologic therapy is a potential alternative to ICDs in patients in whom ICD implantation is not feasible. Gaita et al evaluated multiple antiarrhythmic agents to determine the potential of these drugs to prolong the Q-T interval and reduce the risk of ventricular arrhythmias. Six patients were tested with flecainide, sotalol, ibutilide, and hydroquinidine. The class IC and class III agents did not produce a significant prolongation of the Q-T interval. Hydroquinidine was the only agent to cause prolongation of the Q-T interval, which increased from a mean of 263 ms to a mean of 362 ms. When performing ventricular programmed stimulation after administration of hydroquinidine, the ventricular ERP increased to 200 ms or more, and VF was no longer inducible.[21,22] Quinidine blocks slow and rapid delayed rectifying potassium channels, which explains the prolongation of the APD and the Q-T interval. It has been found to be effective in the SQT1 variant.[23]

Wolpert et al showed that a mutation in the *KCNH2* gene (*N588K* mutation) resulted in a 5.8-fold decrease in blocking potency in the I_{Ks} channel. Class III agents such as sotalol or ibutilide may not be effective secondary to a mutation in the I_{Ks} channel, which reduces the affinity of the I_{Ks} channel for a class III agent. Sotalol was found to have a 20-fold attenuation with *N588K* mutation in its ability to block the I_{Kr} channel. Disopyramide was shown, in vitro, to be less affected by the blocking of the I_{Kr} channel by *N588KL* mutation (1.5-fold decrease in blocking potency) and may be a rational treatment option for SQTS.[24] Propafenone was shown to be effective in preventing paroxysms of AF in a small study of two patients with SQTS for more than 1 year.

Conclusion

SQTS is a new, distinct clinical entity. Our understanding of the genetics, pathophysiology, and therapeutic options of this entity has advanced rapidly in the last 7 years. To date, three different genetic variants have been discovered, all involving gain in function mutations and a part played by potassium channels in phase 3 repolarization. Patients who present with atrial or ventricular arrhythmias in the setting of a short Q-T interval, especially in the presence of a family history of SCD, should be referred to an electrophysiologist for further management. Young patients presenting with lone AF should be evaluated for SQTS.

Aggressive risk stratification in family members is crucial given the high risk of SCD at a very young age. ICD therapy is the treatment of choice in patients with the clinical syndrome, especially in those who have had resuscitated cardiac arrest and syncope or have a family history of SCD.

Pharmacologic therapy is a potential alternative for patients in whom ICD therapy is contraindicated. Quinidine is the only agent that has been demonstrated to be efficacious; however, no long-term data on its efficacy in preventing SCD are available. As the understanding of the genotype-phenotype correlation improves, recommendations for specific therapies based on genotype may be developed.

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CHAPTER 65

Genetic Diseases: Catecholaminergic Ventricular Tachycardia

Marina Cerrone, Carlo Napolitano, and Silvia G. Priori

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is one of the most malignant inherited arrhythmogenic diseases, with a high incidence of sudden cardiac death among affected individuals. The first report of a patient with this disease was published in 1975, but the first systematic description came in 1978 with the work of Coumel et al and was further refined by the same group in 1995.[1-3] In 2001, the authors of this chapter reported for the first time that the autosomal dominant form of the disease was caused by mutations in the gene of the cardiac ryanodine receptor.[4] Shortly thereafter, the gene for an autosomal recessive form of CPVT was identified as the gene encoding cardiac calsequestrin[5]; overall, it became clear that CPVT is caused by abnormal calcium (Ca^{2+}) homeostasis.

After the identification of the underlying genetic causes, basic science studies in cellular systems and animal models provided major advancements to the understanding of arrhythmogenic mechanisms in this disease.

In this chapter, the clinical and genetic aspects of CPVT will be reviewed together with the most important experimental observations on CPVT pathophysiology that provide the rationale for the development of novel therapies.

Clinical Presentation and Diagnosis

The initial presentation of CPVT is syncope or cardiac arrest occurring during adrenergic stress.[3,4] The mean age of onset of the first syncope is 12 years.[6-8] In the absence of treatment, the disease is highly lethal: The estimated incidence of sudden death is of 30% before age 40 years.[9] Sudden death may be the first manifestation of the disease, thus making prevention of lethal events a difficult task.

The diagnostic challenge in CPVT is that in contrast to other inherited channelopathies such as long QT syndrome (LQTS) or Brugada syndrome, the surface electrocardiogram (ECG) is unremarkable. Since patients with CPVT often seek medical attention for the evaluation of unexplained syncope with a normal ECG and no structural abnormalities, they may be misdiagnosed as being affected by vasovagal syncope or epilepsy.

Minor, nondiagnostic features are resting sinus bradycardia and prominent U waves, but their diagnostic value has never been systematically addressed.[3,10] Furthermore, mild QT prolongation in some CPVT cases has been reported[2,3]; thus the differential diagnosis for CPVT should include LQTS. Some patients with LQTS do have a mild phenotype (borderline QT interval and no symptoms), but their prognosis is completely different from that of patients with CPVT, which presents a higher incidence of sudden death and a limited response to β-blocker therapy.[6,11]

In the authors' series of patients with CPVT, a positive history of sudden death, stress-induced syncope, or seizures was present in 30% of patients, suggesting that careful collection of family history plays an important role in the correct identification of this condition.[6]

Exercise stress testing is the single most important tool, since CPVT arrhythmias are often reproducible during graded exercise (Figure 65-1). The typical behavior of CPVT arrhythmias is that of a progressive worsening on increase in workload; isolated premature beats or couplets initially appear between 90 and 110 beats per minute (beats/min) followed by runs of nonsustained or sustained ventricular tachycardia (VT) when the heart rate further increases (see Figure 65-1).[12] Supraventricular arrhythmias are also a common finding and often precede the onset of ventricular arrhythmias.[13] The morphology of VT is a hallmark of the disease: the so-called bidirectional VT, which is characterized by a 180-degree beat-to-beat rotation of the axis of the QRS complexes on the frontal plane.[4,6] Although this pattern is recognizable in the majority of patients, it is important to be aware that some patients also present with irregular polymorphic VT. Furthermore, the initial presentation of the disease may also be that of ventricular fibrillation (VF) triggered by sudden adrenergic activation that may be interpreted as idiopathic VF in the absence of documentation of typical CPVT arrhythmias.[6] Holter monitoring and implantable loop recorders are helpful for diagnosis, especially in those patients in whom emotional triggers (alone or in combination with exercise) are more arrhythmogenic than exercise alone.[14,15]

Programmed electrical stimulation does not contribute to clinical assessment; conversely, epinephrine infusion may often induce the typical pattern of VT, although its diagnostic sensitivity does not appear to be higher than that of exercise stress test.

Genetic Bases

The majority of familial CPVT cases present an autosomal dominant pattern of inheritance. In 1999, Swan et al identified a significant linkage with some microsatellite markers at locus 1q42-q43.[16] On the basis of this information, the authors of this chapter undertook a candidate gene screening in the critical region and identified the cardiac ryanodine receptor (*RyR2*) as the mutant CPVT gene.[4] In the same year, Lahat et al described an autosomal recessive transmission pattern on the chromosomal

locus 1p13-21 in a large Bedouin CPVT family.[17] Subsequently, they also succeeded in identifying a mutation on the cardiac calsequestrin (*CASQ2*) gene, encoding for cardiac calsequestrin.[5]

Autosomal dominant (*RyR2*) CPVT is, by far, the most frequent variant, and *CASQ2* mutations represent 1% to 2% of all genotyped CPVT. More recently, on the basis of the evidence that the patients with Andersen-Tawil syndrome may have bi-directional VT, it has been suggested that some CPVT cases can be explained by *KCNJ2* mutations.[18,19] A detailed discussion of the link between *KCNJ2* mutations and CPVT is beyond the scope of this chapter, but it is relevant to note here that preliminary experimental studies on adenoviral-infected cardiac myocytes with *KCNJ2*-CPVT mutations show a cellular phenotype very similar to that observed in *RyR2*-mutant myocytes.[20]

In 2007, a new autosomal recessive form of CPVT mapping on the chromosomal locus 7p14-22 was reported by Bhuiyan et al, but the gene disease has not yet been discovered.[21] So far, more than 70 different mutations have been associated with CPVT, and they all are single–base pair substitutions causing the replacement of an amino acid. As expected with regard to autosomal recessive disorders, the number of families with CPVT linked to *CASQ2* mutations is fairly small. At present, only seven mutations have been discovered, and they can be inherited in homozygous or compound heterozygous form. A recent analysis from the authors' group has demonstrated that genetic screening on the *RyR2* gene can identify at least 62% of probands who present with a clinical picture suggestive for the disease[22]; genetic testing helps identify silent mutation carriers and for reproductive counseling (Figure 65-2). Furthermore, *RyR2*-negative and *CASQ2*-negative patients should undergo *KCNJ2* screening. *KCNJ2* mutations are associated with a favorable outcome (sudden death is an exceptional event in this case).

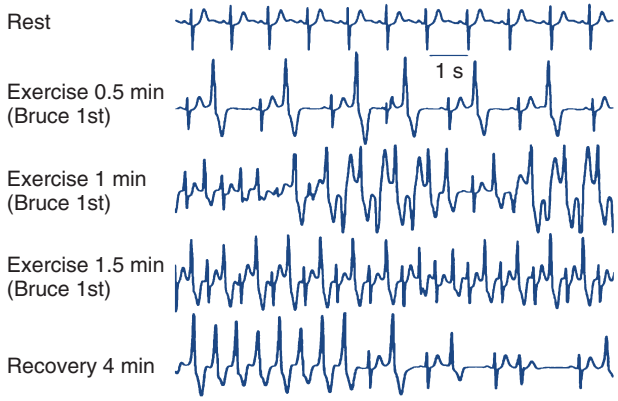

FIGURE 65-1 Continuous lead II electrocardiogram tracing of a patient affected by catecholaminergic polymorphic ventricular tachycardia during treadmill stress test. With the increase in the workload, the complexity of ventricular arrhythmias increases. *(Modified from Liu N, Ruan Y, Priori SG: Catecholaminergic polymorphic ventricular tachycardia,* Prog Cardiovasc Dis *51:23–30, 2008.)*

Mechanisms of Arrhythmias in Autosomal Dominant CPVT: From Cellular Studies to Engineered Murine Models

Summary of RyR2 Physiology

The cardiac ryanodine receptor, RyR2, is a tetrameric channel that regulates the release of Ca^{2+} from the sarcoplasmic reticulum (SR) to the cytosol during the plateau phase of the cardiac action potential. Clearly, this is an important physiological function that allows coupling the electrical activation with the contraction of myofibers (so-called *electro-mechanical coupling*). Abnormal RyR2 function leads to changes in the amount of Ca^{2+} released

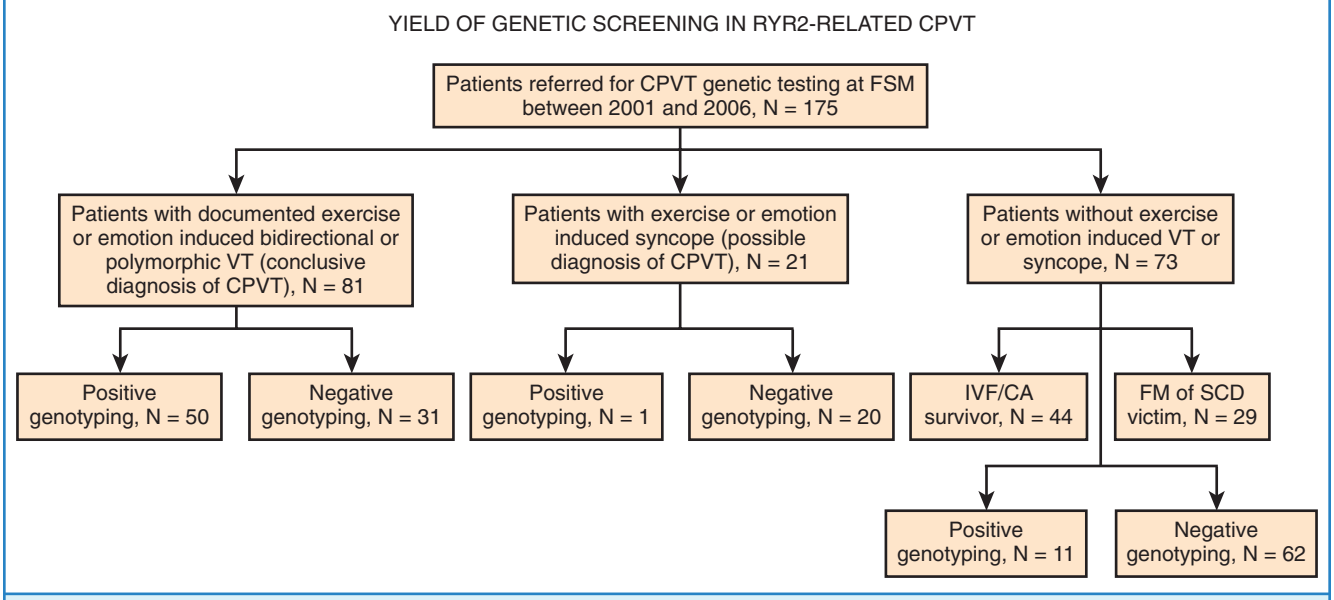

FIGURE 65-2 Yield of genetic testing in the autosomal dominant form of catecholaminergic polymorphic ventricular tachycardia (*CPVT*). *FSM*, Fondazione S. Maugeri Laboratories, Pavia, Italy; *IVF/CA*, idiopathic ventricular fibrillation/cardiac arrest; *FM*, family members; *SD*, sudden death. *(Modified from Rong B, Napolitano C, Bloise R, et al: Yield of genetic screening in inherited cardiac channelopathies: How to prioritize access to genetic testing,* Circ Arrhythmia Electrophysiol *2:6–15, 2009.)*

from the SR and consequently both SR and cytosolic Ca^{2+} concentrations may vary (the other important player for intracellular Ca^{2+} control is the adenosine triphosphate [ATP]–dependent Ca^{2+} pump [SERCA], which, by controlling the uptake of Ca^{2+} from the cytoplasm to the SR, has an impact on the amount of "releasable" Ca^{2+}). RyR2 malfunction often causes increased SR release and cytosolic Ca^{2+} overload; this induces compensatory phenomena that tend to restore the balance, such as the activation of the sodium-calcium exchanger (NCX). Unfortunately, such compensatory mechanisms may be arrhythmogenic (see below).

Since Ca^{2+} is not only important for electrical and mechanical activation but also for a wide range of enzymatic and metabolic pathways, it is clear that *RyR2* abnormalities may exert additional (and, so far, not thoroughly investigated) consequences on cell physiology.[23]

RyR2 function (SR Ca^{2+} release) is regulated by several accessory proteins such as calsequestrin, triadin, junctin, and FKBP12.6. Furthermore, the adrenergic tone controls the RyR2 channel through phosphorylation, which is a crucial function determining the amount of Ca^{2+} released from the SR. Catecholamines activate protein kinase-A (PKA) and calcium-calmodulin–dependent kinase (CaMKII) that phosphorylate RyR2 at different sites (e.g., serine 2008, 2808, and 2914) and act as a throttle on the Ca^{2+} release process.

RyR2 Mutations and Catecholaminergic Polymorphic Ventricular Tachycardia

The effects of *RyR2* mutations have been studied in vitro and in vivo by using different experimental models (expression in lipid bi-layers, heterologous cell expression, and knock-in murine models).

RyR2 mutations can affect both the activation and the inactivation of the channel in several manners. It is also likely that different mutations have different consequences (mutation-specific effects) similar to what was demonstrated for plasmalemmal ion channel causing other inherited arrhythmogenic conditions. Of note, independently from subcellular mechanisms, the final common effect of CPVT mutations (both *RyR2* and *CASQ2*) is similar to that of digitalis intoxication: Ca^{2+} overload, activation of NCX in the forward mode, generation of transient inward current (I_{ti}), and delayed after-depolarizations (DADs) (see below).

The proposed "primum movens" for RyR2-CPVT mutations to lead to Ca^{2+} overload is uncontrolled release (leakage) during diastole, which could be detected, according to different authors, only on adrenergic activation (phosphorylation) or already in the unstimulated condition.[24-26] Given the complexity of the SR Ca^{2+} release process, the leakage could, in principle, be caused by several mechanisms.[24,25,27] The hypotheses so far advanced are summarized in the following paragraphs (Figure 65-3).

Subcellular Mechanisms for *RyR2* Dysfunction in Catecholaminergic Polymorphic Ventricular Tachycardia

FKBP12.6 Dissociation with *RyR2* Mutants

FKBP12.6, also known as *calstabin*, is thought to play a role as a "stabilizer" of the channel in the closed state during diastole. Hints for the possible role of FKBP12.6 in CPVT were initially collected in experimental studies in heart failure. During congestive heart failure, chronic adrenergic hyperactivation may lead to weaker FKBP12.6 binding that can be the cause of Ca^{2+} overload-mediated arrhythmogenesis in this common disease.[28] The FKBP12.6 hypothesis, originally developed by Andrew Marks and co-workers, was subsequently extended to CPVT pathophysiology; these authors demonstrated that some *RyR2* mutants may cause a reduced binding affinity for FKBP12.6, which is further increased by sympathetic stimulation (see Figure 65-3).[27] More recently, the same group performed an FKBP12.6 binding assay in a *RyR2* knock-in mouse engineered with the *R2474S* mutation which has a CPVT-like phenotype[29]; they confirmed their initial hypothesis by demonstrating reduced FKBP12.6 binding in the presence of adrenergic stimulation. In parallel with these studies, Marks' group also tried to pharmacologically treat the binding defect by using K201, a benzothiazepine derivative that was expected to increase FKBP-RyR2 binding. Long-term administration of this drug (or of its novel derivative, S107) was able to restore binding and to prevent the occurrence of arrhythmias both in the FKBP12.6 knock-out murine model and in the $RyR2^{R2474S/WT}$ knock-in murine model.[29,30]

Despite the large amount of evidence provided by the Andrew Marks group, other authors either were not able to replicate their results or provided conflicting evidence when they used alternative approaches. George et al and Jiang et al reported normal FKBP12.6-RyR2 interaction in vitro.[24,31] Chronic treatment with K201 did not prevent arrhythmias in vivo or the occurrence of DADs in isolated myocytes in a CPVT knock-in mouse $RyR2^{R4496C/WT}$ in a study by the authors of this chapter (Figure 65-4).[32] Furthermore, in this model, Western blot experiments also demonstrated physiological interaction between RyR2 and FKBP12.6.[32] Along these lines, Zissimopulos et al demonstrated that FKBP12.6 binding is either unaltered or even increased in the presence of CPVT-*RyR2* mutations.[33] Another report by Hunt et al provided evidence that K201 may modulate RyR2 independently from FKBP12.6.[34] For example, these authors showed that K201 abolished spontaneous Ca^{2+} release in cardiac myocytes in the presence of FK506 that dissociates FKBP12.6 from RyR2.

Overall, considering the limited availability of effective medical therapy for patients with CPVT, the possibility of exploring new treatment options such as K201 and S107 remains appealing; the fact that K201 might be effective independently from its action on FKBP12.6 justifies further studies on this drug.

Defective Interdomain Interaction

RyR2 is a large molecule with a complex tertiary and quaternary structure, in which interactions between domains are important for channel function. Indeed, domain-domain interactions ensure proper folding during the opening and closing of the channel.[35]

Several *RyR2*-CPVT mutations occur in the N-terminal (residue 70-466) and the central domains (residues 2246-2543).[36] The N-terminal and central domains interact, and their relative conformational change from zipped (tight interaction) to unzipped (loose interaction) is involved in the channel gating process.[35] Recent data have highlighted how some CPVT-related mutants may affect this mechanism by inducing a shift toward a mostly unzipped interaction that destabilizes the channel (see Figure 65-3). To test this hypothesis, Oda et al generated a synthetic peptide, DPc10, encompassing the Gly2460-Pro2495 region of RyR2 that mimics an *RyR2* mutant: The peptide destabilizes the N-terminal–central region interaction through competitive activity and reproduces the biophysical effect of CPVT mutations.[37] The same group engineered several other peptides, mimicking mutations located either in the N-terminal or in the central region

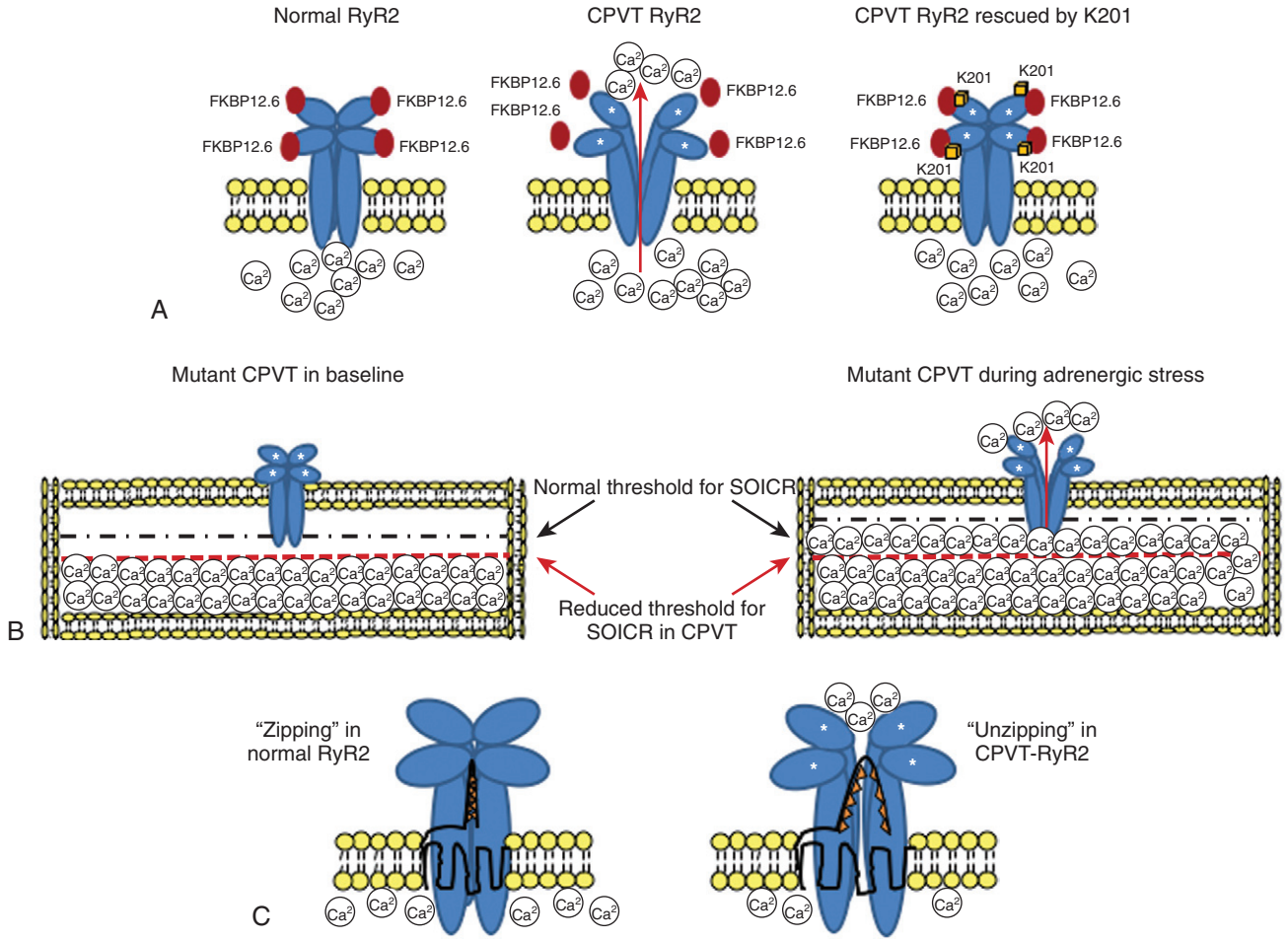

FIGURE 65-3 Different hypotheses of *RyR2* dysfunction caused by catecholaminergic polymorphic ventricular tachycardia (*CPVT*)–related mutations. **A,** FKBP12.6 disassociation caused by CPVT mutations and its rescue by drugs as K201. **B,** The threshold of store overload–induced calcium release (*SOICR*) is reduced in CPVT mutants. **C,** CPVT mutations destabilize interdomain interactions, affecting proper folding of the protein that ultimately causes Ca^{2+} leakage.

of the protein, demonstrating that the mutations caused Ca^{2+} leakage through the disruption of interdomain interaction.[38] Independent support to the hypothesis of unzipping has been provided by George et al by means of high-resolution confocal microscopy and fluorescence resonance energy transfer analysis.[39]

Store Overload–Induced Calcium Release

The open-state probability of RyR2 increases as the SR Ca^{2+} increases. If SR Ca^{2+} reaches a critical threshold, spontaneous Ca^{2+} leakage may occur even in the absence of membrane depolarization (i.e., calcium-induced calcium release). Chen et al proposed the hypothesis that some *RyR2* mutants increase channel sensitivity to luminal Ca^{2+} (in other words, reduce the threshold for spontaneous Ca^{2+} release) (see Figure 65-3).[25,26,31] This phenomenon was termed *store overload–induced calcium release* (SOICR). A reduced SOCIR threshold was shown for nine *RyR2* mutations. Interestingly, while luminal (i.e., inside the SR) Ca^{2+} sensitivity was increased, no evidence for an increased sensitivity to cytosolic Ca^{2+} was observed. On the contrary, Thomas et al reported increased sensitivity of the receptor to cytosolic Ca^{2+} in L433P and R176Q/T2504M *RyR2* mutants.[40] While the role of cytosolic Ca^{2+} sensitivity has still to be determined, it appears evident that a reduced threshold for release has an important role, since, as shown by Venetucci et al, increasing ryanodine receptor open probability alone does not produce arrhythmogenic diastolic Ca^{2+} release because of the accompanying decrease of SR Ca^{2+}content (and reduced driving force).[41,42]

Insights from *RyR2*-CPVT Murine Models

Knock-in murine models have been pivotal to the understanding of the cellular and whole-heart pathophysiology of CPVT.[29,43,44] In 2005, the chapter authors' group provided initial evidence that by engineering a *RyR2*-CPVT mutation in the mouse genome (at variance with what observed for several other murine models of inherited arrhythmias), it is possible to reproduce the phenotype observed in the clinical setting. By homologous recombination, a conditional knock-in mouse harboring the R4496C mutation (a frequent mutation found in CPVT families) was created.[43] The typical CPVT bi-directional VT can be generated in this mouse with adrenergic stimulation in the absence of structural abnormalities.[43] Furthermore, it was demonstrated that the presence of adrenergic-dependent DADs increased NCX-transient inward

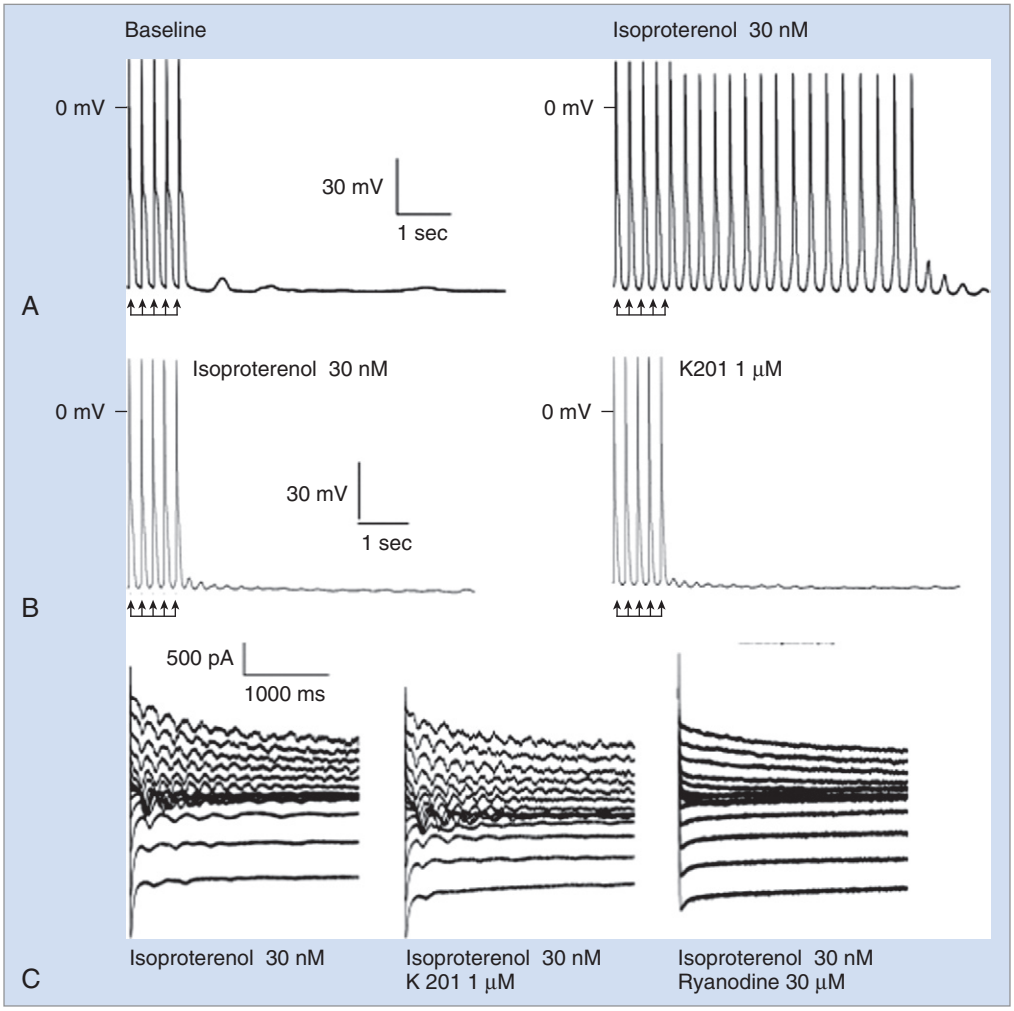

FIGURE 65-4 Patch-clamping recording in RyR2$^{R4496C/WT}$ ventricular myocytes. **A,** Delayed after-depolarizations in baseline and triggered activity elicited by superfusion with isoproterenol. **B,** K201 fails to prevent the occurrence of DADs. **C,** I_{ti} current recording in an RyR2$^{R4496C/WT}$ cardiomyocyte in the presence of isoproterenol and after addition of K201 or ryanodine. *(Modified from Liu N, Colombi B, Memmi M, et al: Arrhythmogenesis in catecholaminergic polymorphic ventricular tachycardia: Insights from a RyR2 R4496C knock-in mouse model,* Circ Res *99:292–298, 2006.)*

current (I_{ti}) and triggered activity as the cellular mechanisms for CPVT (see Figure 65-4).[32] In a subsequent study, the same group observed the onset of abnormal Ca^{2+} waves during diastole, which paralleled the occurrence of DAD development both at baseline and during isoproterenol superfusion.[45] Increased propensity to DAD development in RyR2-R4496C mice was demonstrated also in isolated Purkinje cells by Cerrone et al (Figure 65-5).[46]

Finally, additional data supporting the concept that DADs are the arrhythmogenic mechanisms in CPVT were provided in an elegant study by Paavola et al in patients with CPVT; they used monophasic action potential recordings that showed DAD-like humps originating from the right ventricular septal wall and preceding the occurrence of ventricular arrhythmias.[47]

Transgenic models of CPVT have also provided information on the mechanisms of CPVT arrhythmias at the whole-heart level in studies using the optical mapping technique. In collaboration with José Jalife, the authors of this chapter showed that the arrhythmic beats of both polymorphic and bi-directional VT have a focal origin.[46] Epicardial optical mapping demonstrated that during bi-directional VT, the beats alternately originate from the right ventricle and from the left ventricle and arise from an area coincident with the anatomic insertion of the major bundle branches of the conduction system (Figure 65-6).[46] Additionally, administration of Lugol's solution to chemically ablate the Purkinje network in the right ventricle converts bi-directional VT to monomorphic left-sided VT (see Figure 65-6).[46] Endocardial optical maps have also shown that during polymorphic VT, the site of origin of the beats mapped on the endocardial right ventricular wall corresponded to free-running Purkinje fibers (Figure 65-7).[46] Overall, these experiments support the relevant role of the Purkinje network in the pathogenesis of CPVT arrhythmias.

Mechanisms of Altered Ca^{2+} Homeostasis in CPVT Linked to *CASQ2* Mutations

Mutations in cardiac calsequestrin (*CASQ2*) that cause the autosomal recessive CPVT represent a minority of cases. Current evidence based on limited experience shows no major phenotypic difference between *CASQ2*-CPVT and *RyR2*-CPVT. The few

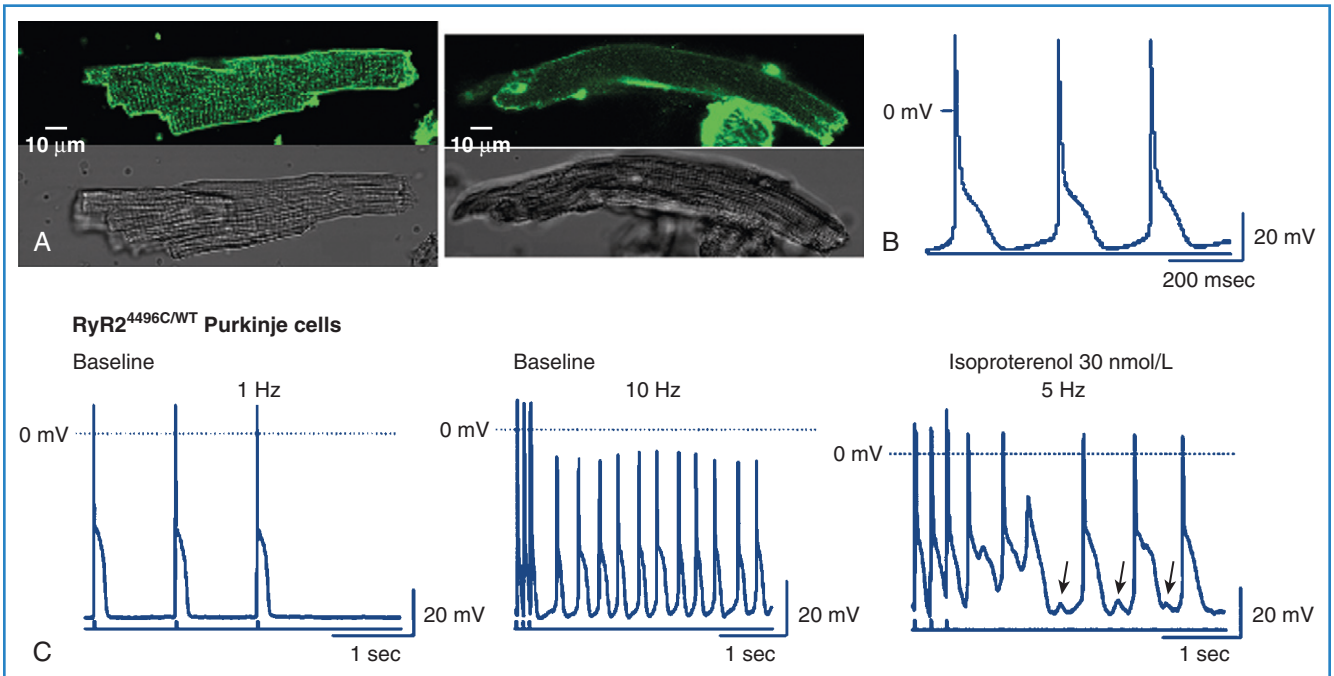

FIGURE 65-5 Patch-clamping recording in isolated RyR2$^{R4496C/WT}$ Purkinje cells. **A,** Confocal and transillumination images of a ventricular myocyte and a Purkinje cell from the same heart. Di-8- ANEPPS staining remarks the lack of transverse T-Tubule system in the Purkinje cell. **B,** Spontaneous pacemaker activity recorded in an isolated Purkinje cell. **C,** Delayed after-depolarizations and triggered activity in baseline and after perfusion with isoproterenol in an RyR2$^{R4496C/WT}$ Purkinje cell. *(Modified from Cerrone M, Noujaim SF, Tolkacheva EG, et al: Arrhythmogenic mechanisms in a mouse model of catecholaminergic polymorphic ventricular tachycardia,* Circ Res *101:1039–1048, 2007.)*

CASQ2 mutations reported so far have been extensively studied in vitro and through transgenic models.

Summary of CASQ2 Physiology

CASQ2 has been initially described as a Ca^{2+} buffering protein resident in the SR lumen. It exists in monomeric and polymeric form; polymerization occurs at high Ca^{2+} and the polymerized protein presents higher Ca^{2+} buffering capacity. When luminal Ca^{2+} is low, CASQ2 binds to junctin and triadin and inhibits RyR2. In the presence of a rise in luminal SR Ca^{2+}, the binding among CASQ2, triadin, and junctin is weakened by the replacement of the binding sites by Ca^{2+}, and this process gradually increases the open probability for the RyR2 channel.[48] Thus, CASQ2 is both a Ca^{2+} buffer molecule and a RyR2 modulator.

Subcellular Mechanisms for CASQ2 Dysfunction in Catecholaminergic Polymorphic Ventricular Tachycardia

Seven CASQ2 mutations have been reported so far, four leading to a truncated protein (nonsense or frameshifts) and three missense mutations. In vitro studies have highlighted three classes of effects: (1) impaired CASQ2 polymerization, (2) altered buffering properties, and (3) altered CASQ2-RyR2 interaction.

Terentyev et al suggested that a reduction or absence of CASQ2, as it happens with the truncation mutants, leads to a decrease of the time necessary to re-establish Ca^{2+} storage, thus facilitating a premature activation of the RyR2 and, as a consequence, diastolic Ca^{2+} leakage.[49]

The D307H was the first missense mutation to be linked to the disease.[5] In in vitro studies, the mutant protein was not able to form properly oriented dimers, and this affected the Ca^{2+} binding capacity.[50] Adenoviral-mediated overexpression of D307H in rat cardiomyocytes showed that Ca^{2+} binding capacity is impaired despite the presence of endogenous native protein (dominant-negative effect)[51,52]; similar results have been obtained in CASQ2^{D307H} myocytes from a transgenic murine model.[53] In contrast, CASQ2-R33Q increases diastolic SR Ca^{2+} release, without affecting Ca^{2+} storing capacity, and it may cause CPVT through a loss of CASQ2-inhibiting effect on RyR2 (Figure 65-8).[54,55] The L167H mutation was identified in a patient with compound heterozygosity (Figure 65-9), and it appears to cause a complex phenotype including abnormal (increased) Ca^{2+} buffering properties, impaired polymerization, and loss of RyR2 inhibitory properties.[55,56]

Insights from CASQ2-CPVT Murine Models

As in the case of RyR2-CPVT, the mouse models reproducing the autosomal recessive CASQ2-CPVT have provided important pathophysiological information but also are of great value in the unraveling of some molecular mechanisms of cardiac Ca^{2+} regulation.

Knollmann et al created a CASQ2 knock-out murine model, in which VT and VF could be induced by β-adrenergic stimulation (isoproterenol).[57] In isolated CASQ2 null myocytes, increased diastolic Ca^{2+} leakage leading to DADs and triggered activity was observed, thus proving the similarities between RyR2-CVPT and CASQ2-CVPT. Interestingly, analysis of this model proved that even in the absence of CASQ2, the SR Ca^{2+} storage capacity was not changed. The authors of this study pointed to the ultrastructural abnormalities involving the increase of the SR volume,

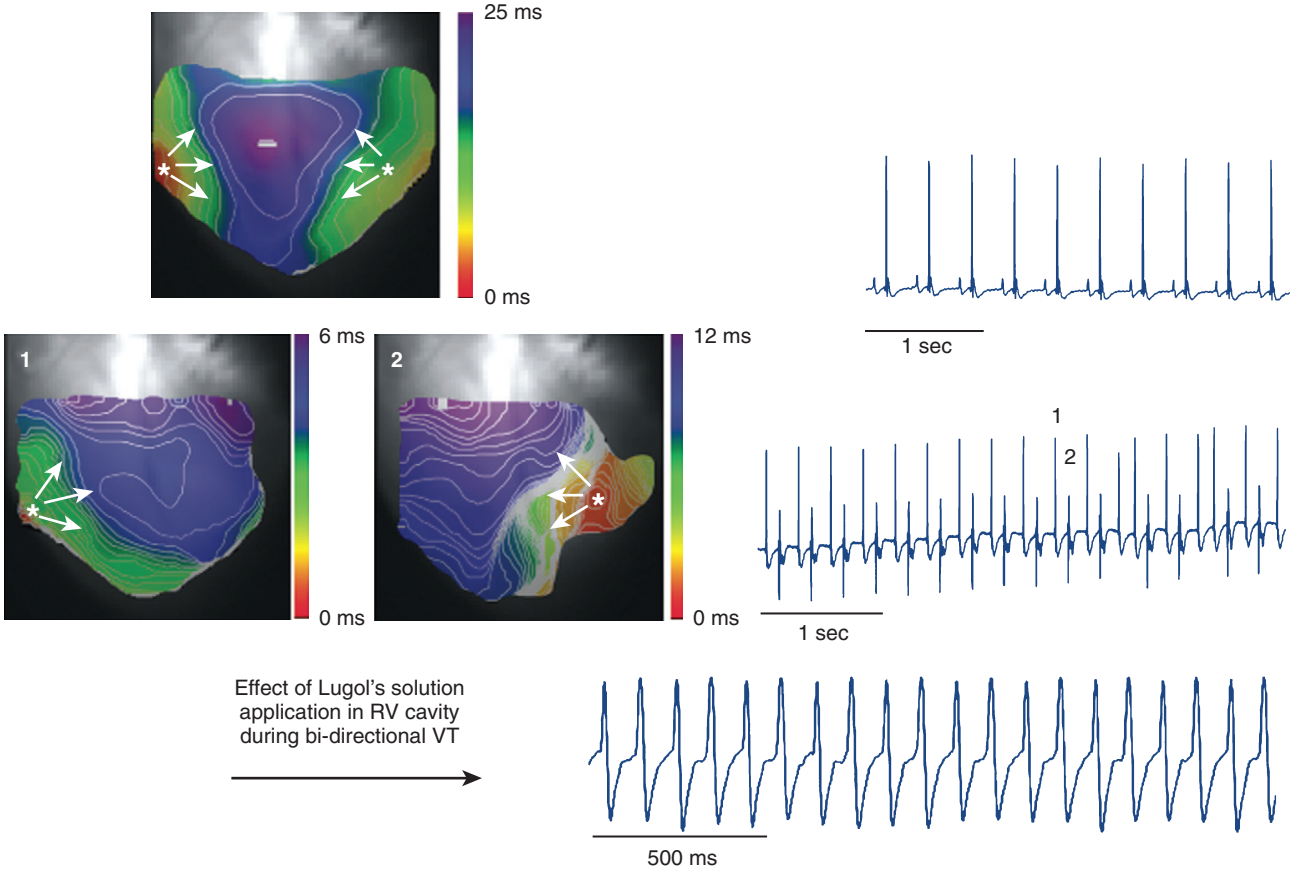

FIGURE 65-6 Bi-directional ventricular tachycardia (VT) elicited in an RyR2$^{R4496C/WT}$ mouse. **A,** Activation map in isolated Langendorff-perfused mouse heart during sinus rhythm and its corresponding volume-conducted electrocardiogram (ECG). **B,** Activation maps in the same heart during bi-directional VT elicited by perfusion with calcium and isoproterenol and corresponding volume-conducted ECG. Map 1 and 2 correspond to the two alternating QRS complexes indicated on the ECG. **C,** Volume-conducted ECG after injection of Lugol's solution in the right ventricular cavity in one anesthetized RyR2$^{R4496C/WT}$ mouse after induction of bi-directional VT. The rhythm converts into monomorphic VT after ablation of the right bundle branch. *RV*, Right ventricular; *VT*, ventricular tachycardia. *(Modified from Cerrone M, Noujaim SF, Tolkacheva EG, et al: Arrhythmogenic mechanisms in a mouse model of catecholaminergic polymorphic ventricular tachycardia,* Circ Res *101:1039–1048, 2007.)*

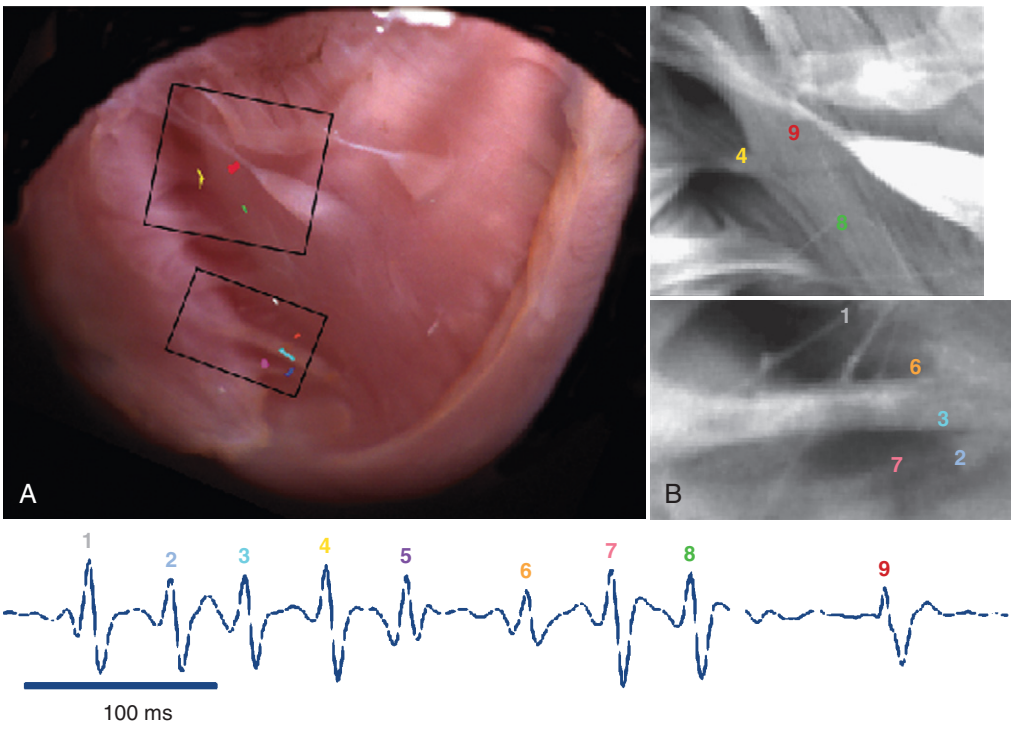

FIGURE 65-7 Polymorphic ventricular tachycardia in an RyR2$^{R4496C/WT}$ mouse. **A,** Each color corresponds to the earliest activation of each beat on the volume-conducted electrocardiogram shown, superimposed on an image of the right endocardial wall. **B,** Magnification of the boxed areas, emphasizing the correspondence of each beat with Purkinje fibers. Beat 5 originates outside the field of view. *(Modified from Cerrone M, Noujaim SF, Tolkacheva EG, et al: Arrhythmogenic mechanisms in a mouse model of catecholaminergic polymorphic ventricular tachycardia,* Circ Res *101:1039–1048, 2007.)*

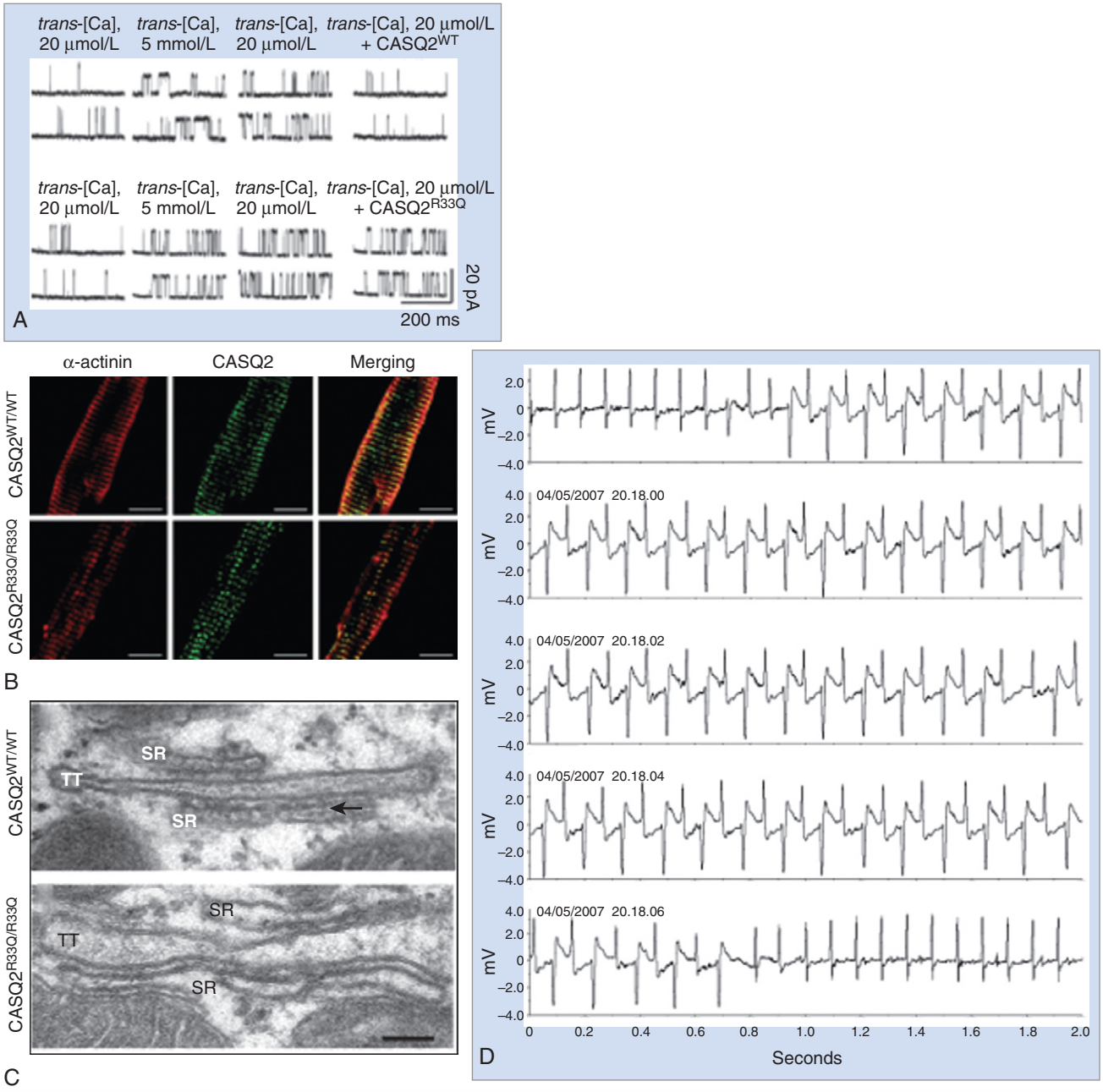

FIGURE 65-8 Effect of the *CASQ2*^{R33Q} mutation. **A,** Single-channel recording of RyR2 activity and its disruption by the *CASQ2*^{R33Q} mutation compared with wild type (WT). **B,** Immunostaining of CASQ2$^{R33Q/R33Q}$ and WT cardiomyocytes emphasizing the decreased amount of CASQ2 in the mutant. Bars: 20 μm. **C,** Electron microscopy showing the lack of electrondense chain-like CASQ2 molecules clustered parallel to the CASQ2$^{R33Q/R33Q}$ sarcoplasmic reticulum (SR) membrane (the *arrow* shows their presence in the WT). Bars: 0.1 μm. **D,** Spontaneous bi-directional-VT in the CASQ2$^{R33Q/R33Q}$ mouse during acoustic stimulation. *TT*, Transverse tubule. *(Modified from Terentyev D, Nori A, Santoro M, et al: Abnormal interactions of calsequestrin with the ryanodine receptor calcium release channel complex linked to exercise-induced sudden cardiac death,* Circ Res *98:1151–1158, 2006; and Rizzi N, Liu N, Napolitano C, et al: Unexpected structural and functional consequences of the R33Q homozygous mutation in cardiac calsequestrin: A complex arrhythmogenic cascade in a knock in mouse model,* Circ Res *103:298–306, 2008.)*

which may represent a compensatory phenomenon to preserve SR Ca^{2+} storing capacity.[57]

More recently, the chapter authors' group developed the CASQ2$^{R33Q/R33Q}$ knock-in model (R33Q was found in a severe case of recessive CPVT), which reproduces the CPVT phenotype.[58] In contrast to the RyR2-R4496C model, in this model arrhythmias occur even spontaneously in the presence of mild stressors (i.e., loud sudden noise) (see Figure 65-8). CASQ2$^{R33Q/R33Q}$ cardiomyocytes showed DADs and triggered activity not only during adrenergic stimulation but also in resting conditions.[58] In contrast to the CASQ2 knock-out model, SR Ca^{2+} is reduced (see Figure 65-8). Rather unexpectedly for a missense mutation, this model is also characterized by reduction of CASQ2 protein (both in the total cell homogenate and in the microsomal fraction) in

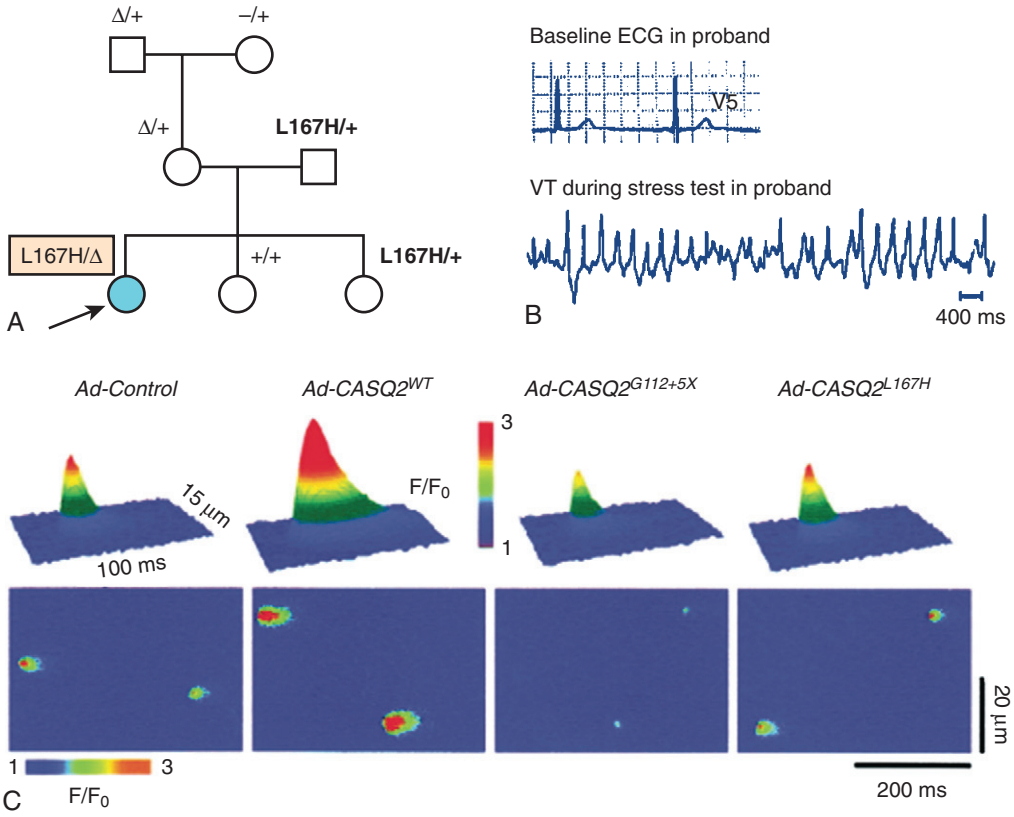

FIGURE 65-9 Effect of two CASQ2 mutations inherited in compound heterozygosis. **A,** Pedigree of the family. *Black circle* indicated by the *arrow* is the case-index who inherited two mutations, one from each of the parents. **B,** Baseline electrocardiogram and ventricular tachycardia elicited by exercise in the case-index. **C,** Ca^{2+} sparks recorded in rat ventricular myocytes infected with wild-type G112+5X or L167H CASQ2 protein. *Top*: Surface plot of averaged Ca^{2+} sparks. *Bottom*: Representative line-scan images. *(Modified from di Barletta MR, Viatchenko-Karpinski S, Nori A, et al: Clinical phenotype and functional characterization of CASQ2 mutations associated with catecholaminergic polymorphic ventricular tachycardia,* Circulation *114:1012–1019, 2006.)*

the presence of normal expression at the mRNA level. Further investigations showed that the mutant R33Q protein, compared with the wild type, is significantly more prone to proteolysis.[58]

Song et al studied two additional murine models, one carrying a null mutation (knock-out) and the other with the D307H mutation.[53] No significant phenotypic differences between the two models, including increased levels of RyR2 and calreticulin, were detected.[53] Calreticulin is a fetal protein that shows Ca^{2+} binding capacity but is not present in adult hearts; the authors thus inferred that its increase in their model should be interpreted as a compensatory mechanism to balance the lack of CASQ2.

Neither the CASQ2 knock-out model generated by Knollmann nor the $CASQ2^{R33Q/R33Q}$ mouse showed altered expression of RyR2 or calreticulin.[57,58] Therefore, until further data are available, it remains unclear why these two different models present a common compensatory mechanism that is not evident in other models, in particular in the knock-out model.

In summary, cellular and animal studies seem to agree in concluding that *CASQ2* mutations cause CPVT by a common final pathway: a critical reduction in protein levels, with increased propensity for diastolic calcium leak.

Current Therapy and Future Directions

Catecholaminergic Polymorphic Ventricular Tachycardia Therapy in the Clinical Setting

On the basis of the clear evidence of the critical role of adrenergic stimulation as a trigger for arrhythmias in CPVT, β-blockers were proposed as a reasonable therapeutic approach following the initial reports on this disease.[2,3] β-Blockers should be started immediately when CPVT is diagnosed; agreement in the scientific community seems to indicate nadolol as the first choice among the available options—for its once-daily dosing and nonselective inhibition of adrenergic stimuli. Asymptomatic bradycardia in these patients should not be used as a reason to reduce the dosage of β-blocker therapy. In fact, the demonstration that DAD-induced arrhythmias are facilitated by faster heart rates provides the rationale to consider the bradycardic effect of β-blockers as an additional antiarrhythmic benefit, along with their inhibitory effect on the sympathetic drive.[59]

More recently, larger epidemiologic studies showed that β-blockers may fail to provide protection from life-threatening events in a relevant proportion of patients.[6,8] In the Italian CPVT Registry, the incidence of recurrent arrhythmia while on therapy is as high as 30%.[6] In case of recurrences of syncopal episodes or VT while on therapy, an implantable cardioverter-defibrillator (ICD) should be considered. Obviously, after ICD implantation, β-blocker treatment should be maintained to minimize the risk of device interventions. Indeed, in the series by the authors of this chapter, 50% of implanted patients received an appropriate ICD therapy during a 2-year follow-up.[9]

The incomplete protection afforded by β-blockers calls for the need of identifying adjunctive effective therapies. Calcium channel blockers, in particular verapamil, have been studied in a limited patient series as a possible alternative to β-blocker therapy by Swan et al and Sumitomo et al.[60,61] The study of Rosso et al evaluated the efficacy of a combined association between β-blockers and verapamil. In their series, the combination of therapies reduced or even suppressed the recurrences of exercise-induced arrhythmias, ICD shocks, or both.[62]

Preliminary data on the possible efficacy of flecainide have been recently published.[63] Flecainide has been shown to prevent stress-induced arrhythmias in CASQ2 knock-out mice and spontaneous SR Ca^{2+} release in isolated myocytes. It was also tested in two patients with CPVT who were implanted with an ICD and were refractory to conventional therapy, and it prevented arrhythmias during exercise test. Although presented only in an anecdotal report, these data are opening encouraging paths to be explored in the attempt to find new therapeutic strategies for treating CPVT.

Wilde et al provided preliminary evidence for the long-term effectiveness of left sympathetic cardiac denervation (LCSD) in three patients with CPVT. However, patients on β-blockers and LCSD who still experience recurrences of sustained VT and syncope do also exist (Priori SG, personal communication).[64] Thus, caution is needed before considering this approach as an effective therapy for high-risk CPVT patients.

Experimental Therapies for Catecholaminergic Polymorphic Ventricular Tachycardia

Experiments in cell systems and CPVT animal models have been carried out to explore new therapeutic possibilities. As mentioned above, attempts to use FKBP12.6-stabilizing drugs (S107[29]and K201[30]) have yielded conflicting results.

Another interesting approach is that of inhibiting the effects of β-adrenergic stimulation by acting on the downstream targets of RyR2 phosphorylation. The pharmacologic inhibition of CAMKII (which phosphorylates RyR2 during adrenergic activation) is a promising approach. CAMKII phosphorylates RyR2 at different sites. Moreover, it is known that CAMKII inhibition reduces diastolic Ca^{2+} leakage and the transient inward I_{ti} current (the transmembrane current generating DADs).[65] Preliminary observations from the chapter authors' group in the $RyR^{R4496C/WT}$ murine model suggest that a specific CAMKII inhibitor, KN93, could prevent arrhythmias both in vitro and in vivo, which provides encouraging support for novel therapeutic strategies involving this pathway.[66]

Conclusion

CPVT is a unique and malignant inherited form of arrhythmia and sudden death caused by the malfunction of Ca^{2+}fluxes from the SR to the cytosol. Such abnormal intracellular Ca^{2+} handling creates a very unstable substrate that manifests primarily with the onset of arrhythmias on adrenergic stimulation in the absence of macroscopic structural changes. Although relatively uncommon, the in-depth analysis of CPVT pathophysiology is relevant to understanding not only CPVT itself but also Ca^{2+}-mediated arrhythmogenesis in general. While several important bits of information are available to piece together the puzzle of CPVT pathogenesis, the development of novel therapeutic strategies to reduce the burden of life-threatening events in high-risk patients who do not respond adequately to β-blockers is still much farther away.

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CHAPTER 66

Heart Rate Variability and Heart Rate Turbulence

Iwona Cygankiewicz and Wojciech Zareba

Heart Rate Variability

Heart rate variability (HRV) refers to beat-to-beat changes in R-R intervals and is believed to reflect the continuous interplay between sympathetic and vagal tones.[1-4] Under normal physiological conditions, a sinus node plays a role of a heart's pacemaker, possessing its own intrinsic activity and being under the influence of the autonomic nervous system. A variety of internal and external stimuli are known to change the balance between sympathetic and vagal tones. Consequent changes in heart rate may therefore occur in response to mental or physical stresses, cardiac or noncardiac disease conditions, or medications. Autonomic nervous system imbalance, which is generally defined as an increased sympathetic tone and decreased vagal tone, has been proven to be associated with increased risk of cardiac mortality. Therefore, HRV has become an important tool in identifying patients at risk of cardiovascular death.[1-7]

Heart Rate Variability Measurements

Assessment of HRV is performed by several methods, including time-domain and frequency-domain analyses as well as nonlinear techniques.[1-7] The analysis is usually based on long-term (at least 18-hour) Holter electrocardiogram (ECG) recordings. Short-term analyses could be performed on recordings of as short as 5 minutes' duration, which usually are obtained under controlled, standardized conditions to avoid the influence of external stimuli that may affect the autonomic nervous tone.

Time-Domain Heart Rate Variability Analysis

Time-domain HRV parameters can be derived from direct measurements of N-N intervals or from the differences between N-N intervals.[1-3,5] The simplest, and most commonly used HRV parameter is the standard deviation of all N-N intervals (SDNN) calculated over a long-term period (Figure 66-1). rMSSD and pNN50 (defined in Table 66-1, along with other parameters derived from the time-domain analysis) are considered as measurements predominantly reflecting parasympathetic modulation of the heart.[1,2] SDNN, SDANN, and SDNNIX (also defined in Table 66-1) reflect the overall variability as well as the variability with a predominant parasympathetic influence. Among time-domain HRV parameters, no parameter could be considered to represent predominantly sympathetic modulation of the heart. Values of time-domain HRV parameters are frequently decreased in patients with cardiac (post-infarction status, cardiomyopathies) and noncardiac conditions (diabetes) and may indicate increased risk of mortality.[1-5]

Geometric methods convert a series of R-R intervals into geometric patterns such as sample density distribution of N-N intervals or the Lorenz plot of N-N intervals.[5,8] Geometric methods create histograms of various interval frequencies and are believed to be less affected by noise and artifacts during computerized processing of ECG recordings. The HRV triangular index is determined by dividing the total number of N-N intervals by the maximum of the density distribution.[8] This index represents overall HRV, and lower values are associated with increased mortality. In the case of Lorenz or Poincaré plots, subjects with preserved HRV are characterized by a fan-shaped plot, whereas those with depressed HRV are characterized by narrow plots.[1-3] Heart rate asymmetry is a recently discovered physiological phenomenon that reflects the larger contribution of heart rate decelerations compared with accelerations to short-term heart rate variability. (Figure 66-2).[9] An abnormal structure of heart rate asymmetry has been shown to be associated with increased risk of all-cause mortality in patients with previous myocardial infarction (MI).

It is recommended that for time-domain measurement over the long term, at least 18-hour ECG recordings encompassing morning and night hours should be used. It is also emphasized that time-domain measurements of HRV, obtained from periods of different durations, should not be compared because the length of recording significantly influences the overall variability values.[1,10,11] The task force on HRV analysis recommends the following measures for time-domain assessment: SDNN, HRV triangular index, SDANN, and rMSSD.[1] It is assumed that SDNN and HRV triangular index estimate the overall HRV, SDANN reflects the long-term component of HRV, and rMSSD and pNN50 estimate predominantly parasympathetic modulation.

Frequency-Domain Heart Rate Variability Analysis

Spectral analysis provides information on how the power of HRV is distributed as a function of frequency and is usually performed on the basis of short-term recordings (5 minutes), even though long-term recordings may also be used.[1,6] Such analysis aims to separate the different frequency components of an entire R-R interval modulation (Figure 66-3). The most frequently used approach to compute spectral indexes is based on the fast Fourier transformation. The total power of R-R interval variability is the total variance and corresponds to the sum of the four spectral bands: low frequency (LF), high frequency (HF), very low

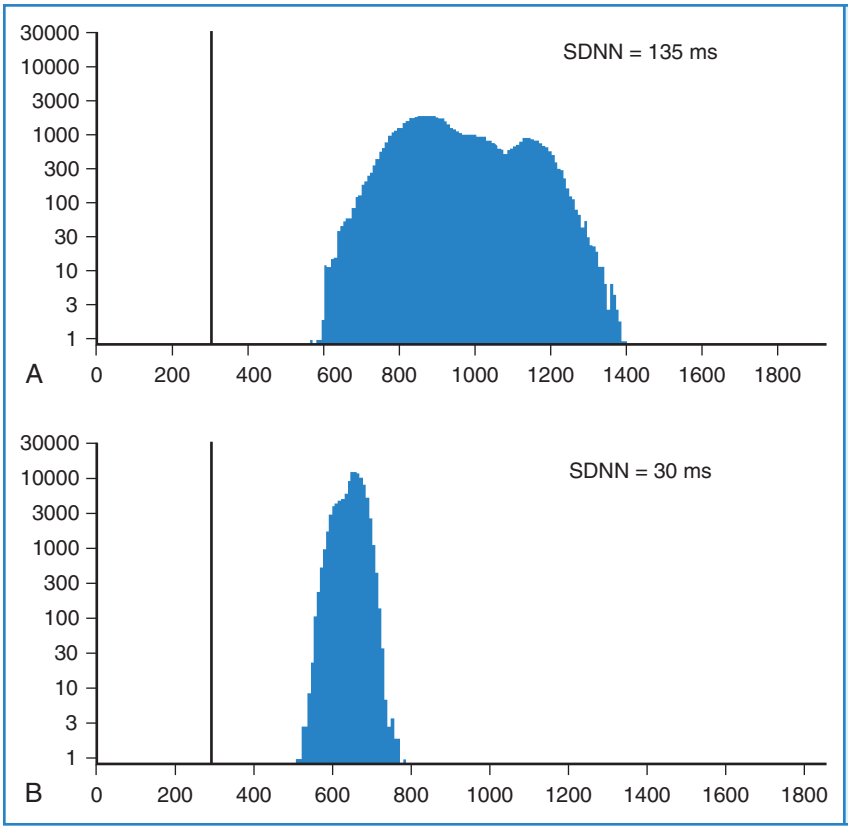


FIGURE 66-1 Exemplary heart rate variability measures in a healthy subject (**A**) and in a patient with depressed left ventricular function and heart failure (**B**). Significantly lower heart rate variability values are observed in a patient with heart failure. *SDNN*, Standard deviation of all N-N intervals.

Table 66-1 Time-Domain and Frequency-Domain Heart Rate Variability Parameters

VARIABLE	UNITS	DESCRIPTION
TIME-DOMAIN		
SDNN	ms	Standard deviation of all N-N intervals
SDANN	ms	Standard deviation of the averages of N-N intervals in all 5-minute segments of the entire recording
SDNNIX	ms	Mean of all the 5-minute standard deviations of N-N during the entire recording intervals
rMSSD	ms	Square root of the mean of the sum of the squares of differences between adjacent N-N intervals
pNN50		Percent of difference between adjacent N-N intervals >50 ms
FREQUENCY-DOMAIN		
Total power	ms^2	Variance of all N-N intervals <0.4 Hz
ULF	ms^2	Ultra-low frequency <0.003 Hz
VLF	ms^2	Very low frequency <0.003 to 0.04 Hz
LF	ms^2	Low frequency power 0.04 to 0.15 Hz
HF	ms^2	High frequency power 0.15 to 0.4 Hz
LF/HF	Ratio	Ratio of low-/high-frequency power

frequency (VLF), and ultra-low frequency (ULF) (see Table 66-1). Spectral analysis obtained from short-term recordings is characterized by three major components: (1) the HF component, (2) the LF component, and (3) the VLF component. Although vagal tone is considered a major contributor to the HF component, LF is believed to reflect both sympathetic and vagal influences. Sympathovagal balance is frequently expressed by an LF/HF ratio. In a healthy subject during resting, controlled conditions, a slight predominance of LF over HF is seen; therefore, the LF/HF ratio is usually between 1 and 2. VLF represents the numerous influences on the heart, including thermoregulation, the renin-angiotensin system, and endothelial factors, but it is also considered a measure of sympathetic activity. The ULF spectral component represents very low oscillations and might reflect circadian and neuroendocrine rhythms. The power of the spectral components may be expressed in absolute (ms^2) and normalized units (nu). Normalized units are obtained as follows:

$$\text{LF or HF norm (nu)} = (\text{LF or HF}\,[ms^2]) \times 100/(\text{total power}\,[ms^2] - \text{VLF}\,[ms^2])$$

For frequency-domain methods, at least a 1-minute recording is needed to assess the HF component, whereas 2 minutes are required for LF analysis. Nevertheless, for standardization, 5-minute recordings in controlled conditions are recommended.[1,10]

Despite different techniques of analysis, time and frequency parameters are strongly correlated to each other. Time-domain methods are preferred for long-term recording analysis. Currently, the majority of commercial Holter devices provide an automatic measurement of HRV parameters. It should be considered,

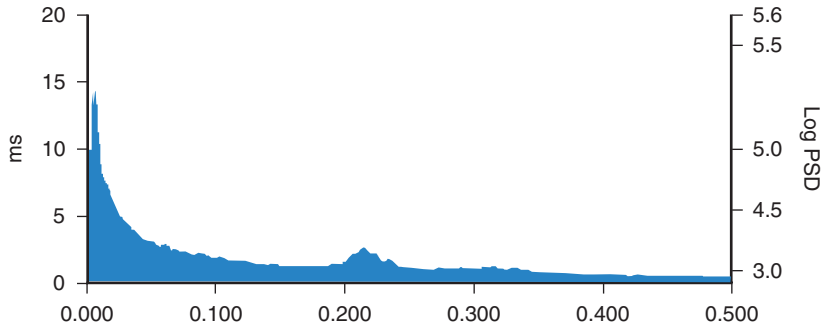


FIGURE 66-2 A sample spectral analysis of a healthy subject (5-minute recording).

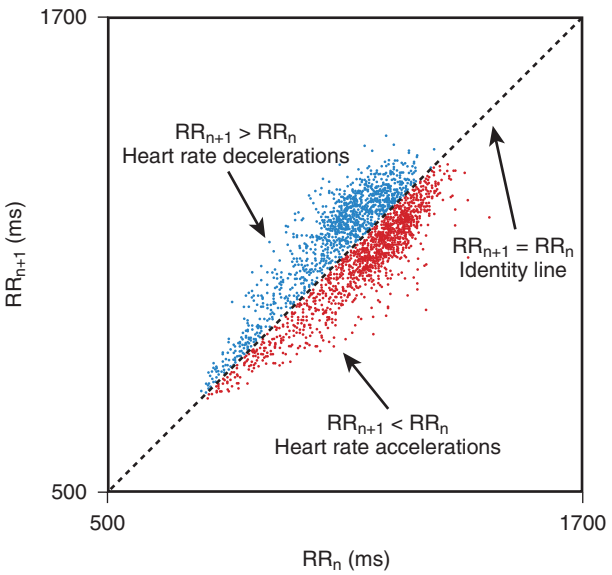


FIGURE 66-3 A sample Poincaré plot of R-R intervals from a 30-minute electrocardiogram taken from a healthy young man. All heart rate decelerations (lighter points described by RRn+1 > RRn) are above the identity line, whereas all heart rate accelerations (darker points described by RRn+1 < RRn) are below this line. Points localized on the identity line correspond to two consecutive R-R intervals of the same duration (RRn+1 = RRn). Note that the upper and lower parts of Poincaré plots are different shapes; that is, they are asymmetrical. *(Courtesy Dr. P. Guzik.)*

however, that independent of the method applied, careful editing of R-R intervals is needed. The task force on HRV recommends that for standardization of physiological and clinical studies, two types of recordings should be used: (1) short-term 5- minute recordings in stable conditions with frequency domain analysis; and (2) 24-hour recordings with time-domain analysis. Spectral analysis could also be performed on the entire 24-hour period, from 5-minute segments yielding LF and HF values and averaged over the entire 24-hour period. The methodology of HRV measurement was standardized in a special report of the Task Force of the European Society of Cardiology/Heart Rhythm Society (ESC/HRS) in 1999 and in the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for ambulatory electrocardiography.[1,10]

Nonlinear Heart Rate Variability Analysis

The last decade brought an increasing interest in nonlinear methods to analyze heart rate variability. Nonlinear analysis is believed to be less dependent on the pre-processing edition of beats and to express a more complex nature of R-R interval variability. Even though the exact pathophysiological background of nonlinear indices has not been fully clarified, evidence exists that a more complicated mathematical approach may be superior to conventional HRV parameters in risk stratification. Methods that have been proven to provide prognostic information are detrended fluctuation analysis, power law relationship analysis, and approximate entropy.[7,11-13]

Clinical Covariates of Heart Rate Variability

Numerous conditions affect sympathovagal status and influence heart rate and its variability. Age has been reported as a major determinant of HRV with constant decline in time-domain and frequency-domain parameters over the course of a person's life.[14] Approximately, a 15% decline in LF and HF power was reported for every 10 years, with an early fall in the HF component.[15] Women tend to have lower SDNN and LF but higher HF values compared with men. Nevertheless, these differences weaken with age and gender; the diminishing of differences around menopausal age suggests a potential hormonal influence on the autonomic nervous system.[16]

Decrease in HRV has consistently been observed in patients after MI and is reported to contribute to both structural changes of the left ventricle and to a decrease in vagal activity or to blunted response of a sinus node to autonomic regulation.[17] Consequently, it has been postulated that such a shift toward increased sympathetic activity and loss of vagal protection may contribute to enhanced arrhythmogenesis and subsequent sudden cardiac death (SCD) caused by lethal arrhythmias. Patients with previous MI are therefore characterized by a significant reduction in SDNN, which is correlated with the degree of left ventricular dysfunction and parallel decrease in spectral components.[18,19] Decreased HRV parameters have been observed not only in patients after MI but also in nonischemic cardiomyopathy and in a steadily growing population of patients with heart failure, including those with preserved left ventricular function. The extent of HRV reduction correlates with the advancement of heart failure expressed by measurements of ejection fraction (EF), New York Heart Association (NYHA) class, or B-type natriuretic peptide (BNP) levels.[20-23]

HRV is known to be modified by a variety of drugs, reperfusion strategies, regular exercise training, and cardiac resynchronization. The initial impact of thrombolysis on HRV in patients with acute MI was confirmed more recently by studies involving patients undergoing invasive reperfusion procedures with percutaneous coronary angioplasty.[24] Recent years have brought additional information that in patients with heart failure changes in HRV after cardiac resynchronization therapy (CRT), implantation may identify CRT responders. Low HRV values before implantation and no increase during postprocedural follow-up identify patients at risk of progression to heart failure.[25,26]

Clinical Applications of Heart Rate Variability

The association between abnormal HRV, impaired autonomic nervous tone, and cardiovascular mortality is well documented (Table 66-2). Even though experimental data indicated an association between impaired HRV and the preponderance toward ventricular arrhythmias, data on the association between decreased HRV and SCD are conflicting. Most post-infarction and heart failure studies indicate that depressed HRV mainly identifies patients at risk of overall mortality, with less evidence for the association with arrhythmic death. Evidence linking depressed HRV with implantable cardioverter-defibrillator (ICD)–documented ventricular tachycardia (VT) or ventricular fibrillation (VF) is limited.[1-7]

Patients with Previous Myocardial Infarction

The clinical relevance of HRV as a prognostic tool was first appreciated in 1965 by Hon and Lee.[27] Nevertheless, its history in cardiac risk stratification came about in the late 1980s when the first publications on HRV as a risk stratifier in patients with previous MI were published.[28,29] In 1987, Kleiger et al, of the Multicenter Post-Infarction Project (MPIP), reported than an SDNN of less than 50 ms was associated with more than a fivefold higher risk of mortality during a 31-month follow-up of more than 800 survivors of MI, compared with those with SDNN greater than 100 ms.[29] Low HRV remained a significant predictor of mortality after adjustment for other significant stratifiers such as EF, Killip Kimball class, and ventricular premature beats (VPBs). However, a combination of reduced SDNN with any of a group of risk markers (≥10 VPBs per hour, left ventricular ejection fraction [LVEF] <30%, failure to perform exercise test, or heart rate >80 beats/min) identified patients with a mortality rate of 50% during a follow-up.

Multiple publications from the 1990s consistently confirmed the predictive value of HRV parameters in patients with previous MI.[30-32] The Grupo Italiano per 10 Studio della Sopravvivenza nell'Infarto miocardico (GISSI) study in 567 males treated with thrombolysis revealed that SDNN, pNN50, and rMSSD were independently associated with all-cause mortality during a 3-year follow-up and thus confirmed the predictive value of HRV in the thrombolytic era.[30] The Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) study enrolled low-risk patients with previous MI and demonstrated that SDNN less than 70 ms was associated with a threefold higher mortality rate (relative risk [RR], 3.2).[31] Both SDNN less than 70 ms as well as low baroreflex sensitivity (BRS; <3 ms/RR) were significantly associated with an adverse outcome, and a combination of having both decreased SDNN and decreased BRS identified patients with a 17% mortality rate compared with 2% in patients with both parameters within higher value.[31] Predictive accuracy of SDNN was further significantly improved when analyzed together with low EF. In the placebo arm of the Azimilide Post-Infarct Survival Evaluation (ALIVE) trial of patients with previous MI and depressed LVEF, low HRV triangular index (<20 U) was found to identify patients at higher risk for death at 1 year compared with those with HRV index greater than 20 U (15 vs. 9.5%, $P < .005$).[32] Nevertheless, no significant relationship with arrhythmic events was observed. The majority of studies focused on time-domain parameters assessed from 24-hour Holter recordings; however, other reports have provided information on the prognostic role of spectral HRV measurements.[33-35] Bigger et al found that 5-minute time-domain and frequency-domain parameters calculated on the basis of randomly chosen 5-minute periods, provided significant, although weaker, prognostic information compared with the same parameters calculated over a 24-hour period in patients from MPIP.[33]

Acute coronary syndromes are currently managed with the wide use of primary angioplasty and β-blockers. Makikallio et al

Table 66-2 Selected Clinical Studies of Heart Rate Variability Parameters Predicting Death

	NO. PATIENTS	STUDIED POPULATION	FOLLOW-UP	RESULTS
PATIENTS WITH PREVIOUS MI				
Kleiger et al[29]	808	MPIP Patients with previous MI	31 months	Mortality rate 34% vs. 9% for SDNN <50 ms vs. >100 ms; RR = 2.8 for SDNN <50 vs. >50 ms Combination of low SDNN with other risk markers (LVEF <30% or VPBs >10/h): mortality up to 50% during follow-up
Bigger et al[33]	715	MPIP Patients with previous MI	2.5 years	All frequency measures (ULF, VLF, LF, and HF) predictive for all-cause and cardiac mortality Decreased ULF as the strongest multivariate risk marker for all-cause mortality (RR = 2.3) Decreased VLF as the strongest risk marker for arrhythmic deaths (RR = 2.94) Combination of decreased ULF or VLF with LVEF <40%; mortality up to 50%

Continued

Table 66-2 Selected Clinical Studies of Heart Rate Variability Parameters Predicting Death—cont'd

	NO. PATIENTS	STUDIED POPULATION	FOLLOW-UP	RESULTS
Bigger et al[34]	331	CAPS 1 Year after MI	3 years	ULF, VLF, LF, and HF significant univariate predictors VLF the strongest risk predictor
Odemuyiwa et al[8]	433	Post-infarction, mean LVEF = 47%	4 weeks to 5 years	HRV triangular index <20 U predictive for all-cause mortality Independent predictor of cardiac death only during first 6 months
Zuanetti et al[30]	567	GISSI-2 MI, thrombolysis	1000 days	NN50: RR = 3.5; SDNN: RR = 3.0; rMSSD: RR = 2.8 for all-cause mortality
La Rovere et al[31]	1284	ATRAMI Mean LVEF = 49%	21 months	SDNN <70 ms: RR = 3.2 (CI = 1.42–7.36) for all-cause mortality (multivariate analysis) SDNN <70 ms + LVEF <30%: RR = 6.7 Combination of SDNN <70% and BRS <3.0 ms/mm Hg: 17% mortality vs 2% in patients with both parameters preserved
Huikuri et al[35]	446	DIAMOND-MI Post-infarction, LVEF ≤35%	2 years	$\alpha 1$ <0.75: RR = 3.0, CI = 2.5–4.2, $P < .05$ for all-cause mortality
Camm et al[32]	1690	ALIVE placebo arm Post-infarction, mean LVEF = 29%	1 year	Mortality rate 15% vs 9.5% for HRV triangular index <20 U vs. >20 U HR = 1.46, CI = 1.10–1.97, $P < .005$ in multivariate analysis
Makikallio et al[36]	2130	FINGER and ISAR Post-infarction, reperfusion in 70%	1012 days	SDNN, VLF, LF, and $\alpha 1$ predictive for non-SCD Only $\alpha 1$ <0.75 predictive for SCD (HR = 1.9, $P = .044$) HRV particularly useful for risk stratification in a subgroup of LVEF >35%
Huikuri et al[38]	312	CARISMA Post-infarction, mean LVEF = 31%	2 years	lnVLF <5.7 ms^2: HR = 7.0, CI = 2.4–20.3, $P < .001$ for predicting ECG-documented VT/VF in multivariate analysis
HEART FAILURE				
Nolan et al[40]	443	UK Heart Study Congestive heart failure (NYHA class I-III; mean LVEF = 41%)	482 days	SDNN <50 ms: annual mortality of 51.4%; RR = 9.4, CI = 4.1–20.6 for total mortality and RR = 2.54, CI = 1.50–4.30 for heart failure death; not predictive for SCD
Ponikowski et al.[41]	102	Congestive heart failure, NYHA class II-IV, mean LVEF = 26%; 76% ischemic etiology	584 days	SDNN, SDANN, and LF predictive for mortality SDNN <100 ms: 1-year mortality 22%
Boveda et al[42]	190	CHF, NYHA class II-IV, mean LVEF = 28%, 45% ischemic etiology	22 months	SDNN <67 predictive for all-cause mortality; RR = 2.5, CI = 1.0–4.2 lnLF <3.3 predictive for SCD; RR = 2.8, CI = 1.2–8.6
Bilchnick et al[45]	127	CHF-STAT study NYHA class II-III, mean LVEF = 26%, 75% ischemic etiology	34 months	SDNN <65.3 predictive for all-cause mortality (RR = 3.72) and borderline significant ($P = .08$) for SCD (RR = 2.40)
Fauchier et al[44]	116	Idiopathic dilated cardiomyopathy, mean LVEF = 34%	53 months	SDNN <100 ms predictive for SCD
La Rovere et al[43]	202	CHF mild to moderate, mean LVEF = 24%	3 years	Controlled breathing LF <13 ms^2 predictive for SCD
Hadase et al[46]	54	CHF, mean LVEF = 40% in survivors	19.8 months	lnVLF <6 predictive for all-cause mortality

ALIVE, *Azimilide Post-Infarct Survival Evaluation trial;* ATRAMI, *Autonomic Tone and Reflexes After Myocardial Infarction trial;* BRS, *baroreflex sensitivity;* CAPS, *Cardiac Arrhythmia Pilot Study;* CI, *confidence interval;* CHF-STAT, *Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy;* CARISMA, *Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance study;* DIAMOND, *Danish Investigations of Arrhythmia and Mortality on Dofetilide;* FINGER, *Finland and Germany Post-Infarction study;* GISSI-2, *Grupo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico;* HF, *high-frequency;* HR, *hazard ratio;* HRV, *heart rate variability;* ISAR, *Innovative Stratification of Arrhythmic Risk;* LVEF, *left ventricular ejection fraction;* LF, *low-frequency;* MI, *myocardial infarction;* MPIP, *Multicenter Post-Infarction Project;* NYHA, *New York Heart Association;* pNN50, *percent of difference between adjacent N-N intervals >50 ms;* rMSSD, *square root of the mean of the sum of the squares of differences between adjacent N-N intervals;* RR, *relative risk;* SCD, *sudden cardiac death;* SDANN, *standard deviation of the averages of N-N intervals in all 5-minute segments of the entire recording;* SDNN, *standard deviation of all N-N intervals;* ULF, *ultra-low-frequency;* VLF, *very low-frequency;* VPB, *ventricular premature beat;* VT/VF, *ventricular tachycardia/ventricular fibrillation.*

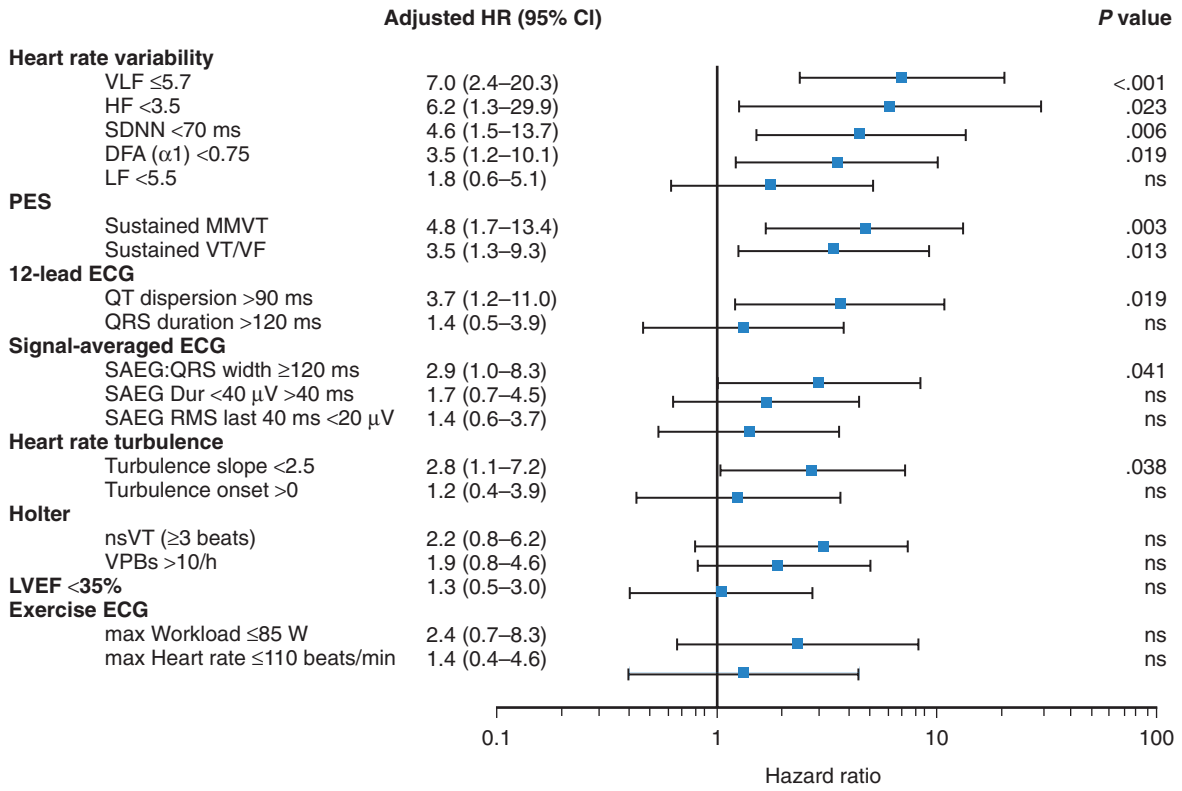


FIGURE 66-4 Prognostic value of electrocardiogram (*ECG*) parameters in predicting a primary endpoint defined as electrocardiogram-documented ventricular tachycardia/fibrillation (*VT/VF*) in patients with previous myocardial infarction from the Cardiac Arrhythmias and Risk Stratification after Acute Myocardial Infarction (CARISMA) study. *DFA,* Degree of frequency analysis; *Dur,* duration; *HF,* high frequency; *HR,* hazard ratio; *LF,* low frequency; *LVEF,* left ventricular ejection fraction; *MMVT,* monomorphic ventricular tachycardia; *nsVT,* nonsustained ventricular tachycardia; *PES,* programmed electrical stimulation; *RMS,* root-mean-square; *SAEG,* signal-averaged electrocardiogram; *SDNN,* standard deviation of all N-N intervals; *VLF,* very low frequency; *VPBs,* ventricular premature beats; *VT/VF,* ventricular tachycardia/ventricular fibrillation. *(From G Huikuri HV, Raatikainen MJ, Moerch-Joergensen R, et al, and Cardiac Arrhythmias and Risk Stratification after Acute Myocardial Infarction study group. Prediction of fatal or near-fatal cardiac arrhythmia events in patients with depressed left ventricular function after an acute myocardial infarction,* Eur Heart J *30:689–698, 2009.)*

addressed the prognostic role of Holter-derived risk parameters in the stratification of patients with previous MI treated according to current guidelines.[36] On the basis of a study of 2130 patients, of whom 70% underwent invasive coronary revascularization and 94% were treated with a β-blocker, the authors documented that all HRV parameters except HF (SDNN <70 ms, lnVLF <5.3, lnLF <3.85, and degree of frequency analysis [DFA, α_1]) were significant univariate predictors of SCD and non-SCD deaths, but only LF and α_1 predicted non-SCD mortality when adjusted for significant clinical covariates. Only reduced α_1 was able to independently identify patients at risk of SCD during a median of 1012 days of follow-up (hazard ratio [HR], 1.9; 95% confidence interval [CI], 1.0 to 3.6; $P = .0444$). Of note, HRV parameters (α_1 and VLF) were able to predict SCD among patients with previous MI who had an LVEF greater than 35%. Nevertheless, it should be stressed that in concordance with recent observations on lower incidence of SCD in patients with previous MI undergoing aggressive reperfusion, only 52 SCDs occurred in a studied population (2.5%), with the majority in patients with LVEF greater than 35%. The Risk Estimation Following Infarction Non-invasive Evaluation (REFINE) study failed to demonstrate the usefulness of decreased SDNN in predicting cardiac death or resuscitated cardiac arrest in 322 patients with an acute infarction and LVEF less than 50%.[37]

The recently published Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CARISMA) study is the first study to evaluate a variety of ECG markers in predicting arrhythmic events (VF or VT) documented by the implantable loop recorder.[38] In patients evaluated 6 weeks after an acute MI, SDNN, VLF, LF, and the fractal scaling component analyzed as continuous variables were independently associated with all-cause mortality as well as primary arrhythmic endpoint documented by the implantable loop recorder. It is worth emphasizing that only α_1 was associated with arrhythmic events when risk stratifiers were evaluated in an early post-infarction period (1 week). When categorized values were used, a decreased VLF component (VLF ≤5.7) had the highest HR (7.0, $P < .001$), followed by HF less than 3.5 (HR, 6.2; $P = .023$), SDNN less than 70 ms (HR, 4.6; $P = .006$), and α_1 less than 0.75 (HR, 3.5; $P = .019$) (Figure 66-4).

Patients with Heart Failure

Decreased HRV has been considered for years to be an independent and strong marker of risk for all-cause mortality or death caused by heart failure, whereas data on predicting SCD in this population are limited.[38-44] Early reports on the predictive value

of HRV showed that reduced HRV parameters were related to a 20-fold increased risk of death in patients awaiting heart transplantation.[39] In the UK-Heart Study SDNN, less than 50 ms was associated with death from progressive heart failure but failed to predict SCD.[40] SDNN is the most extensively studied HRV risk stratifier, but no consensus on the cut-off has been achieved so far. The other studies indicated SDNN less than 100 ms, 67 ms, or 65.3 ms as predictors of death in patients with heart failure.[41,42] Despite different cut-offs, a constant trend is seen in all the published studies toward the high prognostic value of depressed HRV in predicting death from heart failure and all-cause mortality.

More controversies exist in terms of frequency-domain components. The findings of these studies are difficult to compare, mainly because of different methodologic approaches. Decreased LF and VLF components are the most frequently reported HRV spectral measures related with poor outcome in patients with heart failure.[43-47] La Rovere et al reported that low-frequency power measured from short-term recordings during controlled breathing was a powerful predictor of SCD in 202 patients with moderate to severe congestive heart failure.[43] It should also be emphasized that different components of spectral analysis were documented to be related to different types of death. In a group of 330 patients with congestive heart failure in NYHA class I to III, decreased nighttime VLF was related to progressive heart failure, whereas decreased nighttime LF values were associated with SCD.[47] Nonlinear HRV measures were also reported to provide prognostic information on mortality in patients with CHF.[11-13] Maestri et al, who aimed to compare several nonlinear HRV methods in predicting mortality in patients with congestive heart failure, demonstrated that despite differences in prognostic values, assessment of nonlinear indexes provides important prognostic information in addition to clinical data.[13]

The prognostic role of HRV in the prediction of SCD in patients with congestive heart failr remains controversial. Most studies support the prognostic value of HRV in predicting the progression of heart failure. Only a study of Fauchier et al showed that reduced SDNN (less than 100 ms) was an independent risk predictor of SCD and arrhythmic events in patients with dilated cardiomyopathy.[44] Rashba et al in the Defibrillators in Non-ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial demonstrated that SDNN greater than 113 ms identified patients with 0% mortality during a 3-year follow-up.[48] Preserved SDNN also identified patients with 0% SCD and ICD shocks rates (Figure 66-5). It is therefore plausible that preserved function of the autonomic nervous system may serve to identify low-risk patients with previous MI. It cannot be excluded that the paucity of clear evidence for the association between depressed HRV parameters and SCD might be associated with difficulty in categorizing the sudden or arrhythmic nature of death. The autonomic nervous system operates differently in various patients, depending on the disease as well as the advancement of the disease process. HRV parameters successfully predict worsening of the congestive heart failure and total mortality in patients with congestive heart failure, indicating that autonomic dysfunction is part of the overall clinical picture in such patients, but these parameters seem to have little or no prognostic significance for predicting arrhythmic events in these patients.

Several conditions may be associated with the impairment of the autonomic nervous system; however, the current clinical role of HRV assessment seems to be restricted to risk stratification in patients with previous MI and heart failure and for early detection of autonomic neuropathy in patients with diabetes.

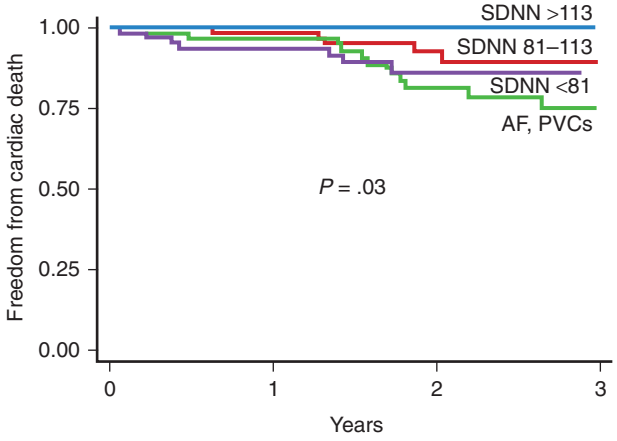


FIGURE 66-5 Risk stratification for the combined incidence of sudden death and implantable cardioverter defibrillatory shocks according to the standard deviation of all N-N intervals (*SDNN*) value. SDNN is categorized into tertiles. Patients with atrial fibrillation or frequent ventricular ectopy are analyzed in a separate group. Note the 0% event rate among patients with preserved heart rate variability. *(From Rashba EJ, Estes NA, Wang P, et al: Preserved heart rate variability identifies low-risk patients with nonischemic dilated cardiomyopathy: Results from the DEFINITE trial,* Heart Rhythm *3:281–286 2006.)*

Heart Rate Turbulence

Heart rate turbulence (HRT), a heart rate–derived noninvasive parameter that tracks the response of heart rate to ventricular arrhythmias, was introduced into electrocardiology in 1999.[49] Since then, abnormal HRT reaction has been proven to provide significant and independent prognostic information in various populations, including patients with MI and heart failure.[50]

Heart Rate Turbulence Measurement

Schmidt et al described HRT as a pattern of the response of a sinus node to a VPB, which, under normal physiological conditions, consists of a biphasic reaction characterized by an early acceleration phase and subsequent deceleration of heart rate following VPB.[49] The above-mentioned changes in sinus rhythm are observed within 15 R-R intervals following VPB and, because of their subtle nature, these changes require computer algorithms for detection (Figure 66-6). HRT reaction is described by two numeric parameters: (1) turbulence onset (TO), reflecting the initial acceleration, and (2) turbulence slope (TS), describing subsequent deceleration of sinus rhythm. TO is defined is a percentage of relative change of the mean of 2 R-R intervals before and two R-R intervals after a VPB, whereas TS is described as a maximum regression line computed in every five consecutive R-R intervals following VPB and is expressed in ms/RR. TO is calculated as a mean of all TO values corresponding to subsequent VPBs, and TS is calculated on the basis of a local averaged VPBs tachogram (see Figure 66-6). Special algorithms are applied to calculate a reliable HRT reaction. An ECG strip, including a VPB with neighboring 20 R-R intervals free of artifacts and other premature beats, is required for analysis. In addition, because it was considered that only a VPB provoking a long compensatory pause may trigger the classic biphasic HRT reaction, different

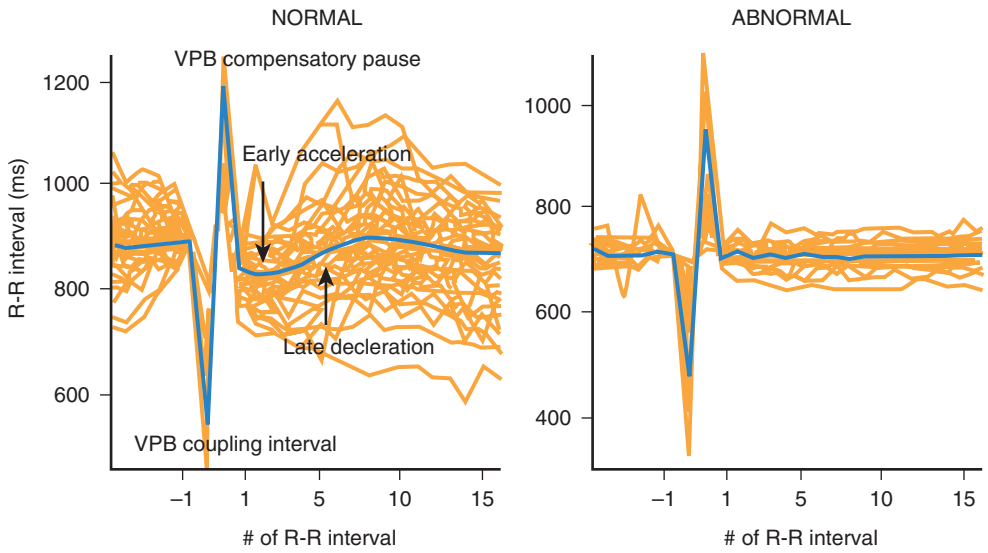


FIGURE 66-6 Heart rate turbulence calculation. Ventricular premature beat (*VPB*) tachograms showing normal (*left*) and abnormal (*right*) heart rate turbulence. Heart rate turbulence in a low-risk subjects consists of an early acceleration and subsequent deceleration of R-R intervals. In high-risk patients (*right*) this reaction is abolished. *(From Bauer A, Malik M, Schmidt G, et al: Heart rate turbulence: Standards of measurement, physiological interpretation, and clinical use: International Society for Holter and Noninvasive Electrophysiology Consensus,* J Am Coll Cardiol *52:1353–1365, 2008.)*

algorithms were applied to exclude interpolated VPBs. Recent guidelines on HRT measurements suggest that at least five VPBs should be present in the entire recording to consider HRT analysis as reliable. Nevertheless, it should be noted that early papers that reported a high prognostic value of HRT in predicting outcome in patients with previous MI and heart failure included patients with at least one VPB present.[49,51-54] HRT analysis was developed and primarily applied to 24-Holter recordings; nevertheless, data indicating that HRT may also be assessed from shorter recordings (e.g., 10 minutes) or from R-R data retrieved from implanted devices are available. A possibility to assess HRT parameters using induced VPBs during electrophysiological studies or via ICDs also exists.[55–57]

A detailed methodology of HRT calculation is available at www.h-r-t.org, and standards of measurement, physiological interpretation, and clinical use are summarized in the consensus statement written under the auspices of the International Society for Holter and Noninvasive Electrocardiology.[50]

Pathophysiological Mechanism of Heart Rate Turbulence

Even though the exact mechanism of the HRT phenomenon has not been fully clarified, most data have indicated that it may be mediated via the baroreceptor reflex. Baroreceptors, localized in the aortic arch and carotid sinus, are constantly stimulated by tonic arterial blood pressure and, being more responsive to sudden hypotonia than to an increase in blood pressure, they constitute one of the basic mechanisms of heart rate and blood pressure control. VPBs result in a short transient drop in blood pressure, which triggers the activation of baroreceptors, leading to immediate withdrawal of parasympathetic activation and predominance of sympathetic activation, resulting in heart rate acceleration. The subsequent increase in blood pressure, explained also by augmented myocardial contractility following the premature contraction, leads to an opposite reaction—activation of the parasympathetic arch and decrease in heart rate.[58-60] These two subsequent phases therefore create a biphasic curve of HRT reaction. Post-extrasystolic potentiation is the other mechanism possibly interplaying with different HRT patterns, such as that documented in patients with dilated cardiomyopathy.[61]

A significant correlation between HRT and baroreflex reaction was confirmed by numerous experimental and clinical studies.[51,60,61] Retrospective analysis of ATRAMI data documented a significant correlation between spontaneous as well as phenylephrine-induced baroreflex sensitivity and heart rate turbulence.[51] Abnormal HRT is also believed to reflect the loss of vagal protection against arrhythmic events, which may explain its role as an SCD risk stratifier. As documented by a few small clinical studies, HRT parameters remain significantly attenuated (decreased TS and increased TO) after atropine-induced blockade.[60,62]

Clinical and Electrocardiogram Covariates of Heart Rate Turbulence

HRT parameters were found to correlate with a variety of clinical (age, LVEF, coexisting diabetes) and ECG covariates (mean heart rate, HRV, BRS).[63-67] Age-related changes include decrease in TS and increase in TO, which might be explained as an effect of a reduced arterial compliance. Attenuated HRT parameters are observed in patients with autonomic nervous system disorders such as diabetes. Lower TS values and higher TO values are observed in patients with decreased LVEF. In patients with chronic heart failure, HRT was significantly correlated with not only LVEF but also with parameters reflecting heart failure advancement, such as NT-proBNP or NYHA class, giving insight into hemodynamic changes.[68] In a small clinical study, abnormal HRT parameters attributed to heart failure were restored by 3 months of β-blocker therapy in 10 patients with heart failure. The evolution of TS was accompanied by parallel changes in HRV parameters reflecting parasympathetic tone.[69]

HRT parameters, especially TS, were found to correlate with mean heart rate and the number of VPBs.[64,70] Patients with a

slower heart rate and a low number of VPBs present with a steeper TS. Whether this is a pure mathematical relationship or the expression of real lower risk remains controversial. HRT was also found to be significantly correlated to HRV parameters both in time domain and frequency domain.[71] HRT dependence on heart rate, number of VPBs, strong correlations with baroreflex sensitivity, and HRV should not be surprising because HRT combines all these factors. Whether these correlations strengthen or weaken the predictive value of HRT remains controversial. On one hand, the optimal risk predictor should be independent. On the other hand, a combination of risk predictors reflecting the different mechanisms participating in the chain of events leading to SCD may increase the positive predictive value and lead to more accurate identification of high-risk patients.

Temporal and circadian changes in HRT parameters were observed.[70,72] Turbulence slope values were reported to be lowest in the afternoon hours in coronary in-patients, whereas no significant changes in TO values were observed.[72] According to Hallstrom et al, ECG recording during daytime hours (8 AM to 6 PM) should be chosen for TS evaluation for prognostic purposes. HRT parameter dynamics after the acute phase of MI and after coronary revascularization were observed.[73-75] Restoration of blunted TO values were observed 12 months after acute MI, whereas TS remained unchanged over this period.[73] Percutaneous coronary intervention resulted in the restoration of HRT parameters assessed within 12 hours after the procedure compared with preprocedure values, but only in patients with Thrombolysis in Myocardial Infarction (TIMI) grade 3 and not TIMI grade 2 flow, suggesting that attenuated microcirculation might be responsible for this finding.[74] However, significant attenuation of HRT parameters, more likely because of the impairment of autonomic nervous fibers in the course of aorta clamping, was observed in patients undergoing coronary artery bypass grafting.[75] TO returned to preoperative values after 12 months, whereas TS remained attenuated. This observation suggests that HRT should not be used for risk stratification purposes during the 12 months after coronary artery bypass grafing.

Heart Rate Turbulence in Risk Stratification

The concept of HRT as a risk marker is based on a fact that the above-mentioned biphasic reaction of a sinus node may be observed in healthy subjects, whereas in high-risk patients, this pattern is blunted or entirely missing (see Figure 66-6). Therefore, high-risk patients are characterized by weaker HRT reaction expressed as the absence of an immediate acceleration or even deceleration of a sinus rhythm (positive values of TO) and a weaker rate of subsequent deceleration with lower TS values (flattened slope). The original report by Schmidt et al proposed TO of 0% or greater and TS of 2.5 ms/RR or less as the abnormal values cutoffs. For risk stratification purposes, patients are categorized into three groups: (1) HRT0: both HRT parameters (TO and TS) normal; (2) HRT1: one of the parameters abnormal; and (3) HRT2: both parameters abnormal. Patients in whom HRT analysis cannot be performed because of lack of VPBs in the ECG recording are placed in the HRT0 category; for risk stratification, they are usually merged with the HRT0 group and are therefore considered to be at low risk of subsequent events.

Patients with Previous Myocardial Infarction

The post-infarction population is a group in which the prognostic value of HRT is particularly well documented (Table 66-3). The prognostic value of abnormal HRT reaction for predicting death was first confirmed in patients with previous MI enrolled in MPIP studies.[49] In these populations, a blunted HRT reaction was independently associated with total mortality. Patients with abnormal TO and TS (HRT2) had a higher risk of death than could be evaluated just on the basis of EF assessment. In the MPIP population, 2-year mortality rates were 9%, 15%, and 32% in patients with HRT0, HRT1, and HRT2, respectively. Analysis of the placebo arm of the European Myocardial Infarct Amiodarone Trial (EMIAT) showed a similar pattern of mortality rates of 9%, 18%, and 34%, respectively (Figure 66-7).

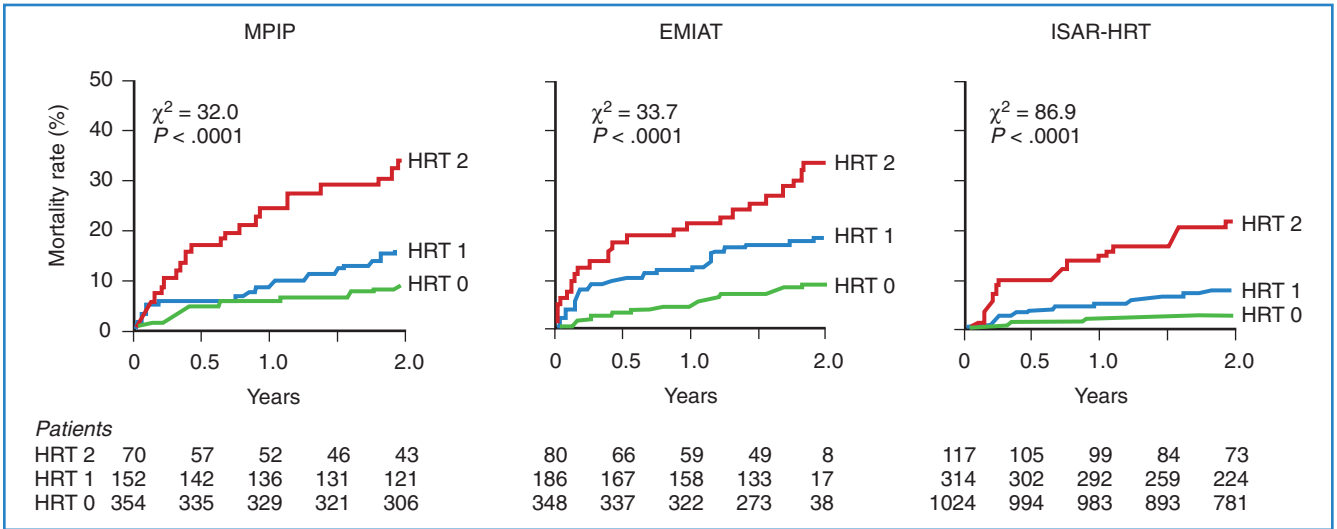


FIGURE 66-7 Cumulative mortality rates of patients stratified by heart rate turbulence (*HRT*) categories in the populations of the Multicenter Post-Infarction Project (*MPIP*) (*left*), European Myocardial Infarct Amiodarone Trial (*EMIAT*) (*middle*), and Innovative Stratification of Arrhythmic Risk trial (*ISAR-HRT*) (*right*). *(From Bauer A, Malik M, Schmidt G, et al: Heart rate turbulence: Standards of measurement, physiological interpretation, and clinical use: International Society for Holter and Noninvasive Electrophysiology Consensus,* J Am Coll Cardiol *52:1353–1365, 2008.)*

Table 66-3 Selected Clinical Studies on Heart Rate Turbulence as a Predictor of Death

HRT	NO. PATIENTS	STUDIED POPULATION	FOLLOW-UP	RESULTS
PATIENTS WITH PREVIOUS MI				
Schmidt et al[49]	577	MPIP Post-infarction	22 months	For all-cause mortality in multivariate analysis: HRT2: HR = 3.2 Abnormal TS: HR = 2.5
Schmidt et al[49]	614	EMIAT Post-infarction LVEF ≤40% (average, 30%)	21 months	For all-cause mortality in multivariate analysis: HRT2: HR = 3.2 Abnormal TO: HR = 1.7 Abnormal TS: HR = 1.9
Ghuran et al[51]	1212	ATRAMI Post-infarction, average LVEF = 49%	21 months	For combination of fatal and nonfatal cardiac arrhythmia: TS: HR = 2.47 HRT2: HR = 4.07
Barthel et al[53]	1455	ISAR-HRT Post-infarction 90% PCI	22 months	HRT2: HR = 5.9 for predicting total mortality
Makikallio et al[36]	2130	FINGER Post-infarction, mean LVEF = 51%	33 months	Abnormal TS: HR = 2.9 in predicting SCD, HR = 3.2 in predicting non-SCD Abnormal TS: >35% (HR = 4.7) predictive for sudden death in patients with LVEF
Exner et al[37]	322	REFINE MI and LVEF <50%	47 months	HRT assessed 10-14 weeks after MI predictive for cardiac death or resuscitated cardiac arrest (HRT1: HR = 2.91) Not predictive if evaluated 2-4 weeks after MI HRT and abnormal TWA: HR = 3.58 (for exercise TWA) and 4.18 for Holter TWA Abnormal HRT with abnormal TWA and low LVEF had highest predictive value
Huikuri et al[38]	312	CARISMA Post-infarction	2 years	TS evaluated 6 weeks after MI predictive for a primary endpoint of ECG-documented VT/VF Abnormal TS: HR = 2.8 TO not predictive No prognostic value for HRT evaluated 1 week after MI
Berkowitch et al[55]	884	MADIT II	22 months	HRT assessed from 10-min recording not predictive
NONISCHEMIC CARDIOMYOPATHY AND HEART FAILURE				
Grimm et al[52]	242	Marburg Study Dilated idiopathic cardiomyopathy, mean LVEF = 30%	41 months	TO as predictor of transplant-free survival TO and TS: only univariate predictor of major arrhythmic events
Koyama et al[78]	50	Congestive heart failure, mean EF = 39%, 32% ischemic etiology	26 months	Abnormal TS (≤3 ms/RR) predictive for death and hospitalizations for heart failure (HR = 10.2, CI = 3.2–37.5)
Kawasaki et al[80]	104	Hypertrophic cardiomyopathy	27 months	HRT failed to predict death and arrhythmic events
Moore et al[81]	358	UK Heart Study Congestive heart failure (I-III NYHA class; mean LVEF = 41%)	5 years	Abnormal TS (≤2.5 ms/RR) predicts heart failure decompensation
Klingenheben et al[79]	114	Frankfurt Dilated Cardiomyopathy database, mean LVEF = 28%	22 months	HRT not predictive for arrhythmic events
Cygankiewicz et al[77]	607	MUSIC study CHF in NYHA class II-III, mean LVEF = 37%, 50% ischemic etiology	44 months	Abnormal TS (≤2.5 ms/RR) and HRT2 predictive for all-cause mortality, SCD, and heart failure death (HRT2: HR = 2.52, 2.25, and 4.11, respectively, for modes of death)

CARISMA, *Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance study;* ECG, *electrocardiogram;* EF, *ejection fraction;* EMIAT, *European Myocardial Infarct Amiodarone Trial;* FINGER, *Finland and Germany Post-Infarction study;* HR, *hazard ratio;* HRT, *heart rate turbulence;* HRT1, *one abnormal HRT parameter;* HRT2, *two abnormal HRT parameters;* ISAR, *Innovative Stratification of Arrhythmic Risk;* LVEF, *left ventricular ejection fraction;* MADIT II, *Second Multicenter Automated Defibrillator Implantation Trial;* MI, *myocardial infarction;* MPIP, *Multicenter Post-Infarction Project;* MUSIC, *Multicenter Ultrasound Stenting In Coronaries study;* NYHA, *New York Heart Association;* PCI, *percutaneous coronary intervention;* REFINE, *Risk Estimation Following Infarction Non-invasive Evaluation study;* SCD, *sudden cardiac death;* TO, *turbulence onset;* TS, *turbulence slope;* TWA, *T-wave alternans;* VT/VF, *ventricular tachycardia/ventricular fibrillation.*

Retrospective analysis of HRT in the ATRAMI trial showed that abnormal HRT reaction can identify patients with previous MI at risk of arrhythmic events during follow-up.[51] In this study, the combination of abnormal TO and TS parameters was found to be the strongest risk predictor (RR, 4.07) of cardiac arrhythmic death. Barthel et al, in the Innovative Stratification of Arrhythmic Risk (ISAR-HRT) study, documented a high predictive value of abnormal HRT parameters in 1455 patients with acute MI treated mostly with percutaneous coronary angioplasty.[53] Patients from this population were treated according to recent guidelines; thus, 93% received β-blockers, 90% rceived angiotensin-converting enzyme inhibitors, and 85% received statins. In this study, HRT2 was found to be an independent predictor of 2-year mortality, providing the highest HR (5.9) followed by decreased LVEF, age, diabetes, and HRT class 1 (one abnormal parameter). Of note, HRT was found to be an independent predictor of death in patients with significantly decreased LVEF (<30%) as well as in those with LVEF greater than 30%. Because HRT2, analyzed in combination with LVEF, increased the positive predictive value to 40%, the simultaneous assessment of HRT with other parameters, especially those reflecting the myocardial substrate, could be recommended. These observations were confirmed by a study by Makikalio et al, who analyzed patients from the Finland and Germany Post-Infarction (FINGER) study and documented that abnormal TS was related with an almost threefold higher risk (HR, 2.9; CI, 1.6 to 5.5; $P = .0008$) of sudden death during the 33 months of follow-up in more than 2000 patients assessed in the early post-infarction period.[35] Similar to what was observed in the ISAR-HRT population, TS 2.5 ms/RR or less, which was of special interest in a subgroup of patients with relatively preserved LVEF, was related to a 4.7 higher risk of SCD in patients with LVEF greater than 35%.

The results of further prospective trials strengthen the position of HRT as a strong and independent prognostic value in identifying patients at risk for mortality. The REFINE trial aimed to assess the prognostic value of noninvasive combined evaluation of autonomic nervous tone and electrical instability in predicting a primary endpoint of cardiac death or resuscitated cardiac arrest.[37] The trial enrolled 322 patients with LVEF less than 50% who were followed up for a median of 47 months. Impaired HRT, abnormal T-wave alternans (TWA), and LVEF less than 50% assessed beyond 8 weeks after acute MI were significant predictors of a primary endpoint. Abnormal HRT in this study was defined as having either TO or TS abnormal versus both parameters being normal. The noninvasive parameters were analyzed twice: 2 to 4 weeks after MI and 10 to 14 weeks after an event. Only HRT analyzed between 10 and 14 weeks after MI was predictive for cardiac death of resuscitated cardiac arrest, with the highest hazard ratio among significant ECG predictors (HR, 2.91; CI, 1.13–7.48; $P = .026$). Interestingly, a combined assessment of HRT and abnormal TWA increased the predictive value of studied parameters significantly. Patients with abnormal HRT and TWA were characterized by a fourfold higher risk of a primary endpoint. When noninvasive ECG parameters were further combined with low LVEF, the predictive value reached a hazard ratio of 6.22, providing the highest accuracy in detecting the high-risk group. Of note, none of the ECG markers assessed in an early post-infarction phase predicted outcome. Similar findings were observed in the CARISMA study, which, for the first time, documented an arrhythmic endpoint by means of an implantable loop recorder.[38] A variety of noninvasive ECG risk markers were assessed at the first and sixth weeks after an MI, and patients were followed up at 3-month intervals for up to 24 months after MI. The turbulence slope, evaluated both as a continuous as well as dichotomized value (≤2.5 ms/RR) at 6 weeks after MI, was predictive for a primary endpoint defined as ECG-documented VF or symptomatic VT. Abnormal TS was related to a 2.8 higher risk of arrhythmic event when adjusted for other significant covariates. The association was nonsignificant when HRT was assessed in an early post-infarction phase (1 week after MI). Furthermore, it should be stressed that similar to what was observed in other studies, TO alone did not provide prognostic information. Of note, combined data from the REFINE and CARISMA studies indicated that HRV and HRT improved over time following an acute MI. Attenuated recovery of HRT, defined as change in TS less than 2.0 ms/RR, identified patients at the highest risk of arrhythmic events during follow-up.[76]

Nonischemic Cardiomyopathy and Chronic Heart Failure

HRT, which was primarily designed to predict mortality in patients with previous MI, was subsequently applied in patients with heart failure (see Table 66-3). Unlike in patients with previous MI, contradictory risk stratification results exist in patients with chronic heart failure and nonischemic cardiomyopathies.[52,77-82] In a study by Koyama et al, in a population of 50 patients with heart failure (72% with nonischemic cardiomyopathy), HRT was highly predictive for death from progression of heart failure and for rehospitalization rate but failed to predict arrhythmic events.[78] The Magdeburg study showed that HRT was predictive for total mortality and heart transplantation in a group of 242 patients with idiopathic dilated cardiomyopathy; nevertheless, no significance was found to predict arrhythmic events in this group of patients.[52] Analysis based on the Frankfurt dilated cardiomyopathy database did not document the prognostic value of HRT.[79] In patients with hypertrophic cardiomyopathy, HRT parameters did not differ from the control group and were not predictive for clinical prognosis.[80]

Most of the papers on HRT in patients with heart failure show that an abnormal HRT reaction identifies patients at risk of progression of heart failure during follow-up.[78,80,82] It is not surprising, when considering that, as mentioned above, HRT parameters are strongly correlated to advancement of heart failure. In the study by Moore et al, based on 358 patients with CHF in NYHA class II to III with available HRT, decreased TS was predictive for decompensated heart failure but not for SCD at 5-year follow-up.[80] Our group documented for the first time that abnormal HRT, especially TS, predicts not only heart failure progression but also SCD in patients with mild to moderate heart failure in the Multicenter Ultrasound Stenting In Coronaries (MUSIC) study.[77] MUSIC included ambulatory patients with congestive heart failure of both ischemic and nonischemic origin who presented with NYHA class II to III at the time of enrollment. HRT was analyzed in 607 patients in sinus rhythm. Abnormal HRT response based on at least one HRT parameter was found to be abnormal in 57% of patients, which is much higher than the percentage observed in post-infarction populations. During a median follow-up of 44 months, 129 patients died, 52 of them from SCD. Abnormal TS and HRT2 were independently associated with increased all-cause mortality (HR, 2.10; CI, 1.41-3.12; $P < .001$; and HR, 2.52; CI, 1.56-4.05; $P < .001$, respectively), SCD (HR, 2.25; CI, 1.13-4.46; $P = .021$ for HRT2), and death from heart failure progression (HR, 4.11; CI, 1.84-9.19; $P < .001$ for HRT2) after adjustment for clinical covariates in multivariate analysis. Similar

to what was reported in post-infarction studies, the predictive value was driven by TS and not TO (Figure 66-8). In our study, abnormal HRT was found to be predictive for all modes of death. Consistent with the postulated mechanisms of HRT relating this phenomenon to abnormal baroreflex sensitivity and autonomic imbalance, abnormal HRT showed a trend toward a stronger association with death from heart failure than with SCD. Importantly, HRT seems to be particularly useful in identifying high-risk patients with preserved left ventricular function, the group of patients not covered by current indications for ICDs. A combination of abnormal HRT, decreased HRV, and impaired repolarization dynamics provided the highest accuracy in identifying the high-risk group among patients with heart failure and relatively preserved LVEF (>35%).[82]

Other Applications

HRT was found to be impaired in various cohorts of patients characterized by autonomic nervous system abnormalities, such as patients with connective tissue diseases, diabetes mellitus, or obstructive sleep apnea.[83-85] The CARISMA investigators documented that abnormal TS, associated with altered cardiac autonomic regulation, was associated with an increased risk of new-onset atrial fibrillation as documented by ILRs.[86]

Heart Rate Turbulence Assessment: Limitations

HRT is considered one of the most useful Holter-derived ECG risk predictors. Nevertheless, such an HRT-based risk assessment has several limitations. First, this method is limited to patients with sinus rhythm presenting with VPBs and certain VPB characteristics and R-R pattern allowing for HRT calculation. Therefore, a high percentage of patients (20% to 40%), despite the presence of sinus rhythm and VPB detected on Holter monitoring, cannot undergo HRT analysis because of the elimination of all VPBs by filtering algorithms. Whether HRT should be corrected for heart rate or for a number of VPBs is a matter of debate.

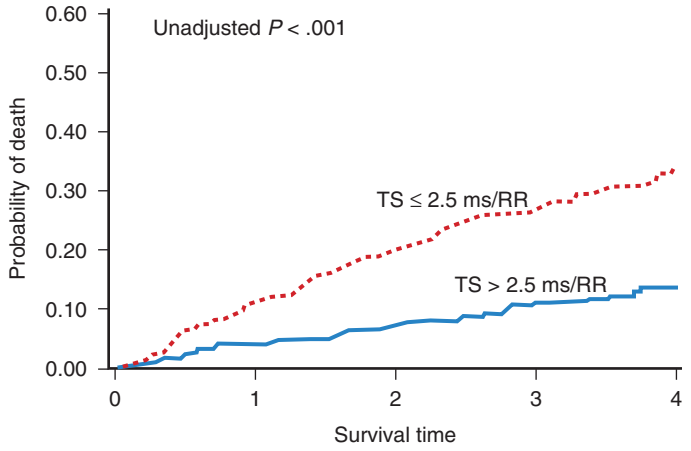
Deceleration Capacity and Severe Autonomic Failure

In 2006, Bauer at al proposed a novel risk predictor called *deceleration capacity* (DC), which was based on the assessment of deceleration-related modulations of heart rate believed to reflect the vagal activity of the autonomic nervous system.[87] The authors postulated that such a selected analysis of HRV exclusively related to deceleration moments may provide information on the autonomic nervous system balance. To calculate DC, a signal processing technique of phase-rectified signal averaging is used to process sequences of R-R intervals obtained from Holter recordings. The technique provides separate characterizations of deceleration-related and acceleration-related modulations, quantified by DC and acceleration capacity (AC). For computation of DC, heart beat intervals longer than the preceding interval are identified as anchors. For computation of AC, heart beat intervals shorter than the preceding interval are identified as anchors. Detailed explanation of the DC calculation process is provided at www.prsa.eu as well as in original reports. For risk stratification purposes, patients are categorized, according to original publication, into low-risk (>4.5), medium-risk (4.5 to 2.5), and high-risk (≤2.5) groups, taking cut-offs of DC published in the original paper by Bauer et al. This study demonstrated that decreased DC was a significant risk predictor of death in patients with previous MI, which encompassed the prognostic value of LVEF and standard HRV measures. Of note, decreased DC (≤2.5 ms) identified high-risk patients in a group with LVEF greater than 30%.[87]

A few years later, the same group presented the results of the Improved Stratification of Autonomic Regulation for Risk Prediction in Post-Infarction Patients with Preserved Left Ventricular Function (ISAR-Risk) study, which demonstrated that a combination of abnormal HRT and abnormal DC may be defined as severe autonomic failure (SAF) and was able to identify a subset of patients with previous MI and LVEF greater than 30%, with a mortality risk comparable with a high-risk group of patients with significantly depressed LVEF during 5 years of follow-up. The 5-year mortality rate in SAF-positive patients was 38.6% compared with 6.1% in a SAF-negative group ($P < .001$), with similar patterns observed for cardiac death and SCD.[88] These findings were further confirmed by a retrospective analysis of four trials (ISAR-Risk, St George Hospital Medical School Post-Infarction Survey, placebo arm of the EMIAT trial, and Multiple Risk Factor Analysis Trial [MRFAT]).[89] It is believed that merging DC and HRT into SAF provides an insight into an overall status of the autonomic nervous system, expressed by DC with the reflex reactivity of a system reflected by HRT reaction; such a combination of abnormal tone and reflex significantly increases the accuracy of risk stratification.

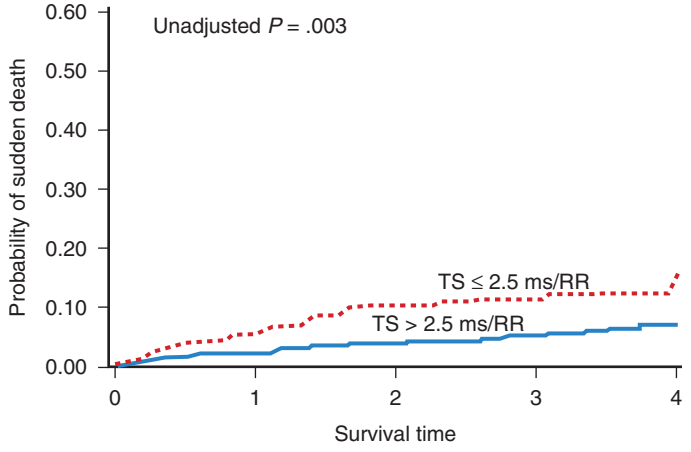
Further Directions

Despite extensive research in the field of noninvasive electrocardiology and several reports that documented the predictive value of HRV and HRT in predicting death, neither of these two techniques is currently recommended for SCD stratification. The ACC/AHA statement on ventricular arrhythmias recommends HRV and HRT as class IIb for risk stratification.[90] According to the recently published AHA/ACC/HRS Scientific Statement on noninvasive risk stratification techniques for identifying patients at risk of SCD, data on short-term HRV that link HRV to risk of SCD are limited; therefore, the use of HRV for risk stratification is not recommended.[91] Depressed HRV from long-term recordings is predictive for all-cause mortality but is not specific for SCD. In the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT), patients with previous MI and an EF less than 30% and depressed HRV or elevated heart rate, randomized to ICD implantation in the early post-infarction period did not benefit from ICD implantation, even though the arrhythmic mortality was significantly lower.[92] It is therefore plausible that low HRV selected a subpopulation of patients who were more likely to develop heart failure. It seems that HRV assessment will play a role in the selection of patients who might benefit from CRT to prevent hemodynamic deterioration and in SCD risk prediction. HRT is a likely SCD risk factor. Nevertheless, its clinical utility to guide ICD implantation has not been demonstrated yet. Therefore, the need to find whether HRT may serve as a marker to guide prophylactic ICD implantation or heart failure progression persists. The ongoing Deceleration Capacity and Heart Rate Turbulence in Decompensated Heart Failure study (DECIDE-HF), aims to predict heart failure decompensation by DC and HRT assessment based on 8-hour R-R intervals from implanted devices in patients with congestive heart failure in NYHA class II to III.The REFINE-ICD trial aims to evaluate whether high-risk patients



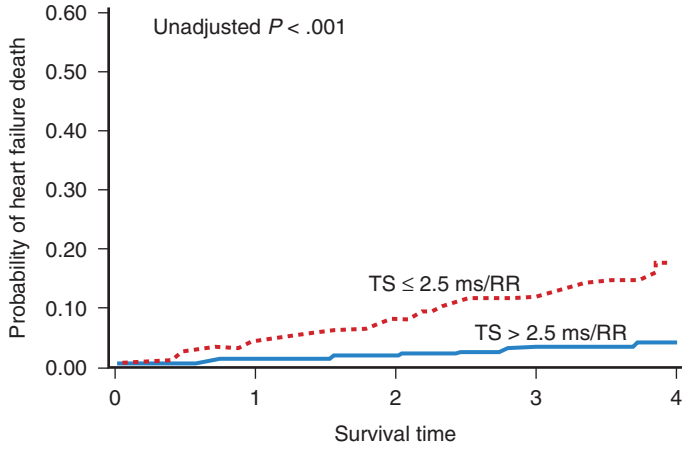
PATIENTS AT RISK

A	TS > 2.5 ms/RR	320	308 (0.03)	207 (0.07)	281 (0.11)	40 (0.13)
	TS ≤ 2.5 ms/RR	287	253 (0.10)	221 (0.20)	198 (0.27)	50 (0.36)



PATIENTS AT RISK

B	TS > 2.5 ms/RR	320	308 (0.02)	207 (0.03)	281 (0.06)	40 (0.07)
	TS ≤ 2.5 ms/RR	287	253 (0.06)	221 (0.10)	198 (0.11)	50 (0.15)



PATIENTS AT RISK

C	TS > 2.5 ms/RR	320	308 (0.01)	207 (0.01)	281 (0.04)	40 (0.04)
	TS ≤ 2.5 ms/RR	287	253 (0.04)	221 (0.08)	198 (0.12)	50 (0.17)

FIGURE 66-8 Cumulative probability of survival with total mortality (**A**), sudden death (**B**), and heart failure death (**C**) as endpoints in patients with congestive heart failure from the Multicenter Ultrasound Stenting In Coronaries (MUSIC) study stratified by abnormal turbulence slope (*TS*). *(From Cygankiewicz I, Zareba W, Vazquez R, et al, Muerte Subita en Insuficiencia Cardiaca Investigators: Heart rate turbulence predicts all-cause mortality and sudden death in congestive heart failure patients,* Heart Rhythm *5:1095–1102, 2008.)*

selected on the basis of the presence of abnormal HRT and abnormal TWA assessed at 8 weeks after an acute MI will benefit from prophylactic ICD implantation. Inclusion criteria are based on the results of the REFINE study, which documented a combination of parameters reflecting the autonomic nervous system and electrical instability in the best manner to predict unfavorable outcome in post-infarction patients. The authors also report two planned studies ISAR-ICD and CAF-HEFT trials to be initiated soon. The ISAR-ICD will assess the benefit of ICD in patients with preserved LVEF stratified by abnormal SAF, whereas CAF-HEFT will test the ability of a noninvasive ECG risk marker to guide pharmacotherapy in HF patients with NYHA class II and LVEF of 45% or less and heart failure–related hospitalization within the last year.[93]

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CHAPTER 67

Clinical Use and Mechanistic Implications of Microvolt T-Wave Alternans and Signal-Averaged Electrocardiography

MICROVOLT T-WAVE ALTERNANS

Elizabeth S. Kaufman, Michael J. Cutler, David S. Rosenbaum

Microvolt T-wave alternans (MTWA), a subtle beat-to-beat alternation of T-wave morphology, is a heart rate–dependent phenomenon that can be detected in normal subjects at rapid heart rates. When it occurs at heart rates of 110 beats/min or less in patients with structural heart disease, it is associated with increased risk of ventricular tachyarrhythmias and sudden cardiac death (SCD). Conversely, patients without abnormal MTWA have a very low risk of SCD. In experimental models, surface MTWA corresponds to alternation of action potential duration, which is most likely mediated by alternans of intracellular calcium cycling. When cellular alternans occurs heterogeneously in different regions of the myocardium, this dispersion of repolarization can lead to ventricular fibrillation (VF). Initially, MTWA was used to detect arrhythmic risk in patients with structural heart disease. More recently, it has been used to identify a low-risk subgroup (among patients with moderate to severe left ventricular dysfunction) who may not require implantable cardioverter-defibrillator (ICD) therapy. In the future, MTWA may be used to detect arrhythmic risk in patients with relatively well-preserved ventricular function.

Introduction

The significance of repolarization alternans, a beat-to-beat alternation in T-wave morphology, was described almost a century ago by Sir Thomas Lewis, who noted that "alternation occurs either when the heart muscle is normal but the heart rate is very fast or when there is serious heart disease and the rate is normal."[1] In the past 25 years, clinicians have learned to exploit the phenomenon of T-wave alternans to identify serious heart disease, especially to detect patients who are at high risk of ventricular tachyarrhythmias and SCD. Whereas earlier investigators observed visible T-wave alternans in patients at risk of imminent SCD, including patients with Prinzmetal's angina, electrolyte disorder, or QT prolongation, more recent investigators have used techniques capable of detecting invisible MTWA during modestly increased heart rate to identify patients with a significantly increased long-term risk of SCD.[2-4] In the recent past, there has also arisen a need to identify patients with advanced structural heart disease whose risk of SCD is low. That is, in an age when the ICD is widely accepted as an effective (albeit expensive) means of preventing SCD, the perception of a need to identify low-risk patients who may not require an ICD is also growing.[5,6] There are two major reasons for this. First, a strategy that can divert low-risk patients away from ICD implantation will increase the cost-effectiveness of ICD therapy. Second, the ability to identify low-risk patients could lead to an increase in the appropriate use of ICD therapy. There is evidence that patients who meet current criteria for primary prevention ICD implantation (based on ejection fraction alone) often do not receive ICDs.[7] It is reasonable to think that both physicians and patients are more likely to accept ICD therapy if the need for such therapy can be more clearly defined. MTWA testing has shown promise for detecting patients at low risk for SCD.

In parallel with advances in the understanding of the clinical implications of MTWA testing, new insights into the cellular and tissue-level mechanisms of T-wave alternans have also become available. Experimental models have shown that T-wave alternans occurs during alternation of action potential morphology, which may occur heterogeneously throughout the heart and lead to electrical instability.[8] Evidence suggests that alternans of calcium cycling within the sarcoplasmic reticulum may underlie T-wave alternans.[9]

This section of the chapter reviews the following aspects of MTWA: experimental evidence for the cellular and tissue mechanisms of T-wave alternans, technical aspects of MTWA recording in clinical practice, and the usefulness of MTWA as a tool for risk stratification.

Mechanisms of T-Wave Alternans

In 1999, Pastore et al used high-resolution optical mapping with voltage-sensitive dye in a guinea pig model to measure alternans of action potential duration in different areas of the myocardium.[8] Above a critical heart rate, groups of cells alternated out of phase with other nearby cells (i.e., short-long-short action potentials in one area coincided with long-short-long action potentials nearby). This situation led to re-entry and VF, demonstrating the mechanism linking alternans with ventricular tachyarrhythmias and SCD.

Two leading hypotheses for the underlying electrophysiological mechanism of action potential duration alternans have been proposed. (1) The restitution hypothesis states that alternans occurs when the cell membrane's ion channels are not able to produce complete repolarization in time for the next action potential. Although this may be one mechanism involved in

alternans, it fails to explain some observations (e.g., why alternans is seen in ischemia when the restitution slope is flat).[10] (2) The other hypothesis is that alternans occurs when the heart rate exceeds the capability of cellular calcium cycling mechanisms to maintain intracellular calcium homeostasis. Pruvot et al measured simultaneous action potentials and calcium (Ca^{2+}) transients in the guinea pig model and found consistent parallels between action potential and Ca^{2+} alternans both spatially and temporally. They concluded that T-wave alternans is closely associated with Ca^{2+} cycling. To further support the Ca^{2+} cycling hypothesis, reduced expression of SR Ca^{2+}-adenosine triphosphatase, which reclaims cytosolic Ca^{2+}, or impaired ryanodine receptor function, which is responsible for the release of Ca^{2+} from the sarcoplasmic reticulum, are associated with Ca^{2+} alternans and action potential duration alternans.[11,12]

Measurement of Microvolt T-Wave Alternans in Clinical Practice

Although MTWA is relatively common in high-risk patients, there are several obstacles to detecting such small (microvolt-level) fluctuations in the T wave and, in particular, to distinguishing MTWA from other sources of fluctuation in the electrocardiogram (ECG) signal. Sources of confounding signal variation include variation in heart rhythm (such as sinus arrhythmia or atrial or ventricular ectopy), respiration (a periodic source of noise), and noise at the patient-electrode interface. To detect MTWA and distinguish it from other signal variations, the spectral method was developed.[13] This method involves measuring the amplitude of the T wave in sequential beats to create a time series, which is then analyzed using fast Fourier transform to produce a power spectrum (Figure 67-1). The power at 0.5 cycles/beat corresponds to every-other-beat MTWA. MTWA is reported in microvolts as alternans voltage, the square root of the power. Along with alternans voltage, alternans ratio (k) is also reported. This is alternans power divided by the standard deviation of the background noise. In contrast, a nonspectral method, called *modified moving average analysis*, divides beats into even and odd bins and averages the morphology of T waves in each bin over several beats at a time.[14] The difference in amplitude of the odd beats versus the even beats is a measure of alternans. The modified moving average technique is susceptible to false detection of alternans in the presence of noise.[15] Moreover, this technique has not yet been validated adequately as a long-term clinical risk predictor.

The onset of MTWA occurs when an individual's heart rate exceeds a particular threshold heart rate, and MTWA tends to persist while the heart rate remains higher than that threshold heart rate.[13,16] The threshold heart rate is specific to an individual. Whereas in normal subjects, MTWA may appear at high heart rates, in patients with structural heart disease and high risk of death or sustained ventricular arrhythmias, the threshold heart rate for MTWA tends to be less than 110 beats/min (Figure 67-2).[17-19] The higher the heart rate at which MTWA is measured, the higher the sensitivity and the lower the specificity for detecting individuals at high risk of ventricular arrhythmia.[18] By convention, MTWA that occurs at heart rate of 110 beats/min or less has been defined as abnormal.[20] To detect abnormal MTWA, it is therefore necessary to increase the heart rate into the range of 105 to 110 beats/min.

Initial studies of MTWA used atrial pacing to elevate heart rate.[21] Subsequently, exercise testing was adopted, and most large clinical trials assessing the value of MTWA testing have been done with exercise. Because the magnitude of MTWA oscillates over time, even at a constant heart rate, in an MTWA study it is important to maintain a subject's heart rate in the target zone between 100 and 110 beats/min for several minutes.[17] Most standard work-based exercise protocols such as the Bruce protocol elevate heart rate too quickly through this critical zone. The performance of a diagnostic MTWA test requires a heart rate–guided exercise protocol tailored to an individual's level of fitness and heart rate response.

Traditionally, MTWA tests have been classified as positive, negative, or indeterminate.[20] A MTWA test is considered "positive" when MTWA appears at an onset heart rate of 110 beats/min or less, with a magnitude of more than 1.9 μV and an alternans ratio greater than 3, and is sustained for at least 1 minute while the heart rate remains over the heart rate threshold. MTWA study results are negative if there is no sustained MTWA at an onset heart rate of 110 beats/min or less and there is at least 1 minute of recording of sinus tachycardia at a heart rate 105 beats/min or greater, during which time there is a low noise level

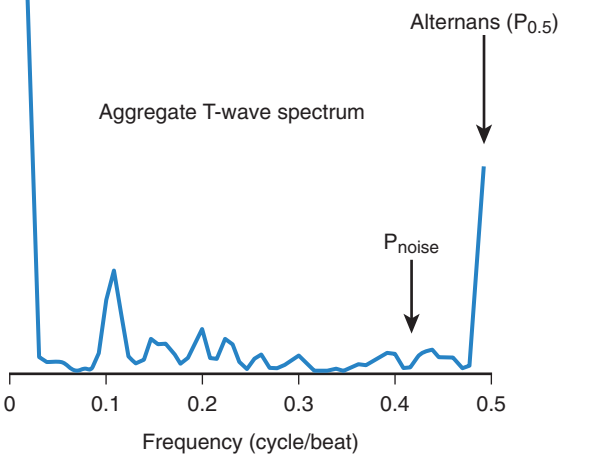

FIGURE 67-1 Aggregate T-wave spectrum.

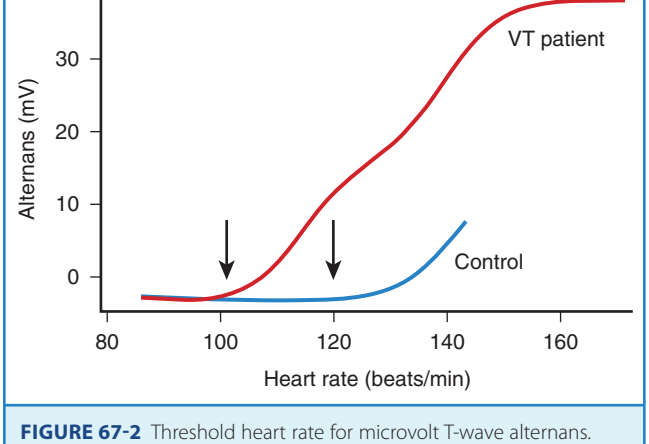

FIGURE 67-2 Threshold heart rate for microvolt T-wave alternans. *VT,* Ventricular tachycardia.

(<2 μV), fewer than 10% ectopic beats, and no nonsustained MTWA. Study results that do not meet either of these criteria are considered indeterminate.

Several factors may interfere with the measurement of MTWA and result in indeterminate study results. Two of these are technical issues: (1) high levels of noise (which can be reduced by careful skin preparation and use of high-resolution electrodes) and (2) rapid elevation of heart rate through the target heart rate zone (which can be avoided by a modified exercise protocol tailored to heart rate). In addition, several patient-related factors interfere with the measurement of MTWA. Failure to elevate heart rate to at least 105 beats/min, dense (usually ventricular) ectopy that persists during exercise, and the occurrence of nonsustained MTWA can also lead to what has been termed an indeterminate test result. Recently, a detailed analysis[22] of the causes and outcomes of indeterminate MTWA test results showed that only about 6% of "indeterminate" tests were so classified because of technical factors (noise or rapid heart rate rise); the other 94% were caused by patient factors. The prognostic significance of an indeterminate test was as bad as a positive test result, lending support to the practice of combining positive and indeterminate results into a single abnormal category for the purpose of risk stratification.

There has been debate among MTWA investigators regarding whether β-blocker therapy should be held before testing. When pacing is used to elevate heart rate, β-blockade decreases alternans voltage and converts a substantial number of positive tests to negative.[23] β-Blocker therapy may also interfere with achieving the target heart rate of 105 beats/min during an exercise study. However, continuing β-blocker therapy is convenient, and testing on β-blocker may more accurately assess risk in patients who will continue long-term therapy with these medications.[24] In the large study by Bloomfield et al, of which the analysis of indeterminate results was a substudy, more than 80% of patients were taking β-blocker medications, which were not held before MTWA testing.[22,25] Nevertheless, MTWA testing had excellent predictive accuracy in that study. A meta-analysis by Chan et al showed a much higher predictive power of MTWA in studies that did not withhold β-blockers than in those that did.[26]

Measurement of MTWA is reproducible when testing is repeated within a short time span.[27,28] Few data regarding the long-term stability of MTWA are available. The large studies that have led to the acceptance of MTWA as a prognostic indicator have required sinus rhythm and have been performed with exercise. Preliminary studies suggest that AV sequential pacing and pharmacologic elevation of heart rate may provide additional methods for assessing MTWA, although the prognostic value of such testing has not been validated.[29,30] A study by Kraaier et al showed low concordance among exercise, atrial pacing, and AV sequential pacing; the predictive value of these methods has not been established.[31]

Development of Microvolt T-Wave Alternans as a Tool for Clinical Risk Stratification

Studies Establishing Microvolt T-Wave Alternans as a Marker of Susceptibility to Sudden Cardiac Death

After initial studies in animals showed a relationship between MTWA and vulnerability to ventricular fibrillation, Rosenbaum et al published the first prospective study of MTWA as a predictor of clinical risk.[13,21] In this study, atrial pacing was used to elevate heart rate in patients undergoing electrophysiological studies. The presence of MTWA at a paced heart rate of 100 beats/min was related to inducibility of ventricular tachycardia (VT) and to the risk of future arrhythmic events. Subsequently, Hohnloser and Estes demonstrated that noninvasive exercise testing could yield MTWA results that were comparable with those seen with atrial pacing.[16,32] Additional studies showed that MTWA assessed during exercise performed well as a predictor of future ventricular arrhythmic events compared with other noninvasive risk stratifiers, even with invasive electrophysiological studies.[33-36] A consistent finding in these studies was the strong negative predictive value of a negative MTWA test.

However, not all studies showed a high positive predictive value of the MTWA test. Tapanainen et al assessed MTWA in patients with acute myocardial infarction during the predischarge exercise test (when many patients could not or were not pushed to achieve an adequate heart rate) and found that an indeterminate or incomplete MTWA study was strongly associated with risk of death; the negative predictive accuracy of an MTWA study was 99%.[37] In the Marburg Cardiomyopathy Study, a positive MTWA was not a significant risk predictor, although an indeterminate test was associated with significant ventricular arrhythmia.[38] Interestingly, the patients in the Marburg study had MTWA analysis performed off β-blocker therapy. It may be that MTWA testing performed on β-blocker therapy correlates better with chronic risk for patients on this background therapy, as suggested by Klingenheben et al.[24] As noted above, a recent meta-analysis by Chan et al showed a much higher predictive power of MTWA in studies that did not withhold β-blockers than in those that did.[26]

Microvolt T-Wave Alternans in Patients with Depressed Ejection Fraction After Myocardial Infarction

The results of the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) showed a reduction in the mortality rate of patients with chronic ischemic heart disease and ejection fraction 0.30 or less with prophylactic ICD implantation, but at a great cost (approximately 17 ICDs needed to be implanted to save 1 life). Following this, investigators began to explore the use of MTWA to find a low-risk subset of "MADIT-like" patients who might have event-free survival without protection by an ICD. Studies by Hohnloser and Bloomfield pointed out the very high negative predictive value of MTWA in this population and proposed that patients with negative MTWA results (positive and indeterminate results were grouped as "non-negative" or "abnormal") might safely avoid ICD implantation.[39,40] Chow et al studied 768 patients with ischemic cardiomyopathy and, by using propensity analysis, determined that ICD implantation offered a much higher mortality benefit in patients with non-negative MTWA results.[41]

In the Alternans Before Cardioverter Defibrillator (ABCD) trial, a 95% negative predictive value of MTWA at 1 year was comparable with the negative predictive value of invasive electrophysiological testing; at 2 years the negative predictive value of MTWA was not as high.[42] This study showed that (1) noninvasive MTWA testing can be used to improve primary prevention (separating higher risk patients from lower risk patients) without the risk or cost associated with invasive electrophysiological testing, (2) risk stratification may need to be repeated periodically because the myocardial substrate changes over time, and (3) the value of MTWA plus electrophysiological testing was superior to that of either test alone, suggesting that multiple risk markers should be

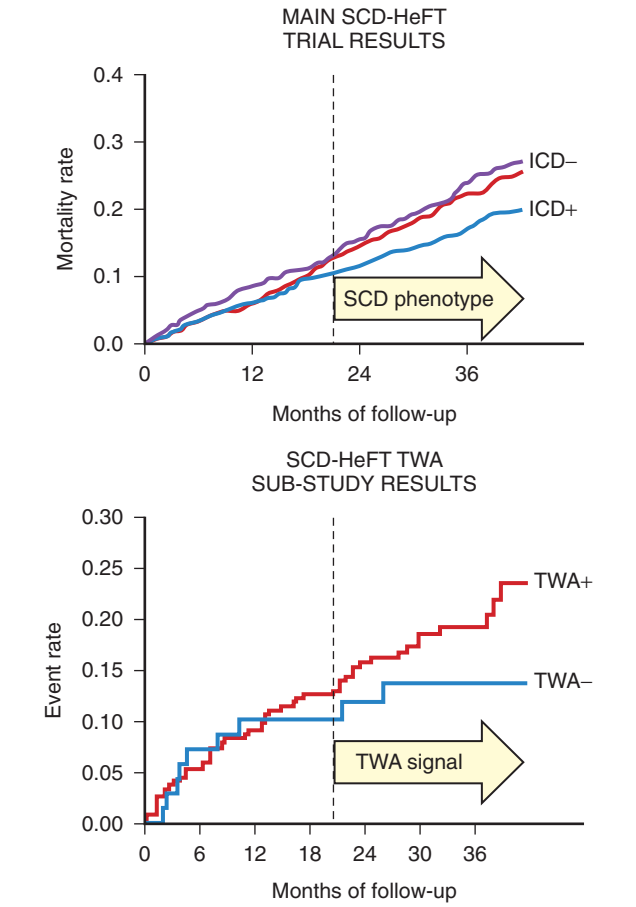

FIGURE 67-3 Synergistic value of electrophysiological study and microvolt T-wave alternans (*TWA*) testing. *SCD-HeFT,* Sudden Cardiac Death in Heart Failure Trial.

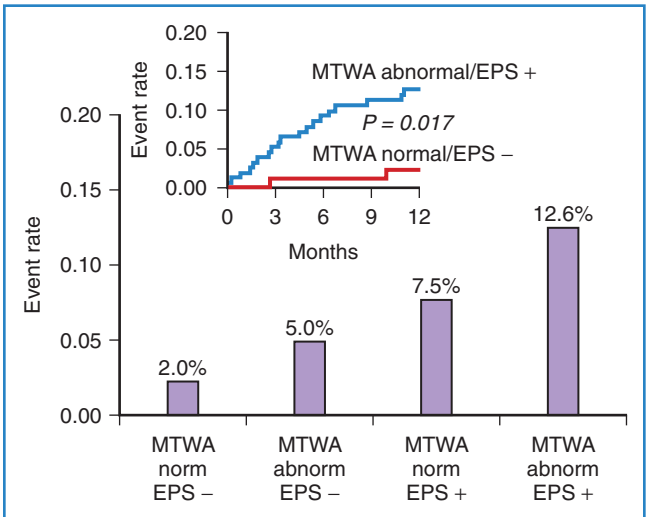

FIGURE 67-4 T-wave alternans tracking the sudden cardiac death phenotype. *MTWA,* Microvolt T-wave alternans; *EPS,* electrophysiology study.

used in combination for optimal risk stratification (Figure 67-3). A subanalysis of the ABCD data showed that an abnormal MTWA predicted unstable ventricular arrhythmia, whereas a positive electrophysiological test predicted monomorphic VT.[43]

The Noninvasive Risk Assessment Early After a Myocardial Infarction (REFINE) study reaffirmed the advantages of combining multiple risk markers.[44] In this study of patients who had an MI, impaired heart rate turbulence, abnormal MTWA, and low ejection fraction were combined to identify patients at high risk. Of note, this was true when patients were assessed 10 to 14 weeks but not 2 to 4 weeks after the MI. A study by Huikuri et al also showed that MTWA performed early after MI was not a useful risk predictor.[45]

In contrast to the studies that showed a high negative predictive value of MTWA in stable post-MI patients, the Microvolt T-Wave Alternans Testing for Risk Stratification of Post-Myocardial Infarction Patients (MASTER) trial failed to show that MTWA status could predict ventricular tachyarrhythmic events (of which 90% were appropriate ICD therapies).[46] Published in the same year, the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) alternans substudy, which randomized both patients with MI and those with nonischemic cardiomyopathy to ICD, amiodarone, or placebo therapy, reported that MTWA testing did not predict arrhythmic events or death.[47] As pointed out in the editorial that accompanied this report, however, the survival benefit of the ICD in SCD-HeFT only emerged between 18 and 24 months after randomization, at exactly the time that a difference in event-free survival became apparent in the populations with normal and abnormal MTWA results (Figure 67-4).[48] Hohnloser showed that in prospective clinical trials evaluating MTWA as a risk predictor, trials with a low rate of ICD implantation showed a consistently high negative predictive value of MTWA.[49] In contrast, trials that used ICD therapies as a surrogate endpoint for SCD found MTWA to be less useful. Hohnloser concluded that MTWA has a high negative predictive value for SCD but that ICD therapies are an unreliable surrogate endpoint for SCD.

Microvolt T-Wave Alternans in Patients with Other Types of Cardiomyopathy

Several studies have shown MTWA to be a valuable risk predictor in patients with heart failure.[25,50] These studies, which combined patients with ischemic cardiomyopathy and those with nonischemic cardiomyopathy, showed a high negative predictive value of MTWA, as did additional studies that focused only on patients with nonischemic dilated cardiomyopathy.[36,51,52] The usefulness of MTWA for predicting the risk of ventricular tachyarrhythmias in the nonischemic cardiomyopathy population stands in contrast to the insensitivity of other risk stratifiers, including invasive electrophysiological testing. However, a recent study of 286 patients with ejection fraction of 35% or less (ischemic and nonischemic cardiomyopathies) raised questions about the adequacy of MTWA for identifying a low-risk subgroup.[53] In this study, the negative predictive value of MTWA for 2-year total mortality rate was only 90%. It should be noted, however, that patients in this study had nonsustained VT, syncope, or both and therefore had a higher baseline risk than most primary prevention populations.

Microvolt T-Wave Alternans as a Marker of Risk in Patients with Preserved Ejection Fraction

Recently, Ikeda et al showed that MTWA can identify a high-risk subgroup among patients with well-preserved ejection fraction after myocardial infarction (MI).[54] MTWA has also shown promise

as a risk predictor in hypertrophic cardiomyopathy.[55,56] In contrast, MTWA has not been helpful as a risk discriminator in congenital long QT syndrome (LQTS) or in Brugada syndrome.[57-59] Thus MTWA appears to be of value in disease states associated with structural heart disease.

Directions for Further Study

MTWA has been well established as a valuable predictor of risk for SCD among patients with structural heart disease. However, significant questions remain. MTWA is a dynamic phenomenon that is affected, for example, by heart rate and by β-blockade. It is not known how early MTWA should be measured after MI for the best long-term risk prediction and how often MTWA testing should be repeated. Because a patient's arrhythmogenic substrate may change over time (because of scar maturation, ischemic events, changes in left ventricular function), serial MTWA testing will likely add value to risk assessment. The value of MTWA measurement during dual-chamber pacing or during pharmacologic heart rate elevation requires further study, as does the modified moving average technique. The magnitude of MTWA and its onset heart rate may contribute additional prognostic information to the traditional MTWA test. The usefulness of MTWA as a prognostic tool in lower risk populations (such as patients with preserved left ventricular function after MI) has only begun to be explored.[54] Finally, genetic polymorphisms that underlie susceptibility to MTWA (and to ventricular arrhythmia) require exploration.

SIGNAL-AVERAGED ELECTROCARDIOGRAPHY

Gioia Turitto, Raushan Abdula, and Nabil El-Sherif

Introduction

Signal-averaged electrocardiography (SAECG) is one of several proposed methods for noninvasive risk stratification for SCD. The term *signal-averaged electrocardiography* refers to techniques for improving the signal/noise ratio, thus allowing analysis of signals that are too small to be detected by routine measurement. Among such signals are those arising from areas of slow and inhomogeneous conduction in diseased ventricular myocardium (usually referred to as *late potentials* [LPs]). These potentials are small because the activation front is slow and fractionated, the mass of tissue undergoing depolarization is small, or both. LPs are of clinical relevance because they may identify a substrate for re-entrant ventricular excitation.[60]

Important technical advances in the field of SAECG in the early 1980s included the introduction and refinement of filtering techniques, the selection of bipolar orthogonal leads, and their combination into a vector magnitude for maximal sensitivity as well as the use of computer algorithms to identify QRS offset and provide numeric values for signals in the terminal part of the QRS.[61] In 1991, a Task Force of the American College of Cardiology (ACC), the American Heart Association (AHA), and the European Society of Cardiology (ESC) published standards for the acquisition and analysis of LPs and attempted to define clinical indications for the SAECG.[62] The Task Force original recommendations were updated by an ACC Expert Consensus Document.[63] The recommended applications consisted of risk stratification for future arrhythmic events and SCD in survivors of MI and prediction of malignant ventricular tachyarrhythmias in patients with coronary artery disease (CAD) and syncope or asymptomatic nonsustained VT. Other groups of patients with organic heart disease in whom SAECG has been used for risk stratification for SCD include patients with idiopathic dilated cardiomyopathy, hypertrophic cardiomyopathy, right ventricular cardiomyopathy. More recently, the prognostic value of SAECG was examined in a statement prepared by a Joint ACC/AHA/Heart Rhythm Society Writing Group on noninvasive risk stratification techniques for identifying patients at risk of SCD.[64] This Expert Consensus Document acknowledged that an abnormal SAECG may identify patients with prior MI at risk of SCD. Given its high negative predictive accuracy, SAECG could be useful for the identification of low-risk patients. However, the document noted that routine use of SAECG to identify patients at high risk for SCD is not adequately supported by existing data and further studies would be required to assess the usefulness of this test.

Technical Aspects of Signal-Averaged Electrocardiogram

For the time-domain analysis of SAECG, data acquisition consists of several steps: proper recording, amplification, digitization, identification and alignment of the signal of interest, time-ensemble averaging, and filtering. Typically, 200 to 600 cardiac cycles are acquired. The QRS selection process uses a cross-correlation algorithm in which each detected QRS is compared with a preselected template. A correlation coefficient of more than 0.98 is typically required for a good match; this allows rejection of abnormal QRS such as ventricular premature complexes or noisy beats. Time-ensemble averaging is used because the signal of interest, that is, the QRS, is repetitive, whereas much of the interfering noise (environmental noise, electromyographic noise, etc.) is random. Thus, time-ensemble averaging results in an improved signal/noise ratio. Filtering is also applied to reduce the residual noise and improve identification of LPs. A bi-directional Butterworth filter has been recommended for analysis of LPs.[61] By using this filter, the first part of the QRS is bandpass filtered, and the second part of the QRS as well as the ST segment are filtered in reverse time, starting from the end of the data and moving toward the middle of the QRS. A bipolar orthogonal lead system is used to optimize the recording of LPs because of their unknown distribution on the body surface. The three leads are processed separately and then combined into a vector magnitude of the form $\sqrt{X2 + Y2 + Z2}$ and used for subsequent analysis. Bandpass filtering of the signal-averaged vector magnitude may further discriminate LPs from noise. Early studies of the frequency signature of LPs showed that they predominantly contain high frequencies and that filters that eliminate low frequencies may expose LPs more clearly. Commercial SAECG systems apply bandpass filtering with a low-pass setting of 250 Hz and a high-pass setting of 25 to 40 Hz. Computer algorithms are used to identify QRS onset and offset. These algorithms depend on the signal/noise ratio.[61] Once the QRS offset is defined, time-domain analysis of an SAECG mainly consists of the determination of three parameters: (1) the duration of the filtered QRS complex (QRSD), (2) the duration of low-amplitude signals of less than 40 μV, that is, the time that the filtered QRS voltage remains below 40 μV (LAS40), and (3) the root mean square voltage of the terminal 40 ms of the QRS (RMS40). The ad hoc Task Force recommended that for adequate LP analysis, a low noise level of less than 1 μV with a 25-Hz high-pass cutoff

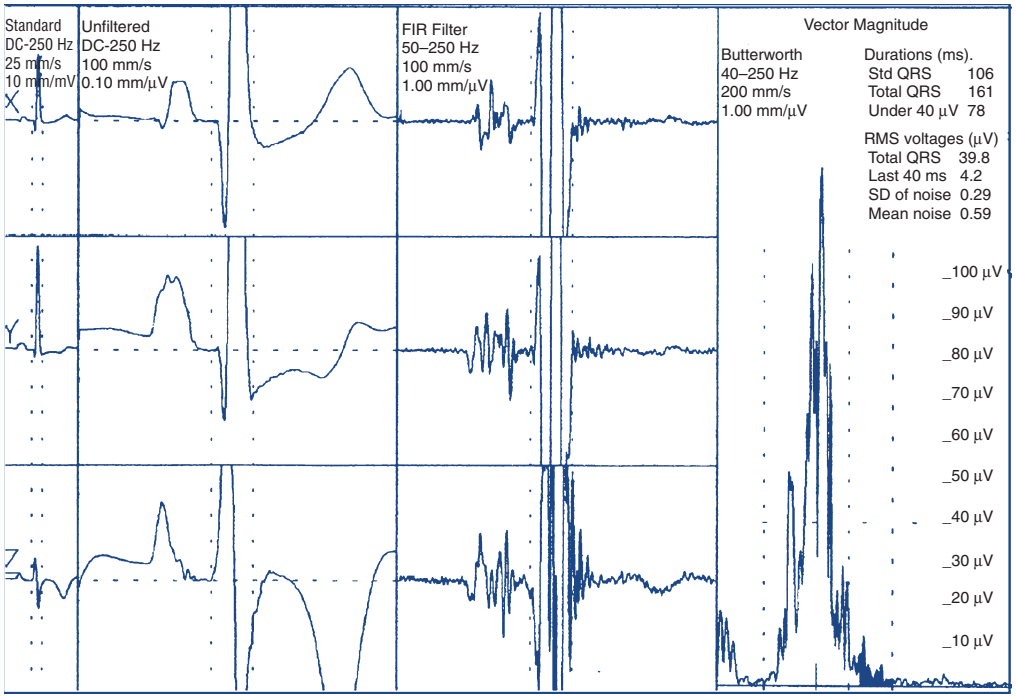

FIGURE 67-5 Example of abnormal time-domain analysis of the signal-averaged electrocardiogram. Filtered QRS duration and duration of low-amplitude signals are prolonged, whereas voltage of the terminal QRS is decreased, at a filter setting of 40 to 250 Hz. *Total QRS*, High-frequency QRS duration; *Under 40 μV*, duration of low-amplitude signals less than 40 μV; *RMS*, root mean square; *Last 40 ms*, RMS voltage of the terminal 40 ms of the QRS.

or less than 0.7 μV with a 40-Hz high-pass cutoff be obtained.[62] The Task Force also acknowledged that the definition of an LP and the scoring of an SAECG as normal or abnormal have not been standardized. Representative criteria include that an LP exists (using a 40-Hz high-pass filter) when (1) QRSD is greater than 114 ms; (2) LAS40 is greater than 38 ms; and (3) RMS40 is less than 20 μV (Figure 67-5).[62] It has been suggested that gender-specific criteria may be required for optimal test performance because men have, on average, longer QRSD compared with women.[65] The presence of intraventricular conduction defects may also hinder the recognition of LPs on the SAECG.[63,64] Time-domain analysis remains the mainstay for SAECG analysis because of its proven diagnostic accuracy and high reproducibility. More recently, ambulatory electrocardiography has been proposed to record and examine the SAECG for risk stratification in patients who have had MI.[66,67]

Techniques for frequency-domain analysis were devised to overcome some of the limitations of time-domain analysis, namely the inability to detect abnormal and delayed conduction within the QRS complex or in the presence of intraventricular conduction defects. The rationale for frequency-domain analysis is the observation that the QRS, LPs, and ST-segment waveforms in the SAECG have different spectral characteristics. Various techniques have been described under different names, including spectro-temporal mapping, spectral turbulence analysis, wavelet decomposition analysis, and acceleration spectrum analysis.[68] At the present time, none of these techniques has gained widespread acceptance because of a lack of standardization, suboptimal reproducibility, and the lack of convincing evidence that frequency-domain analysis results in greater diagnostic and prognostic accuracy compared with conventional time-domain analysis.

Table 67-1 Prevalence of an Abnormal Signal-Averaged Electrocardiogram in Normal Subjects and in Post-Infarction Patients with or Without Malignant Ventricular Tachyarrhythmias

	Prevalence (%)	
STUDY GROUPS	**TIME-DOMAIN**	**FREQUENCY-DOMAIN**
Normal subjects	0-10	4
Recent MI (<2 weeks), no VTA	14-29	26
Remote MI (>1 month), no VTA	18-33	23
Remote MI (>1 month), VTA	52-90	73-92

MI, Myocardial infarction; VTA, ventricular tachyarrhythmias.
From Cain ME: Signal-averaged electrocardiography. ACC Expert Consensus Document, J Am Coll Cardiol 27:238–249, 1996, with permission from the American College of Cardiology Foundation.

Clinical Applications of Signal-Averaged Electrocardiography

Patients with Prior Myocardial Infarction

The prevalence of an abnormal SAECG in normal subjects and in patients with prior MI with or without ventricular tachyarrhythmias is described in Table 67-1. The reported wide range in the prevalence of LPs after MI may be related to differences in the diagnostic criteria for LPs as well as in the time of recording of

Table 67-2 Prognostic Value of Signal-Averaged Electrocardiography after Myocardial Infarction in the CAST Substudy

VARIABLE	χ^2	*P* VALUE
QRSD/25 Hz	32.4	.0000
RMS40/25 Hz	4.1	.0433
LAS/25 Hz	23.8	.0000
QRSD/40 Hz	37.1	.0000
RMS40/40 Hz	4.5	.0344
LAS/40 Hz	10.3	.0001

All parameters were measured at high-pass filter settings of 25 Hz and 40 Hz.
CAST, Cardiac Arrhythmia Suppression Trial; LAS, duration of low-amplitude signals of <40 μV; QRSD, high-frequency filtered QRS duration; RMS40, root mean square voltage of the terminal 40 ms of the QRS.
From El-Sherif N, Denes P, Katz R, et al: Definition of the best prediction criteria of the time domain signal-averaged electrocardiogram for serious arrhythmic events in the postinfarction period, J Am Coll Cardiol 25:908–914, 1995, with permission from the American College of Cardiology Foundation.

Table 67-3 Prognostic Value of Signal-Averaged Electrocardiography for Serious Arrhythmic Events after Myocardial Infarction

Studies (n)	22
Patients (n)	9883
Follow-up (mo)	22
Arrhythmic events (%)	7.2
Sensitivity (%)	62
Specificity (%)	77
Positive predictive accuracy (%)	19
Relative risk	4.8
Odds ratio	5.7

From Bailey JJ, Berson AS, Handelsman H, Hodges M: Utility of current risk stratification tests for predicting major arrhythmic events after myocardial infarction, J Am Coll Cardiol 38:1902–1911, 2001, with permission from the American College of Cardiology Foundation.

the SAECG and to the site of MI. For instance, LPs may be more common in patients who have had inferior MI compared with patients who have had anterior MI.[69] This could be related to the fact that the inferoposterior segments of the left ventricle depolarize later compared with the anteroseptal and anterior segments. Thus in patients with inferior MI, delayed regional activation is likely to outlast normal ventricular depolarization and appear as LPs after the QRS offset. In contrast, in patients with anterior MI, the abnormal myocardial region is activated early during the QRS complex, resulting in partial obscuring of LPs.

Risk stratification of survivors of MI has been extensively performed with time-domain SAECG. There is increased likelihood of malignant ventricular tachyarrhythmias and SCD in post-MI patients with an abnormal SAECG.[64,70-72] A multicenter substudy of the Cardiac Arrhythmia Suppression Trial (CAST) sponsored by the National Institutes of Health (NIH) was conducted to define the best predictive criteria of time-domain SAECG in the post-MI period.[72] A total of 1158 patients were recruited and followed up for an average of 10 ± 3 months. Forty-five patients (4%) had serious arrhythmic events (nonfatal VT or SCD). A Cox regression analysis with six SAECG variables indicated that QRSD filtered at 40 Hz greater than 120 ms was the most predictive criterion of arrhythmic events (Table 67-2). An abnormal SAECG, defined as QRSD at 40 Hz greater than 120 ms, was present in 12% of the study population. The positive, negative, and total predictive accuracy of an abnormal SAECG was 17%, 98%, and 88%, respectively.[72]

A review of studies in which the SAECG was performed in approximately 5000 patients within 1 month of MI, with an average follow-up of 13 months, showed that the SAECG was abnormal in 29% of patients and that arrhythmic events occurred in 7% of patients. The positive predictive accuracy of the SAECG was low (mean, 17%; range, 8% to 29%), whereas its negative predictive accuracy was high (mean, 96%; range, 81% to 99%).[11] In a comprehensive meta-analysis, including almost 10,000 post-MI patients, Bailey et al confirmed the high sensitivity and specificity of the test, as well as its low positive predictive accuracy (Table 67-3).[71] Because of the low predictive accuracy of the test, no intervention is justified in post-MI patients based solely on the presence of an abnormal SAECG.[64]

The predictive value of the SAECG could be increased by combining its results with other clinical data such as left ventricular ejection fraction (LVEF), degree of ventricular ectopy, heart rate variability, and T-wave alternans. According to Bailey et al, it may be feasible to stratify as many as 90% of post-MI patients into "high risk" (>30%) and "low risk" (<3%) categories by using combinations of four noninvasive tests (Table 67-4).[71] With this approach, the first step would be performance of both SAECG and LVEF. If the both tests were negative or both positive (as would be true for 64.2% of the patients), further testing would not be done because the 2-year probability of a major arrhythmic event (MAE) would be very low in the former situation (2.2%) and high enough in the latter situation (38.7%) to warrant consideration of ICD implantation. The second step would be performance of a 24-hour ambulatory ECG in the 35.8% of patients with only a positive SAECG or only a low LVEF, resulting in an intermediate risk for an MAE (10.6% over 2 years). If the ambulatory ECG and heart rate variability were both normal or both abnormal (25%), no further testing would be needed because in the former situation, the posterior probability would still be below the original prior probability despite either an abnormal SAECG or a low LVEF, and in the latter case, the posterior probability would again be high enough to warrant consideration of ICD implantation. As a result of this noninvasive approach, approximately 90% of patients would be accurately risk stratified into low-risk (80%) and high-risk (10%) groups for MAE, and the unstratified group would include only 10% of post-MI patients.[71]

A recently noted limitation of risk stratification studies in post-MI patients may be the reduced ability to predict arrhythmic events in the era of aggressive treatment of MI, including reperfusion or revascularization strategies and pharmacotherapy (i.e., β-blockers). In this setting, the prognostic value of LPs may be diminished. However, the recently published Cardiac Arrhythmias and Risk Stratification after Acute Myocardial Infarction (CARISMA) study confirmed the ability of SAECG to predict arrhythmic events after MI.[73] In total, 312 patients with a mean

Table 67-4 Staged Application of Tests for Prediction of Major Arrhythmic Events Following Myocardial Infarction

TEST COMBINATION	RESULTS OF TESTS	PROPORTION OF POPULATION (%)	PROBABILITY OF MAE OVER 2 YEARS (%)
Stage 1: SAECG and LVEF	Both negative	56.6	2.2
	Only one positive	35.8	10.6
	Both positive	7.6	38.7
Stage 2: AECG (SVA and HRV)*	Both negative	23.3	4.7
	Only one positive	10.8	17.5
	Both positive	2.6	48.2

Based on a 2-year prior probability of 7.9%.
**Performed on only one positive patient of stage 1.*
AECG, *Ambulatory (Holter) electrocardiogram;* HRV, *heart rate variability;* LVEF, *left ventricular ejection fraction;* MAE, *major arrhythmic event;* SVA, *serious ventricular arrhythmias on ambulatory (Holter) electrocardiogram.*
From Bailey JJ, Berson AS, Handelsman H, Hodges M: Utility of current risk stratification tests for predicting major arrhythmic events after myocardial infarction, J Am Coll Cardiol *38:1902–1911, 2001, with permission from the American College of Cardiology Foundation.*

LVEF of 31% ± 6% were included in the study. Heart rate variability and turbulence, Holter monitoring for ambient arrhythmias, SAECG, T-wave alternans, and programmed electrical stimulation were performed 6 weeks after MI. The primary endpoint was ECG-documented VF or symptomatic sustained VT. To document these arrhythmic events, the patients received an implantable ECG loop recorder. There were 25 primary endpoints (8%) during the follow-up of 2 years. QRS duration on the SAECG was a significant predictor of the primary endpoint, along with several heart rate variability measures (Figure 67-6). A QRSD greater than 120 ms on the SAECG had a sensitivity, specificity, and positive and negative predictive values for arrhythmic events of, respectively, 44%, 85%, 20%, and 95%.[73]

Patients with Nonsustained Ventricular Tachycardia

SAECG was initially used to predict the outcome of programmed ventricular stimulation in patients with CAD and asymptomatic nonsustained VT. In a study from Turitto et al, LPs proved to be the single most accurate predictor for the induction of sustained monomorphic VT in 105 patients with nonsustained VT.[74] In this study, concordance between the results of programmed stimulation and those of SAECG was observed in 84% of cases. The largest subgroup consisted of patients who had a normal SAECG and no induced sustained monomorphic VT (70%). In these patients, the spontaneous arrhythmia may have been caused by mechanisms other than re-entry. The group with both abnormal SAECG and induced sustained VT accounted for 14% of cases. The results of the two tests were discordant in the remaining 16% of cases. This may be explained by electrophysiological limitations of both programmed stimulation and SAECG techniques.[74] Subsequent studies have shown that the SAECG may also predict the results of programmed stimulation in patients with nonischemic dilated cardiomyopathy.[75]

The most compelling data on the predictive accuracy of SAECG in patients with CAD, prior MI, left ventricular dysfunction, and asymptomatic nonsustained VT originated from the SAECG substudy of the Multicenter Unsustained Tachycardia Trial (MUSTT).[76] In this large, prospective, multicenter study, SAECG data from 1268 patients were entered in a Cox proportional hazards modeling to examine individual and joint relations between SAECG parameters and arrhythmic death or cardiac arrest (primary endpoint), cardiac death, and total mortality. In all patients, SAECG quantitative variables were processed at 40 to 250 Hz and included filtered QRSD, RMS40, and LAS40. First, to assess the prognostic content of a "normal" versus "abnormal" SAECG, the SAECG parameters were analyzed as continuous variables and as dichotomized at standard cut points. A QRSD greater than 114 ms was the single most powerful independent predictor of the primary endpoint and cardiac death and was thus defined as an abnormal SAECG (Table 67-5).[76] The SAECG variables remained significant predictors after adjustment for prognostic clinical and treatment factors. Second, to illustrate the ability of the SAECG to stratify risk, patients were divided by QRSD (>114 ms [abnormal SAECG] vs. <114 ms [normal SAECG]) and Kaplan-Meier survival curves were generated for each outcome (Figure 67-7).[76] With an abnormal SAECG, the 5-year rates of the primary endpoint (28% vs. 17%, $P = .0001$), cardiac death (37% vs. 25%, $P = .0001$), and total mortality (43% vs. 35%, $P = .0001$) were significantly higher. The combination of LVEF less than 30% and abnormal SAECG identified a particularly high-risk subset that constituted 21% of the total population. Of the patients with this combination, 36% experienced arrhythmic events and 44% experienced cardiac death during a 5-year follow-up. In contrast, 13% and 20% of patients without this combination experienced arrhythmic events and cardiac death, respectively, during a 5-year follow-up. The authors concluded that an abnormal SAECG (defined as a filtered QRS duration >114 ms) is a strong predictor for both arrhythmic events and cardiac mortality in patients with ischemic cardiomyopathy.[76]

Patients with Nonischemic Dilated Cardiomyopathy

Studies investigating the prognostic value of SAECG in nonischemic dilated cardiomyopathy are relatively scarce. In some studies, SAECG was found to be a predictor of survival. The heterogeneity of the study populations with respect to the presence of spontaneous ventricular tachyarrhythmias and bundle branch block as well as the empirical use of antiarrhythmic drugs, which could have

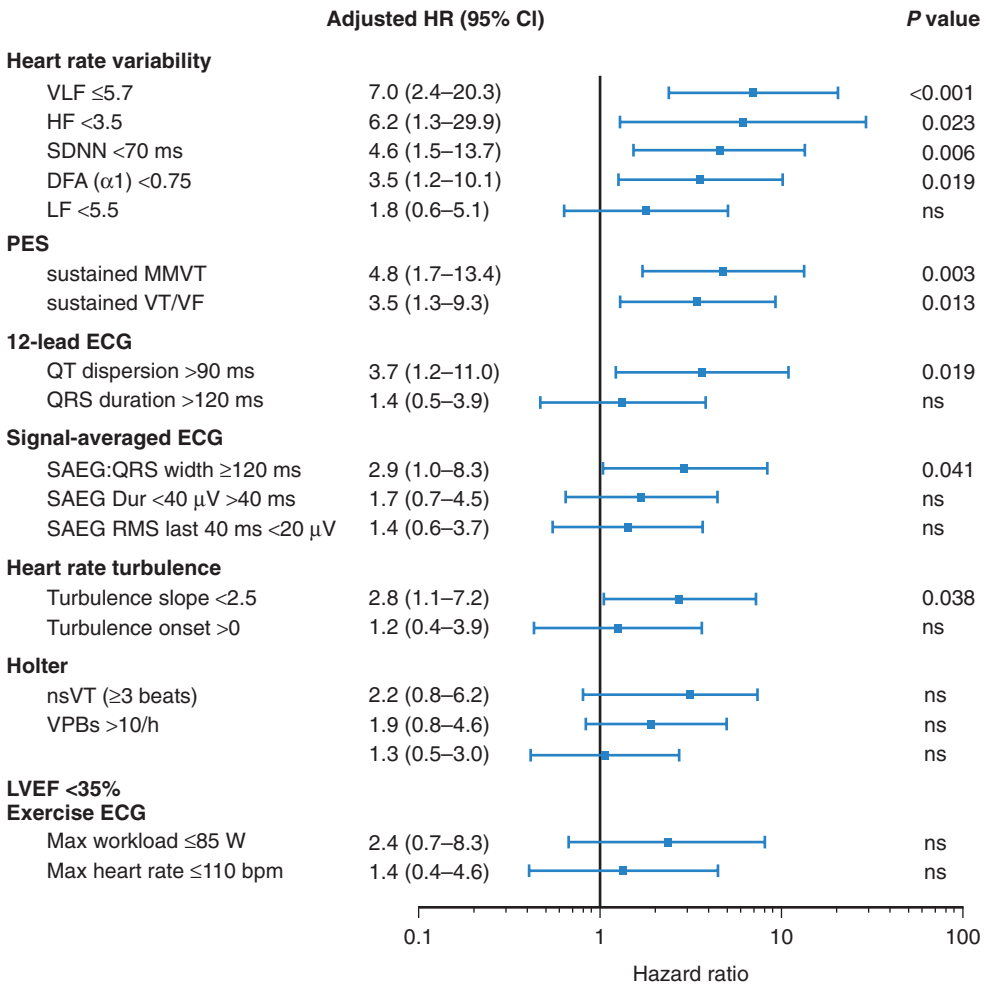

FIGURE 67-6 Adjusted hazard ratios (*HRs*) with 95% confidence intervals of the variables as predictors of primary endpoint. HRs are calculated from predefined threshold values of continuous variables. HRs are adjusted for age, prior myocardial infarction, history of congestive heart failure, and diabetes. The variables are listed in descending order starting with the highest HR for each risk stratification method. *DFA*, Fractal scaling exponent of heart rate variability; *Dur*, duration; *HF*, high frequency; *LF*, low frequency; *MMVT*, monomorphic ventricular tachycardia; *nsVT*, nonsustained ventricular tachycardia; *PES*, programmed electrical stimulation; *SDNN*, standard deviation of N-N (R-R) intervals; *VF*, ventricular fibrillation; *VLF*, very low frequency; *VPBs*, ventricular premature beats. *(From Huikuri HV, Raatikainen MJP, Moerch-Joergensen R, 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 *30:689–698, 2009.)*

influenced both the results of SAECG and clinical outcome, may explain the discrepancies between these reports and other series that did not find any correlation between an abnormal SAECG and prognosis in patients with dilated cardiomyopathy.[77,78]

Turitto et al performed SAECG and programmed ventricular stimulation in a group of 80 subjects with nonischemic dilated cardiomyopathy and spontaneous nonsustained VT, with a mean follow-up of 22 months.[77] Survival analysis with Cox proportional hazards model demonstrated that no test result was significantly associated with arrhythmic events or total cardiac mortality. When 2-year survival analysis was based on the results of SAECG, there were no significant differences in arrhythmia-free survival or cumulative survival between patients with abnormal SAECG and those without abnormal SAECG (Figure 67-8). The presence of a normal SAECG and lack of inducibility of sustained monomorphic VT did not portend a favorable prognosis in patients with nonischemic dilated cardiomyopathy and spontaneous nonsustained VT.[77]

In the Marburg Cardiomyopathy Study, arrhythmia risk stratification was performed prospectively in 343 patients with idiopathic dilated cardiomyopathy.[78] This included analysis of LVEF by echocardiography, SAECG, arrhythmias on ambulatory ECG, QTc dispersion, heart rate variability, baroreflex sensitivity, and T-wave alternans. During 52 ± 21 months of follow-up, MAEs, defined as sustained VT, VF, or SCD, occurred in 46 patients (13%). On multivariate analysis, LVEF was the only significant arrhythmia risk predictor in patients with sinus rhythm, with a relative risk of 2.3 per 10% decrease of EF (95% confidence interval, 1.5 to 3.3; $P = .0001$). In patients with atrial fibrillation, multivariate Cox analysis identified LVEF and absence of β-blocker therapy as the only significant arrhythmia risk predictors. SAECG, baroreflex sensitivity, heart rate variability, and T-wave alternans did not appear to be helpful.[78] These results strongly support the recommendation that novel risk stratification strategies be sought in patients with nonischemic dilated cardiomyopathy.

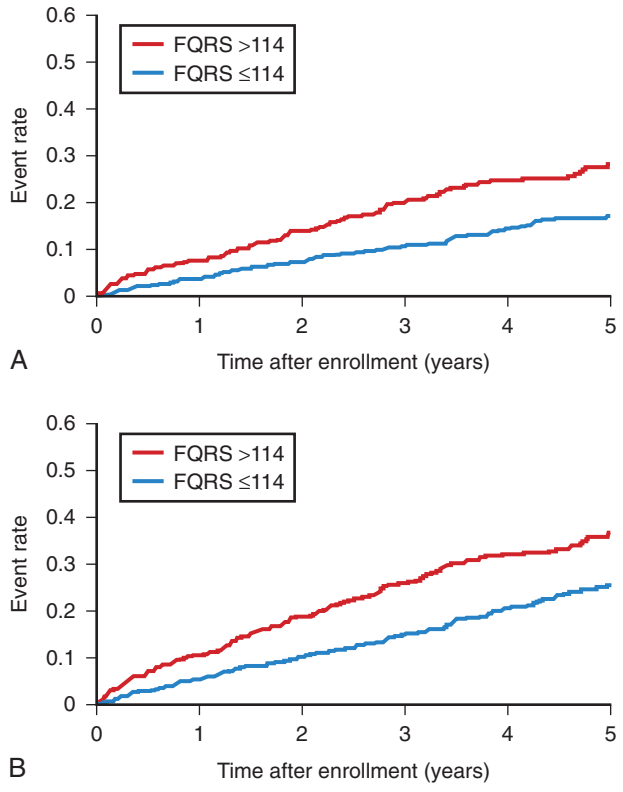

FIGURE 67-7 Kaplan-Meier estimates of arrhythmic death or cardiac arrest (**A**) and cardiac death (**B**) by SAECG result in the Multicenter UnSustained Tachycardia Trial (MUSTT) substudy. *P* < .001 between groups; *FQRS*, high-frequency QRS duration. *(From Gomes JA, Cain ME, Buxton AE, et al: Prediction of long-term outcomes by signal-averaged electrocardiography in patients with unsustained ventricular tachycardia, coronary artery disease, and left ventricular dysfunction,* Circulation *104:436–441, 2001, with permission from the American Heart Association.)*

Table 67-5 Multivariate Analysis of Signal-Averaged Electrocardiography Quantitative Values as Predictors of Outcome in the MUSTT Substudy

	Arrhythmic Death/Cardiac Arrest		Cardiac Death	
PREDICTOR	χ^2	***P* VALUE**	χ^2	***P* VALUE**
CONTINUOUS VARIABLES				
Filtered QRS duration	29.2	<.001	34.0	<.001
RMS voltage	14.3	.004	17.0	<.001
Duration of LAS	0.3	.59	0.2	.62
DICHOTOMOUS VARIABLES				
Filtered QRS duration (>114 vs. ≤114 ms)	23.1	<.001	20.8	<.001
RMS voltage (<20 vs. ≥20 μV)	0.3	.59	0.1	.73
Duration of LAS (<38 vs. ≥38 ms)	1.6	.21	0.3	.58

SAECG parameters were analyzed at a 40- to 250-Hz filter setting.
MUSTT, *Multicenter Unsustained Tachycardia Trial;* LAS, *Low-amplitude signals of <40 μV;* RMS, *root mean square voltage of the terminal 40 ms of filtered QRS. From Gomes JA, Cain ME, Buxton AE, et al: Prediction of long-term outcomes by signal-averaged electrocardiography in patients with unsustained ventricular tachycardia, coronary artery disease, and left ventricular dysfunction,* Circulation *104:436–441, 2001, with permission from the American Heart Association.*

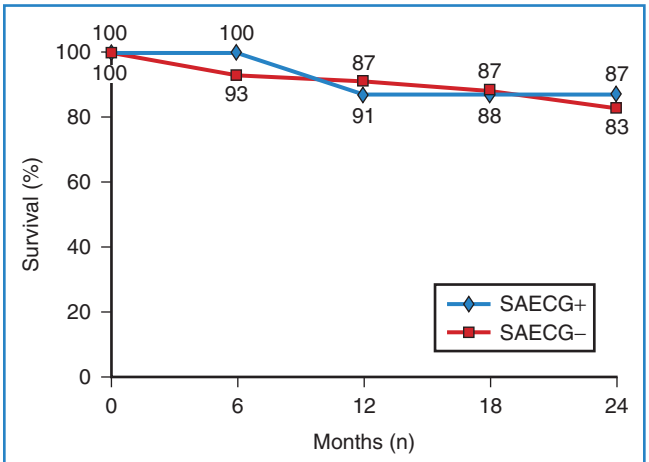

FIGURE 67-8 Two-year actuarial survival curves for arrhythmic events in 80 patients with nonischemic dilated cardiomyopathy classified by signal-averaged electrocardiography (SAECG) results. *SAECG+,* Abnormal recording; *SAECG–,* normal recording. Data are expressed as mean value ± standard error. *(From Turitto G, Ahuja RK, Caref EB, et al: Risk stratification for arrhythmic events in patients with nonischemic dilated cardiomyopathy and nonsustained ventricular tachycardia: Role of programmed ventricular stimulation and the signal-averaged electrocardiogram,* J Am Coll Cardiol *24:1523–1528, 1994, with permission from the American College of Cardiology Foundation.)*

Conclusion

The SAECG is a valuable noninvasive test for risk stratification for SCD, especially in survivors of MI. It has a very high negative predictive accuracy but a relatively low positive predictive accuracy. It is possible that improved risk stratification may be accomplished if this test is used as part of an algorithm in conjunction with other risk stratifiers. For this purpose, new ambulatory monitoring devices using digital recordings with high sampling rate may permit the simultaneous analysis of several noninvasive parameters (e.g., LPs, heart rate variability, T-wave alternans, heart rate turbulence) from the same recording.

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CHAPTER 68

Q-T Interval, QT Dynamicity, and QT Variability

Wojciech Zareba, Iwona Cygankiewicz, and Antonio Bayes de Luna

The last 2 decades have witnessed increasing research in the field of cardiac repolarization, which was predominantly triggered by breakthroughs in understanding of ion channel function in relation to long QT syndrome (LQTS) and subsequently few other channelopathies. At the same time, technological advances in electrocardiology led researchers to development of computerized methods quantifying QT duration, T-wave morphology, T-wave alternans, QT variability, and adaptation of the Q-T interval to the R-R interval. The Q-T interval is measured by electrocardiogram (ECG) on a daily basis, and although it is recognized as a routine procedure, some challenges regarding proper methodology and interpretation of Q-T interval measurements and T-wave morphology still remain.

Q-T Interval

The Q-T interval includes the QRS complex; nevertheless, the entire Q-T interval is considered a measure of repolarization because the repolarization process already takes place during the QRS complex for the early activated regions of the myocardium.[1,2] Because the process of depolarization and repolarization in the myocardium is sequential, certain regions are depolarized earlier and repolarization starts earlier in them compared with other regions. The most optimal approach to quantify the duration of repolarization represented as the Q-T interval is to obtain this measurement simultaneously from all 12 leads of the standard ECG.[1,2] The Q-T interval should be measured from the earliest onset of the QRS complex in any lead to the latest offset of the T wave in any lead, thereby providing a total measure of repolarization duration.[1-3] This approach is exercised in some automatic algorithms incorporated in ECG machines, but manual measurements of the Q-T interval usually rely on a single lead (most often lead II), which under-represents Q-T interval duration. In the case of a flat T wave in lead II, lead V5 is most frequently chosen as an alternative because electrical forces of V5 resemble those of lead II.

The end of the T wave is defined as the point at which the descending or ascending arm of the T wave terminates, usually at the level of the isoelectric line, or as the nadir between the T and U waves.[1-4] When the T and U waves merge or when the T wave has a bifid appearance with two components, careful inspection of repolarization duration in all 12 leads may be helpful in determining the proper approach to quantify the Q-T interval.[5,6] In some cases, a QTU duration should be reported, with acknowledgment that the measurement includes a second component that may be part of the T wave or superimposed U wave (Figure 68-1). In case of repolarization morphologies, with the presence of a second component of the T wave or the U wave, some investigators suggest using the rule that the U wave usually should be at least 150 ms behind the peak of the T wave, whereas closer deflections may be considered the second component of the T wave.[5,6] However, no systematic data are available to validate this rule.

The Q-T interval duration is different among standard 12 leads, and QT dispersion has been measured in numerous studies as a possible marker of arrhythmogenic conditions.[7,8] However, because of the conceptual and methodologic limitations of QT dispersion, this method has not been approved as a standard tool in clinical practice or drug studies. Inter-lead differences in repolarization morphology, rather than just Q-T interval duration, seem to better reflect the complexity of the repolarization process.[9-11] Inter-lead differences in repolarization morphology could be quantified by using various methods, including principal component analysis and area-based analysis of the repolarization segment.[9-11] Principal component analysis of the repolarization segment allows quantifying the length (λ_1) and width (λ_2) of the T-wave loop.[9,10] The roundness of the T-wave loop in its preferential plane (λ_2/λ_1) has been considered an index of increased T-wave complexity.

QTc Formulas

Bazett's formula, describing a curvilinear association between the Q-T and R-R intervals ($QTc = QT/[RR^{1/2}]$), is most frequently used.[12] Fridericia's formula ($QTc = QT/[RR^{1/3}]$), or the cubic root formula, is used in studies evaluating the effects of medications on the Q-T interval.[13] Both formulas adjust the Q-T interval to reflect repolarization duration at a heart rate of 60 beats/min. Bazett's QTc formula has limitations of overestimating the repolarization duration at fast heart rates and underestimating it at slow heart rates. Fridericia's formula causes less misjudgment; however, clinicians are not comfortable using this formula on a daily basis because of the need for a cubic root equation and, more importantly, because of limited clinical data on normal values and the diagnostic and prognostic significance of this measurement. Other QTc formulas have been proposed (Box 68-1).[12-17]

QTc formulas provide a good estimation of the Q-T interval duration at heart rates close to the normal resting range of 55 to 80 beats/min, as observed in the majority of ECGs. However, below and above those limits, risks of misclassification of the QTc value do exist. Heart rates less than 55 beats/min or more than 80 beats/min usually are recorded by Holter monitoring and exercise testing; for these ranges of heart rates, Fridericia's (cubic)

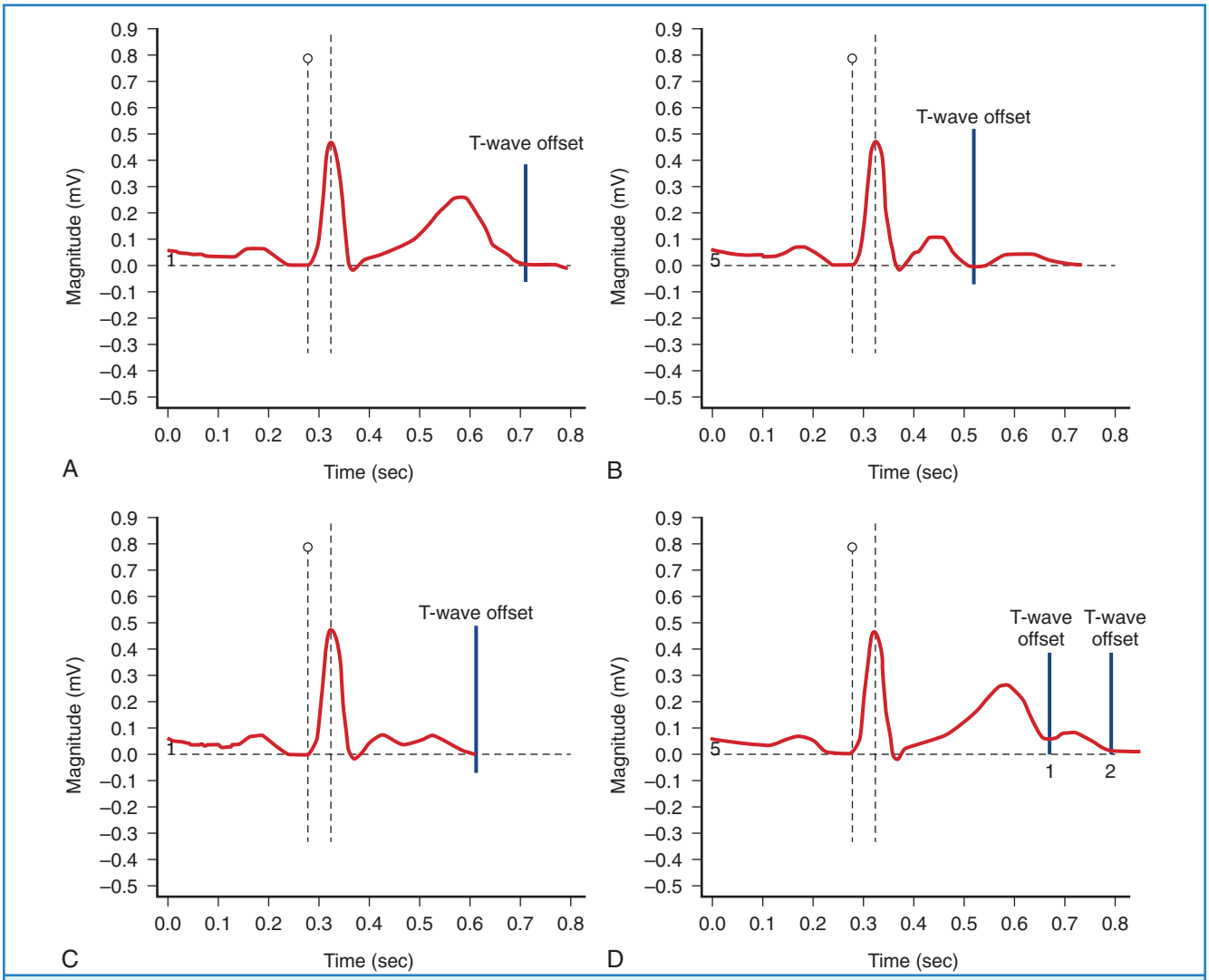


FIGURE 68-1 Q-T interval measurement in different T-wave morphologies. **A,** When the T-wave morphology is normal, the T-wave offset is identified when the descending limb returns to the TP baseline. **B,** When the T wave is followed by a distinct U wave, the T wave offset is identified when the descending limb of the T wave returns to the TP baseline before the onset of the U wave. **C,** when the T wave is biphasic with T1 and T2 waves of similar amplitude, the T-wave offset is identified as when T2 returns to baseline. **D,** When a second low-amplitude repolarization wave interrupts the terminal portion of the larger T wave (whether it should be categorized as T2 wave or a U wave), the T-wave offset should be measured at the nadir of the two waves and at the final return to baseline. *(From Goldenberg I, Moss AJ, Zareba W: QT interval: How to measure it and what is "normal," J* Cardiovasc Electrophysiol *17:333–336, 2006.)*

Box 68-1 Examples of QT Correction Formulas

Bazett[12]: a square root formula: $QTc = QT/(RR^{1/2})$
Fridericia[13]: a cubic root formula: $QTc = QT/(RR^{1/3})$
Framingham[14]: a linear formula: $QTc = QT + 0.154(1 - RR)$
Hodges[15]: using the heart rate: $QTc = QT + 1.75$ (Heart rate − 60)
Rautaharju[16]: QT is entered in milliseconds; the formula is different for males and females depending on age:
For all females and males aged <15 years and >50 years: QTI = QT(HR + 100)/656 ms
For males aged 15–50 years: QTI = (100 × QT)/([656/(1 + 0.01 HR)] + 0.4 (Age − 25)
Karjalainen[17]: QT and RR are entered in milliseconds; the formula varies by heart rate:
For heart rate <60 beats/min: $QT_{Nc} = (QT \times 392)/0.116 (RR + 277)$
For heart rate 60–99 beats/min: $QT_{Nc} = (QT \times 392)/0.156 (RR + 236)$
For heart rate ≥100 beats/min: $QT_{Nc} = (QT \times 392)/0.384 (RR + 99)$

formula is preferred because of its simplicity of application, although other more complex formulas, including Rautaharju's and Karjalajnen's formulas, could be used as well.

In drug studies, QTc corrected by Fridericia's formula is the most frequently used, but the analysis of QT-RR regression based on the subject-specific QT-RR relationship plots is attracting increasing interest.[18,19] The RR bin method is yet another approach that measures the Q-T interval in absolute value for matched R-R intervals for recordings off and on drugs without the need for correction formulas.[20,21] Both methods are particularly valuable when evaluating drugs affecting heart rates.

Reference QTc Values

Table 68-1 shows abnormal QTc values (using Bazett heart rate correction) by age and gender. Women and children have a longer

Table 68-1 QTc Values by Age and Gender

QTC VALUE (SEC)	CHILDREN (1–15 YEARS)	MEN	WOMEN
Normal	<0.44	<0.43	<0.45
Borderline	0.44–0.46	0.43–0.45	0.45–0.46
Prolonged	>0.46	>0.45	>0.46

From Moss AJ, Robinson J: Clinical features of the idiopathic long QT syndrome, Circulation *85(1-Suppl): I140–I144, 1992.*

duration of repolarization than men.[22] Gender-related differences in QT are predominantly caused by a shorter Q-T interval duration in men than women at age 15 to 55 years, not because of Q-T interval prolongation in women.[16] Data from a large cohort of more than 46,000 healthy individuals participating in pharmaceutical QT studies, as reported by Mason et al, are fully supportive of the initial ranges of QTc values reported by Moss et al.[22,23] Table 68-2 shows values for QTcB (Bazett corrected QTc) and QTcF (Fridericia corrected QTc) for age-specific and gender-specific groups from this large cohort. In general, the 98th percentile value for QTcF is approximately 10 ms shorter than the respective value for QTcB for a given age and gender group. Factors influencing gender differences in QTc duration may include slower heart rate in men, different density of potassium

Table 68-2 QTcB and QTcF Reference Values by Age and Gender Based on More than 70,000 Individuals

		QTcB Interval (ms)			QTcF Interval (ms)		
	N	2%	MEDIAN	98%	2%	MEDIAN	98%
All	46,129	361	409	457	359	400	445
Male	21,567	356	401	449	355	394	438
Female	24,562	369	414	460	365	405	450
MALES							
M, 0–9	579	368	408	452	346	388	428
M, 10–19	776	352	403	448	354	391	430
M, 20–29	2528	347	390	436	351	387	426
M, 30–39	3411	353	396	443	353	389	430
M, 40–49	4316	357	401	446	356	393	435
M, 50–59	4460	361	405	451	359	397	438
M, 60–69	3275	362	407	456	361	399	444
M, 70–79	1718	362	406	456	363	401	446
M, 80–89	483	361	409	455	366	407	452
M, 90–99	21	363	421	442	369	414	448
FEMALES							
F, 0–9	384	365	411	461	347	387	428
F, 10–19	569	371	408	457	362	396	437
F, 20–29	2469	364	409	454	362	400	440
F, 30–39	3954	367	412	455	364	403	441
F, 40–49	6047	371	414	460	367	405	447
F, 50–59	4899	370	416	463	367	407	450
F, 60–69	3323	370	416	462	367	407	452
F, 70–79	2072	370	417	467	369	410	459
F, 80–89	801	370	417	467	366	411	464
F, 90–99	44	373	423	476	370	416	454

Both lower (2%) and upper (98%) percentiles are shown because the lower boundary may identify short QTc and the upper boundary may identify long QTc.
From Mason JW, Ramseth DJ, Chanter DO, et al: Electrocardiographic reference ranges derived from 79,743 ambulatory subjects, J Electrocardiol *40:228–234, 2007.*

ion channels in the male myocardium versus the female myocardium, effects of female hormones contributing to longer Q-T interval duration in women, and possibly the effect of male hormones contributing to the shorter Q-T interval duration in men. Differences by age also exist, with healthy older adults demonstrating a longer QTc duration compared with younger individuals.

T-Wave Morphology

Changes in T-wave morphology are frequently observed in association with myocardial ischemia, hypertrophy, overload, and genetic alterations in repolarization. LQTS shows variations of T-wave morphology, which could be related to the type of affected ion channel and the magnitude of ion channel dysfunction as well as other factors, such as age, heart rate, and the status of the autonomic nervous system. Specific genetic types of LQTS could be associated with distinct ECG patterns of repolarization.[24,25] Figure 68-2 shows specific patterns associated with distinct genetic types of the disorder: LQT1, characterized by wide, broad-based T waves; LQT2, usually showing low-amplitude and frequently notched T waves; and LQT3, characterized by a relatively long ST segment followed by a peaked, frequently tall T wave. In the Rochester ECG Core Lab, we use a 3-digit code (Box 68-2), which is a classification to characterize the T wave and the Q-T interval visually.[26] The first digit represents a description of T-wave morphology, the second digit provides information about its polarity, and the third digit indicates whether the U wave is present or whether the TU complex should be measured because of the presence of the second component of the T wave or the U wave merging with the T wave. Recognizing abnormal T-wave morphology may be particularly useful in diagnosing patients with borderline QTc duration (420 to 470 ms). In such patients, the presence of an abnormal (notched, flat) T wave may indicate the possibility of LQTS (Figure 68-3).

Decreased T-wave amplitude with an increased presence of notches may be observed in drug-induced changes in repolarization. Drug-induced changes in T-wave morphology reflect changes in the transmural gradient of repolarization with propensity to arrhythmogenesis (Figure 68-4).[27,28] Therefore the identification of drug-induced changes in repolarization morphology in clinical studies should always trigger attention because those changes may indicate a propensity to proarrhythmia.

Box 68-2 Coding of QT/T-Wave Morphology

FIRST DIGIT: TU WAVE SHAPE
1. Smooth normal configuration
2. Flat
3. Broad slow activation
4. Peaked
5. Biphasic
6. Bifid, notches
7. Other more complex morphology
8. Indeterminate
9. Lead not available

SECOND DIGIT: TU WAVE PHASE
1. Positive
2. Negative
3. Biphasic positive/negative
4. Biphasic negative/positive
5. Polyphasic
6. Isoelectric
7. Other
8. Indeterminate
9. Lead not available

THIRD DIGIT: REPOLARIZATION MORPHOLOGY
1. T wave without visible U wave
2. T wave with independent U wave (separated from T wave by isoelectric line)
3. TU wave (U wave present, not separated by isoelectric line)
4. Indeterminate
5. Lead not available

From Zareba W, Moss AJ, Rosero SZ, et al: Electrocardiographic findings in patients with diphenhydramine overdose, Am J Cardiol *80:1168–1173, 1997.)*

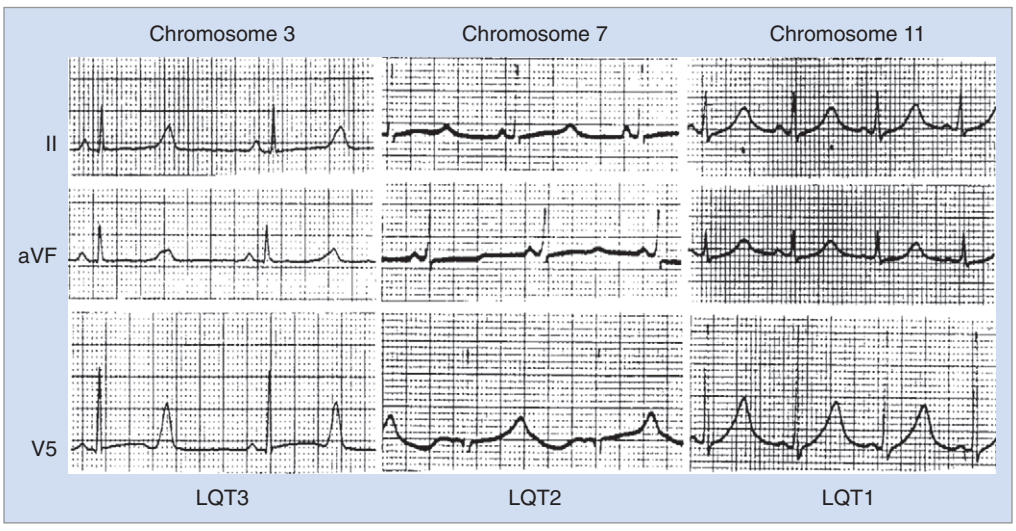


FIGURE 68-2 T-wave morphology in electrocardiogram recordings from leads II, aVF, and V5 from patients with long QT syndrome types 1, 2, and 3. *(From Moss AJ, Zareba W, Benhorin J, et al: ECG T-wave patterns in genetically distinct forms of the hereditary long QT syndrome,* Circulation *92:2929–2934, 1995.)*

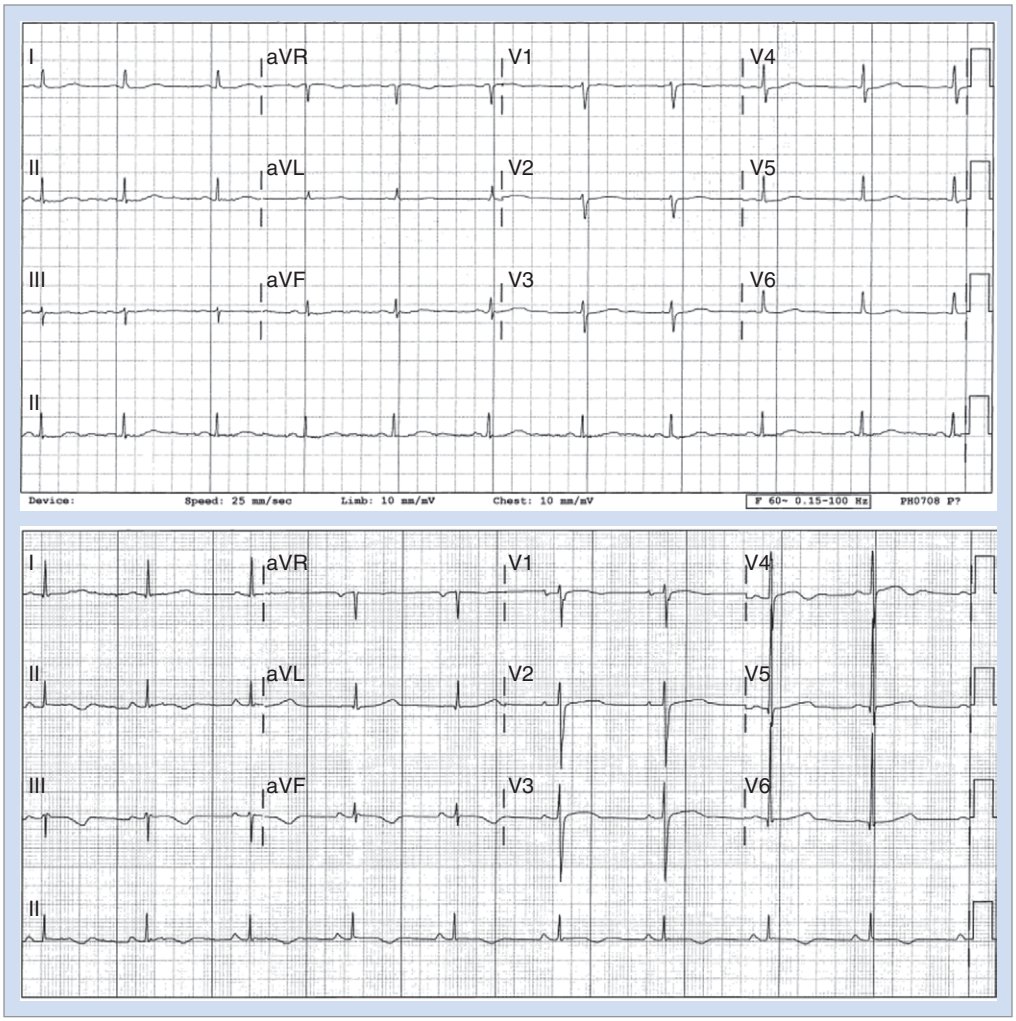


FIGURE 68-3 Electrocardiogram of genetically confirmed cases of long QT syndrome with borderline QTc duration. *Top*, Note the flatness of the T wave in leads V2 to V4. *Bottom*, Abnormal T-wave morphology in several leads: an inverted T wave is shown in leads II and V4, a broad dome-like T wave in the right precordial leads, and subtle notches of the T wave in V5.

Drug-Induced Q-T Interval Prolongation

Several cardiac and noncardiac medications may cause QTc prolongation and cause torsades de pointes (TdP) (Table 68-3).[29] They usually block the I_{Kr} current, whereas others exert such action if administered together with a drug affecting the function of the cytochrome P-450 enzymatic system. A number of quinidine-induced sudden cardiac deaths (SCDs) and, subsequently, the results of the Cardiac Arrhythmia Suppression Trial (CAST) brought further attention to the proarrhythmic effects of antiarrhythmic drugs.[30] The antihistamine drug terfenadine was recognized as the first noncardiac medication causing TdP and SCD.[31] Terfenadine blocks the I_{Kr} current (as well as the Na^+ current and the L-type calcium channel), causing a mean 6-ms QTc prolongation, which should not have clinical implications. Cardiac events were reported in patients taking terfenadine, almost exclusively when used in combination with other medications (ketoconazole, antibiotics) also metabolized by the same enzymatic system of the cytochrome P-450 3A4. Such a combination causes an increase in plasma concentration of terfenadine because of inhibition of its metabolism by a concomitantly administered drug with subsequent substantial QTc prolongation (>60 ms in the majority of reported cases) and TdP. Among noncardiac drugs, several antipsychotic drugs block the I_{Kr} current and cause QTc prolongation, and some of them were reported to be associated with SCD.[32]

Box 68-3 lists common factors predisposing to QTc prolongation and TdP.[29] Females with faster resting heart rates and a longer QTc interval compared with men are particularly prone to drug-induced TdP. Older patients and those with underlying heart diseases (cardiomyopathies) or electrolyte abnormalities, especially hypokalemia and bradycardia, are particularly at an increased risk for drug-induced QTc prolongation and TdP.

The U.S. Food and Drug Administration (FDA) and the Committee for Proprietary Medicinal Products (CPMP) of the European Agency for the Evaluation of Medicinal Products mandate evaluating all new drugs for their potential QTc-prolonging effects.[33,34] Each drug must be evaluated individually after full consideration of the drug's risks in relation to its benefits for the

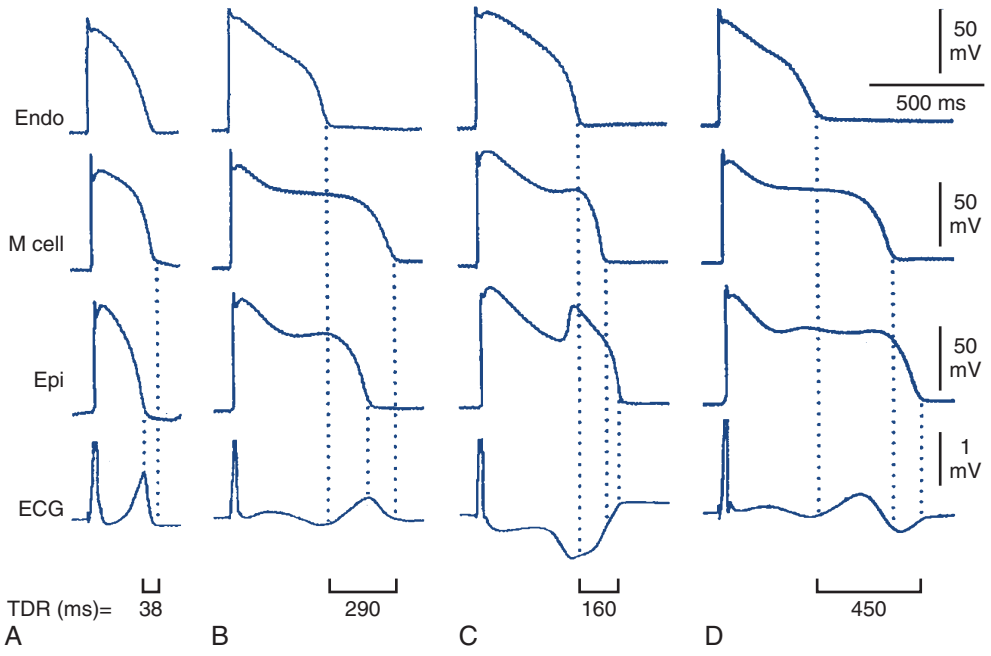


FIGURE 68-4 Transmural dispersion of action potentials and changes in T-wave morphology on the electrocardiogram. **A,** Normal T wave with normal transmural gradient of repolarization. **B,** Biphasic T wave. An increase in transmural gradient with the end of the endocardial action potential coincides with the negative phase of the T wave. **C,** Inverted T wave. The epicardial layer shows the longest repolarization duration contributing to an increased and inverted transmural gradient. **D,** Polyphasic T wave with markedly increased transmural gradient. Negative phases of the T wave coincide with the end of action potential in endocardial and M cell layers. *(From Emori T, Antzelevitch C: Cellular basis for complex T waves and arrhythmic activity following combined I_{Kr} and I_{Ks} block,* J Cardiovasc Electrophysiol *12:1369–1378, 2001.)*

Box 68-3 Factors Associated with Increased Risk of QTc Prolongation and Torsades de Pointes

PROLONGED QTC
Female sex
Advanced age
Bradycardia
Hypokalemia
Hypomagnesemia
Congestive heart failure (low ejection fraction)
Cardiac arrhythmias
Combinations of drugs (cytochrome P450 enzyme inhibitors)
Genetic polymorphisms of gene coding cardiac ion channels or enzymes in liver metabolizing drugs

From Zareba W: Drug induced QT prolongation, Cardiol J *14:523–533, 2007.*

population at risk. Drugs that show some QTc-prolonging effects in phase I or phase II studies may require further testing in a thorough QT study. The thorough QT study consists of repeated monitoring of QT and RR parameters as well as T-wave morphology during administration of a tested drug and during administration of moxifloxacin, an antibiotic with known QTc-prolonging effects used as a positive control (to validate the ability of the ECG core lab to detect the expected repolarization changes). Drugs with QTc prolongation showing upper confidence intervals exceeding 10 ms may require additional safety measures during the next phases of development, such as specific labeling with regard to the QTc-prolonging effect, or may not be recommended to enter the market.

QTc Prolongation in Risk Stratification

LQTS was the first entity in which the association between QTc prolongation and arrhythmic events was appreciated.[35-39] For every 10-ms increase of QTc duration, a 5% to 7% exponential increase of the risk of cardiac events exists.[35-37] LQTS patients with QTc greater than 500 ms are particularly prone to developing cardiac events defined as *aborted cardiac arrest or death*.[40] However, approximately one third of LQTS gene carriers have normal or borderline QTc values, and they may also experience these events.[35–40] This indicates that the magnitude of QTc duration is not the only factor when evaluating the risk of arrhythmic events. QTc duration above 500 ms or prolongation by more than 60 ms in response to a drug indicates an increased risk of TdP in the case of drug-induced QTc prolongation.[41]

Prolonged QTc is also considered a risk factor in other patient populations. In the Rotterdam Study, a cohort of 3105 men and 4878 women aged 55 years and older was observed over several years.[42] An abnormal QTc prolongation (>450 ms in men, >470 ms in women) was found to be associated with a threefold increased risk of SCD after adjustment for age, gender, body mass index, hypertension, cholesterol or high-density lipoprotein (HDL) ratio, diabetes mellitus, myocardial infarction (MI), heart failure, and heart rate (Figure 68-5). Data from The Framingham study, however, did not support this association.[43] The Cardiovascular Health Study showed an association between QTc of greater than 450 ms and total mortality, and the Strong Heart Study showed that a QTc of 460 ms or greater was associated with a twofold increased risk of SCD and total mortality.[44,45]

The predictive value of QTc prolongation in patients with coronary artery disease (CAD) and heart failure is inconsistent.[46-51]

Table 68-3 Drugs That Prolong the Q-T Interval

CATEGORY	DRUGS
Antihistamines	Astemizole, terfenadine
Anti-infectives	Amantadine, clarithromycin, chloroquine, erythromycin, grepafloxacin, moxifloxacin, pentamidine, sparfloxacin, trimethoprim-sulfamethoxazole
Anti-neoplastics	Tamoxifen, arsenic trioxide
Anti-arrhythmics	Quinidine, sotalol, procainamide, amiodarone, bretylium, disopyramide, flecainide, ibutilide, moricizine, tocainide, dofetilide, ranolazine, vernakalant, and dronedarone
Anti-lipemic agents	Probucol
Calcium channel blockers	Bepridil
Diuretics	Indapamide
Gastrointestinal agents	Cisapride
Hormones	Fludrocortisone, vasopressin
Anti-depressants	Amitriptyline, amoxapine, clomipramine, imipramine, nortriptyline, protriptyline
Anti-psychotics	Chlorpromazine, haloperidol, perphenazine, quetiapine, risperidone, sertindole, thioridazine, ziprasidone, doxepin, methadone

Updated information on QT prolonging drugs can be found at www.qtdrugs.org. From Zareba W: Drug induced QT prolongation, Cardiol J *14:523–533, 2007.*

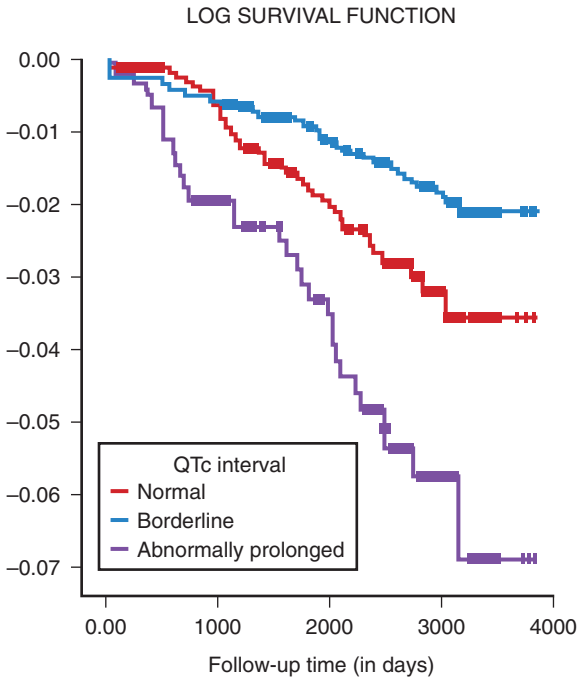


FIGURE 68-5 Risk of sudden death and QTc in older subjects enrolled in the Rotterdam study. *(From Straus SM, Kors JA, De Bruin ML, et al: Prolonged QTc interval and risk of sudden cardiac death in a population of older adults,* J Am Coll Cardiol *47:362–367, 2006.)*

Most of the studies are not able to confirm the practical usefulness of QTc prolongation for predicting cardiac events in patients with underlying coronary disease and cardiomyopathy because these conditions alter repolarization; therefore QTc prolongation reflects the severity of the disease rather than the risk of cardiac events.[46-51]

QT Dynamicity

The dependency of the repolarization process on heart rate represents a repolarization dynamic. During exercise, the uncorrected Q-T interval shortens with decreasing R-R intervals. In the case of progressively increasing or decreasing heart rate, the Q-T interval shows a linear correlation with heart rate within physiological limits. However, in cases of abrupt RR changes, the Q-T interval does not change adequately, and a lag of QT adaptation to changing heart rate exists. Abrupt R-R interval changes, especially caused by ventricular premature beats, may precede the onset of ventricular tachycardia (VT). The presence of a short-long-short sequence may prolong the action potential duration (reflected as QTc prolongation on surface ECG), facilitating early afterdepolarizations (EADs) and triggering VT. Adjustment of the QT to changing heart rate is a dynamic phenomenon consisting of fast adaptation and slow adaptation phases. Franz et al showed that after a rapid change in heart rate, the fast adaptation phase of repolarization usually lasts 30 to 60 seconds and is followed by a 2-minute slow adaptation.[52] This adjustment also seems highly individual and, among other factors, depends on the nature of heart rate changes. Repolarization adapts faster to increasing heart rate than it does to decreasing heart rate. This differential response is known as *repolarization hysteresis*.[53] Measures of repolarization hysteresis are proposed for diagnosing LQTS in patients who usually show a larger difference in QT duration between exercise and recovery compared with control subjects.[54]

Continuous recording of R-R intervals and corresponding Q-T intervals in Holter recordings brought an increased interest in the analysis of the dynamic behavior of repolarization: the slope of the linear regression between Q-T and R-R intervals (Figure 68-6). Usually, R-R and Q-T intervals included in a 30- or 60-second epoch of the ECG are calculated and averaged to diminish the possible influence of erroneous measurements and to decrease the effect of sudden and short-acting changes in R-R interval on Q-T interval duration.[55] These averaged Q-T and R-R intervals may then be linearly fitted from the period of prolonged recording, typically 24 hours of Holter monitoring. Both the QT apex (QTa) and QT end (QTe) can be measured. A steeper slope indicates excessive prolongation of QT at longer R-R cycle lengths and adequate or excessive shortening of QT at shorter R-R cardiac cycles (see Figure 68-6). A flat slope indicates that the Q-T interval is less dependent on the R-R cycle and fails to adequately shorten at faster heart rates (shorter cycle). Both features may contribute to an increased risk of arrhythmias. A steeper QT/RR slope indicates decreased vagal tone and increased sympathetic

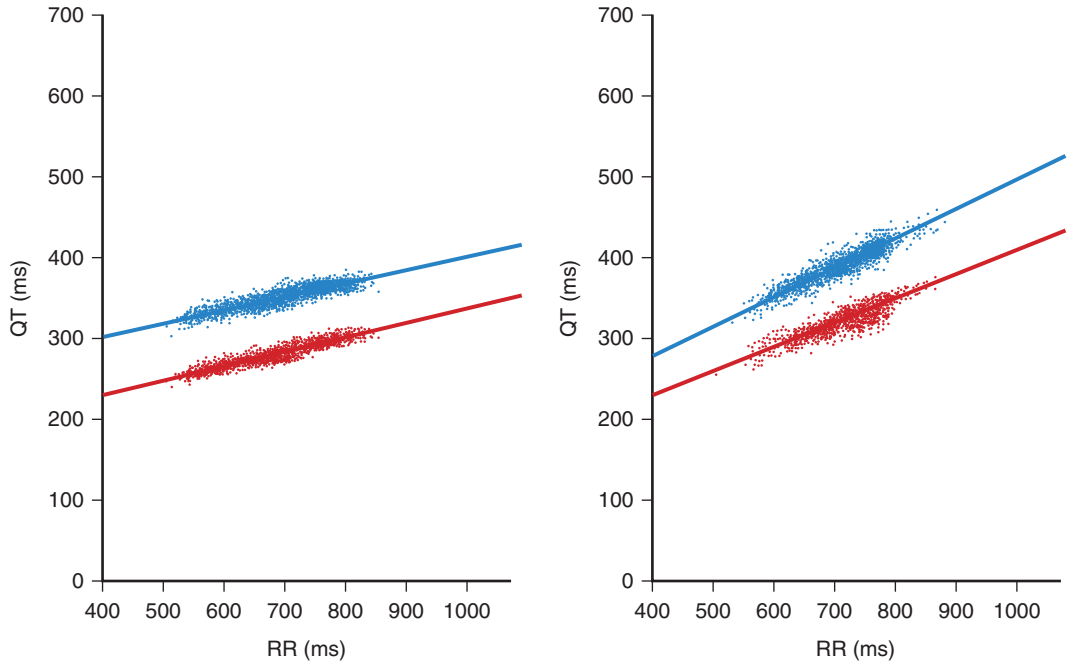


FIGURE 68-6 Repolarization dynamics measured by QT/RR slopes.

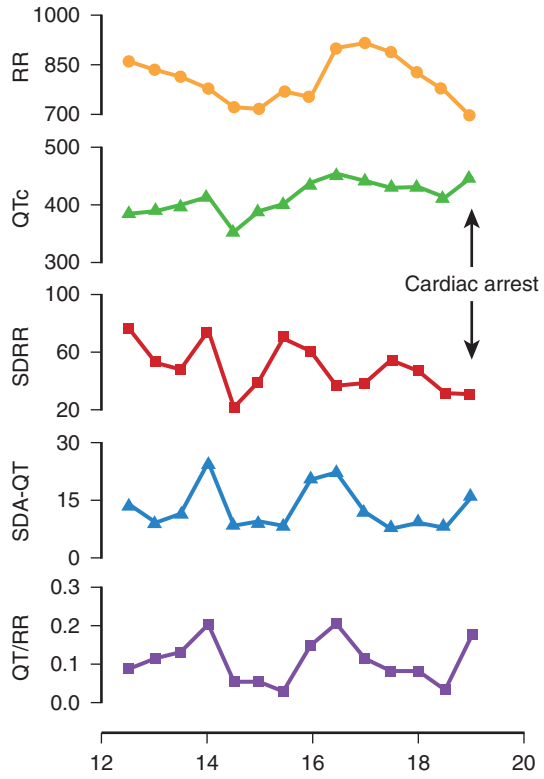
activity, which may contribute to a higher vulnerability of the myocardium to arrhythmias. Lengthening of the QT at slower rates may be associated with an arrhythmogenic increase in the dispersion of refractoriness in the myocardium, whereas excessive shortening of QT at fast heart rates may facilitate arrhythmia by diminished heterogeneity of refractoriness. QT dynamics reflect both the rate dependence of ventricular repolarization as well as the modulation of this dependence by a variety of factors, such as the autonomic nervous system, hormones, metabolic equilibrium, disease entities, and drugs. A significant diurnal variation of QT/RR has been reported with the QT/RR slope usually evaluated separately for day and night.[56]

Prognostic Value of QT/RR Slopes

Analysis of Q-T interval duration only by surface ECG may not correspond to what happens in the period directly preceding malignant arrhythmias. Singh et al reported an abrupt increase in the QT/RR slope associated with a prolonged QTc and reduced heart rate variability in the interval immediately preceding the onset of ventricular fibrillation (VF) that led to cardiac arrest in a 71-year old man with hypertension and chronic renal failure.[57] The QT/RR slope increased from 0.032 at 60 minutes before VF to 0.293 minutes, as observed 10 minutes before cardiac arrest (Figure 68-7). Sredniawa et al described an abrupt increase in the QT/RR slope (from 0.223 to 0.483) in the period preceding a burst of frequent ventricular ectopic beats on Holter monitoring in patients with CAD and documented cardiac arrest caused by sustained VT.[58] Transitory QT lengthening may express a temporal imbalance of the autonomic nervous system, which may lead to heterogeneity of the ventricular refractory periods and may predispose to the development of re-entry phenomena.

The prognostic value of QT dynamics in predicting cardiac and arrhythmic events was evaluated in several studies. The prognostic value of the QT/RR slope in the prediction of SCD was evaluated by the Groupe d'Etude du Pronostic de l'Infarctus (GREPI) study.[59] Abnormal QT/RR slope, evaluated 9 to 14 days after infarction, was found to be an independent risk marker for SCD during an average 7-year follow-up. A steeper QT/RR slope (>0.18 during the day) was associated with total mortality and SCD, indicating that excessive shortening at fast rates, excessive lengthening at slow rates, or both may contribute to arrhythmic events (Figure 68-8). The increased QT/RR slope was the most powerful predictor when tested simultaneously with clinical variables in the Cox multivariate model. Of note, the hazard ratio (HR) was three times higher for SCD than for all-cause mortality (HR, 6.07 vs. 2.25, respectively). In the European Myocardial Infarct Amiodarone Trial (EMIAT) study, QT dynamicity was assessed in patients with prior MI and a left ventricular ejection fraction (LVEF) of 40% or higher and was compared between patients with arrhythmic cardiac death (ACD) and non-ACD during a mean follow-up of 21 months.[60] The QT slopes were significantly higher in the ACD group, but only an increased morning QT/RR slope differentiated patients with ACD from those with non-ACD (QT/RR slope, 0.272 vs. 0.239, respectively). Therefore QT dynamicity distinguished patients with prior MI who died of ACD from survivors and also predicted the type of death.

Pathak et al demonstrated that an increased QT/RR slope (>0.28) assessed over 24 hours was predictive for SCD in patients with chronic class II to III heart failure caused by ischemic (43%) or idiopathic (57%) cardiomyopathy with a mean LVEF of 28%.[61] Of note, similar to studies in patients with prior MI, abnormal QT dynamicity was related more to SCD than to total mortality. The HR of 24-hour QT dynamicity (QTe) was more than 50%



QT/RR slope and SDRR in the hour preceding the terminal rhythm

Time (min)	QT/RR slope	SDRR (ms)
–60	0.032	43.2
–50	0.043	37.3
–40	0.068	56.8
–30	0.026	40.5
–20	0.018	25.3
–10	0.293	33.1

FIGURE 68-7 Half-hourly distribution of the electrophysiological parameters assessed before cardiac arrest. *SDRR*, Standard deviation of the consecutive R-R intervals over 5-minute segments; *SDA*-QT standard deviation of the average of consecutive uncorrected Q-T intervals over 5-minute segments; *QTc*, corrected Q-T interval; *QT/RR*, the slope of the regression line between Q-T and R-R intervals. *(From Singh JP, Sleight P, Kardos A, Hart G: QT interval dynamics and heart rate variability preceding a case of cardiac arrest,* Heart *77:375–377, 1997.)*

higher for SCD than for total mortality (HR, 3.4 vs. 2.2 in univariate analysis). Analysis of repolarization dynamics was performed in the Multicenter Ultrasound Stenting in Coronaries (MUSIC) study, which analyzed 542 patients with mild to moderate heart failure (49% with ischemic cardiomyopathy; mean LVEF, 37%).[62] The mean value of the QTa/RR slope was 0.172, and that of QT/RR was 0.193. During the 44-month follow-up, 119 deaths occurred, including 47 classified as SCDs. Nonsurvivors were characterized by steeper QT/RR slopes. In this study, increased QT/RR slopes during the daytime (>0.20 for QTa and >0.22 for QTe) were independently associated with increased total mortality during an average 44-month follow-up (HR, 1.57 and 1.58 for QTa and QT, respectively) (Figure 68-9). None of the dynamic repolarization parameters was associated with increased risk of SCD.

The independent prognostic value of QT dynamicity in patients with idiopathic dilated cardiomyopathy was reported by Iacoviello et al, who found that abnormal QT dynamicity was significantly associated with arrhythmic events (VT, VF, or SCD) during a mean 39-month follow-up.[63] At multivariate analysis, only the QT slope (>0.19), decreased LVEF, and nonsustained VT were independent predictors of poor outcome.

Evidence that an abnormal QT/RR slope is a powerful predictor of cardiac events, mainly death in various groups of patients with ischemic heart disease and nonischemic cardiomyopathies, is growing. Holter algorithms allow automatic computation of the QT/RR slope, with preprocessing and filtering essential to decrease the effects of outliers and the effects of instantaneous changes of QT/RR behavior. However, apart from the overall pattern of QT/RR behavior, beat-to-beat changes in the Q-T interval (QT variability) have also evoked much interest, especially because such instantaneous changes may lead to the development of life-threatening VT. QT dynamics expressed as the overall QT/RR slope representing the overall underlying substrate for arrhythmia may be complemented by analyses of QT variability reflecting transient changes in the vulnerability of the myocardium to arrhythmias.

QT Variability

QT variability consists of beat-to-beat changes in repolarization duration and morphology appearing without the 2:1 pattern typical of T-wave alternans. Beat-to-beat changes in QT duration and T-wave morphology can easily be seen in post-extrasystolic pauses or significant variations in the R-R interval. However, QT duration varies by milliseconds on a beat-to-beat basis even in healthy subjects with regular heart rates. These beat-to-beat changes in QT duration and T-wave morphology can be quantified by computerized ECG methods. A healthy person has a small level of beat-to-beat variation of action potential duration, mostly related to fluctuations of autonomic modulation.[64] QT variability depends on both Q-T and R-R interval duration; QTc prolongation, R-R shortening, or both occurring simultaneously may contribute to excessive QT variability and T-wave alternans (Figure 68-10). QT variability cannot be entirely explained by changes in the autonomic nervous system. Beat-to-beat changes in the action potential duration depend on instantaneous changes in ion channel activity. Even with a stable R-R interval, repolarization changes, caused by variations in the number of involved channels, are possible.[65] Cardiomyopathy, ischemia, and LQTS may alter the number of involved channels, and changes in cycle length may further potentiate the beat-to-beat variability of repolarization.

A time-stretching algorithm was developed by Berger et al to quantify changes in repolarization duration and morphology.[66] In this method, beat-to-beat Q-T interval variability is measured by 256-second recordings of surface ECGs. A QT variability index (QTVI) is calculated as the logarithm of the ratio of normalized QT variance to heart rate variance. These authors demonstrated that patients with dilated cardiomyopathy had higher QT variability compared with control subjects. Couderc et al developed a T-wave endpoint-independent method to quantify repolarization variability based on wavelet transformation.[67] The wavelet-based method showed that patients with LQTS (*SCN5A* carriers)

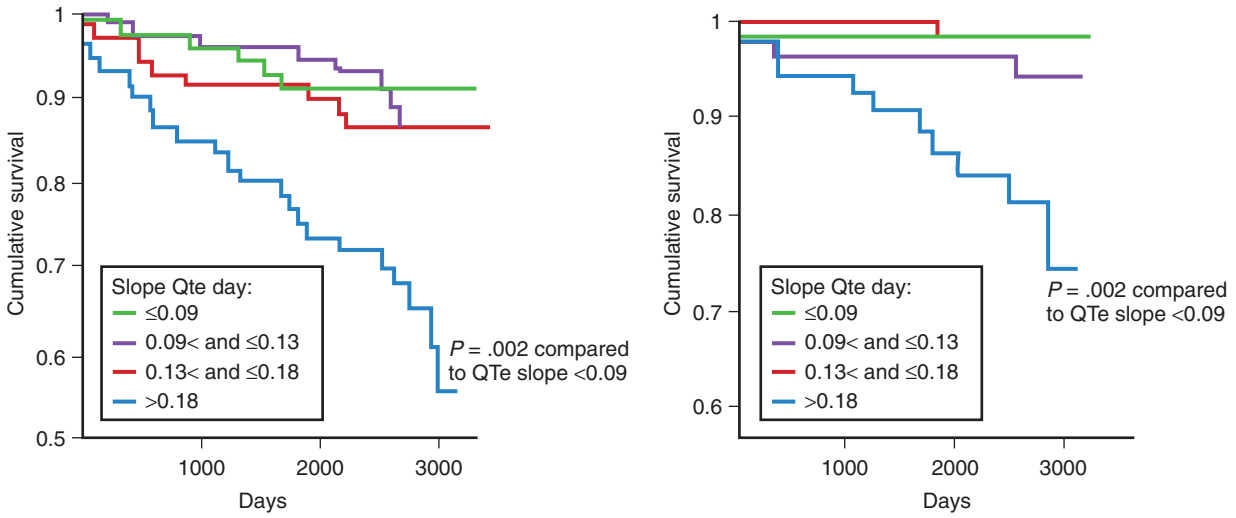
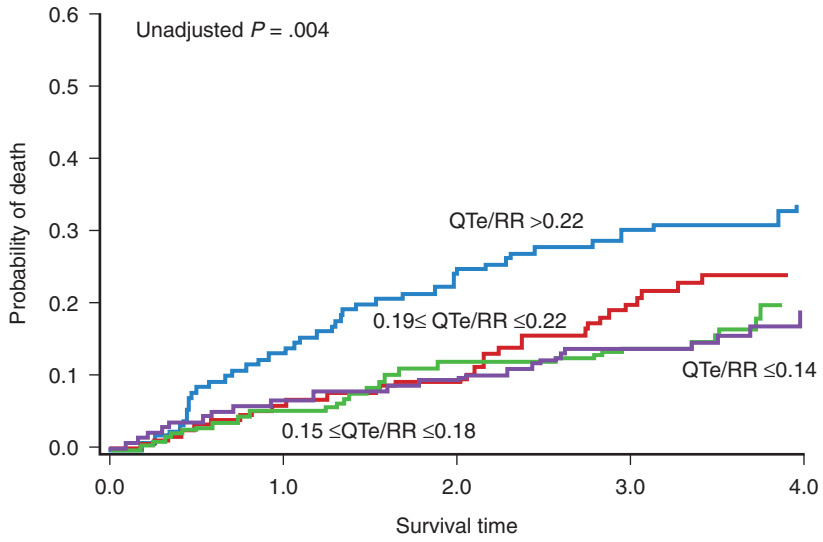


FIGURE 68-8 Event-free curves of total mortality (*left*) and sudden cardiac death (*right*) according to daytime slope of QTe/RR (QTe represents the QT end measured to the end of T wave) using the Kaplan-Meier method. *(From Chevalier P, Burri H, Adeleine P, et al: QT dynamicity and sudden death after myocardial infarction: Results of long term follow up study,* J Cardiovasc Electrophysiol *14:227–233, 2002.)*



Patients at risk

QTe/RR ≤0.14	139	129 (0.06)	125 (0.09)	118 (0.14)	23 (0.20)
0.15≤ QTe/RR ≤0.18	152	143 (0.05)	137 (0.09)	128 (0.14)	25 (0.20)
0.19≤ QTe/RR ≤0.22	118	109 (0.06)	102 (0.12)	91 (0.20)	17 (0.24)
QTe/RR >0.22	133	114 (0.13)	97 (0.25)	90 (0.30)	20 (0.36)

FIGURE 68-9 Probability of death according to the QTe/RR slope value in patients with congestive heart failure. *(From Cygankiewicz I, Zareba W, Vazquez R, et al: Prognostic value of QT/RR slope in predicting mortality in patients with congestive heart failure,* J Cardiovasc Electrophysiol *19:1066–1072, 2008.)*

have significantly increased repolarization variability both in time and amplitude compared with noncarriers.[67] Subsequently, our group developed a time-domain technique to quantify T-wave variability based on a beat-to-beat change in T-wave amplitude without the need to identify the end of the T wave.[68] The variation of mean amplitude inside each of the four windows encompassing the repolarization segment is analyzed across beats, and the level of variability is computed in each window on the basis of the estimated variance of the average amplitude across beats in the selected window. The square root value is reported and expressed in microvolts. The prognostic significance of this method was validated in the second Multicenter Automatic Defibrillator Implantation Trial (MADIT II) cohort.[68] Increased QT variability has been demonstrated in patients with heart failure, dilated

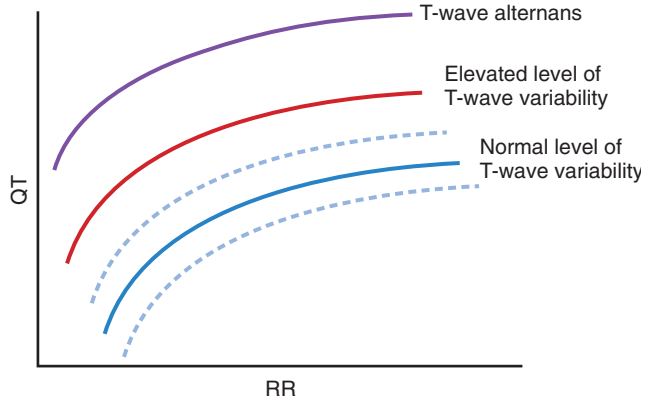


FIGURE 68-10 Conceptual link between electrocardiographic measures of myocardial vulnerability: QT/RR relationship, T-wave (or QT) variability, and T-wave alternans. *(From Zareba W: QT-RR slope: Dynamics of repolarization in the risk stratification,* J Cardiovasc Electrophysiol *14:234–235, 2003.)*

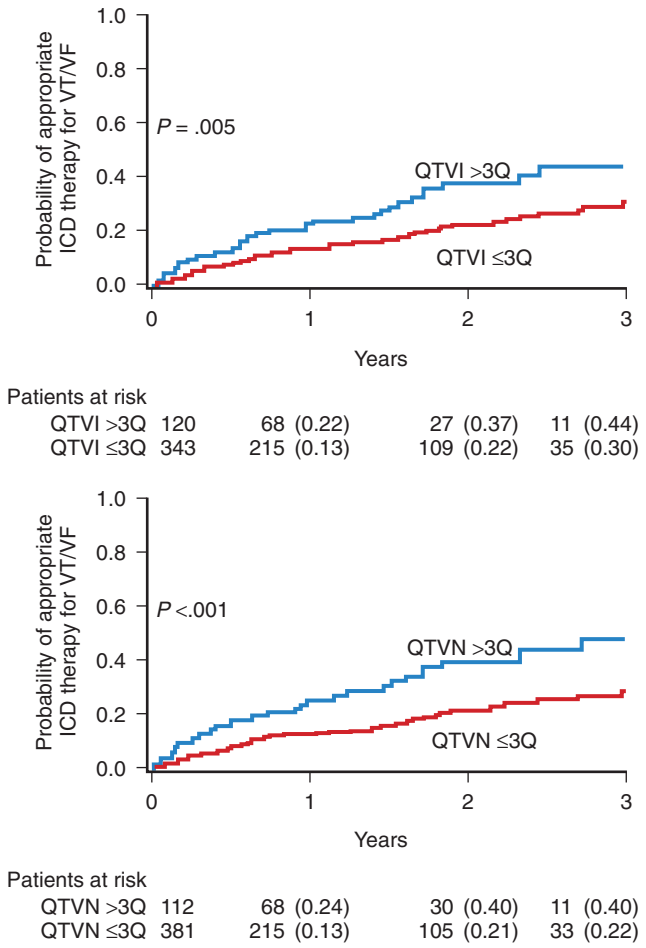


FIGURE 68-11 Cumulative probability of first appropriate defibrillator therapy for ventricular tachycardia or ventricular fibrillation in patients with QT variability (QTVN) in the highest quartile versus the lower three quartiles for QT variability index (*top*) and QTVN (*bottom*). *(From Haigney MC, Zareba W, Gentlesk PJ, et al, and the MADIT II Investigators: QT interval variability and spontaneous ventricular tachycardia or fibrillation in the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II patients,* J Am Coll Cardiol *44:1481–1487, 2004.)*

cardiomyopathy, hypertrophic cardiomyopathy, coronary disease, or LQTS as well as in patients with anxiety, depression, or panic disorders.[69-75] QT variability increases before drug-induced TdP in experimental conditions.[76,77] QT variability was also reported to be influenced by external factors such as air pollution.[78]

Prognostic Value of QT Variability

In 1998, Atiga et al analyzed QTVI in 95 patients undergoing electrophysiological study.[79] The QTVI was higher in patients with structural heart disease than in controls (–0.7 ± 0.7 vs. –1.1 ± 0.5; $P < .05$). It also was higher in patients who died suddenly during a 2-year follow-up period than in other patients with heart disease (0.0 ± 0.6 vs. –0.8 ± 0.5; $P < .05$). After adjustment for significant clinical covariates, increased QTVI (≥0.1) was the only parameter identifying patients at risk of arrhythmic events (odds ratio [OR], 12.5; $P = .004$). The event-free survival rate was 67% in patients with QTVI of 0.1 or higher compared with 85% in those with QTVI less than 0.1. Of note, as a predictor, QTVI outperformed the following parameters tested simultaneously in studied patients: QT dispersion, T-wave alternans during atrial pacing, VT inducibility, signal-averaged ECG, heart rate variability, and ejection fraction.

In the MADIT II substudy by Haigney et al, QT variability was assessed in a 10-minute resting ECG recording.[80] A high-risk QT variability subgroup was defined by identifying patients from the highest QTVI distribution (>75th percentile). This analysis showed an independent prognostic value of QTVI (>–0.52 log units) to predict an increased risk of arrhythmic events in patients with prior MI and severe left ventricular dysfunction (LVEF <30%). The mean QTVI and QTVN (QT variability numerator) were significantly higher in patients requiring an appropriate therapy for VF or VT (–0.80 ± vs. –0.94 ± 0.60; $P = .037$; and 0.39 ± 0.59 vs. 0.25 ± 0.56; $P = .001$ for QTVI and QTVN, respectively) (Figure 68-11). Multivariate Cox analysis showed that both QTVI and QTVN were independent risk factors for VT or VF (HR, 1.80 and 2.18, respectively), after adjustment for significant clinical covariates. Our group developed a new method to estimate T-wave variability that was tested in a group of 275 patients with ICDs from the MADIT II trial. T-wave variability greater than 0.59 μV was an independent risk predictor of ICD therapy for VT or VF.[68] Patients with increased T-wave variability had a 47% probability of appropriate ICD therapy compared with 29% in those with T-wave variability of 59 μV or less during a mean 3-year follow-up.

Piccirillo et al demonstrated that abnormal QT variability can identify a high risk of SCD among 396 asymptomatic patients with congestive heart failure caused by ischemic cardiomyopathy with an LVEF between 35% and 40% and New York Heart Association (NYHA) class I.[81] A QTVI of 80th percentile or greater (–0.47) indicated a high independent risk for SCD (HR, 4.6; CI, 1.5 to 13.4; $P = .006$).

QT/RR slope analyses require precise identification of the end of the T wave, whereas both the above-mentioned methods of QT variability—QT variability or lability developed by Berger et al and T-wave variability developed by Couderc et al—do not

require precise identification of the end of the T wave because they both rely on quantifying QT and T-wave morphology on a beat-to-beat basis.[66,68] At the same time, it must be noted that limitations to quantifying beat-to-beat QT or T-wave variability in recordings with flat T waves, with non-sinus rhythms, or with excessive noise, do exist. T-wave alternans is yet another case of T-wave variability with a 2:1 pattern, but this phenomenon is covered elsewhere in this text. Nevertheless, recent data indicate that QT variability, not T-wave alternans, is associated with post-infarction remodeling of the myocardium predisposing to arrhythmogeneicity, further supporting the concept that QT variability is a natural phenomenon suitable for analysis in dynamic ECGs.[82]

Summary

The growing interest in analysis of the Q-T interval, T-wave morphology, QT dynamics, QT variability, and parameters evaluating repolarization in its static and dynamic form is driven by tremendous progress in our understanding of the genetics and physiology of ion channel function and ion channel abnormalities present in rare genetic disorders (LQTS, Brugada syndrome, short QT syndrome, etc.) and in common disorders (post-infarction myocardium, cardiomyopathies). At the same time, technological progress, including computerized methods, in the previous decade has enabled the acquisition of high-quality signals in everyday ECG or Holter recordings, opening the door for further innovation in this field.

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CHAPTER 69

Ambulatory Electrocardiography: Long-Term Monitors and Event Recorders

Robert W. Rho and Richard L. Page

Palpitations, shortness of breath, fatigue, syncope, and other intermittent arrhythmic events pose a diagnostic challenge to clinicians. The etiology of such events may remain elusive and result in significant patient anxiety, morbidity, and, in some cases, even death. Ambulatory electrocardiogram (ECG) monitoring may be an important tool in achieving a diagnosis. In addition to providing a rhythm diagnosis, ambulatory ECG monitoring may be used to quantify and characterize the frequency and duration of the arrhythmia and to evaluate the efficacy of therapies directed at the arrhythmia. Since the initial description of the first continuous ambulatory ECG monitor by Neil Holter, significant advances in ambulatory ECG technology and its role in clinical practice have been made. This chapter will review the types of ambulatory monitors available and discuss the efficacy and limitations of ambulatory ECG monitors in common clinical settings.

Types of Ambulatory Electrocardiography Monitors

Ambulatory ECG monitors can be classified as continuous short-term monitors, event recorders (looping and nonlooping), outpatient telemetry, and implantable loop recorders. The following is a description of each type of ambulatory ECG monitors.

Continuous Short-Term Monitors

The Holter monitor, invented by Neil Holter in 1941, is the prototype for continuous ambulatory ECG monitors. Modern continuous monitors provide three to 12 high-quality surface ECGs with full disclosure for a period of 24 to 48 hours. These are battery-operated, self-contained devices that comprise electrodes and leads connected to a compact, lightweight box that can be worn on the patient's belt or placed in a pouch. These devices are capable of storing high-quality ECG data on a cassette tape, which can then be turned in and analyzed at a workstation. More recently, continuous monitors store high-fidelity digital ECGs on a flash card or a PC card. Time stamps correlating patient symptoms to the ECG, extended battery and memory capacity (up to 96 hours), ability to transmit digital recordings over the Internet, and software packages facilitating "advanced" digital ECG analyses are also available. This type of monitor is ideal for patients who have symptoms that occur frequently (at least once per day) but has limited application in situations where patients experience rare and sporadic symptoms. An example of a Holter monitor is shown in Figure 69-1.

Event Monitors

Event monitors are ambulatory ECG monitors that are designed to be worn or carried for up to 30 days. Two types of event monitors are available: (1) *Loop recorders* (before symptom onset) constantly store and dump ECG data for 30 seconds to 4.5 minutes (depending on the manufacturer); when activated by the patient, ECG data from this buffer are stored for analysis, along with an interval of ECG that is recorded after activation. This type of monitor requires that the patient wear electrodes and leads constantly. (2) *Nonlooping event recorders* (after symptom onset) do not require that the patient wear electrodes continuously. These are small recording devices that are kept by the patient nearby (pocket or purse), and when the patient has symptoms, the electrodes on the device are placed on the chest, and the ECG is then recorded. These devices typically have 5 to 10 minutes of memory, but more advanced devices may have up to 30 minutes of memory capacity. Event recorders are ideal monitors for identifying a symptom/rhythm correlation for intermittent symptoms that are long enough to allow time for recording. The limitations of event recorders are that patient-triggered recorders cannot detect asymptomatic arrhythmias. Looping event recorders with automatic triggers may allow the detection of very slow or very rapid arrhythmias but may "miss" some arrhythmias such as rate-controlled atrial fibrillation (AF) or supraventricular tachycardia (SVT) that are slower than the detection rate of the device. The primary limitations of looping event recorders are patient discomfort, poor patient compliance, and premature termination of monitoring (since patients often complain about having to wear electrodes and leads for extended periods). The limitations of nonlooping event recorders include their inability to detect short-lived arrhythmias or event initiation and occasional poor ECG quality. Examples of a looping event recorder and a nonlooping event recorder are shown in Figures 69-2 and 69-3, respectively.

Outpatient Telemetry

Continuous ambulatory monitors that provide full-disclosure ECGs for up to 21 to 31 days are available (Mobile Cardiac Outpatient Telemetry Cardionet, Philadelphia, PA; and External Cardiac Ambulatory Telemetry Mednet, Ewing, NJ). Continuous ECGs from three leads are recorded and transmitted by a cell phone to a central headquarter, where ECGs are stored and trained technicians evaluate each rhythm. The devices have an algorithm-based auto-triggering feature that, when activated, transmits ECGs to a monitoring station, where they are evaluated

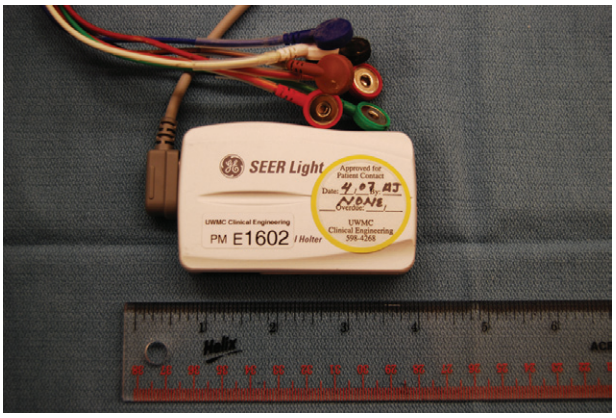

FIGURE 69-1 An example of a Holter monitor.

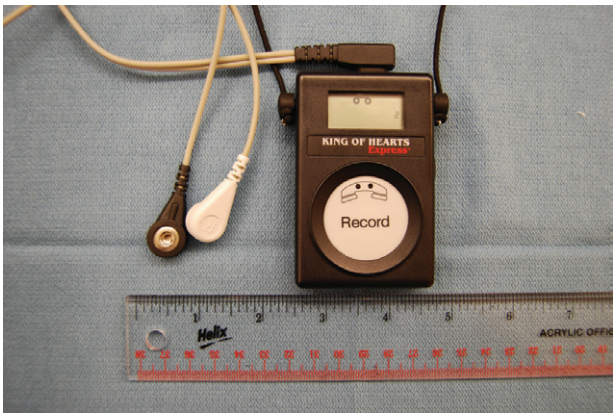

FIGURE 69-3 An example of a looping event recorder. In order to store electrograms preceding the event, the patient wears electrodes continuously during the monitoring period.

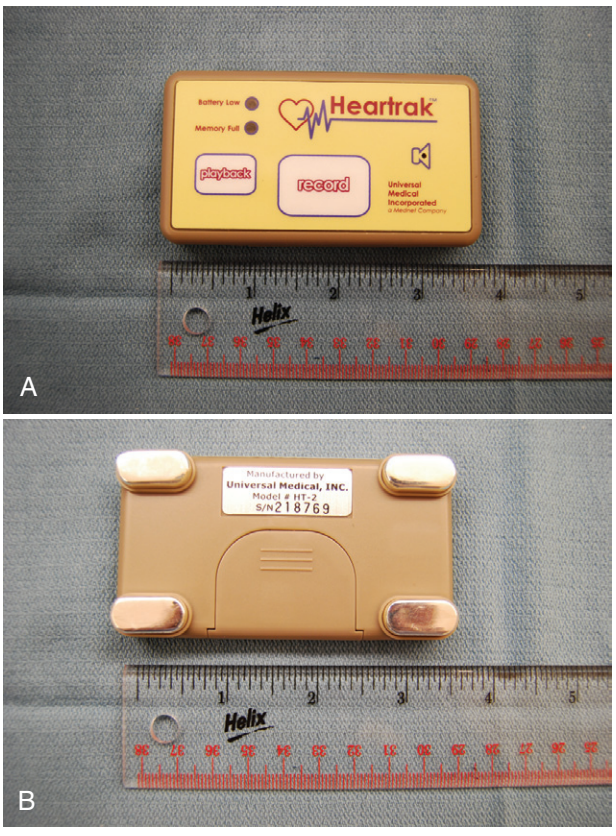

FIGURE 69-2 An example of an event recorder. This device is carried with the patient and applied to the chest wall during symptoms. **A,** Front of the device. **B,** Back of the device with electrodes applied to the chest.

by trained technicians; physicians are then notified about any significant arrhythmias. Auto-triggering algorithms within the monitoring system include low-rate and high-rate triggering as well as triggering for AF. Because the monitor records continuously, AF burden can be reported, in addition to significant bradyarrhythmias and tachyarrhythmias. The main limitations of the device are patient intolerance to wearing the device and irritation from the electrodes.

Implantable Loop Recorders

Implantable loop recorders (ILRs) are small, lightweight devices that are placed in the subcutaneous space in a minor procedure and provide high-quality ECGs. The earlier-generation ILRs were equipped with patient-activated storage only (Medtronic Reveal; Medtronic, Inc., Minneapolis, MN). Subsequent models have implemented programmable auto-triggering based on high and low heart rate thresholds (Reveal Plus [Medtronic]; Confirm [St Jude Medical, St. Paul, MN]; Sleuth [Transoma Medical, Arden Hills, MN]). The most-recent-generation ILRs are equipped with AF detection algorithms (Reveal XT, AF [Medtronic]). These devices provide 1 to 3 years of monitoring with 48 to 630 minutes of storage and can be patient activated or automatically activated by programming a low rate and a high rate for detection. In the case of patient-activated recordings, these devices store 60 to 240 seconds of ECGs before (usually 60 seconds of ECGs) and after the patient has triggered the device. The ECGs corresponding to these events can be reviewed noninvasively. Some devices are equipped with remote recording capabilities, by which ECGs from the recorder can be sent transtelephonically to a receiving station (Confirm) or can be manually or automatically transmitted from a home-based station to a secure Web site (Reveal Plus and Carelink [Medtronic]) or to a monitoring station manned by trained ECG technicians (Sleuth). These devices are ideal for rare, but significant, events that are worrisome in the case of a cardiac arrhythmia such as syncope. The limitations of these monitors include failure of the patient to activate the device during symptoms, availability of only one lead for analysis, discomfort associated with the implantation and removal of the device, a small risk of infection, and minor cosmetic alteration of the chest wall. An example of an ILR is shown in Figure 69-4.

Implantable Pacemakers and Implantable Defibrillators

Implantable defibrillators and pacemakers are placed for therapeutic, rather than diagnostic, reasons, but they do have

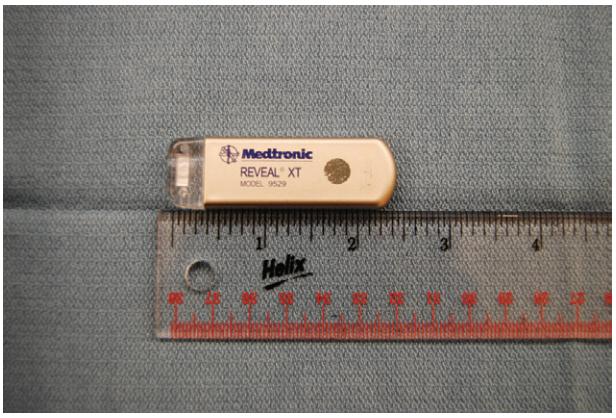

FIGURE 69-4 An example of an implantable loop recorder. This device is implanted subcutaneously, usually in the anterior chest wall.

sophisticated diagnostic capabilities that allow for storage of intracardiac ECGs during tachyarrhythmias. Diagnostic information available from implantable devices includes rate histograms, atrial high-rate episodes, ventricular high-rate episodes, and stored intracardiac ECGs (depending on the model and vendor of the device). The accuracy of the information available in the device depends on appropriate sensing parameters and programmed detection parameters. Diagnostic information about arrhythmic events that are available in cardiac pacemakers and implantable defibrillators is discussed in Chapters 22 and 92 and therefore will not be covered in this chapter.

Diagnostic Efficacy of Ambulatory Electrocardiography Monitors

The diagnostic efficacy of ambulatory ECG monitors depends on the clinical scenario in which the monitor is used, the risk profile of the patient being studied, the frequency of the event, and the type of monitor used. The following is a discussion on the efficacy of various types of ambulatory ECG monitoring for the evaluation of palpitations and syncope.

Palpitations

Palpitations, defined here as an awareness of one's heart beat, are a symptom commonly encountered in clinical practice. Although possibly a manifestation of arrhythmias, palpitations are often caused by noncardiac factors. When arrhythmias are the cause of palpitations, the most common rhythms recorded during symptoms are premature atrial contractions, premature ventricular contractions, SVTs, and AF. In a prospective cohort study, 190 patients who presented at an academic medical center with palpitations were evaluated and followed up for 1 year. A diagnosis of the etiology of their palpitations was established in 84%. Among these patients, 40% experienced palpitations because of cardiac arrhythmias and 33% because of anxiety and panic disorder, and the remaining patients had nonarrhythmic causes.[1] Patients with palpitations associated with structural heart disease (including complex congenital heart disease), presyncope, or syncope are at higher risk of having a cardiac arrhythmia, which may even be life threatening.

Interpretation of studies evaluating the diagnostic yield of ambulatory ECG monitors in the workup of palpitations requires carefully assessing whether the monitor provided a symptom–rhythm correlation. While it does not provide a diagnosis of an arrhythmia, the finding of sinus rhythm or sinus tachycardia during palpitations is still important in diagnosis, as it provides useful clinical information and can be reassuring to the patient. The evaluation of palpitations is difficult because of several inherent limitations: (1) Noncardiac factors are the cause of palpitations in a significant number of patients; (2) arrhythmias in some patients may be associated with palpitations, while some others may be asymptomatic; and (3) for a given patient, the palpitations may arise from multiple arrhythmic causes as well as nonarrhythmic causes (the patient may not be able to discern the differences between the causes).

A limitation of some studies evaluating the diagnostic efficacy of continuous 24- to 48-hour monitors for the workup of palpitations is that some of these studies report the number of times these monitors provide an arrhythmia diagnosis but not the number of times the palpitations are associated with sinus rhythm. This underestimates the diagnostic yield of the 24-hour Holter monitor because multiple recordings of sinus rhythm associated with palpitations may help rule out cardiac arrhythmia as the cause of the palpitations (Tables 69-1, 69-2, and 69-3).

Diagnostic Yield of 24-Hour Continuous Electrocardiography Monitors

In general, the likelihood of a 24-hour Holter monitor documenting arrhythmias in patients with intermittent palpitations is low. In a large retrospective study of consecutive patients who received Holter monitors for symptoms of palpitations, the 24-hour Holter monitor demonstrated sinus rhythm in 2247 of 2688 Holter recordings (83.6%). Two hundred seventy-six patients had a second Holter monitoring performed, and 210 of 276 were negative (76.1%). Among patients with arrhythmias corresponding to palpitations detected on 24-hour Holter monitoring, 4.4% had frequent ectopic beats (>15 per 10,000 beats), 6.6% had AF, 2.8% had narrow-complex tachycardia, and 2.6% had ventricular tachycardia (VT). The frequency of cardiac arrhythmias detected by 24-hour Holter monitoring is especially low among patients younger than 50 years, in whom 93.1% of Holter monitors demonstrated no arrhythmias. Cardiac arrhythmias were observed in 29% of patients older than 70 years, with 15% of recordings demonstrating AF.[2] This study provided information about the type of arrhythmias recorded during continuous 24-hour monitoring among patients with palpitations. The study did not provide insights into the diagnostic yield of the Holter monitor (the ability to provide a symptom/rhythm correlation).

Diagnostic Yield of Continuous Monitors and Event Recorders

In a randomized cross-over study of 43 patients with intermittent palpitations, patients were randomized to a 48-hour Holter monitor versus a 3-month (nonlooping) event recorder and then crossed over to the other monitor. The 48-hour Holter monitor recorded ECGs during symptoms in 15 (35%) of 43, and none of these recordings demonstrated an arrhythmia. The event recorder was able to record ECGs during symptoms in 29 (67%) of 43 and diagnosed an arrhythmia in 8 (28%) of 29. Among the arrhythmias recorded on the event recorder, SVT, premature ventricular beats,

Table 69-1 Palpitations: Diagnostic Yield of Holter Monitors

AUTHOR	N	STUDY DESIGN	RECORDING DEVICE	DURATION	DX YIELD	ARRHYTHMIAS DETECTED*
Sulfi[2]	2688	Retrospective	Holter monitor	24 hours	NA	16.4%
Kinlay[3]	43	Randomized cross-over	Holter (n = 24) Event recorder (n = 19)	48 hours 3 months	35% 67%	0% 19%
Scalvini[4]	310	Randomized	Holter (n = 155) Event recorder (n = 155)	24 hours 7 days	48% 77%	34% 52%

Dx, *Diagnostic.*
**Percentage of total patients monitored.*

Table 69-2 Palpitations: Diagnostic Yield of Event Recorders (Nonlooping)

AUTHOR	N	STUDY DESIGN	RECORDING DEVICE	DURATION	DX YIELD	ARRHYTHMIAS DETECTED*
Rindqvist[6]	89	Retrospective	Event recorder	NA	65%	54%
Wu[7]	396	Retrospective	Event recorder	NA	66%	33%
Barrionuevo[8]	227	Prospective	Event recorder	15 days	92.5%	55%

Dx, *Diagnostic.*
**Percentage of total patients monitored.*

Table 69-3 Palpitations: Diagnostic Yield of Event Recorders (Looping)

AUTHOR	N	STUDY DESIGN	RECORDING DEVICE	DURATION	DX YIELD	ARRHYTHMIAS DETECTED*
Zimetbaum[9]	105	Retrospective	Loop recorder	2 weeks	83%	28%
Fogel[10]	122	Prospective	Loop recorder	4 weeks	66%	42%

Dx, *Diagnostic.*
**Percentage of total patients monitored.*

and AF or atrial flutter accounted for 18%, 12%, and 6% of arrhythmias, respectively.[3] Scalvini et al randomized 310 patients with palpitations to initial monitoring with a 24-hour Holter monitor (n = 155) or a looping event recorder for 7 days (n = 155). The diagnostic yield of the Holter monitor was 48% (34% of patients had arrhythmias detected) and 77% for the event recorder (52% of patients had arrhythmias detected, $P < .01$).[4] In a review of studies evaluating the diagnostic yield of ambulatory ECG monitors for palpitations, Zimetbaum et al reported a diagnostic yield (providing a symptom/rhythm correlation) of 66% to 83% for event recorders and 33% to 35% for a Holter monitor.[5]

In noncomparison studies, nonlooping event recorders have demonstrated a diagnostic yield for palpitations of up to 66% with arrhythmias detected in 33% to 54% of patients.[6-8] Studies of looping event recorders have demonstrated a diagnostic yield of 66% to 83% with arrhythmias detected in 28% to 42% of patients.[9,10]

Olsen et al evaluated the role of mobile cardiac outpatient telemetry (MCOT, Cardionet, Philadelphia, PA) in the evaluation of palpitations, syncope, and presyncope. In 18 patients in this study, MCOT was the first monitoring system applied for the evaluation of palpitations. The diagnostic yield was 73% (14 of 18) with all 14 patients recording arrhythmias. In another 58 patients, a previous rhythm diagnosis associated with palpitations was already established with another recording system prior to MCOT monitoring. During monitoring, 34 (59%) of 58 of patients had a symptom/rhythm correlation, with 27 (79%) of 34 demonstrating an arrhythmia associated with palpitations.[11] These data demonstrate the limitations in evaluating patients for palpitations. Only 59% of patients with a previously established "diagnosis" of an arrhythmia had recurrent palpitations during a long-term monitoring period, and an arrhythmia different from the original "diagnosis" was responsible for palpitations in many patients. These observations should be considered when making clinical decisions about arrhythmias detected by any ambulatory monitor and in the interpretation of studies evaluating the diagnostic yield of these monitors for palpitations.

Optimal Duration of Monitoring for Palpitations

Data on the optimal duration of monitoring in providing a symptom/rhythm correlation demonstrate that 2 weeks of

monitoring yields the majority of diagnoses. In a study by Reiffel et al, the weekly yield of an event recorder was evaluated retrospectively in 5052 patients. During the first 2 weeks of monitoring, 87% of patients had transmitted an ECG recording during symptoms. The additional diagnostic yield during the following 2 weeks (weeks 2 to 4) was 9%.[12] Zimetbaum et al demonstrated that 83% of patients had a diagnostic transmission from their event recorder within 2 weeks of monitoring and that the diagnostic yield was low beyond this monitoring period.[13] On the basis of this evidence, a monitoring period of at least 2 weeks and up to 4 weeks is considered to provide a symptom/rhythm correlation in the majority of cases of diagnosis likely to be achieved by an event recorder.

To summarize this section, studies of the etiology of palpitations demonstrate that nonarrhythmic causes of palpitations are common. ECG recordings during palpitations may demonstrate different arrhythmias during different episodes of palpitations within the same patient. With these data in mind, event recorders with patient-triggered events provide better diagnostic yield than does a 24- to 48-hour Holter monitor and will provide a diagnosis in up to 87% of patients within the first 2 weeks of monitoring (Figure 69-5). The continuous 24-hour monitor is associated with a relatively low diagnostic yield (approximately 35%) among patients with intermittent palpitations, and the second 24-hour recording is of especially low yield. ILRs and mobile cardiac telemetry are not indicated in most cases of intermittent palpitations, as they are not likely to provide additional diagnostic yield to external event recorders.

Syncope

Syncope is a common and complex clinical situation with multiple etiologies. Syncope is responsible for 3% of emergency room visits and for 1% of all hospital admissions.[14] Common causes of syncope include reflex-mediated syncope (vasovagal syncope, cough syncope, and micturition syncope), carotid sinus hypersensitivity, orthostatic hypotension, transient ischemic attacks, seizures, aortic stenosis, pulmonary embolism, and cardiac arrhythmias. When syncope is associated with structural heart disease or an ion channelopathy, a higher risk of sudden cardiac death from an arrhythmia is present.[15] Some specific clinical situations that are associated with a high risk of sudden death when accompanied by a history of syncope include long QT syndrome (LQTS), Brugada syndrome, arrhythmogenic right ventricular cardiomyopathy, familial cardiomyopathy, hypertrophic cardiomyopathy, repaired tetralogy of Fallot, family history of sudden death, and severe left ventricular dysfunction. Among patients with structurally normal hearts, however, in most cases, syncope (excluding patients with ion channelopathies) is caused by nonarrhythmic factors, and the majority of these are reflex-mediated (vasovagal) syncope.

Establishing the etiology for syncope can be challenging. A detailed history, physical examination, orthostatic vital signs, and a 12-lead ECG are important for patients with syncope. If all of these are performed thoughtfully, this should lead to a diagnosis in 50% of patients presenting for the evaluation of syncope.[16] In an unselected population of patients with syncope, many remain undiagnosed despite thorough evaluation. Patients with cardiac syncope are a high-risk group, with a 5-year mortality rate of up to 51%.[15] Studies evaluating the diagnostic yield of ambulatory ECG monitors vary widely, largely because of differences in the patient population, such as number of syncopal episodes, age of the patient population studied, presence of structural heart disease, and diagnostic evaluation performed before placement of the monitor.

In a study evaluating the incidence and prognosis of syncope in the Framingham study population, 822 of 7814 patients reported an episode of syncope and had an average of 17 years of follow-up. The etiology of syncope was vasovagal in 29.9%, cardiac in 9.5%, orthostatic in 9.4%, neurologic (stroke, transient ischemic attack, or seizure disorder) in 9%, medication related in 6.8%, and unknown in 36.6%. During follow-up, 78.4% had only incidental episodes of syncope, 7.6% had 1 recurrence, 3.3% had 2 recurrences and 0.9% had 3 or more recurrences. Patients with syncope from a cardiac cause had a higher mortality rate compared with patients without a history of syncope (hazard ratio, 2.01; confidence interval, 1.48 to 2.73). In contrast, patients with vasovagal syncope had a good prognosis.[17]

Because of the unpredictable nature and the infrequency of syncope recurrence, the ability of the ambulatory ECG recording to provide a symptom/rhythm correlation is proportional to the duration of the monitoring period and the pretest suspicion for cardiac arrhythmias (structural heart disease, ion channelopathy, congenital heart disease, etc.). In the study by Linzer et al, 78.4% of patients (unselected population) had only one episode of syncope.[16] In general, the most useful monitoring strategy in patients with infrequent episodes of syncope is an ILR and, to a significantly lesser degree, a looping event recorder. The 24-hour Holter monitor and the nonlooping event recorder are unlikely to provide a diagnosis in this setting.

Continuous Electrocardiography Monitors for Syncope

Studies of the efficacy of the 24-hour Holter monitor for the evaluation of syncope have demonstrated that the likelihood of establishing a symptom/rhythm correlation and demonstrating an arrhythmic cause of syncope with this monitoring strategy is low. In a review by DiMarco et al, a symptom/rhythm correlation among patients with syncope could only be established in 22% of patients on a Holter Monitor.[18] Sarasin et al evaluated the diagnostic yield of Holter monitors among 140 patients with a high likelihood of arrhythmias. Overall, the diagnostic yield for the 24-hour Holter monitor was 11.4% (16 of 140 patients had syncope [n = 7] or presyncope [n = 15] during the 24-hour monitoring period). Nine of the 16 patients who had symptoms during the monitoring period had a serious arrhythmia recorded.[19] Sivakumaran et al evaluated 100 patients with syncope (n = 21), presyncope (n = 29), or both (n = 50) by first randomizing them to either a 24-hour Holter monitor or to a looping event recorder. The diagnostic yield for patients randomized to a loop recorder first was 63%, with 8% of these patients demonstrating an arrhythmia as a cause of their symptoms. For patients randomized to a 24-hour Holter monitor, the diagnostic yield was 24% with no abnormal arrhythmias recorded as a cause of their syncope. When the initial monitoring strategy did not yield a diagnosis, cross-over to the other monitor was performed in some. Four patients were crossed over to the 24-hour Holter monitor after nondiagnostic loop recording, and 29 patients were crossed over to a loop recorder after nondiagnostic Holter monitoring. The overall diagnostic yield for the Holter monitor (n = 56) and the loop recorder (n = 78) was 22% and 56%, respectively.[20] Taken together with the review by Dimarco et al, these studies and two other studies established the low diagnostic yield (15% to 24%) of

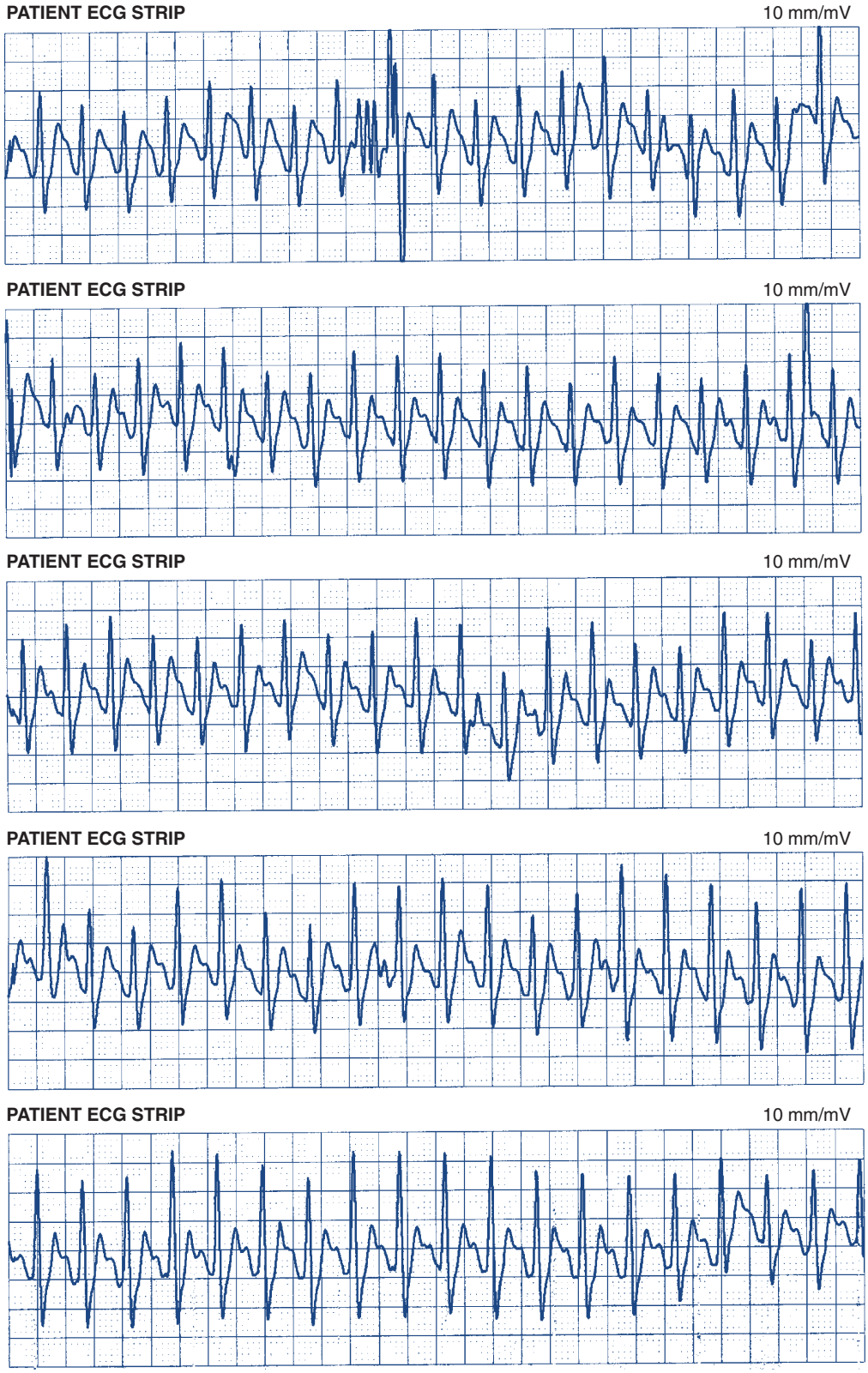

FIGURE 69-5 A patient with palpitations who was provided with a nonlooping event recorder. A recording of her ambulatory electrocardiogram (*ECG*) during symptoms provided a diagnosis of supraventricular tachycardia. She was referred to Cardiac Electrophysiology for further management.

Table 69-4 Syncope: Diagnostic Yield of Holter Monitors

AUTHOR	N	PRIOR WORKUP	STRUCTURAL HEART DISEASE	STUDY DESIGN	MONITOR	DURATION	DX YIELD
Sarasin[19]	140	EPS (27%)	34%	Prospective	Holter monitor	24 hours	12%
Sivakumaran[20]	100*	Orthostatic (100%)	32%	Prospective, randomized, cross-over	Holter monitor (n = 51)	48 hours	24%
					Loop recorder (n = 49)	1 month	63%
					Holter monitor (n = 55)	48 hours	22%
					Loop recorder (n = 78)	1 month	56%
Croci[21]	308	NA	†	Prospective	Holter monitor	24 hours	16%
Farwell[22]	195	NA	NA	Prospective	Holter monitor	24 hours	18.4%

Dx, *Diagnostic;* EPS, *electrophysiological study.*
**Included patients with presyncope (number of patients with syncope/presyncope/both).*
†A total of 158 of 308 patients had "known or certain structural heart disease or an abnormal 12-lead electrocardiogram."

Holter monitors in providing a diagnosis among patients with unexplained syncope (Table 69-4).[17,18,21,22] The primary reason for the poor performance of the Holter monitors is that, in general, it is unlikely that a syncopal episode will recur during the relatively short monitoring period. For this reason, a long-term monitoring strategy is more likely to provide a diagnosis among patients who have a high clinical probability of cardiac arrhythmias.

Event Recorders

Nonlooping event recorders are unlikely to be useful in the evaluation of syncope because the patient would not be conscious to self-record the event. However, a looping event recorder allows patients to activate the monitor on regaining consciousness. Furthermore, looping event recorders with auto-triggering would automatically store bradyarrythmias or tachyarrhythmias in the event that the patient is not able to trigger the monitor himself or herself (Figure 69-6). Although looping event recorders can provide much longer monitoring periods than a 24-hour Holter monitor can, studies of loop recorders have been disappointing. Inherent limitations diminish the diagnostic yield of this monitoring strategy. In many patients, a 30-day monitoring period may not be long enough to capture a recurrent event. Another significant limitation is poor patient tolerance and compliance (failure to activate the loop recorder or failure to wear the device consistently).

Linzer et al evaluated 57 patients with syncope who had a negative Holter monitor recording and compared them with the recording from a looping event recorder.[23] After a monitoring period of 1 month, 14 (25%) of 57 patients had a definitive diagnosis for the cause of syncope. Four (28%) of 14 patients had a primary cardiac arrhythmia diagnosed as the cause of their syncope, including VT (1 patient), high-grade atrioventricular (AV) block (2 patients), and SVT (1 patient). Neurally mediated syncope was observed in 3 patients, and normal cardiac rhythm was recorded in 7 patients. Schuchert et al evaluated 24 patients (50 ± 14 years) with a history of 3 ± 4 recurrent syncopal events over the last 6 months, no structural heart disease, and a negative tilt-table test with a looping event recorder. The average monitoring period was 50 ± 22 days. During the monitoring period, 26 device activations occurred in 14 patients, but only 1 of these was caused by syncope (and this was associated with sinus tachycardia recorded on the monitor). Overall, 8 patients had 90 episodes (1 patient had 80 episodes) of recurrent syncope with 2 episodes prior to monitoring, 2 during monitoring, and 4 after monitoring (15 ± 10 months after termination of monitoring). Of the 2 patients who had syncope during monitoring, 1 patient inadvertently erased the stored ECGs before transmitting. Overall, the diagnostic yield of the event recorder was only 1 (4%) of 24 in this highly selected population of patients with a structurally normal heart and a history of multiple episodes of syncope within the previous 6 months.[24]

In general, studies evaluating the diagnostic efficacy of looping event recorders reported that these devices provided a symptom/rhythm correlation in 4% to 24% of patients presenting with syncope of unknown cause (Table 69-5).[23-26] A major limitation of the looping event recorder is related to patient compliance. Up to 25% of patients may fail to activate the loop recorder while experiencing symptoms during the monitoring period, and early termination of monitoring may occur because of patient intolerance or adverse skin reactions to the electrodes.[20,23,24]

Implantable Loop Recorders

Because of its long-term monitoring capabilities and its improved tolerability (no external electrodes, wires, and boxes), the ILR has emerged as an important tool for establishing or excluding an arrhythmic cause for syncope. Table 69-6 provides data on some recent studies evaluating the efficacy of ILRs in diagnosing or rejecting arrhythmias as a cause of syncope.[27-33] In the Randomized Assessment of Syncope Trial (RAST), Krahn et al randomized patients referred to their arrhythmia center to "conventional" testing versus an ILR with 1-year follow-up. Patients with a left ventricular ejection fraction (LVEF) of less than 35%, those with a history consistent with vasovagal syncope, and those unlikely to survive 1 year were excluded. The etiology of syncope was diagnosed in 52% of patients randomized to an ILR versus 20% in the "conventional" testing arm ($P < .012$).[27] In an observational study of "high-risk" patients (high risk defined in this study as syncopal episodes being recurrent, unpredictable, or frequent, or occurring during high-risk activities), ILRs were implanted in 103 patients,

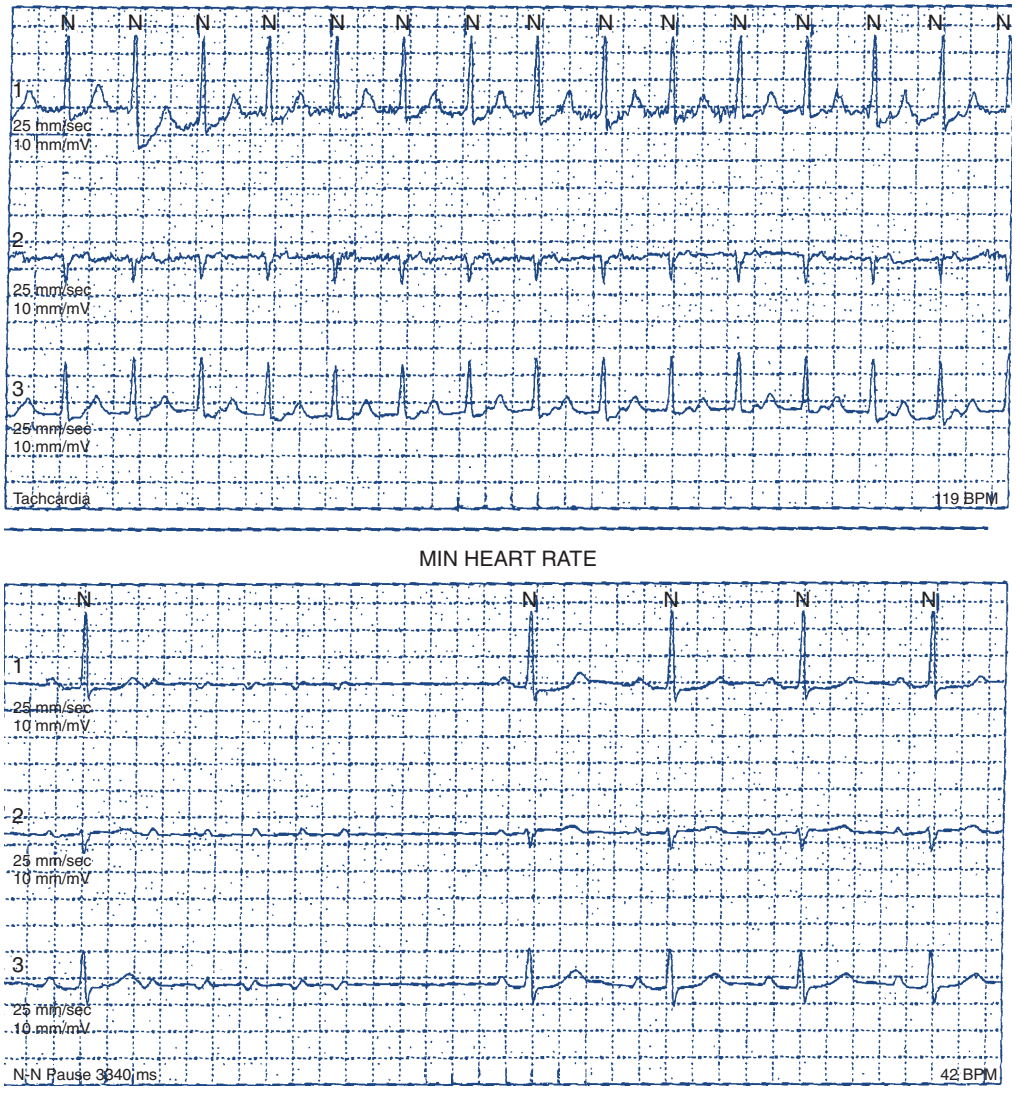

FIGURE 69-6 A 68-year-old man with a history of syncope and a structurally normal heart. A looping event recorder is triggered by the patient during an episode of presyncope. The recording demonstrates atrial tachycardia with high-grade atrioventricular block.

Table 69-5 Syncope: Diagnostic Yield of Loop Recorders

AUTHOR	N	PRIOR WORKUP*	STRUCTURAL HEART DISEASE	STUDY DESIGN	MONITOR	DURATION	DX YIELD
Linzer[23]	57	Holter (100%)	NA	Prospective	Loop recorder	1 month	25%
Schuchert[24]	24	Tilt-table (100%)	0%	Prospective	Loop recorder	50 ± 22 days	8.3% (2/24)
Fogel et al[25]	62†	EPS (29%)‡ Tilt-table (16%)§	42%	Prospective	Loop recorder	NA	32%
Zimetbaum[26]	172	NA	36%	Retrospective	Loop recorder	20 ± 10 days	6%

Dx, *Diagnostic.*
**Workup performed before enrollment (% of patients in whom the study was performed).*
†Includes patients with syncope and presyncope.
‡Electrophysiological study (EPS) was negative in 18 of 26 patients with structural heart disease.
§Tilt-table testing was negative in 10 of 36 of patients with no structural heart disease.

Table 69-6 Syncope and Presyncope: Diagnostic Yield of Implantable Loop Recorders

AUTHOR	N	PRIOR WORKUP	STRUCTURAL HEART DISEASE (%)	STUDY DESIGN	MONITOR	DURATION	DX YIELD	ARRHYTHMIAS*
Entem[29]	144	Holter (100%) EPS (62%) Tilt-table (32%)	32%	Retrospective	ILR	346 ± 160 days	36.5%	64.5%
Inamdar[30]	100	Holter (100%) EPS (100%) Tilt-table (100%)	25%	Retrospective	ILR	9 ± 8 months	45%	84%
Krahn[31]	16	Holter (100%) EPS (100%) Tilt-table (100%)	37%	Prospective	ILR	4.4 ± 4.2 months	94%	56%
Krahn[27]	60	Holter (100%)	38%	Randomized	ILR Conventional	NA	52% 20%	40% 8%
Farwell[28]	103	Holter (100%)	0%	Randomized	ILR Conventional	17 months	43% 6%	NA NA
Mason[32]	43	EPS (39%) Tilt-table (74%)	67%	Retrospective	ILR	11.1 ± 10.4 months	60%	50%
Brignole[33]	103	"Conventional" Workup	38%	Prospective	ILR	14 ± 10 months	50%	81%

ILR, *Implantable loop recorder;* EPS, *electrophysiological study.*
**Includes the percentage of patients with symptoms who are found to have an arrhythmia on the ILR.*

who were followed up for 14 ± 10 months. Overall, a symptom/rhythm correlation was demonstrated in 52 patients (50%). Four additional patients had recurrent syncope during follow-up, but they were not able to activate the recorder. Among patients who were older than 65 years (n = 78), 56% had a symptom/rhythm correlation provided by the ILR, and 42 of 44 of these episodes were caused by an arrhythmia. Among patients younger than 65 years (n = 25), 32% had a symptom/rhythm correlation provided by the ILR, and 20% of the patients were found to have an arrhythmia during their syncopal event. Arrhythmias recorded were AV block in 23%, sinus node dysfunction in 14%, atrial arrhythmias in 4%, and ventricular tachycardia or ventricular fibrillation (VT/VF) in 3% of patients older than 65 years. Among patients younger than 65 years, recorded arrhythmias were AV block in 12% and sinus node dysfunction in 8%. No atrial or ventricular tachyarrhythmias were recorded among patients less than 65 years. During follow-up, 4 patients (all >65 years) died during monitoring; in 1 patient, recording was unavailable because of the occurrence of sudden death, and the others had noncardiac causes. Five syncope-related traumatic episodes occurred in 3 patients during follow-up.[28]

Firm evidence supports the early use of the ILR in selected higher-risk patients who have unexplained syncope after a conventional workup fails to determine the cause and who have recurrent syncope. Studies demonstrating a diagnostic yield of 36% to 94% for ILRs have included patients with negative EPS and negative tilt-table test results and a significant number of patients with structural heart disease. A more general approach to using an ILR will likely have a lower yield because of the lower incidence of syncope from arrhythmic causes in an unselected population of patients with syncope.

Outpatient Telemetry

Outpatient telemetry is a new monitoring technology that provides continuous, full-disclosure ECGs with patient and auto-triggering algorithms, which can be worn for up to 21 to 31 days. This technology also provides continuous surveillance monitoring (by trained ECG technicians, 24 hours per day) of ECGs that are transmitted daily and instantly by a hand-held cellular device when events are triggered. The unique features of this device, as compared with current looping event recorders, are as follows: (1) Outpatient telemetry provides full disclosure of ECGs during the monitoring period, (2) it can provide information about the AF burden, and (3) ECGs can be evaluated in real time and physicians notified about significant arrhythmias. Retrospective studies evaluating the ability of continuous outpatient telemetry to provide a symptom/rhythm correlation among patients with a variety of indications have established it as a useful tool.[29] However, published studies on the ability of outpatient telemetry to significantly improve the diagnostic yield, as compared with auto-triggered looping event recorders, are lacking. In a retrospective study, Olson et al evaluated the diagnostic efficacy of MCOT in 122 consecutive patients in a variety of clinical settings (palpitations, presyncope, syncope, drug efficacy monitoring).[10] Ten (59%) of the 17 patients who were evaluated for presyncope or syncope in this study had a diagnosis made with MCOT. In a randomized, multi-center study, 305 patients were randomized to a looping event monitor versus MCOT (Cardionet, Philadelphia, PA). Patients with syncope, presyncope, or severe palpitations occurring less frequently than 1 per 24 hours and a nondiagnostic Holter monitor recording were included in this study. Patients with severe heart failure symptoms, myocardial infarction within

3 months, unstable angina, history of sustained VT or VF, and an ejection fraction of less than 35% were excluded. The primary endpoint of the study was confirmation or exclusion of an arrhythmic cause for the symptoms. Of the 305 patients randomized, results from 266 patients were analyzed (MCOT [n = 134], loop recorder [n = 132]). The overall diagnostic yield reported in the study was 88% for patients monitored by MCOT and 75% for patients monitored by a loop recorder (P = .008). In the subset of patients with syncope (n = 43) and presyncope (n = 91), the diagnostic yield for MCOT was 89% versus 69% for the loop recorder (P = .008).[34] The diagnostic yield was significantly better than that of a loop recorder despite the fact that the reported diagnostic yield of the loop recorder was higher in this study than reported by others. A potential explanation for this is that patients who could not tolerate the MCOT monitor or the loop recorder were not included in the analysis. Among the 39 patients who did not complete the protocol, 20 patients (MCOT [n = 13], loop recorder [n = 7]) were noncompliant and did not wear the device for the entire duration of the study. These patients were not accounted for in the reported diagnostic yield of this study. An accurate assessment of a monitoring system should take into account all the factors impacting the diagnostic yield of a monitor. Another important shortcoming of this study is that the majority of loop recorders did not have the auto-triggering feature. Previous studies had demonstrated that auto-triggered loop recorders are superior to loop recorders without this feature in diagnosing the underlying symptom provoking arrhythmia and in the detection of asymptomatic episodes.[35] Although MCOT has some theoretical advantages (continuous monitoring) over the loop recorder, currently evidence that MCOT provides significant improvements over the diagnostic yield of looping event recorders with auto-triggering for the evaluation of syncope is insufficient.

To summarize the role of ambulatory ECG monitors for the evaluation of syncope, clinical evidence consistently demonstrates that the 24-hour Holter monitor is associated with a low diagnostic yield for patients with unexplained syncope. Looping event recorders may have a limited role in select patients who can reliably activate the monitor and who have very frequent episodes of presyncope or syncope. Studies evaluating the role of outpatient telemetry (MCOT, ECAT) in syncope are promising, but it has not been established whether outpatient telemetry provides significant improvements in diagnostic yield over currently available auto-triggered loop recorders. In most cases of unexplained syncope, the literature supports the use of an ILR as the monitoring strategy of choice after conventional testing fails to provide a diagnosis. A selective list of studies evaluating the diagnostic capabilities of various ambulatory ECG monitoring strategies in syncope is provided in Tables 69-4, 69-5, and 69-6.

Monitoring in Atrial Fibrillation

AF is the most common cardiac rhythm disturbance encountered in clinical practice. Ambulatory ECG monitors have numerous potential roles in the diagnosis and management of patients with AF. Patients may have symptoms of palpitations, fatigue, lightheadedness, and shortness of breath, but because of its paroxysmal nature, AF may escape diagnosis. Asymptomatic AF is common even among patients with known symptomatic bouts of AF; in one study, AF was found to be 12 times more common than symptomatic recurrences.[36-38] When continuous monitoring is possible with an implantable pacemaker, the incidence of asymptomatic episodes among patients with a history of AF may be as high as 50%. Israel et al evaluated asymptomatic episodes of AF in 110 patients with implanted atrial defibrillators for the treatment of AF. These devices have sophisticated algorithms with excellent sensitivity and specificity for detecting AF. In this study, 38% of patients had asymptomatic bouts of AF during continuous monitoring. Furthermore, 1 in 6 patients had asymptomatic AF that persisted for 48 hours or longer.[39] These data confirm that symptoms are a poor indication of the onset, frequency, and duration of episodes among patients with AF. The best monitoring strategy for the detection of asymptomatic AF in a variety of clinical situations has not yet been established (see Figure 69-6).

Patients with AF may suffer symptoms of exercise intolerance, dyspnea on exertion, and fatigue caused by inadequate rate control. Achieving rate control in patients with AF is important because inadequate rate control may contribute to, or be the sole cause of, depressed left ventricular function from a tachycardia-mediated cardiomyopathy. Grogan et al reported significant improvement in left ventricular (LV) function in 10 patients who presented with severe LV dysfunction and AF with poor rate control. After treatment with rate control, the mean LVEF improved from 25% (range, 12% to 30%) to 52% (range, 40% to 64%).[40] In the assessment of rate control among patients with AF, a resting heart rate alone is inadequate. The goal of rate control is to improve symptoms, optimize hemodynamics through a range of activities, and prevent tachycardia-mediated cardiomyopathy. The target heart rate defining adequate rate control at rest and with exercise has not yet been well established. In the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study, patients randomized to the rate control arm of the study were defined as adequately rate controlled when their resting heart rate was less than 80 beats/min and less than 110 beats/min during a 6-minute walk test.[41] Optimal rate control targets are controversial. In general, goals are to alleviate symptoms and prevent tachycardia-mediated cardiomyopathy. Among asymptomatic patients with normal LV systolic function, a more lenient strategy (resting heart rate <110 beats/min) may be reasonable.[42] A 24-hour Holter monitor may be a useful tool in assessing rate control in patients with persistent or chronic AF throughout a range of patient activities. The 24-hour Holter reports minimum, maximum, and average heart rates and can provide useful clinical information to guide treatment. Among patients with LV dysfunction or symptoms, a reasonable goal is to achieve a 24-hour average heart rate of less than 90 beats/min and a maximum heart rate of less than 120 beats/min (Figure 69-7). Elderly patients with normal LV function and minimal symptoms may benefit from a more lenient rate control target (<110 beats/min at rest). The usefulness of a 24-hour Holter monitor for the assessment of rate control is limited in patients with paroxysmal AF, especially among patients who experience infrequent episodes.

Recent studies have demonstrated the important role of ambulatory ECG monitoring in evaluating the efficacy of rhythm control strategies. Although the major goal in any rhythm control strategy is the alleviation of symptoms, for both therapy and ablation, it is clinically useful to establish whether, and to what degree, both symptomatic AF and asymptomatic AF are recurrent. In a study by Senatore et al, 72 patients were followed up for 30 to 120 days after an AF ablation procedure, with scheduled daily event recordings (30 seconds) along with recordings during any

symptoms. All these patients were also evaluated with a 24-hour Holter monitor on days 14, 30, and 120 following the procedure. A detailed history was obtained from the patients, and 12-lead ECG was administered during each follow-up visit. A total of 5585 thirty-second transmissions (mean, 77.5 per patient) were obtained. When patients were evaluated with a Holter monitor and 12-lead ECGs, AF recurrence was detected in 10 patients (13.9%). However, when additional diagnostic information from the event recorder was included, 20 patients were found to have AF recurrences (27.8%).[43] In another study of 114 patients undergoing AF ablation, a continuous 7-day Holter recording was obtained before ablation, immediately following ablation, and

Location: Unknown **HOLTER REPORT**

Patient Name
ID
Age **55 yr** Hookup Date: **23-Mar-2009**
Gender **Male** Hookup Time: **15:34:00**
Date of Birth: **01-Jan-1954** Duration: **24:00:00**

Overreading Physician
Referring Physician
Ordering Physician:
Hook-Up Technician:
Indication/Diagnosis: **ATRIAL FIBRILLATION**
Medications

General

144918 QRS complexes
6001 Ventricular beats (4%)
0 Supraventricular beats (<1%)
100 % of total time in AF/AFL

Heart Rates

55 Minimum at 22:12:26 23-Mar
101 Average
227 Maximum at 11:37:31 24-Mar
69321 Beats in tachycardia (>100 bpm), 48% total
74 Beats in bradycardia (<60 bpm), < 1% total
1.8 Seconds Max R-R at 23:43:30 23-Mar

Supraventriculars (S, J, A)

0 Isolated
0 Couplets
0 Bigeminal cycles
0 Runs totaling 0 beats

Ventriculars (V, F, E, I)

3669 Isolated
644 Couplets
36 Bigeminal cycles
293 Runs totaling 1044 beats
10 Beats longest run 210 bpm 11:38:27 24-Mar
3 Beats fastest run 227 bpm 18:21:55 23-Mar

Interpretation

MECHANISM: ATRIAL FIBRILLATION WITH RAPID VENTRICULAR RESPONSE (MEAN HEART RATE FOR THE RECORDING PERIOD WAS: 101 BPM).
OCCASIONAL PREMATURE VENTRICULAR COMPLEXES AS SINGLETS AND COUPLETS VS ABERRANCY.
THERE WERE 293 PAROXYSMS OF WIDE-COMPLEX TACHYCARDIA OF 3 TO 10 BEATS IN DURATION @ UP TO 227 BPM RECORDED (NSVT vs ABERRANCY).
NO PROLONGED PAUSES NOTED.
NO SYMPTOMS REPORTED BY PATIENT.

SCAN DATE: 04/06/2009 (RF) RECORDING QUALITY: GOOD

Confirmed by_____ (1052) on 4/7/2009 5:50:54 PM

A Signed:_____ Date:_____

FIGURE 69-7 A 73-year-old woman with chronic atrial fibrillation treated with atrioventricular nodal–blocking agents for rate control. Her heart rate in the office was 72 beats/min. A Holter monitor was ordered and demonstrated poor rate control. These data are evident in the reported mean and maximum heart rates (**A**) and the heart rate histogram (**B**). *AF/AFL,* Atrial fibrillation/atrial flutter; *BPM,* beats/min; *NSVT,* nonsustained ventricular tachycardia.

Continued

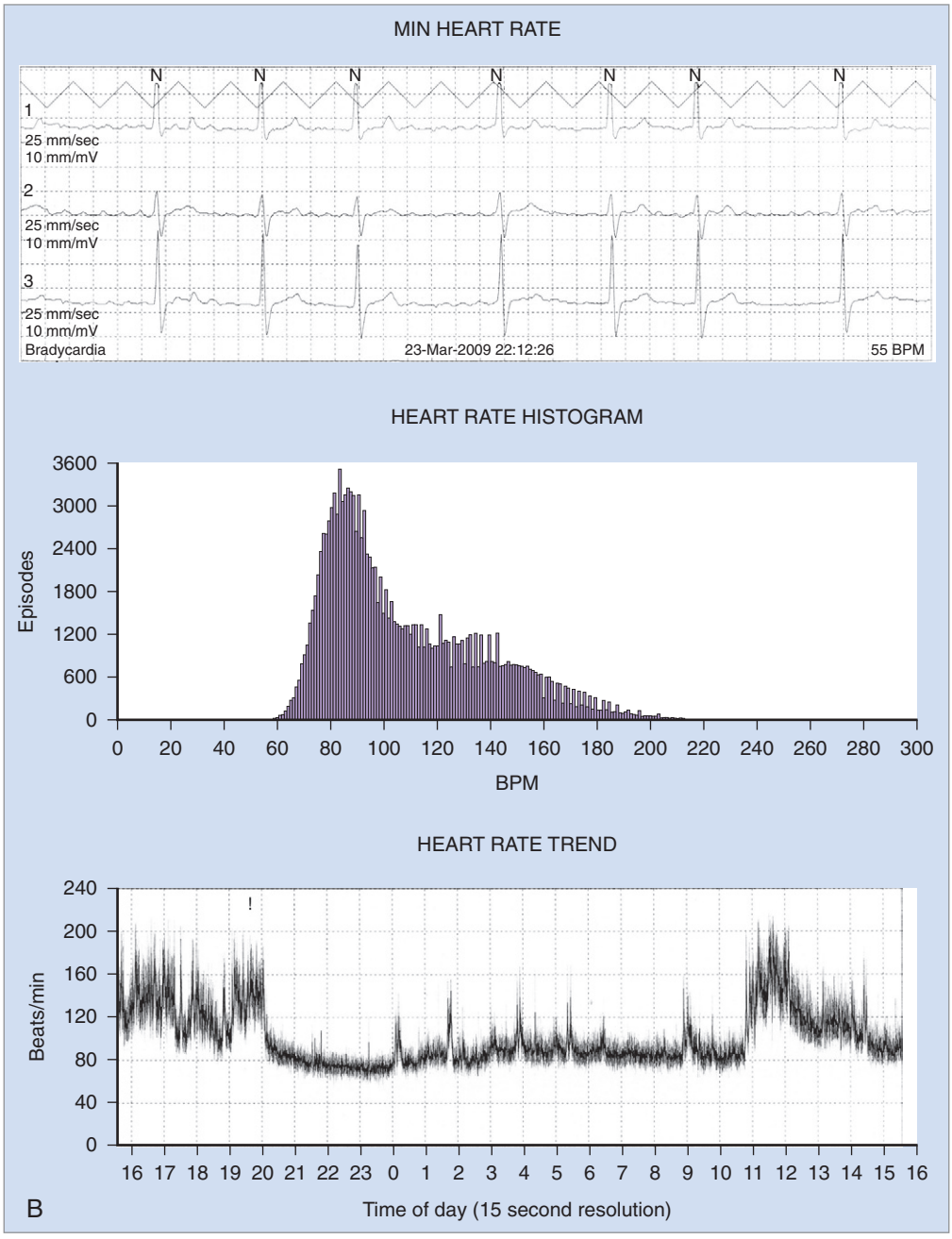

FIGURE 69-7, cont'd

then at 3, 6, and 12 months. On the 7-day Holter monitor before the ablation, episodes of AF were recorded in 92 (81%) of 114 patients. Episodes were entirely symptomatic in 35 (38%) of 114, symptomatic and asymptomatic episodes in 52 (57%) of 114, and entirely asymptomatic in 5 patients (4%). After the ablation, the percentage of patients with only asymptomatic episodes of AF increased from 4% to 37%.[44] These studies demonstrate that a symptom-based follow-up strategy for AF recurrence is inadequate and highlight the importance of long-term ambulatory monitoring in detecting asymptomatic AF following radiofrequency (RF) ablation of AF. Some current ambulatory monitoring systems (MCOT, ECAT, Medtronic Reveal AF, etc.) have sophisticated AF algorithms that may not only detect episodes of AF but also provide the percentage of time a patient is in AF (AF burden) (Figure 69-8). These monitoring systems have not been established as the standard of care for AF surveillance; however, in the future, specific roles for such monitors may be established in AF management, such as guiding antiarrhythmic

drug therapy and determining continuation of anticoagulation in patients with paroxysmal AF.

SUMMARY

Currently, multiple types of recording devices are available to clinicians for the diagnosis of symptoms (syncope, presyncope, palpitations) that may be attributed to cardiac arrhythmias. Careful consideration of the pretest probability of a cardiac arrhythmia, frequency of symptoms, and knowledge of the likely diagnostic yield of each device for different clinical situations will help guide clinicians to the monitoring system that is most likely to provide a diagnosis. The future of ambulatory ECG monitoring will include smaller and better-tolerated devices and more accurate arrhythmia detection algorithms.

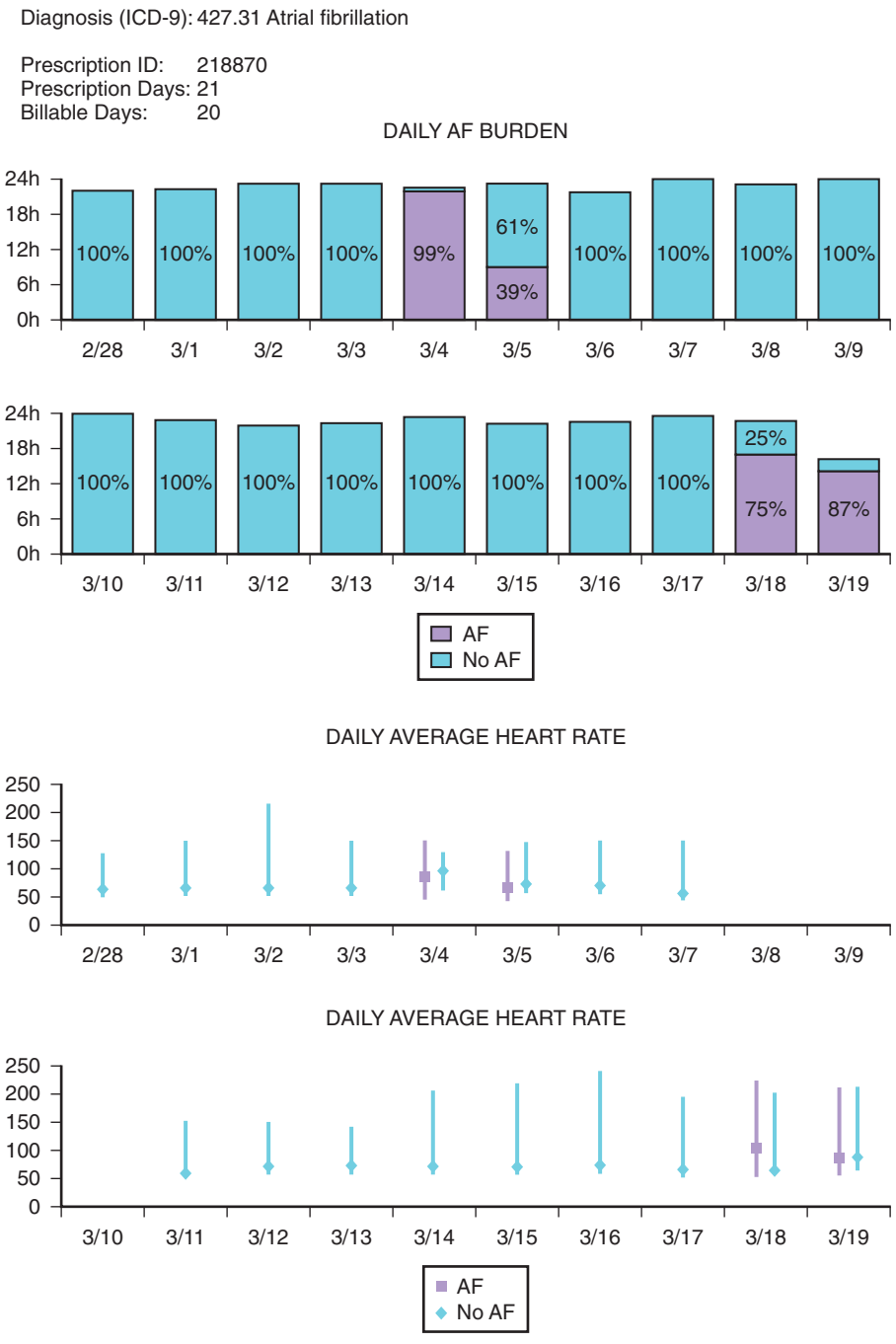

FIGURE 69-8 A 68-year-old man with diabetes as well as hypertension and symptomatic atrial fibrillation (*AF*) who underwent an AF ablation. After the ablation, he felt well and had no symptoms of AF. An outpatient telemetry device demonstrated episodes of asymptomatic AF with one episode that was >24 hours in duration. *PAC,* Premature atrial contraction.

Continued

Emergent/Urgent Reports

Date	Symptom	Findings	HR
No urgent reports found			

Billable Daily Reports

Date	Symptom	Findings	HR
02/24/2009	auto	Baseline - Normal Sinus Rhythm with PAC	70
02/25/2009	auto	Normal Sinus Rhythm	70
02/26/2009	auto	Normal Sinus Rhythm	76
02/27/2009	auto	Normal Sinus Rhythm	63
02/28/2009	auto	Normal Sinus Rhythm	63
03/01/2009	auto	Normal Sinus Rhythm with Artifact	80
03/02/2009	auto	Normal Sinus Rhythm	70
03/03/2009	auto	Normal Sinus Rhythm	75
03/03/2009	auto	Normal Sinus Rhythm with PAC into Atrial Fibrillation/Flutter Onset	67
03/04/2009	auto	New Onset Atrial Fibrillation/Flutter	107
03/04/2009	Heart Racing	Atrial Fibrillation/Flutter	78
03/04/2009	auto	Atrial Fibrillation/Flutter with 2.0 Second Pause	54
03/04/2009	auto	Atrial Fibrillation/Flutter	129
03/05/2009	auto	Atrial Fibrillation/Flutter	73
03/05/2009	auto	Atrial Fibrillation/Flutter with 2.0 Second Pause	57
03/05/2009	auto	Normal Sinus Rhythm	67
03/06/2009	auto	Normal Sinus Rhythm	69
03/07/2009	auto	Normal Sinus Rhythm	74
03/07/2009	auto	Normal Sinus Rhythm	72
03/11/2009	auto	Normal Sinus Rhythm	64
03/12/2009	auto	Normal Sinus Rhythm	74
03/13/2009	auto	Normal Sinus Rhythm	86
03/14/2009	auto	Normal Sinus Rhythm	78
03/15/2009	auto	Normal Sinus Rhythm	71
03/16/2009	auto	Normal Sinus Rhythm	75
03/17/2009	auto	Normal Sinus Rhythm	61
03/17/2009	auto	Normal Sinus Rhythm	62
03/18/2009	auto	Atrial Fibrillation/Flutter	125
03/18/2009	auto	Atrial Fibrillation/Flutter	159

Physician Interpretation

Interpreting Physician

Signature Date

FIGURE 69-8, cont'd

KEY REFERENCES

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CHAPTER 70

Provocative Testing for Arrhythmias

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Diagnosis of arrhythmia is based on the recordings and documentation of abnormal electrical activity in the heart by the surface electrocardiogram (ECG); intracardiac electrogram (EGM); implantable loop recorders, pacemakers, or implantable cardioverter defibrillators (ICDs); or invasive monitoring during electrophysiological study (EPS). However, detection and recording of nonsustained paroxysmal arrhythmias remain a clinical challenge. Arrhythmias such as persistent atrial fibrillation (AF) can easily be detected on the surface ECG, even if the onset of clinical symptoms occurred hours or days earlier. In other arrhythmias, however, an exact diagnosis can be difficult because of a paroxysmal ECG pattern that becomes normal when the patient arrives at the hospital and because potential clinical symptoms such as palpitations or syncope are transient by definition.

Paroxysmal ECG patterns can be observed in potentially life-threatening arrhythmias such as Brugada syndrome or long QT syndrome (LQTS). Therefore an exact diagnosis of the underlying arrhythmia is crucial because of its prognostic and therapeutic consequences. In some cases, the cardiologist will recommend lifestyle modifications only, drug-based therapy, or implantation of a pacemaker or ICD. In the case of hereditary arrhythmias, family members at risk are also tested and treated if necessary.

As a consequence, several provocative test methods have been developed to increase sensitivity in detecting bradyarrhythmia, supraventricular tachycardia (SVT), and ventricular tachycardia (VT).

Bradyarrhythmia

Atrioventricular Block

Treatment and prognosis of atrioventricular (AV) block depends on the exact location, either intranodal or infranodal. Besides invasive electrophysiological measurements, several noninvasive methods are used to identify the site of conduction block.

The AV node and the His-Purkinje system are innervated differently by the autonomic nervous system, with the AV node being highly innervated by sympathetic and parasympathetic nerves and the His-Purkinje system being poorly innervated.[1] These differences are the basis of provocative maneuvers to determine further the exact location of an AV block.

Carotid sinus massage increases vagal tone and worsens AV nodal block.[2] Isoproterenol, exercise, and atropine are known to increase sympathetic tone, improving AV nodal conduction.[2] Because of these changes on rate impulse conduction through the AV node, these maneuvers exert different effects on infranodal block; for example, after carotid sinus massage, the sinus rate drops, and therefore the presence of a functional infranodal block can disappear, depending on whether a lower impulse rate approaches the infranodal conduction system, re-establishing 1:1 conduction. However, increasing the impulse rate (e.g., by atropine) could worsen the functional infranodal block. So in regard to infranodal block, carotid sinus massage improves infranodal block, and exercise and atropine worsen infranodal block.

Some authors have tried to evaluate the role of adenosine or its precursor adenosine 5′-triphosphate (ATP) to diagnose high-degree AV block as the underlying mechanism for unexplained syncope.[3] Adenosine binds to the A1-receptor, thus exerting its effects of depressing sinus node automaticity, slowing or blocking AV node conduction, and shortening and hyperpolarizing the atrial action potential as well as decreasing automaticity in Purkinje fibers.[4,5]

Brignole et al suggested that an ATP test could be valuable for diagnosis of paroxysmal AV block based on a potentially higher ATP susceptibility of patients with syncope.[6] However, the same group published data showing that ATP could predict AV block only in a few patients.[7] Another study by Fragakis et al investigating adenosine in the context of sick sinus syndrome and unexplained syncope failed to demonstrate a valuable role for adenosine in confirming AV block as a cause of syncope as well.[8] As a result, the usefulness of adenosine in detecting AV block has not been established.

During invasive EPS, the class I antiarrhythmic drug ajmaline can be used to unmask infra-Hisian conduction abnormalities.[2] A dose of 1 mg/kg is used in patients with normal systolic function. If the infra-Hisian conduction is pathologic, a second- or third-degree infra-Hisian block or an H-V interval greater than 120 ms occurs a few minutes after ajmaline infusion. Theoretically, ajmaline could be replaced by other class I antiarrhythmic drugs such as flecainide or procainamide, but the elimination half-life of ajmaline is shorter, which is an advantage for its use in a screening test.

Syncope

Carotid sinus hypersensitivity can be the underlying disease leading to syncope caused by a sinus pause. It can easily be tested for by performing carotid sinus massage over the region of carotid bifurcation (i.e., the maximal point of carotid pulsation between the angle of the mandible and the superior border of the thyroid

cartilage) under continuous ECG and blood pressure monitoring for 5 seconds on both sides, one after another, in the supine, 70-degree, head-up tilt position.[9] The test result is assumed to be positive if a sinus pause greater than 3 seconds (cardio-inhibitory subtype), a decrease of systolic blood pressure greater than 50 mm Hg (vasodepressor subtype), or both are observed. However, such sinus pauses can be observed in healthy individuals as well, so carotid sinus massage cannot definitively distinguish healthy individuals from sick individuals.[10,11]

Tilt-table testing (TTT) is a widely used provocative test method for the assessment of syncope. Several protocols have been developed, with the Bruce protocol being the most widely used (see Chapters 48 and 70). In addition, isoproterenol or nitrates are used as provocative agents to increase the sensitivity and decrease the specificity of the TTT.[2]

ATP can be used for the evaluation of cardio-inhibitory syncope.[13] According to a protocol developed by Flammang and colleagues, a rapid bolus of 20 mg ATP is administered. The ATP test result is considered positive if complete AV block greater than 10 seconds occurs or if the longest R-R interval after ATP administration is greater than 6 seconds.[14,15] Head-up TTT and the ATP test do not correlate well, which has led to the hypothesis that the ATP test reveals a form of syncope different from that detected by the head-up TTT or carotid sinus massage.[7,16] The ATP test is not routinely used; additional clinical trials are needed. According to the guidelines published by the European Society of Cardiology, the adenosine test is a class IIb recommendation because of its low predictive value.[17]

Sick Sinus Syndrome or Sinus Node Dysfunction

Sick sinus syndrome is a clinically heterogeneous disease. Underlying pathophysiological mechanisms include changes in intrinsic sinus node properties, sinoatrial (SA) conduction properties, and extrinsic factors such as autonomic regulation.[18] To distinguish endogenous sinus node dysfunction from autonomic dysregulation responsible for sick sinus syndrome, intrinsic heart rate (IHR) can be determined with propranolol and atropine.[19] With the patient under continuous ECG monitoring, 0.2 mg/kg propranolol is administered at 1 mg/min, followed by a single bolus of 0.04 mg/kg atropine over 2 minutes. IHR is determined as the maximum sinus rate after injection of atropine. Based on the formula IHR = 118.1 – (0.57 × Age), normal IHR is assumed to be within ±14% of the 95% confidence interval (CI) for age 45 years or younger or within ±18% for age 45 years or older. An abnormal IHR therefore represents dysfunction of intrinsic sinus node properties. In contrast, autonomically mediated sick sinus syndrome shows a normal IHR after autonomic blockade. By eliminating (para)sympathetic activity, propranolol or atropine testing facilitates discrimination of intrinsic sinus node dysfunction and autonomic dysregulation. Further evaluation of intrinsic sinus node dysfunction can be achieved by determining sinus node recovery time (SNRT) and SA conduction time (SACT) during EPS (see Chapter 39).

Fragakis et al evaluated the diagnostic value of adenosine in detecting sick sinus syndrome in a study with 19 patients, 12 of whom were control patients and 7 with syncope of unknown origin.[8] The investigators measured the maximum corrected SNRT after atrial overdrive pacing at different cycle lengths and compared it with the longest sinus pause after adenosine administration corrected to basic cycle length. With a bolus of 0.15 mg/kg adenosine, they showed that this noninvasive test is at least comparable with the measurement of corrected SNRT in diagnosing sick sinus syndrome. However, they could not show any value for the use of adenosine in the diagnosis of AV block.

Another study by Burnett et al investigated adenosine as a provocative agent in 10 patients with sick sinus syndrome. By validating their results with EPS, they demonstrated that the lengthening of the sinus cycle length corrected to the basic cycle length after adenosine infusion offers a sensitivity of 80% and a specificity of 97% for the diagnosis of sick sinus syndrome.[20]

The adenosine test may therefore be a suitable alternative in the diagnosis of sick sinus syndrome; however, because of the small number of patients enrolled in these studies, additional investigations are still necessary to assess the value of adenosine in the diagnosis of sick sinus syndrome.

Furthermore, administration of ajmaline has been shown to increase the sensitivity of EPS in the detection of sick sinus syndrome.[2] The test result is assumed to be positive if the corrected sinus node time is greater than 550 ms after ajmaline infusion.

Chronotropic Incompetence

Athletes often show resting bradycardia, but they can increase their heart rate adequately with exercise. In contrast, patients with chronotropic incompetence or sinus node dysfunction and resting bradycardia cannot appropriately accelerate their heart rate. A physical exercise stress test can be useful in differentiating nonpathologic bradycardia at rest from chronotropic incompetence. In addition, drug testing can be performed by increasing the heart rate after infusion of isoproterenol and atropine based on the sympathetic stimulation and parasympathetic blockade, respectively. Vavetsi et al studied 100 patients with sinus bradycardia but no obvious cardiac disease.[21] According to their protocol, 2 mg atropine was injected, followed by incremental isoproterenol infusion starting at a dose of 2.4 mg/min up to a maximum of 7.2 mg/min (2 to 3 minutes and 1.2 mg/min isoproterenol per step). By measuring the maximum heart rate, they defined the chronotropic reserve. As a result, they clearly identified patients with deficient chronotropic response who required pacemaker implantation.

Supraventricular Tachyarrhythmias

In the surface ECG, SVTs are easily recognized by narrow-complex tachycardia. However, distinguishing different forms of SVT, as well as identifying SVT with pre-existing bundle branch block presenting as wide-complex tachycardia, remains a clinical challenge. In this regard, adenosine or ATP is widely used for the diagnosis and therapy of tachyarrhythmias (Figure 70-1).

Atrioventricular Nodal Re-entrant Tachycardia and Atrioventricular Re-entrant Tachycardia

Dual conduction properties (fast and slow) exist in the AV node as the basis of AV nodal re-entrant tachycardia (AVNRT).[22] Adenosine is routinely used to terminate AVNRT.[4] However, AVNRT is a paroxysmal SVT that often self-terminates before ECG documentation can be performed. Thus patients with palpitations and tachycardia often remain undiagnosed and do not receive adequate therapy (e.g., ablation). In these cases, adenosine can be used for diagnostic purposes because the two pathways may

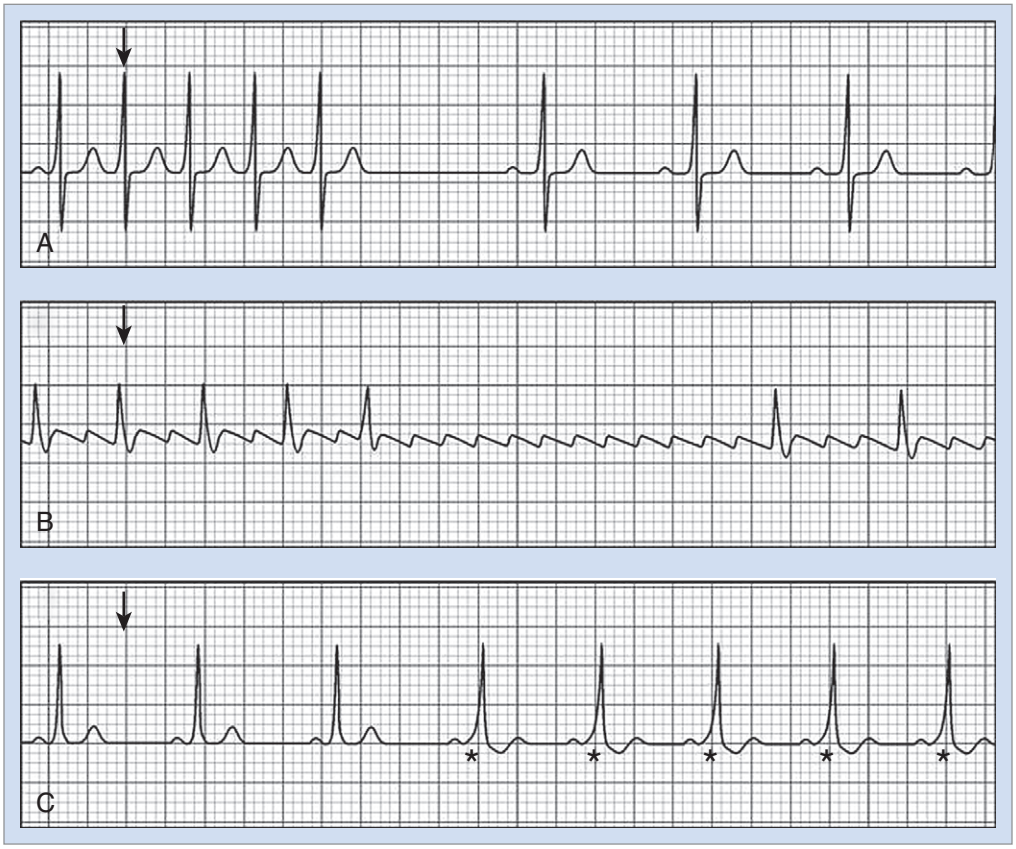

FIGURE 70-1 Bolus injection of adenosine (*down arrow*) causes transient atrioventricular (AV) block, thus terminating AV nodal re-entrant tachycardia as indicated by regular sinus rhythm (**A**), unmasked atrial flutter displayed by typical flutter waves (**B**), or latent pre-excitation demonstrated by occurrence of δ-waves (**C**). δ-Waves are highlighted by *asterisks*.

respond differently to adenosine. A higher dose is necessary to block conduction in the slow pathway compared with the fast pathway, resulting in an abrupt increase in A-H and P-Q intervals detectable in intracardiac or surface ECG recordings, respectively.[23,24]

With the patient under continuous ECG monitoring, adenosine is administered during sinus rhythm as a bolus of 6 mg (followed by a bolus of 0.9% saline) with additional 6-mg doses to a maximum of 18 mg or until second- or third-degree AV block occurs.[4,25] Some authors suggest a starting dose of 3 mg adenosine followed by further 3-mg steps or a dose regimen based on body weight, starting at 0.05 mg/kg with further application of 0.05 mg/kg.[4,24] In general, dose reduction should be considered in patients with concomitant dipyridamole therapy or those with heart transplants because of the increased effect of adenosine in these patients.[4] Dual AV node physiology is considered if a sudden increase greater than 50 ms of the P-Q interval is seen, AV nodal echo beats occur, or AVNRT develops.

Tebbenjohanns et al used adenosine in 37 patients with symptoms of paroxysmal tachycardia but without ECG documentation who underwent EPS.[24] They used an average adenosine dose of 10.3 ± 4.2 mg and identified a sudden increase in the P-Q interval on the surface ECG in 76% of the patients with inducible AVNRT but in only 5% of the patients without AVNRT. Thus the adenosine test had a sensitivity of 76%, a specificity of 95%, a positive predictive value (PPV) of 93%, and a negative predictive value (NPV) of 83%, thus proving to be a suitable noninvasive bedside test for the diagnosis of AVNRT in patients at risk.

Viskin and coworkers developed a test protocol that used ATP to distinguish tachycardias caused by accessory pathways (e.g., AVNRT or AV re-entrant tachycardia [AVRT]) from other forms of tachycardia (e.g., AF).[26] They included 146 patients with palpitations of unknown etiology. The ATP test was performed as a bedside test with the patient under continuous ECG monitoring. The investigators started with a bolus of 10 mg ATP followed by additional injections of 10 mg ATP (to a maximum of 60 mg). The test result was considered positive when a dual AV node physiology or a concealed accessory pathway became obvious by a more than 50-ms P-R interval increment or decrement or by the occurrence of AVNRT or AVRT. The test result was considered negative when second- or third-degree heart block occurred without any of the criteria mentioned above. To confirm the test results, EPS was performed on all patients; it showed a sensitivity of 71%, a specificity of 76%, a PPV of 93%, and an NPV of 37% of the ATP test in regard to predicting AVNRT or AVRT.[26]

Belhassen et al evaluated the diagnostic role of ATP in 96 patients during EPS.[27] They showed that ATP injected during sinus rhythm in an incremental dosage, starting at 10 mg to a maximum of 60 mg, identified dual AV nodal physiology in 75% of the patients with inducible AVNRT. In addition, they demonstrated that ATP can be used to confirm the results of a successful radiofrequency ablation of the slow pathway.

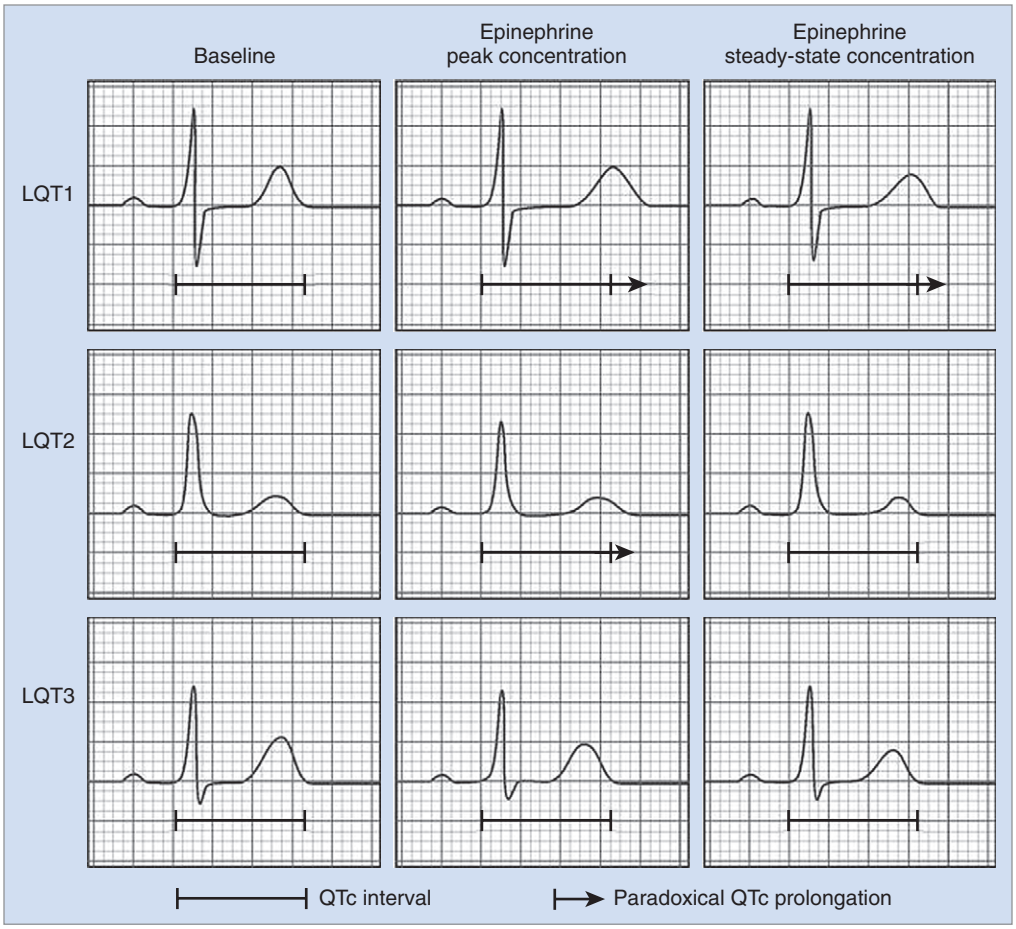

FIGURE 70-2 Schematic illustration of electrocardiogram changes seen in epinephrine stress test (Shimizu protocol). In long QT (*LQT*) syndrome types 1 and 2, a paradoxical QTc prolongation can be seen at epinephrine peak concentration. In LQT1, QTc remains prolonged at epinephrine steady-state concentration, and it returns to normal in LQT2. In contrast, in LQT3, no QTc prolongation can be detected either at peak or at steady-state concentration.

Distinguishing Atrial Flutter from Atrioventricular Nodal Re-entrant Tachycardia or Atrioventricular Re-entrant Tachycardia

Atrial flutter with 2:1 block normally presents with heart rates of 140 to 150 beats/min. Similarly, AVNRT or AVRT displays a comparable heart rate spectrum. Adenosine can be used to discriminate between AVNRT or AVRT and atrial flutter with 2:1 block.[4] Because of the transient AV block caused by adenosine, electrical atrial activity will be unmasked, showing characteristic P waves and leading to the correct diagnosis of atrial flutter (Figure 70-2).

Identification of Accessory Bundles by Adenosine and Adenosine 5′-Triphosphate

Furthermore, adenosine, given during sinus rhythm, has been shown to unmask accessory AV conduction bundles with latent pre-excitation, which have only been apparent during atrial arrhythmia or atrial pacing.[28,29] Despite the absence of pre-excitation in sinus rhythm, these patients are at risk of rapid ventricular heart rate when AF occurs. By slowing or transient block of conduction to the ventricles through an AV node, a concealed accessory pathway can be exposed (see Figure 70-2). Garratt et al investigated 22 patients with a history of documented SVT and a normal ECG at sinus rhythm. They demonstrated that adenosine is capable of unmasking latent pre-excitation with high sensitivity and specificity.[29]

In summary, adenosine is a useful drug for the management and diagnosis of tachycardias. By inducing a transient AV block, re-entry tachycardias involving the AV node are terminated and the ventricular rate is slowed, thus unmasking atrial activity when atrial tachyarrhythmias are present. Adenosine has no influence on VTs.[4,30] Of note, the same effect of transient AV nodal conduction slowing can be achieved by physical methods to stimulate the vagal nerve, including carotid sinus massage, the diving reflex, the Valsalva maneuver, or deep inspiration.[31]

However, adenosine can, as with most drugs, have certain adverse effects. It can induce AF in patients at risk because of its ability to shorten the atrial action potential duration in a dose-dependent and rate-dependent manner.[32] Because of its sympathetic stimulation, adenosine also can cause a 1:1 conduction in atrial flutter.[33] In addition, in patients with AF and accessory pathways, adenosine can enhance antegrade AV conduction of the high atrial rate via the accessory bundle, resulting in a fast ventricular rate with wide QRS complexes ($F_{ast}B_{road}I_{rregular}$ tachycardia), which also can lead to ventricular fibrillation (VF). Therefore adenosine should always be administered with caution and

after taking the required measures to establish the safety of the patient.

Isoproterenol During Electrophysiological Study

Many SVTs are currently treated with radiofrequency ablation procedures. However, inducing the specific arrhythmia during EPS is important before performing an ablation. For this purpose, isoproterenol infusion is widely used in combination with programmed stimulation, especially when programmed atrial stimulation alone fails to induce the clinical arrhythmia.[2] Furthermore, failure of arrhythmia re-induction after ablation (with or without isoproterenol) confirms the successful outcome of the procedure.

Atrial Fibrillation

Oral et al investigated the role of isoproterenol to assess the inducibility of paroxysmal AF during catheter ablation.[34] They enrolled 80 patients with a history of paroxysmal AF and 20 healthy controls receiving an incremental dosage of isoproterenol starting at 5 μg/min followed by 10, 15, and 20 μg/min every 2 minutes or until AF was induced. They induced AF in 84% of patients with AF but in only one of the control subjects (5%). They revealed inducibility of vagotonic AF in 88%, adrenergic AF in 100%, and nonspecific AF in 79%. Overall sensitivity was 88%, and specificity was 95% for induction of AF in patients with paroxysmal AF regardless of the clinical subtype.

In the case of vagally induced AF, carotid sinus massage or ATP at a dosage of 10 to 20 mg can be useful to induce AF.[2,35]

Oral et al were able to demonstrate the value of isoproterenol infusion after catheter ablation of paroxysmal AF in predicting clinical outcome more accurately compared with the widely used rapid atrial pacing.[36]

ATP also can be used for the same purpose.[37] Ninomiya et al used 30 mg of ATP after isolation of all four pulmonary veins during isoproterenol infusion in 21 patients with AF. In all patients, electrical isolation was achieved initially. However, spontaneous reconduction was observed in 12 pulmonary veins, with 8 more pulmonary veins showing re-conduction only after ATP administration. Thus their results indicated the usefulness of ATP to detect early reconduction after pulmonary vein isolation.

Arentz et al performed a study on 29 patients with paroxysmal or persistent AF who underwent pulmonary vein isolation.[38] They used adenosine at a dose of 12 to 18 mg injected after the successful isolation of pulmonary veins to unmask the so-called dormant conduction, that is, restored conduction through a previously isolated pulmonary vein. Adenosine induced transient conduction in 25% of successfully isolated pulmonary veins. However, a second EPS was performed in 14 patients that revealed a non-significant higher rate of restored conduction in previously "adenosine-positive" pulmonary veins. To identify the potential underlying mechanism, Datino and coworkers studied the effects of adenosine on canine pulmonary veins.[39] They illustrated that adenosine selectively hyperpolarized canine pulmonary veins by increasing the inward rectifier potassium current I_{KAdo}, restoring the excitability of isolated pulmonary veins with dormant conduction.

Further studies are needed to evaluate the safety, reliability, and usefulness of ATP and adenosine in predicting clinical outcome after pulmonary vein isolation in a larger cohort of patients.

Ventricular Tachyarrhythmias

Some forms of ventricular tachyarrhythmia are difficult to diagnose because of their transient ECG pattern, in which typical ECG criteria are "concealed." These arrhythmias include Brugada syndrome, LQTS, and catecholaminergic polymorphic ventricular tachycardia (CPVT). Patients with these arrhythmias often present with syncope or (have survived) sudden cardiac death (SCD) without any characteristic ECG recordings. Because these syndromes could potentially result in a lethal arrhythmia, a confirmed diagnosis in patients at risk is very important; multiple provocative testing methods were therefore developed.

General Drug Effects on Inducibility of Ventricular Tachycardia and Differentiation of Ventricular Tachycardia Mechanisms

The most common method to induce VT during EPS is programmed stimulation by specific stimulation protocols. However, in some special variants of VT (e.g., CPVT) or if programmed stimulation fails to induce VT, drugs can be used to induce tachycardia. The drug of first choice in this context is isoproterenol because of its adrenergic stimulation effects. However, data on the use of isoproterenol regarding tachycardia induction rates are highly controversial in the literature, varying from less than 5% to 20%.[40-42] With CPVT or repetitive monomorphic tachycardia, the use of isoproterenol seems to be established mainly on the basis of initiation mechanisms via triggered activity caused by delayed afterdepolarizations (DADs). In addition, epinephrine, atropine, and aminophylline are alternative agents to facilitate induction of these arrhythmias if isoproterenol fails to induce the arrhythmia during programmed stimulation. The use of catecholaminergic drugs also may be a useful alternative to induce tachycardias caused by abnormal automaticity; programmed stimulation is, however, highly unreliable for initiating this type of arrhythmias. In general, tachycardia induction requiring the use of catecholamines or other pharmacologic agents that increase intracellular cyclic adenosine monophosphate (cAMP) suggests an arrhythmia initiation mechanism caused by triggered activity via DADs; these agents should have less or only indirect effects on early afterdepolarization (EAD)–related arrhythmias. Another drug-specific effect based on the DAD-related initiation is hypothesized by the administration of verapamil or adenosine terminating this type of tachycardia and is therefore called *adenosine-sensitive* or *verapamil-sensitive tachycardias*. The following sections focus on specific arrhythmias and arrhythmia syndromes to discuss potential provocation tests in more detail.

Long QT Syndrome

LQTS is characterized by prolonged ventricular repolarization (detectable as QTc prolongation) and polymorphic VT, named *torsades de pointes tachycardia*, which may lead to SCD.[43] By highlighting the predominant underlying pathophysiology in general, two forms of LQTS are described: LQTS caused by mutations in ion channel genes (congenital LQTS) or QTS secondary to therapy with QTc-prolonging drugs (acquired LQTS).[43,44] Diagnosis of LQTS remains difficult because episodes of tachycardia rarely occur and QTc prolongation alone is not sufficient for diagnosis because even healthy individuals can show

a prolonged Q-T interval.[45-47] In contrast, approximately 25% of genetically affected people present with normal or borderline QTc interval.[48] In congenital LQTS, genetic testing is currently the most important step toward establishing diagnosis. However, genotyping results take weeks to months and, according to the technique used, a disease-related mutation may not be detected or a mutation previously not described may be detected. In the latter case, whether this mutation could lead to arrhythmia often is unclear.

Priori et al were able to show that the percentage of concealed LQTS depends on the genotype.[49] Studying 647 patients with genetically diagnosed LQTS, they demonstrated normal ECG recordings in 36%, 19%, and 10% of the patients with LQT1, LQT2, and LQT3, respectively. Thus provocative test methods are still of clinical relevance because these tests are fast and easy to perform and can potentially guide subsequent genetic testing to a certain subtype of LQTS, thus enabling a faster and more economic genetic testing.

In 1984, Schechter et al suggested that LQTS is associated with abnormally large β-adrenergic–mediated after-depolarizations as an underlying mechanism leading to ventricular arrhythmias.[50] This finding resulted in the development of an epinephrine stress test to unmask concealed LQTS. The two established major protocols used in clinical routine were developed by the groups of Ackerman and Shimizu.[51-53]

Epinephrine Testing in Long QT Syndrome

Ackerman Protocol

The protocol developed by Ackerman and coworkers consists of a sequentially increasing infusion of epinephrine, starting at a low dosage of 0.025 μg/kg/min for 10 minutes followed by 0.05, 0.1, and 0.2 μg/kg/min every 5 minutes.[52] The protocol originally started with an epinephrine dosage of 0.05 μg/kg/min increased to a maximum dosage of 0.3 μg/kg/min, but after initial observations of gene-specific responses at low dosages and increased adverse effects at high dosages, the protocol was changed.[51,54] Patients receive epinephrine infusion for 25 minutes in total. The entire procedure is monitored with permanent ECG recordings with a focus on Q-T, R-R, and QTc intervals. Changes in QT and QTc (ΔQT and ΔQTc) were determined by calculating the differences between maximal and minimal QT or QTc between epinephrine infusion and baseline, respectively. The criteria to stop epinephrine infusion are increased systolic blood pressure (>200 mm Hg), nonsustained VT, polymorphic VT, increased premature ventricular contractions (>10/min), T-wave alternans, or clinical symptoms such as headache or nausea.

We conducted epinephrine stress testing in 147 genotyped patients (44 patients negatively tested for LQTS, 40 patients with LQT1, 30 with LQT2, and 11 LQT3). The median baseline QTc intervals were 444 ms, 456 ms, 486 ms, and 473 ms in control subjects, LQT1, LQT2, and LQT3, respectively. The median QTc change during epinephrine infusion was −23 ms in controls, −4 ms in patients with LQT2, −58 ms in patients with LQT3, and +78 ms in patients with LQT1. A paradoxical QT response defined as an increase in ΔQT of more than 30 ms was specific for patients diagnosed with LQT1 (observed in 92% of these patients) but not for patients without LQTS (18%), LQT2 (13%), or LQT3 (0%). In summary, epinephrine testing had a sensitivity of 92.5%, a specificity of 86%, a PPV of 76%, and an NPV of 96% for LQT1.

Epinephrine induces hyperphosphorylation of the slowly activating delayed rectifier potassium channel I_{Ks}, which is an important ion channel for repolarization. Hyperphosphorylation results in increased activity of I_{Ks}, leading to shortening of the Q-T interval.[55,56] Because of mutations in *KCNQ1*, patients with LQT1 display loss of I_{Ks} function with slowed repolarization and reduced response to epinephrine. Thus during epinephrine infusion, an imbalance of ion currents resulting in prolongation of the Q-T interval can be observed in patients with LQT1.[57] Because of different gene mutations, other ion channels are dysfunctional in LQT2 and LQT3, resulting in an epinephrine-induced Q-T interval reduction caused by intact I_{Ks} channels observed in the study mentioned above.

The epinephrine stress test, according to Ackerman, has several advantages compared with other provocative tests in diagnosing LQTS. First, it is easy to standardize and interpret because it does not require the patient's effort. Second, the gradually increasing dosage of epinephrine is better tolerated by patients, and false-positive responses are less frequently observed compared with a bolus-based method. However, disadvantages include induction of hypokalemia by epinephrine and possible adverse effects such as life-threatening arrhythmias. Patients taking β-blockers, who cannot be tested accurately, are excluded from this test type.[52]

Taken together, these study results indicate that epinephrine stress testing may be a useful tool in patients with LQT1 recently diagnosed through genetic testing, especially when the resting ECG is concealed and if the *KCNQ1* mutation is novel.[52]

Shimizu Protocol

The second protocol for epinephrine stress testing is that developed by Shimizu and coworkers.[53] This protocol consists of bolus administration of epinephrine 0.1 μg/kg followed by continuous infusion of 0.1 μg/kg/min for 5 minutes with the patient under ECG monitoring. Of special interest are QTc intervals 1 to 2 minutes after bolus injection, which represent the peak epinephrine effect, and 2 to 3 minutes after starting continuous infusion, which represent steady-state conditions.

This protocol is based on experimental data showing that β-adrenergic stimulation differentially affects the action potential duration and the Q-T interval at peak and steady-state concentrations, depending on the underlying genotype.[58] In LQT1, epinephrine cannot enhance dysfunctional I_{Ks}, leading to paradoxical QTc prolongation at peak epinephrine concentrations as well as under steady-state conditions. In LQT2, β-adrenergic stimulation results in an initial prolongation of the Q-T interval, followed by a Q-T interval shortening at steady-state concentrations. The underlying mechanism is assumed to be an initial enhancement of the sodium-calcium (Na^+/Ca^{2+}) exchange current with subsequent increase of I_{Ks}. In LQT3, however, epinephrine leads to persistent shortening of the Q-T interval at peak and steady-state concentrations (see Figure 70-2). Thus Shimizu's protocol can be used to differentiate between the three most common subtypes of LQTS by monitoring the QTc interval at peak epinephrine concentrations after bolus administration and steady-state concentrations after continuous infusion.[59]

Adenosine Testing in Long QT syndrome

Sudden acceleration of the heart rate, typically seen in exercise and stress conditions, can trigger torsades de pointes tachycardias in LQTS. This is the mechanistic basis of tachycardia-mediated

provocative stress tests as described above. Furthermore, sudden deceleration of heart rate, such as during a pause after a premature complex, can also initiate the onset of torsades de pointes.[60] This knowledge led to the development of another provocative test protocol described by Viskin et al in which adenosine is used.[61] As previously mentioned, adenosine causes transient AV block followed by marked sinus tachycardia when administered in sinus rhythm.[5] In the study by Viskin et al, 38 patients in sinus rhythm (18 patients with diagnosed LQTS or high probability of LQTS and 20 control subjects) received intravenous adenosine starting with a 6-mg bolus.[61] Adenosine administration was continued to a maximum of 24 mg by repetitive boluses until AV block (second or third degree) or sinus bradycardia or arrest of more than 3 seconds occurred. Measurements taken in this protocol are Q-T interval; QT_{peak} interval (from the beginning of QRS to the peak of the T wave); the difference between these two QT measurements, QTc; and the morphology of the T wave at the time of maximal bradycardia and tachycardia. Both groups of subjects developed a similar degree of adenosine-induced bradycardia, but the Q-T interval in patients with LQTS increased significantly. In addition, both groups showed a similar degree of subsequent tachycardia, but QTc prolongation was more pronounced in patients with LQTS.

Thus Viskin et al were able to demonstrate a proof of principle for using adenosine stress testing in the setting of LQTS.[61] Because of the small number of patients enrolled in this study, these results are difficult to transfer to clinical practice. Patients in the LQTS cohort were either diagnosed with or were highly suspected to have LQTS. Hence, it is unclear whether the test could identify patients with lower probability of LQTS or whether the test protocol can discriminate different subtypes of LQTS as with epinephrine testing (according to Shimizu et al).[53] Larger studies are needed to evaluate the potential role of adenosine stress testing in identifying LQTS.

Sotalol Test in Acquired Long QT Syndrome

Acquired LQTS is caused by ion channel mutations. Current concepts postulate an intrinsic susceptibility to challenges of myocardial repolarization. This reduced repolarization reserve, the basis of which is still ill defined, is composed of rare as well as common genetic variants, together with acquired electrical remodeling, as seen during hypertrophy and heart failure. A large number of cardiac and noncardiac drugs induce disproportionate QTc prolongation and cause potentially lethal torsades de pointes arrhythmias in selected patients at risk.[62,63] Therefore it is very important to identify patients at risk in a timely manner. To face this clinical challenge, Kääb and coworkers developed a drug-based provocative test protocol using the class II/III antiarrhythmic drug sotalol.[64] In a pilot study, they conducted sotalol testing on 40 patients (20 control subjects and 20 patients with documented torsades de pointes). All patients fasted for 6 to 8 hours before testing, and blood pressure and heart rhythm were noninvasively monitored continuously from 1 hour before to 24 hours after testing. All patients had sinus rhythm at the beginning. After 1 hour of resting (baseline), intravenous d,l-sotalol was administered at a constant rate of 2 mg/kg (in 50 mL 0.9% saline) for 20 minutes. The longest Q-T and QTc intervals at baseline and 5 to 10 minutes after sotalol infusion were used for analysis. At baseline, no differences in Q-T and QTc intervals could be detected between the two groups. After sotalol infusion, QT increased from 404 ± 39 to 561 ± 68 ms and QTc increased from 434 ± 21 to 541 ± 37 ms, with QT duration in patients with torsades de pointes significantly longer than in control subjects. None of the control subjects had an increase of QTc greater than 480 ms, whereas all patients with torsades de pointes had an increase in QTc resulting in QTc greater than 480 ms after sotalol infusion, indicating 480 ms as a potential cutoff in diagnosing acquired LQTS (Figure 70-3).

Larger clinical trials are needed, however, to validate the results of this pilot study.

Effects of Ibutilide

From a study by Cheng et al, the class III antiarrhythmic ibutilide may be considered suitable for provocative testing in patients at risk for inducible LQTS.[65] In this study, the investigators performed EPS on 21 patients without LQTS receiving 1 mg of the I_{Kr} blocker ibutilide. Ibutilide caused a reduction in baseline heart rates and prolongation of ventricular repolarization during sinus rhythm. They calculated the QT variability index (QTVI), which, when prolonged, was associated with an increased risk for arrhythmogenesis. QTVI remained unchanged during sinus rhythm after ibutilide infusion. Because variations in basic cycle lengths may increase the risk for ventricular arrhythmias, random interval atrial pacing was performed; it revealed a significant increase in QTVI after ibutilide infusion in patients with and without structural heart disease.[60,65,66] On the basis of these results, it was suggested that an increased temporal lability of repolarization was caused by ibutilide during heart rate fluctuations. Therefore, despite some limitations of this study, such as the small number of patients enrolled, ibutilide administration in combination with programmed atrial pacing may be considered a useful tool in patients at risk for inducible LQTS in the future. However, further studies are required to develop an established and standardized test protocol in larger patient cohorts to confirm the validity of this test in patients with latent repolarization disease.

Exercise Stress Test

Another method to unmask concealed LQTS is the exercise test. A widely used protocol was developed by Bruce (see Chapter 53) and can be applied on a treadmill or a bicycle.[12]

Takenaka et al conducted exercise stress testing on 82 patients with genetically identified LQTS and 33 healthy control patients.[67] They showed that the QTc interval and the interval between the peak and the end of the T wave (Tpe) were significantly prolonged in LQT1 associated with a morphologic change of the T wave to a broad-based pattern. In contrast, patients with LQT2 did not show any significant changes in QTc or Tpe interval but revealed a prominent notch on the T wave. LQT1 and LQT2 could be differentiated with an exercise stress test.

In another study by Wong et al, 159 patients with suspected LQTS performed an exercise stress test on a treadmill combined with postural ECG test recordings in the supine position and immediately thereafter in the vertical position.[68] Each patient was genotyped to validate the results of the exercise stress test. These investigators demonstrated that patients with LQTS exhibited a greater prolongation of QTc with postural change compared with healthy subjects. During exercise, patients with LQT1 showed a marked increase in QTc prolongation that significantly differed from the slight prolongation of QTc in LQT2 or the unchanged QTc in healthy individuals. In conclusion, Wong et al validated

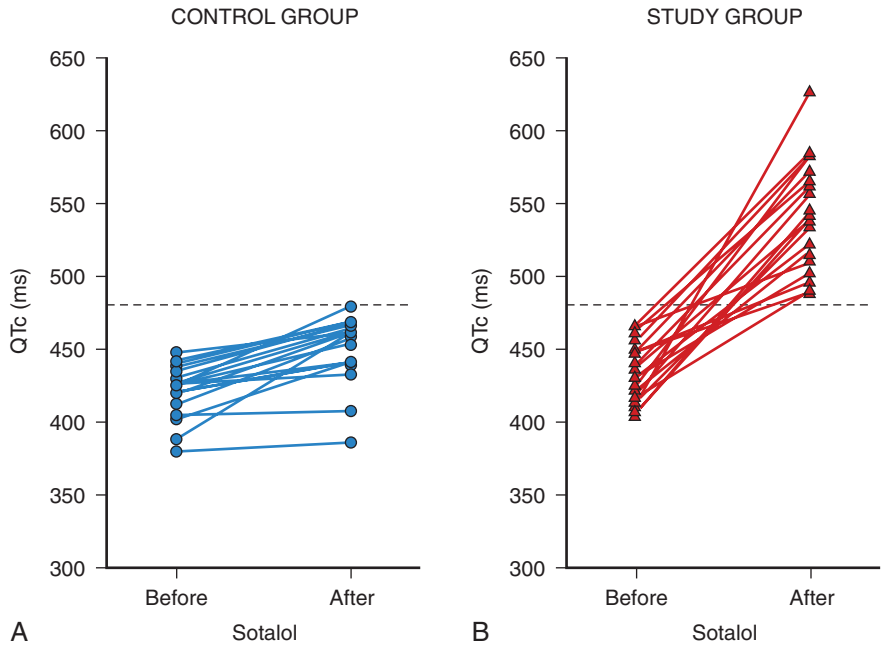

FIGURE 70-3 Individual QTc intervals in control (**A**) and study (**B**) groups before and after sotalol administration. The *dotted line* indicates a cutoff value of 480 ms that is distinguished best between the study population and the control group. *(From Kaab S, Hinterseer M, Nabauer M, Steinbeck 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 *24:649–657, 2003.)*

exercise stress testing as a useful method in predicting LQTS, especially LQT1.

The different results of the various genotypes may support the finding that fatal cardiac events in LQT1 are more often associated with exercise.[67]

Unmasking Concealed Long QT Syndrome by Standing Maneuvers

Recently, investigators studied whether short, transient sinus tachycardia occurring while standing would be able to change the Q-T interval to establish an additional provocative test method to unmask concealed LQTS.[69] Standing leads to sinus tachycardia causing Q-T interval shortening in healthy hearts. However, patients with LQTS often display a pathologic response to heart rate changes, as seen during epinephrine testing. To investigate this phenomenon, Viskin and colleagues conducted a standing test in 68 LQTS patients with different genotypes and 82 healthy control subjects and compared ECG parameters such as heart rate and Q-T and QTc intervals recorded with the patient beginning in the supine position and moving to the vertical position. Upon standing, both groups showed similar heart rate acceleration but significantly different Q-T interval changes. Healthy control subjects exhibited a shortening of the Q-T interval, whereas patients with LQTS showed a prolongation of the Q-T interval. Because of the heart rate acceleration, both groups showed a prolongation of the QTc interval, with both cohorts being significantly different. In a subgroup analysis, Q-T interval changes during sinus tachycardia induced by standing were particularly impaired in patients with LQT2, a finding that helped establish an additional useful test for the diagnosis of LQTS.

Brugada Syndrome

Another channelopathy predisposing to ventricular arrhythmias is Brugada syndrome, which was described for the first time by Brugada et al in 1992.[70] Patients with Brugada syndrome commonly present with syncope, VT, or SCD depending on whether the arrhythmia is (self-)terminating. Interestingly, these patients do not show any structural heart disease but a specific ECG pattern of right bundle branch block (RBBB) with ST-segment elevation in precordial leads. The three types of ECG pattern are a coved ST-segment elevation (type 1), an ST-segment elevation with a saddleback-like T wave (type 2), and an only slightly elevated ST segment with either a coved-type configuration or a saddleback configuration (type 3).[71] However, only the type 1 ECG pattern can be used to diagnose Brugada syndrome if other reasons for ST-segment elevation are excluded.[71] In addition, the ECG in Brugada syndrome can be completely normal. As a consequence, provocative test methods have been developed to unmask concealed Brugada syndrome.[72-74] This testing involves sodium channel blockers, with flecainide, procainamide, pilsicainide, propafenone, and ajmaline being the most frequently used (Figure 70-4). For a detailed description of provocative drug testing in Brugada syndrome, see Chapter 62.

Catecholaminergic Polymorphic Ventricular Tachycardia

CPVT, which is an exercise-induced arrhythmia in patients with structurally normal hearts, causes syncope or SCD.[75] Ventricular arrhythmia occurring during exercise is polymorphic with an alternating beat-to-beat QRS axis, the so-called *bi-directional*

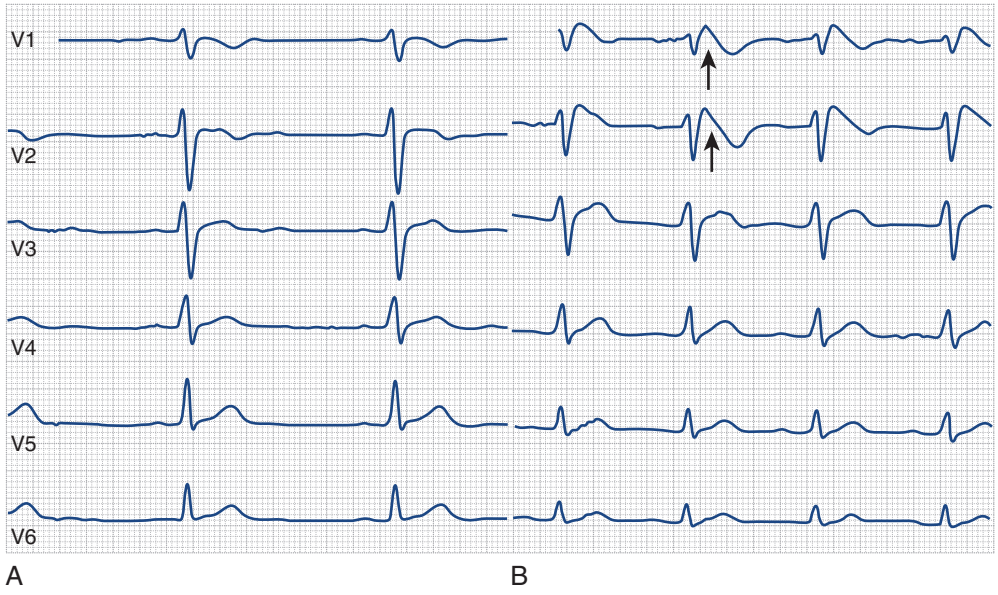

FIGURE 70-4 Positive ajmaline stress test result performed in a 21-year-old man with a history of unexplained syncope. **A,** Electrocardiogram at rest shows no significant abnormalities and only a slightly elevated ST segment. **B,** After administration of ajmaline, a coved-type ST-segment elevation is unmasked (type 1 pattern, indicated by *arrows*), leading to the diagnosis of Brugada syndrome.

ventricular tachycardia (Figure 70-5). The resting ECG, however, is usually normal.[76] Thus diagnosis of CPVT and differentiation from concealed LQTS is difficult. As a consequence, provocative stress testing with exercise or isoproterenol is often conducted.[75]

Beckmann et al reported a family with a history of recurrent SCD that affected nine family members during the past 30 years.[77] Genetic testing revealed LQT1. However, one girl without *KCNQ1* mutation died suddenly at the age of 13. Because other noncarrier family members showed symptoms such as syncope, an exercise stress test was performed by the family members; this led to the diagnosis of CPVT as a second inherited disease in the same family (Figure 70-6).

Krahn et al reported a study on 18 patients with unexplained cardiac arrest in which adrenaline and procainamide were used to unmask ventricular arrhythmias.[78] Under continuous ECG monitoring, adrenaline was administered at a starting dose of 0.05 μg/kg/min followed by incremental doses up to 0.40 μg/kg/min to detect VT or QTc prolongation. After a 30-minute washout period, procainamide at a dose of 15 mg/kg was infused to unmask ST-segment elevations diagnostic for Brugada syndrome. Using this test protocol, 56% of the patients were diagnosed with CPVT, 11% with Brugada syndrome, and 33% with idiopathic VF. Interestingly, 50% of the patients with CPVT did not show any ECG abnormality during exercise stress test performed earlier. Thus the authors concluded that adrenaline was superior to exercise stress testing in unmasking CPVT. They suggested that a combined sympathetic stimulation with vagal blockade during exercise was less arrhythmogenic compared with sole sympathetic stimulation with adrenaline.

Despite the reported inducibility of CPVT with exercise in 100% and by isoproterenol in 75%, but not by programmed stimulation, Brunetti demonstrated one case of CPVT that was detected by continuous ECG recording but was not inducible by exercise.[79,80]

One main characteristic of CPVT is the reproducible provocation of ventricular tachyarrhythmia during exercise.[81] Hence, repeated stress tests (exercise or drugs) can be used to monitor adequate therapy with β-blockers, the most frequently used drugs in CPVT. A tachyarrhythmia that is still inducible during exercise under β-blockade indicates ineffective therapy and should lead to increasing the dose of the β-blocker.[80,82,83]

Repetitive Monomorphic Ventricular Tachycardia (Type Gallavardin)

Another ventricular arrhythmia occurring in patients without an overt cardiac structural abnormality is repetitive monomorphic ventricular tachycardia (type Gallavardin, RMVT). It is defined by numerous monomorphic premature ventricular complexes, couplets, and runs of nonsustained VT. In most cases, a left bundle branch block (LBBB) pattern with normal or rightward axis during tachycardia can be observed.[84] Because RMVT manifestation is exercise dependent, provocative test methods can be used to diagnose and differentiate it, especially from paroxysmal sustained idiopathic VT.

Hoffmann et al characterized 20 patients with RMVT, demonstrating the diagnostic value of exercise stress testing and isoproterenol infusion in these patients.[84] Exercise testing on a treadmill induced runs of tachycardia or sustained VT in 85% of their patients. In addition, sensitivity for verapamil can be tested during exercise testing after induction of tachycardia. Because of its reproducibility, this exercise test can also be used to evaluate the effectiveness of drug therapy and establish the adequacy of therapy when tachycardia is no longer inducible during the same

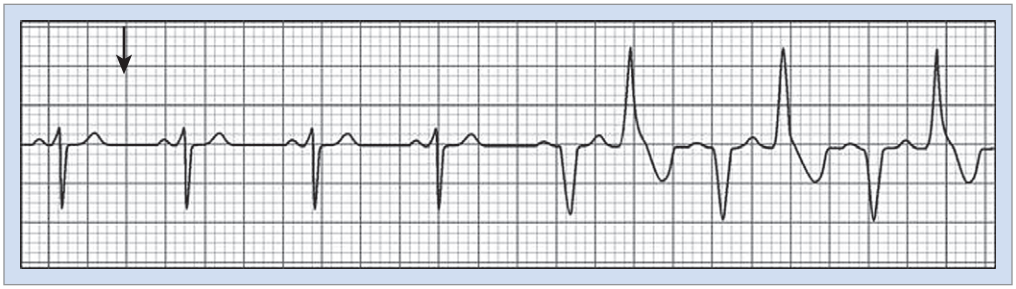

FIGURE 70-5 Bi-directional tachycardia seen in catecholaminergic polymorphic ventricular tachycardia.

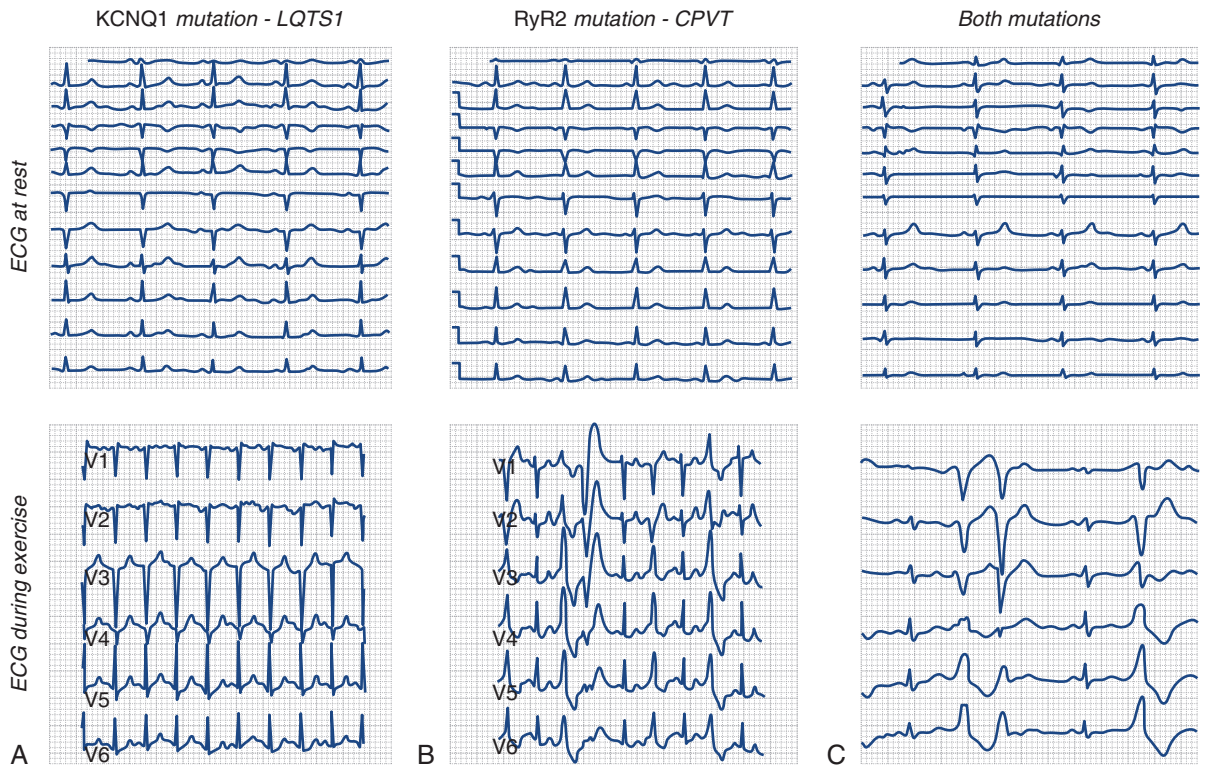

FIGURE 70-6 Electrocardiogram recordings of three different members of a family affected by sudden cardiac death. **A,** A patient with *KCNQ1* mutation (long QT syndrome type 1) shows only a borderline QTc prolongation (450 ms) at rest and no ventricular extra beats during exercise stress test at a heart rate of 150 beats/min. **B,** A patient with *RyR2* mutation (catecholaminergic polymorphic ventricular tachycardia) shows a normal resting electrocardiogram but polymorphic ventricular extra beats during exercise (heart rate, 150 beats/min). **C,** A patient with both mutations shows a borderline QTc prolongation (447 ms) at rest and polymorphic ventricular extra beats during exercise at a heart rate of 100 beats/min.

test protocol. Similar results have also been described for the isoproterenol test. By using 1 to 5 μg/min isoproterenol, tachycardia can be induced in 88% of these patients, but, interestingly, sole programmed right ventricular stimulation induced tachycardia in only 13% of the patients.

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CHAPTER 71

Head-up Tilt-Table Test

Satish R. Raj and Robert S. Sheldon

Definition of the Head-up Tilt-Table Test

The head-up tilt-table test (HUTT) is simply a method of subjecting patients to a prolonged upright position. It provokes a range of normal and abnormal responses and is used most commonly to investigate syncope. Tilt tests induce syncope or presyncope in most patients with otherwise undiagnosed syncope and induce the same endpoints in only a minority of control subjects.[1] HUTTs have been used in diagnostic studies in populations such as those with neurally mediated syncope (NMS[2]; "reflex fainting"), syncope in the setting of structural heart disease, and loss of consciousness that might be caused by epilepsy. These tests are also used for the assessment of orthostatic hypotension, autonomic neuropathy, and postural orthostatic tachycardia syndrome.[2] They have been used as entry criteria in observational studies and clinical trials, mechanistic physiological studies of the neurally mediated reflex, and in pharmacologic treatment studies and have been proposed to be useful for selecting efficacious treatment.[3,4] Tilt tests have made the informed care of syncope patients more accessible and less daunting. By their ability to induce syncope under controlled conditions, they have reassured many patients about a relatively benign diagnosis.

In the first part of this chapter, the physiology of tilt testing and some of the methods of testing will be briefly reviewed and then various aspects of its diagnostic accuracy and clinical uses will be summarized. A series of specific uses and outcomes to illustrate ways to interpret the HUTT will also be presented.

Indications for the Head-up Tilt-Table Test

Syncope is a common problem. Community-based epidemiologic studies have shown that the lifetime prevalence of syncope is over 40% and that many people experience recurrent episodes of fainting.[5] The neurally mediated (vasovagal) reflex is the most common cause, particularly in young people, but other causes are also frequently seen. Syncope is responsible for about 1% of emergency room visits and 1% to 3% of hospital admissions, and syncope patients are frequently referred to internists, cardiologists, and neurologists.[6] A diagnostic process with reasonably high accuracy was needed to discriminate syncope caused by potentially fatal conditions from syncope caused by more benign ones. In the late 1980s, a number of groups reported the usefulness of the HUTT in diagnosing the particularly common neurally mediated reflex, which is the cause of NMS.[7,8] Tilt tests are now widely used for diagnosing syncope, and they have been used as tools for physiological studies, for predicting outcome, and for selecting therapies.

Tilt testing is not the only diagnostic modality that is used for investigating the cause of syncope. Quantitative histories and implantable loop recorders are also under active investigation and are used in clinical practice. The uses of a focused syncope history, tilt tests, and loop recorders are all recommended in clinical guidelines.[2] The cause of syncope can be comfortably determined with a good history in most cases, and the need to proceed with tilt testing or loop recorders should be determined on a case-by-case basis. Commonly, tilt tests are used if a clinical suspicion of some form of autonomic disorder such as NMS or an autonomic neuropathy is present, and loop recorders are indicated for a suspected arrhythmia.

Protocols and Procedures of the Head-up Tilt-Table Test

The core of the HUTT is passive head-upright tilt for 20 to 60 minutes until hypotension, bradycardia, and presyncope or syncope ensues or until the test ends. Variants of this method include the use of intravenous isoproterenol, sublingual nitrates, intravenous clomipramine, or combined lower-body negative pressure to induce an endpoint either earlier or with higher likelihood.[9-13] Consensus conferences have recommended different uniform protocols, but no formal comparison of their diagnostic accuracies has been made.[2] Protocols that use a steeper tilt angle or a longer duration of tilt and drug interventions have higher positive yields and lower specificities.

An example of the tilt testing equipment and protocols at one hospital is outlined in Table 71-1. Patients are studied either after overnight fasting or at least 2 hours after food absorption to decrease the risk of vomiting and aspiration. The patient is placed on a table (that has a footboard), which can rapidly and smoothly incline from a supine position to head-up tilt (between 60 and 80 degrees from baseline) and, more importantly, can rapidly return to the supine position in the event of hypotension or unconsciousness. Restraints are applied to the patient to avoid accidental falls during loss of consciousness. Some centers, but not all, routinely insert an intravenous catheter (after starting electrocardiogram [ECG] monitoring). This allows administration of medications, either for provocation (isoproterenol, nitroglycerin, or clomipramine) or rarely for rescue (saline or atropine). During the test, the ECG values for both heart rhythm and heart rate (HR) and blood pressure (BP) are monitored. While many laboratories measure only arm-cuff BP every 2 to 5 minutes, continuous BP

Table 71-1 Vanderbilt Heart Institute: HUTT Lab Protocol

MATERIALS AND EQUIPMENT NEEDED

- Head-up tilt table with straps
  - Electric or pneumatic table that can rotate to angles of 60 to 90 degrees head-up
  - Must be able to return to horizontal position within 10 to 15 seconds
- Three-lead ECG lead monitoring system
- Continuous noninvasive BP system
  - Finger BP using a photoplethysmography-based system
- IV access with a 20-gauge IV line (normal saline TKVO)
- Automatic BP monitoring (arm cuff) system
  - To calibrate continuous BP readings
- Digital data acquisition
  - ECG and continuous BP
  - Pharmaceutical provocative agent: nitroglycerin 0.4 mg/spray
  - Pharmaceutical rescue agent: atropine 1 mg IV in a predosed ampoule

PERSONNEL NEEDED

- RN with ACLS training
- RN able to establish IV access and give patient medication
- Heart technician to aid in data acquisition
- Physician
  - ACLS-qualified physician in vicinity of testing and available to respond to emergency
  - Physician does not need to be in room during tilt test

PROCEDURE DESCRIPTION

- The patient should be maintained NPO for 3 hours prior to testing.
- In the initial evaluation, patients should have the following medications held for five half-lives before the test or as tolerated (unless specifically requested otherwise by a physician).
  - Disopyramide, scopolamine patch, fludrocortisone, and β-blockers should be administered.
- Informed consent must be obtained before the test.
- The patient is placed on the tilt table in the supine position. The patient's feet are positioned against the foot rest. Strapping is placed around the patient's knees to prevent the knees from buckling and around the chest and hips to support the patient and prevent slumping. Placing straps around the abdomen is avoided because of discomfort or injury to the patient's abdomen or organs.
- The electrodes are applied to the patient and connected to the ECG cable.
- IV access is obtained, and an IV infusion of NS is begun at TVO rate (only after the ECG cables are in place to capture bradycardia/asystole with IV insertion).
- The continuous BP monitor is positioned on the patient's finger.
- An automatic BP cuff is placed and is set to cycle every 3 minutes.
- The lights are dimmed in the room, the door is closed, and the patient is reminded that environmental stimuli will be kept to a minimum (no talking unless to report symptoms).
- The patient is monitored for 10 minutes in the supine position to obtain baseline data.
- The patient is placed in the head-up tilt position at 75 degrees. Automatic cycled BP and HR are obtained every 3 minutes with continuous observation of the ECG monitor and the finger BP and the patient's symptoms throughout the test.

TILT PROTOCOL

- The patient is to remain in the head-up tilt for 30 minutes, plus another 10 minutes following sublingual nitroglycerine 0.4 mg administration for a total of 40 minutes (unless a reason to terminate the study is present).

REASONS FOR TEST TERMINATION

- Frank syncope or severe presyncope with systolic BP <70 mm Hg
- Completion of protocol without syncope or pre-syncope
- Elevation of BP: systolic BP >220 mm Hg, diastolic BP >120 mm Hg, or both, or increase in BP associated with symptoms such as blurred vision, dizziness, or headache
- Worsened bradycardia or tachycardia
- Progressive angina pain
- Ischemic ST changes
- Patient's intolerance or fatigue

HUTT, *Head-uptilt-table test;* ECG, *electrocardiogram;* BP, *blood pressure;* IV, *intravenous;* RN, *registered nurse;* TKVO, *to keep vein open;* ACLS, *Advanced Cardiac Life Support;* NPO, *nothing by mouth;* NS, *normal saline;* HR, *heart rate.*

Table 71-2 Adjunctive Investigations During Head-up Tilt-Table Test

- Transcranial Doppler ultrasound monitoring of the middle cerebral artery velocity during the tilt
- Electroencephalogram monitoring during the tilt
- Carotid sinus massage performed shortly after the upright tilt (and before any provocative agent is given)

Table 71-3 Revised Vasovagal Syncope International Study (VASIS) Classification of Positive Head-up Tilt-Table Test[45]

TYPE 1: MIXED
Heart rate falls at the time of syncope, but the ventricular rate does not fall to <40 beats/min or falls to <40 beats/min for less than 10 seconds with or without asystole of <3 seconds. Blood pressure falls before heart rate falls.
TYPE 2A: CARDIOINHIBITION WITHOUT ASYSTOLE
Heart rate falls to a ventricular rate <40 beats/min for more than 10 seconds, but asystole of more than 3 seconds does not occur. Blood pressure falls before heart rate falls.
TYPE 2B: CARDIOINHIBITION WITH ASYSTOLE
Asystole occurs for more than 3 seconds. Heart rate fall coincides with or precedes blood pressure fall.
TYPE 3: VASODEPRESSOR
Heart rate does not fall more than 10% from its peak at the time of syncope.

measurements (either with an arterial line or with continuous noninvasive technology) provide more information, especially at the time of hypotension and fainting when an automatic arm cuff can sometimes pose difficulties in documenting BP. Adjunctive investigations can be combined with the HUTT in special circumstances, and some are listed in Table 71-2.

Definition of a Positive Head-up Tilt-Table Test

A positive test for NMS requires both the presence of hypotension (usually with relative or absolute bradycardia) *and* the reproduction of some clinical symptoms before and after the faint. Investigators of the VASIS (Vasovagal Syncope International Study) developed a classification scheme to subcategorize positive hemodynamic responses to the HUTT on the basis of the relative roles of bradycardia and vasodepression (Table 71-3), although the clinical usefulness of the classification is not yet clear. Some patients can have a typical hemodynamic pattern for NMS, but the symptoms are not clinically reminiscent. While these patients may be predisposed to this type of fainting, it may be unrelated to their current clinical problems. The HUTT can also demonstrate patterns of orthostatic tachycardia or orthostatic hypotension (immediate or delayed).

Passive Drug-Free Head-up Tilt-Table Test

Protocol

The traditional HUTT protocol involves tilting a subject to at least 60 degrees head-up tilt or more commonly to 70 to 80 degrees head-up tilt for up to 45 minutes', duration.[14-16] Drug-free protocols have reported positive yields of about 50% and specificities of about 90%.[1] The primary advantage of these protocols is that only passive orthostatic stress is involved, without the possible confounding effects of a nonphysiological response to a drug.

Isoproterenol and the Head-up Tilt-Table Test

Rationale

Isoproterenol is administered to mimic the catecholamine response to orthostatic stress.

Protocol

After a short drug-free HUTT phase, patients are infused with incremental doses of isoproterenol ranging from 1 to 3 μg/min for 10 minutes at each level of isoproterenol. Doses of 5 μg/min at an angle of more than 80 degres for more than 10 minutes provoke a high rate of false-positive tests. However, using only a 15-minute drug-free HUTT followed by isoproterenol 1 to 3 μg/min has a reported positive test rate of ~60% and specificity greater than 90%.[9]

Nitroglycerin and the Head-up Tilt-Table Test

Rationale

Nitrates are given to increase venodilation.

Protocol

Intravenous nitroglycerin infusions and sublingual nitroglycerin with tilt testing also provoke the neurally mediated response.[10,11] Sublingual nitroglycerin 0.3 to 0.4 mg following a 45-minute drug-free HUTT has a positive test rate for patients with syncope of unknown origin of 61% and a specificity of 94%.[2] The advantages of sublingual nitroglycerin over isoproterenol are improved convenience, improved tolerance, and ease of use. Although both isoproterenol HUTT and nitroglycerin HUTT have comparable rates of positive tests and true-negative rates, Oraii et al[17] found that 75% of their cases had discordant responses to the two tests, suggesting that the provocative agents may provide complementary information.

Clomipramine and the Head-up Tilt-Table Test

Rationale

Clomipramine is given to increase central nervous system serotonin, which is postulated to be a neurotransmitter central to the reflex.

Protocol

Theodorakis et al[12] reported that a protocol that included infusing intravenous clomipramine 5 mg over 5 minutes was associated with a total positive response rate (both passive phase and with clomipramine) of 80% and a specificity of more than 95%. The putative mechanism involves an acute increase in synaptic serotonin because of acute serotonin reuptake blockade. This has not

been widely used, possibly because of difficulty in obtaining the drug outside Europe.

Physiology Underlying the Head-up Tilt Table Test

Assumption of the upright posture requires prompt physiological adaptation to gravity.[18] About 500 mL of blood rapidly descends from the thorax to the lower abdomen, buttocks, and legs. In addition, a 10% to 25% shift of plasma volume out of the vasculature and into the interstitial tissue occurs, mostly within 10 minutes of upright posture, with a slow ongoing shift after that time.[19,20] This shift decreases venous return to the heart, resulting in a transient decline in both arterial pressure and cardiac filling. This has the effect of reducing the pressure on the baroreceptors, triggering a compensatory sympathetic activation that results in an increase in HR and systemic vasoconstriction (countering the initial decline in BP). Hence, assumption of upright posture results in a 10 to 20 beats/min increase in HR, a negligible change in systolic BP, and an approximately 5 mm Hg increase in diastolic BP.

The most common pathophysiological explanation for NMS is known as the *ventricular hypothesis*.[21] This hypothesis argues that the initiating event is a pooling of blood in the legs (from prolonged sitting or standing) with a resultant reduction in venous return (preload) to the heart. The resultant decrease in BP leads to a baroreceptor-mediated increase in sympathetic tone. This increased sympathetic tone leads to increased chronotropic and inotropic effects. The vigorous contraction, in the setting of an underfilled ventricle, is thought to stimulate unmyelinated nerve fibers (*ventricular afferents*) in the left ventricle. This is then thought to trigger a reflex loss of sympathetic tone and an associated vagotonia (with resultant hypotension, bradycardia, or both).

This hypothesis seems to provide a plausible explanation for the *postural prodrome* to many of the episodes of NMS and provides a rationale for the use of the HUTT. However, even among patients with postural NMS, some experimental observations do not fit completely within this model.[21]

Accuracy of the Head-up Tilt-Table Test

Gold Standard Populations

Tilt testing has a core problem: It has not been validated against a syndrome that has gold standard diagnostic criteria. In essence, the syndrome is *defined* by tilt tests rather than being *diagnosed* by tilt tests. Waxman et al reported that isoproterenol tilt tests induce syncope or presyncope in 75% of subjects with pre-existing classic NMS induced by situations such as the sight of blood or medical procedures.[22] However, Agarwal et al reported that of their 12 subjects who developed the neurally mediated reflex during angioplasty sheath withdrawal, none had positive tilt tests.[23] Therefore, most reports on tilt tests refer to the proportion of positive studies as *positive yield* rather than as sensitivity.

Head-up Tilt-Table Test Sensitivity

A positive response was seen in 49% of drug-free HUTTs and 61% to 69% of drug-provoked tests in patients with prior syncope.[1,2] It is possible that many patients with NMS may have false-negative tilt tests. Even aggressive tilt protocols using isoproterenol appear to be incompletely sensitive in the case of patients who otherwise are similar to those with positive tilt tests.[24]

Specificity of the Head-up Tilt-Table Test

Studies of the specificity of tilt tests are equally difficult to interpret. The first lifetime syncopal spell can occur at any age up to about 45 years, and the lifetime prevalence is around 40%.[5] This raises several problems. First, how many healthy control subjects are predisposed to faint but have simply not yet fainted? Second, if the HUTT identifies people predisposed to fainting, then populations of younger control subjects will appear to have more false-positive tilt tests. This will confound the studies on aging and the autonomic nervous system. Finally, the specificity of a tilt test protocol seems to be inversely related to its positive yield. Thus a "false-positive" tilt may be a mistake (it may be truly false), or it may reflect a physiological propensity to a neurally mediated reaction that has yet to manifest clinically. No ideal protocol exists, but an optimal compromise appears to have both test positivity and specificity around 70% to 75%.

Effect of Protocol Variability on the Head-up Tilt-Table Test Results

Controlled studies have shown that the likelihood of positive tests depends on whether intravenous cannulation is used, the angle and duration of the HUTT, whether and how a drug challenge is used, the number of head-up iterations during the test, the volume status of the subject, and the subject's age.[2,16,25-33] Outcomes can be quite sensitive to subtle changes in tilt conditions. Protocols that use a longer observation period, a steeper tilt angle, and drug interventions have a higher diagnostic yield and lower specificity. Similarly, younger subjects are more sensitive to tilt testing, whether or not isoproterenol is used. While both isoproterenol and nitroglycerin increase the diagnostic yield of the HUTT by the same proportion, the two provocative agents might select different patients.[17]

Reproducibility of the Head-up Tilt-Table Test

Tilt tests are 70% to 87% reproducible over intervals of days to months when both presyncope and syncope are deemed to be positive test outcomes.[2] This may reflect the alterations in testing conditions or reflect a "training effect" with physiological adaptation to the HUTT. On the basis of this observation, Ector et al have developed *orthostatic tilt training* as a treatment for NMS.[34] Given this apparent "training effect," the HUTT should not be used in a serial fashion to assess response to drug therapy for NMS.

Prognostic Utility of the Head-up Tilt-Table Test

Tilt Tests and Clinical Outcomes

HUTTs do not predict the future clinical course of patients. In three studies, patients had similar rates of syncope recurrence after the HUTT whether the test outcome was negative or positive.[24,35,36] As well, the ISSUE (International Study on Syncope of Uncertain Etiology) investigators reported that the degree of bradycardia elicited during a positive tilt test failed to correlate with the degree of bradycardia recorded on an implanted loop recorder during a subsequent syncopal spell in the community.[36] Thus, the HUTT fails to predict the future clinical outcomes of patients.

Ability to Select Efficacious Clinical Therapy

Although some have proposed using tilt-table testing as a way to select efficacious therapy, this strategy has not been shown to work. The fact that β-blockers can prevent syncope during

isoproterenol tilt tests suggests that the need for isoproterenol to obtain a positive tilt test would predict eventual clinical benefits from β-blockers. This was tested as a formal substudy of the Prevention of Syncope Trial and was conclusively disproven.[37] A related hypothesis was that profound bradycardia or asystole on a tilt test would predict eventual clinical benefit from permanent cardiac pacing. This, too, seems unlikely. Two observational, historically controlled studies of pacing and syncope and the Second Vasovagal Pacemaker Study concluded that the degree of bradycardia on baseline tilt tests did not predict the subsequent likelihood of syncope in patients treated with a permanent pacemaker.[38-40] A later meta-analysis that included a patient-specific analysis came to the same conclusion.[41]

Therefore, results of the HUTT are not useful for prognosis. These results do not predict eventual clinical outcome or improvement with either β-blockers (which probably do not work in most patients) or with pacemakers.[37]

Guidelines to Order a Head-up Tilt Table Test

Prior to proceeding to the HUTT, a detailed history of the fainting spells should be taken and a focused physical examination performed. The most recent guidelines for the HUTT come from the European Society of Cardiology (2009).[2] Tilt testing was felt to be appropriate (or at least worthy of consideration) in the following clinical circumstances (the class of recommendation is listed after each item):

1. To assess RECURRENT episodes of syncope, either in the absence of structural heart disease, or in the presence of structural heart disease AFTER other cardiac causes of syncope have been excluded. (class I)

2. An unexplained SINGLE syncopal episode if it was associated with physical injury OR the patient has a high-risk-setting occupation (e.g., pilot). (class I)

3. When there is deemed to be clinical value in demonstrating neurocardiogenic syncope to the patient (education/reassurance). (class I)

4. Differentiating syncope with myoclonic activity from epilepsy. (class IIb)

5. Evaluating patients with recurrent unexplained falls. (class IIb)

6. Assessment of frequent syncope and psychiatric disease. (class IIb)

Authors' Approach to Ordering a Head-up Tilt Table Test

As with many commonly used tests (such as cardiac exercise testing), a Bayesian approach is required for optimal performance. If the pretest probability of NMS is so high (or so low) that a negative (or positive) HUTT would not alter that diagnosis, then the test may not be worthwhile. However, when clinical features of NMS as well as atypical clinical features are present, then the HUTT may provide useful information that makes the diagnosis of NMS more or less likely. This threshold will vary from provider to provider, even for the same patient, depending on the clinical impression (particularly the historical features surrounding the fainting spell and prior spells).

In some cases, a provider may be confident in the diagnosis of NMS, but the patient or family may not be as confident in the provider's clinical acumen. In this circumstance, the HUTT can be very useful to reassure the patient and the family about the diagnosis of NMS, which is a relatively benign cause of syncope.

Although the HUTT was clinically developed largely to diagnose NMS, it can also be useful for diagnosing other disorders. Postural tachycardia syndrome (POTS) is a chronic multisystem disorder that is associated with an excessive (supraphysiological) increase in HR on assuming an upright posture.[18] An HUTT will capture this hemodynamic information, as shown in Case Scenario #5. Orthostatic hypotension has traditionally been defined as a drop in BP greater than 20/10 mm Hg within 3 minutes of standing.[42] In the recently described phenomenon of delayed orthostatic hypotension, the drop in BP occurs only after longer upright posture, such as with the HUTT.[43,44]

Head-up Tilt-Table Test: Shades of Gray

HUTTs have provided mixed benefits with regard to NMS. Unquestionably, they have greatly improved informed care of patients with syncope and have led to a revived interest in the field. They have provided inclusion criteria for study populations for diagnostic studies, long-term observational studies, and randomized clinical trials. Tilt tests have been used as platforms for physiological studies and pilot treatment studies. Unfortunately, HUTTs also have a complex mix of significant methodologic variables and have not been validated against gold standard populations; they are only moderately reproducible and do not provide prognostic predictive power. HUTTs have also not been shown to be useful in selecting efficacious therapies. The usefulness of HUTTs must be understood in the context of these various benefits and limitations.

Case Scenarios: Interpretation of the Head-up Tilt-Table Test

Tilt Scenario 1: Neurally Mediated Syncope

Scenario

V.V. is a 20-year-old male with a 6-month history of recurrent syncope. He has had six spells so far, all of which occurred while he was upright—either walking or standing still. At times, he has had a brief presyncope prior to a frank syncopal spell.

Tilt Results and Interpretation

V.V. underwent a drug-free HUTT at a 75-degree head-up tilt for a planned duration of 45 minutes. Immediately on upright tilt, a small increase in both HR and BP occurred (Figure 71-1, *A*). During the next 30 minutes of ongoing tilt, BP remained stable, although HR slowly increased during prolonged tilt. After 35 minutes, an abrupt decrease occurred in BP over ~20 seconds, immediately preceded by some BP cycling (see Figure 71-1, *B*). The nadir systolic BP was 78 mm Hg and was associated with severe presyncope that *reproduced his clinical symptoms*. BP began to recover as soon as the tilt table was returned to the supine position.

This hemodynamic pattern is typical of NMS. The patient had stable HR and BP for over 30 minutes during the head-up tilt.

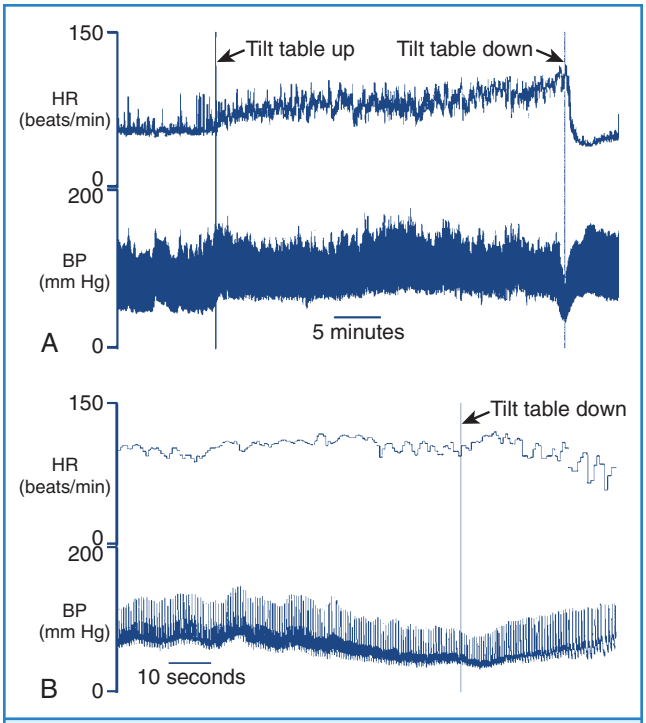

FIGURE 71-1 Neurally mediated syncope. **A,** The heart rate (*HR*) and blood pressure (*BP*) are shown for the duration of the head-up tilt-table test. For over 30 minutes of the head-up tilt, BP was stable and HR increased slightly but was stable. **B,** After 35 minutes, an abrupt decrease in BP occurred over approximately 20 seconds, immediately preceded by some cycling (increasing and decreasing) BP. BP began to recover immediately on return of the tilt table to the horizontal position.

Then a rather precipitous decrease in BP associated with severe presyncope occurred. This is a vasodepressor pattern (VASIS type 3; see Table 71-3).[45] In the authors' laboratory, this is the most commonly seen hemodynamic pattern with a positive HUTT.

NMS is a clinical diagnosis and not one that can be made by the HUTT alone. The diagnosis of NMS is supported in this case, since the presyncopal symptoms during the HUTT were similar to those experienced by the patient prior to his clinical episodes of syncope.

Tilt Scenario 2: Neurally Mediated Syncope with Nitroglycerin Provocation

Scenario

P.A. is a 36-year-old male with a seizure disorder since childhood. He has been free of seizures for over 5 years on a stable antiepileptic regimen. In the last 8 months, however, he had developed a different type of loss of consciousness spell. During an episode, he had a short or absent prodrome before losing consciousness and falling to the ground. His loss of consciousness lasted only 15 seconds, he turned pale, and he woke up feeling warm and diaphoretic. Given that his recent symptoms were different from his prior seizure symptoms, he was referred for an HUTT.

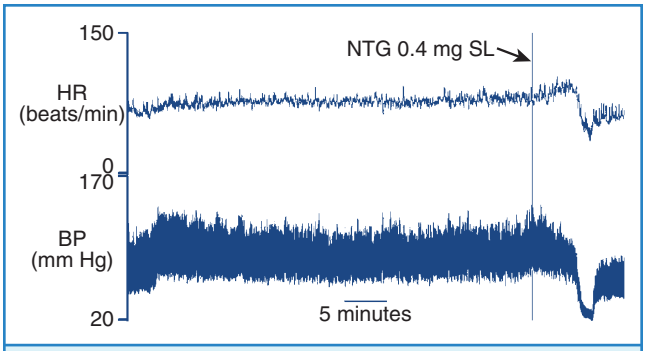

FIGURE 71-2 Nitroglycerin provocation. Heart rate (*HR*) and blood pressure (*BP*) remained stable for the 30 minutes of drug-free tilt. In response to sublingual nitroglycerin 0.4 mg, BP initially decreased slightly and HR increased slightly. After a few more minutes, both HR and BP fell rapidly and the patient developed syncope.

Tilt Results and Interpretation

Immediately on a head-up tilt to 75 degrees, P.A.'s HR and BP increased slightly. This hemodynamic pattern remained stable for the remaining 30 minutes of drug-free tilt (Figure 71-2). He was then given sublingual nitroglycerin 0.4 mg as a provocative agent. As a result of nitroglycerin-induced venodilation, P.A.'s BP decreased slightly and his HR increased slightly. This was not a positive result but a direct hemodynamic response to the nitroglycerin. After a few minutes, both his HR and his BP fell rapidly, and he had an episode of syncope. He felt warm and diaphoretic, which mimicked his clinical spells.

Several drugs have been used to increase the yield or sensitivity of the HUTT. These include isoproterenol, nitroglycerin, and clomipramine. All of these agents increase the sensitivity of the HUTT at the expense of a decrease in specificity (see Protocols and Procedures for the Head-Up Tilt Test for details). Here, the diagnosis was established when his clinical symptoms were reproduced when he had both hypotension and bradycardia.

Tilt Scenario 3: False-Positive Tilt Test Result

Scenario

A healthy 24-year-old female volunteered for a clinical research study and underwent an HUTT as a part of the research protocol. She had no history of either syncope or orthostatic intolerance.

Tilt Results and Interpretation

She underwent a drug-free HUTT at a 60-degree head-up tilt. After 13 minutes, she began to feel lightheaded. Her BP decreased suddenly (Figure 71-3), and she experienced frank syncope after just 14 minutes into the HUTT. The table was returned to the horizontal position, and she rapidly recovered.

Her hemodynamic pattern during the HUTT is very similar to that of the NMS patient (see Figure 71-1, *A*). Both demonstrated a tilt pattern consistent with NMS—a prolonged maintenance of BP followed by rapid hypotension culminating in frank syncope or severe presyncope. She does not have NMS as such, since NMS is a clinical diagnosis and she has not had clinical syncope. This is a false-positive result, although in time she might have clinical syncope.

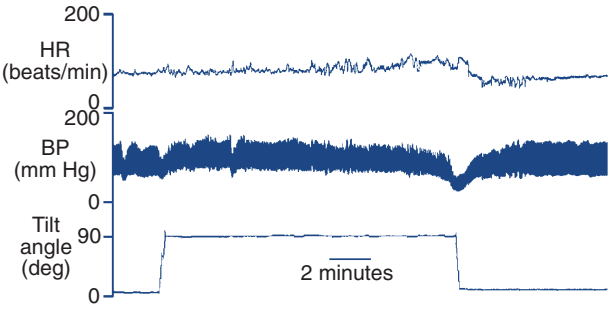

FIGURE 71-3 False-positive tilt test. Heart rate (*HR*) and blood pressure (*BP*) in response to head-up tilt-table test are similar to that seen in Figure 71-1. Since this patient had never fainted clinically outside this test, this is a false-positive response to tilt-table testing.

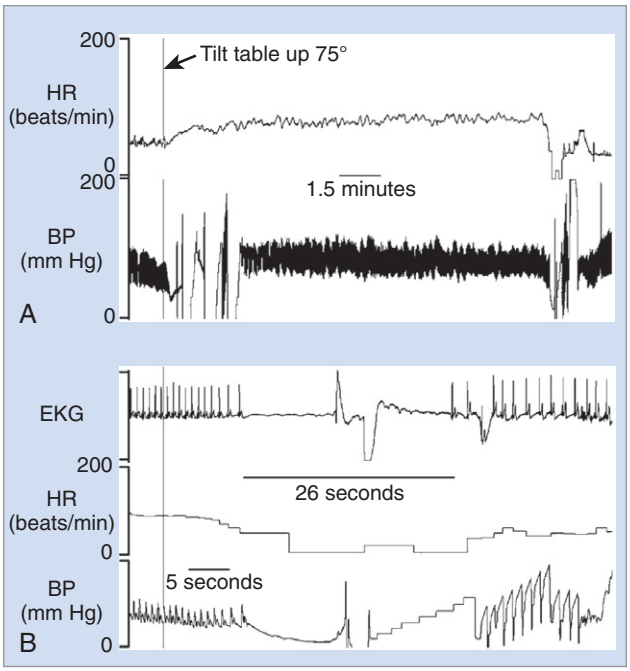

FIGURE 71-4 Convulsive syncope.This tilt test was performed on a boy who had "seizures" during his spell. **A,** Heart rate (*HR*) and blood pressure (*BP*) shown are values recorded during the head-up tilt-table test. **B,** After 14 minutes, he developed 26 seconds of asystole, with loss of consciousness and myoclonic jerks. The artifacts in the BP channel at the time of systole are caused by the myoclonic jerks. Also, a BP signal problem that occurred early during the tilt was not caused by the myoclonic jerks.

Tilt Scenario 4: Convulsive Syncope

Scenario

C.S. is a 17-year-old male who has had six syncopal spells in his lifetime. Each spell occurred in the setting of orthostatic stress (while seated or standing). His actual loss of consciousness lasted only 1 to 3 minutes, and he experienced prolonged fatigue following each spell. He also reported presyncope in response to acute pain. In the last year, he experienced an unusual loss of consciousness when he was on a mission trip to Honduras. He was apparently playing soccer when he was noted to fall backward and hit his head on the ground. He was reported to have "seizures" during this spell, which caused a good deal of anxiety about a possible diagnosis of epilepsy.

Tilt Results and Interpretation

C.S. underwent a drug-free HUTT at a 75-degree head-up tilt, with continuous monitoring of HR and BP. About 14 minutes into tilt, the patient described stomach discomfort and nausea. Shortly after that, his HR slowed, and he developed 26 seconds of asystole (Figure 71-4, *A*). This loss of consciousness was accompanied by myoclonic jerks that resembled a "seizure" (note the artifacts in the BP signal following asystole in Figure 71-4, *B*).

Both the patient and his mother had been concerned about a possible seizure disorder. They were reassured by the reproduction of the seizure-like symptoms during the HUTT.

Tilt Scenario 5: Postural Tachycardia Syndrome

Scenario

O.T. is a 26-year-old female with intolerance to the upright posture. She reports that several times in a day she experiences lightheadedness and presyncope in the upright posture. She reports that while standing she has chest pains, dyspnea, rapid palpitation, and a "graying out" of her vision in addition to lightheadedness. She also suffers from frequent headaches and tremulousness. When she feels very unwell, she assumes a recumbent posture, and her symptoms begin to disappear. Despite the frequent presyncope, she has not experienced frank syncope.

Tilt Results and Interpretation

O.T. underwent a drug-free HUTT at a 60-degree head-up tilt. Immediately after the tilt, her BP increased (Figure 71-5, *A*). A striking increase in her HR from 80 beats/min at baseline to 164 beats/min at 3 minutes following the onset of the tilt was seen. In contrast to the patient with neurally mediated hypotension, O.T. began experiencing significant orthostatic symptoms almost immediately after assuming an upright posture, and these became worse with ongoing upright tilt (see Figure 71-5, *B*). These symptoms and elevated HR improved quickly once the table was returned to the horizontal position. The cardinal criterion for POTS is an excessive increase in HR on assuming an upright posture (>30 beats/min increase within 10 minutes) in the absence of orthostatic hypotension (a drop >20/10 mm Hg). The diagnostic criteria for POTS require the aforementioned hemodynamic criteria *plus* a constellation of typical symptoms that get worse with the upright posture and improve with the recumbent posture.[18,46] Only a minority of patients with POTS report frank syncope.[47]

The presence of excessive orthostatic tachycardia is not adequate to make a diagnosis of POTS. Chronic (>6 months), characteristic symptoms on assuming an upright posture on a daily or an almost-daily basis are also necessary for a diagnosis of POTS.

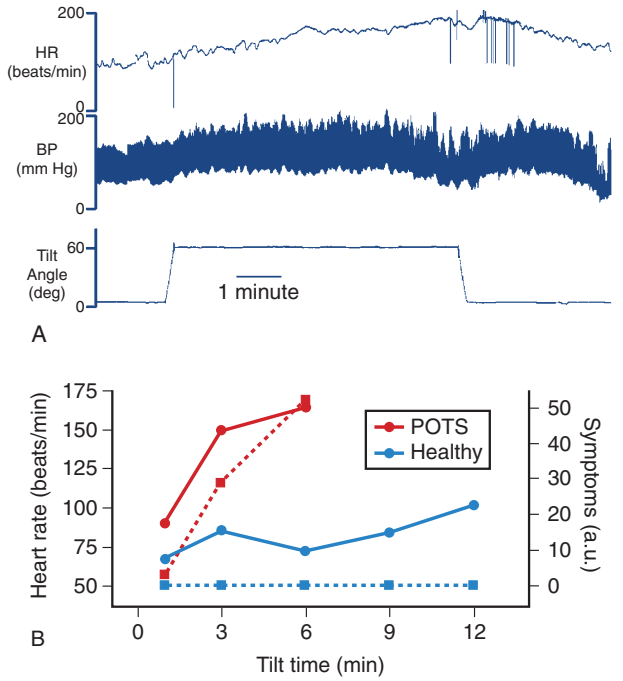

FIGURE 71-5 Postural tachycardia syndrome. **A,** Blood pressure (*BP*) increases in response to head-up tilt, but in this patient with postural tachycardia syndrome (*POTS*), HR increased excessively with the upright posture. This test was terminated early because of severe presyncope with tachycardia in the absence of classic neurally mediated hypotension. **B,** Patients with POTS can become rapidly tachycardic (*solid lines*) and develop severe symptoms (*dashed lines*) on upright tilt. In contrast, healthy subjects have a more modest increase in their HR and are often asymptomatic with the upright tilt.

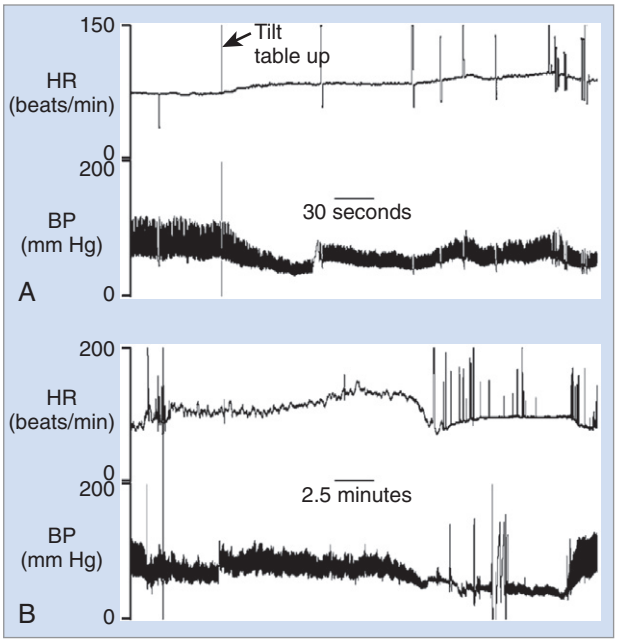

FIGURE 71-6 Neurogenic orthostatic hypotension and delayed orthostatic hypotension. **A,** This patient with neurogenic orthostatic hypotension had a rapid and severe drop in blood pressure (*BP*) almost immediately on upright tilt, with only a modest increase in heart rate (*HR*). The fall in BP was greater than 20/10 mm Hg within 3 minutes of the upright tilt. **B,** The patient with delayed orthostatic hypotension has a slow and gradual decrease in BP. The drop in BP is not greater than 20/10 mm Hg within 3 minutes. In typical neurally mediated syncope, BP is usually stable before it "falls off a cliff," in contrast to the gradual "rolling down a hill" pattern seen in delayed orthostatic hypotension.

Tilt Scenario 6a: Neurogenic Orthostatic Hypotension

Scenario

M.P. is a 79-year-old male who presents with a 1-year history of recurrent presyncope (two per month) but no frank syncope. All of his episodes occurred while he was standing and were also worse in the hot weather. He is unsteady on his feet and prone to falls.

Tilt Results and Interpretation

Within seconds after the table was raised to a 75-degree head-up tilt, M.P.'s BP fell, with only a minimal increase in HR (Figure 71-6, *A*). His BP was 112/74 mm Hg at baseline, and this fell to 69/51 mm Hg within 3 minutes of the HUTT (meeting the criteria for significant orthostatic hypotension). He maintained this BP for the remainder of the test. This hypotension reproduced his clinical presyncope.

This patient has neurogenic orthostatic hypotension with a decrease in BP more than 20/10 mm Hg within 3 minutes of upright posture and only a modest reflex increase in HR.[42] Hemodynamic patterns can be variable. Some patients can maintain their lower BP with ongoing orthostatic stress, while in others BP progressively decreases.[48] Neurogenic orthostatic hypotension can be caused by a peripheral autonomic neuropathy (Bradbury-Eggleston syndrome; pure autonomic failure) or a central autonomic disorder (Shy-Drager Syndrome[49]; multiple systems atrophy). Treatment usually involves a combination of blood volume expansion and vasopressor agents.[50]

Tilt Scenario 6b: Delayed Orthostatic Hypotension

Scenario

S.H. is a 64-year-old female who describes having a typical "sinking feeling" when she is upright for prolonged periods (such as when she must wait in line at a store). She feels better when she sits down. Her severe presyncope is often preceded by nausea.

Tilt Result and Interpretation

Within a few minutes of a 75-degree head-up tilt, her systolic BP fell by 14 mm Hg at 3 minutes (see Figure 71-6, *B*). This does not meet the criterion for orthostatic hypotension.[42] With ongoing tilt, her BP continued to drift downward. Her systolic BP reached a nadir of 52 mm Hg at 24 minutes of head-up tilt. Shortly thereafter, the patient felt nauseated and severely lightheaded, which mimicked her clinical spells.

Delayed orthostatic hypotension is characterized by a slow and gradual decrease in BP that does not occur immediately, as is typically seen with neurogenic orthostatic hypotension. In

contrast to the initially stable BP followed by a sudden drop (falling off a cliff), as is seen with NMS (see Figure 71-1), BP gradually declines in delayed orthostatic hypotension (akin to rolling down a ramp). The exact underlying causes are not known, but the hypotension may be caused by mild failure of the autonomic nervous system in some cases.

Tilt Scenario 7: Syncope with a "Normal" BP—Cerebral Syncope

Scenario

C.T. is a 19-year-old who has suffered from over 20 syncopal spells since age 14 years. All of her loss-of-consciousness (LOC) spells have occurred in the setting of prolonged standing. While undergoing a head-up HUTT at another hospital, C.T. had lost consciousness during the test *while* her systolic BP was approximately 100 mm Hg.

Tilt Result and Interpretation

C.T. underwent a drug-free 75-degree HUTT for a planned duration of 45 minutes. On upright tilt, a small increase in both HR and BP occurred (Figure 71-7, *A*). After 9 minutes of HUTT, C.T. lost consciousness. Her HR was 150 beats/min, and her systolic BP was never below 100 mm Hg (see Figure 71-7, *B*). The table was returned to the horizontal position, and she rapidly regained consciousness.

How could she lose consciousness in the absence of systemic hypotension? Does this mean that her episodes are nonphysiological or nonhemodynamic? The hemodynamic cause of syncope is inadequate cerebral perfusion and not a decrease in the arm or hand BP.

Given her prior history of tilt-table–induced syncope without hypotension, this HUTT was performed with TCD ultrasound of her right middle cerebral artery. Figure 71-7, *C*, shows the TCD velocity signal in addition to the HR and BP at the start of the

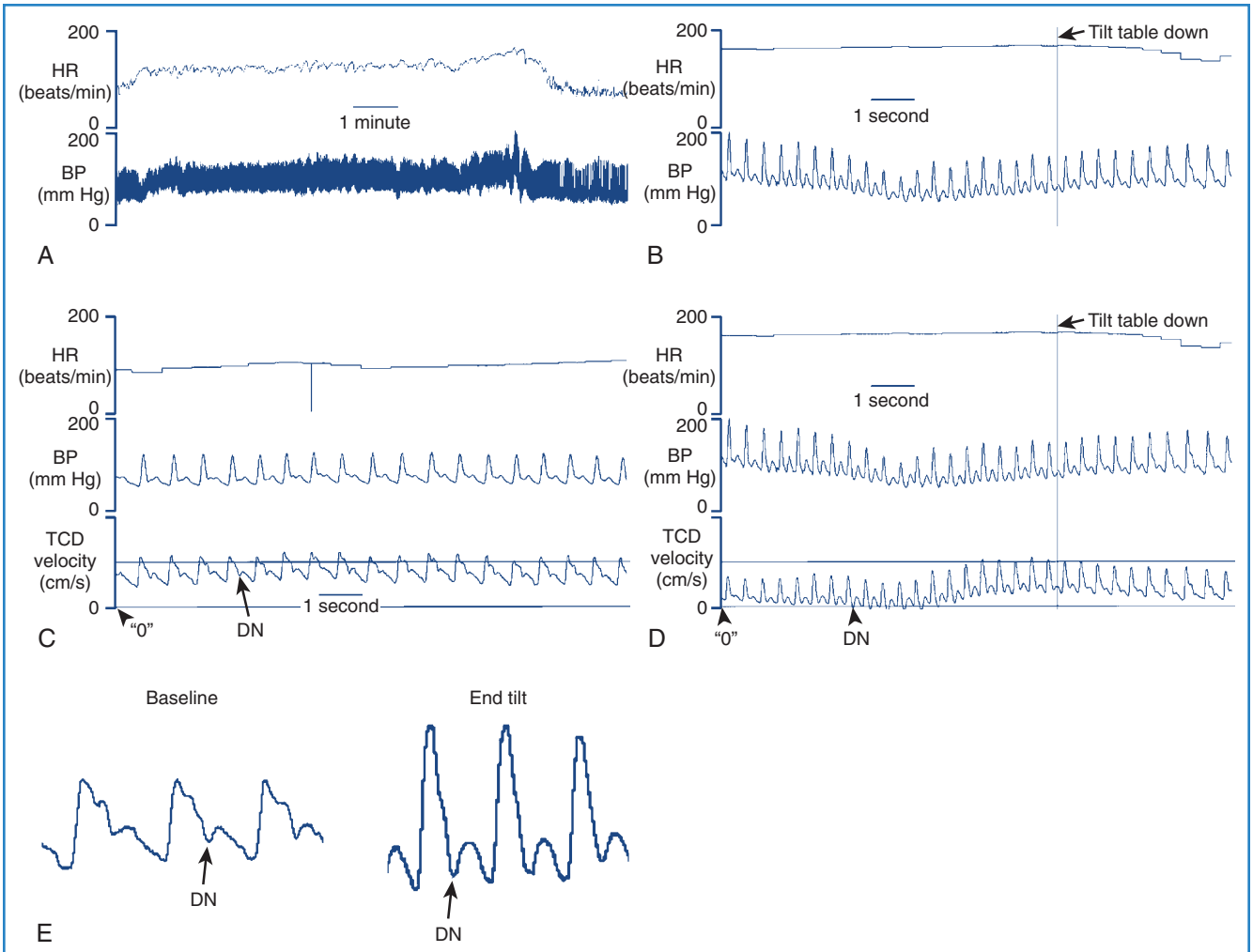

FIGURE 71-7 Cerebral syncope. **A,** This patient had a small stable increase in heart rate (*HR*) and blood pressure (*BP*) on upright tilt. **B,** The patient lost consciousness after 9 minutes, but her BP never fell below 100 mm Hg. **C** to **E,** The same traces with an additional channel showing transcranial Doppler (*TCD*) velocity at the beginning of the tilt (**C**) and end of tilt (**D**). The TCD velocity waveform was clearly different at the time of syncope, with a lower dicrotic notch (*DN*) and a very low diastolic perfusion pressure (**E**) and is thought to be associated with cerebral vasospasm. This TCD waveform can also be seen in typical neurally mediated syncope.

study. The TCD signal has a prominent dicrotic notch in mid-diastole and shows evidence of good diastolic cerebral flow (TCD velocity well above 0 cm/s). Figure 71-7, *D*, shows the end of the tilt. At the time of LOC (just before the table was returned to the horizontal position), the first TCD velocity wave (including systole and the early phase of diastole) narrowed, the dicrotic notch deepened, and the diastolic cerebral flow was negligible (flow velocity approaches 0 cm/s). Almost immediately after the table was returned to the horizontal position, the TCD velocity waveform started to revert to the baseline, with the dicrotic notch and diastolic flows at a higher velocity. The difference between the "baseline" and "end" TCD velocity waveforms can be seen best in Figure 71-7, *E*.

These isolated changes in cerebral blood flow velocity are thought to represent isolated cerebral vasospasms. Syncope caused by this isolated change in cerebral blood flow has been termed *cerebral syncope*.[50] No clinical trial data are available to guide clinicians on the optimal management of patients with cerebral syncope. If an adequate prodrome is present, hyperventilation can be attempted (using a paper bag), as this can cause cerebral vasodilation. Otherwise, traditional pharmacologic and nonpharmacologic approaches to NMS can be attempted.

Tilt Scenario 8: Syncope with a "Normal" BP: Psychogenic Syncope

Scenario

P.S. presents with a 10-year history of recurrent syncope. She has suffered from over 100 spells of LOC. She reports prodromal pallor prior to LOC, a duration of LOC of 5 to 7 minutes, both fatigue and confusion following the spells, and retrograde amnesia for many of the spells. The frequency of her spells is variable, with a clustering of spells. She did not report any variation in the frequency of spells by time of day or body position.

Tilt Result and Interpretation

P.S. underwent a drug-free 75-degree HUTT. On upright tilt, HR and BP increased (Figure 71-8, *A*). After 5 minutes of HUTT, she lost consciousness while her systolic BP was greater than 120 mm Hg. The table was returned to the horizontal position.

Review of the TCD ultrasound signal during apparent LOC at the end of the tilt (see Figure 71-8, *B*) revealed a waveform with a prominent dicrotic notch and diastolic flow velocities (well above 0 cm/s), indicating cerebral diastolic perfusion. A comparison of the TCD waveform from baseline with the end of the tilt does *not* reveal significant changes in morphology (see Figure 71-8, *C*).

Given the absence of hemodynamic perturbation (either systemic hypotension or altered cerebral blood flow) during her apparent LOC, a diagnosis of *psychogenic syncope* was made. In many of these cases, the syncope may be caused by conversion reactions. She was referred to a psychologist for further therapy.

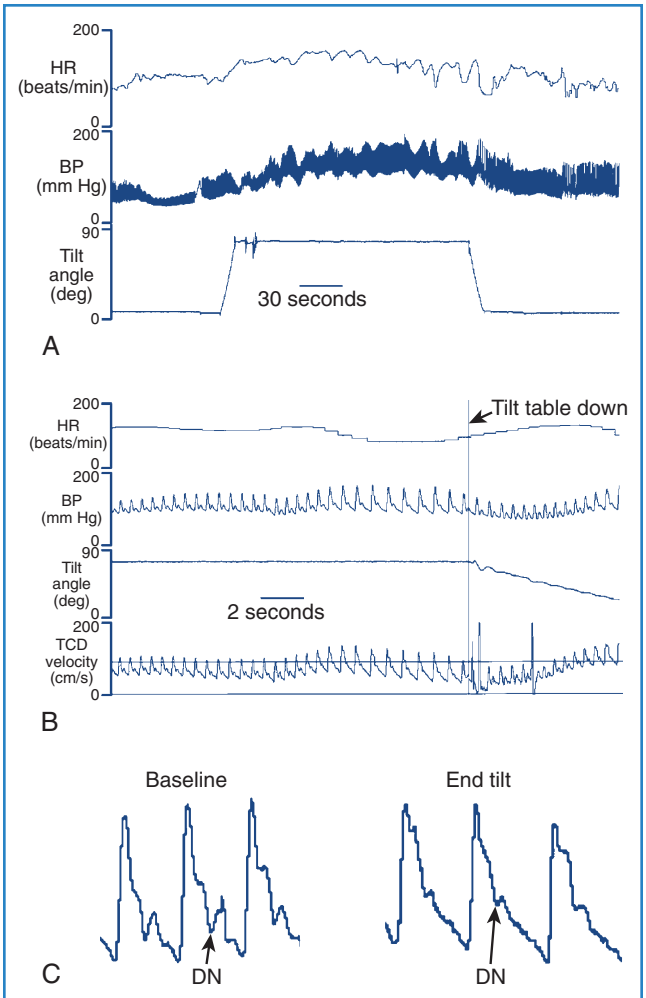

FIGURE 71-8 Psychogenic syncope. **A,** Similar to Case 7, this patient suffered apparent loss of consciousness with a stable heart rate (*HR*) and blood pressure (*BP*) greater than 120 mm Hg. **B** and **C,** Unlike Case 7, the transcranial Doppler (*TCD*) velocity waveform at the time of syncope is not significantly changed from baseline with a prominent dicrotic notch (*DN*) and diastolic flow velocities. These data suggest the absence of a hemodynamic explanation for the apparent loss of consciousness and point to the diagnosis of psychogenic syncope.

Tilt Scenario 9: Hypersensitive Carotid Sinus Syndrome

Scenario

F.T. is a 62-year-old woman with a 2-year history of recurrent syncope. Some of the spells are associated with a prodrome of lightheadedness. She denies any nausea or vomiting. The spells might have been brought on by her turning her head to the right and looking back. While on cardiac monitoring in hospital, left carotid sinus massage could reproducibly cause her to lose consciousness and lose postural tone for approximately minutes, but in the absence of asystole or significant bradycardia.

Tilt Result and Interpretation

F.T. underwent an HUTT with continuous HR and noninvasive BP monitoring. Immediately after tilting to a 75-degree head-up tilt, her HR was 95 beats/min and her BP was 87/64 mm Hg (Figure 71-9). Digital pressure was then applied over the left carotid bulb. Within several seconds, she lost consciousness. An initial decrease in F.T.'s HR was seen, but it then returned to baseline. Her BP, however, decreased to 58/49 mm Hg. Her BP and

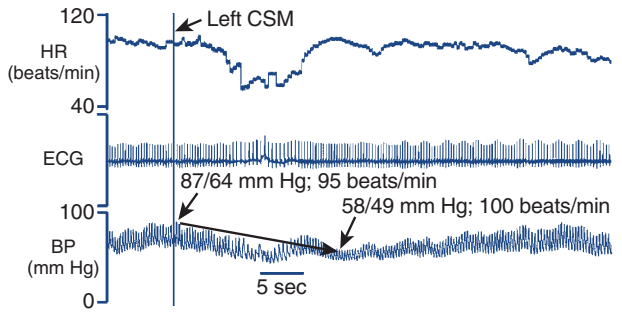

FIGURE 71-9 Hypersensitive carotid sinus syndrome. Heart rate (*HR*) and blood pressure (BP) are stable after the head-up tilt. With digital compression of the left carotid sinus bulb (*CSM*), HR remained stable, but BP dropped significantly with loss of consciousness. Cardioinhibition with CSM can be detected even in the supine patient, but a vasodilatory response to CSM can be difficult to diagnose unless the patient is upright.

consciousness recovered shortly after the table was returned to the horizontal position.

F.T. has hypersensitive carotid sinus syndrome with a prominent vasodepressor component. While HR changes can often be easily diagnosed at the bedside, BP drops are often difficult to diagnose without monitoring of the upright posture and continuous BP monitoring.

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CHAPTER 72

Risk Stratification for Sudden Cardiac Death

Iwona Cygankiewicz and Wojciech Zareba

Sudden cardiac death (SCD) is defined as natural death from cardiac causes that occurs within 1 hour from the onset of symptoms. If unwitnessed, patients should have been seen alive within 24 hours preceding their death. Pre-existing heart disease may be known; nevertheless, SCD frequently affects persons with no previously recognized cardiovascular disorder.[1] However, as documented by autopsy studies of 270 cases of SCD in individuals with no previously known heart disease, pathologic examination revealed structural abnormalities in 95%.[2] The real incidence of SCD is difficult to establish, mainly because of the different definitions of SCD and the sources of data used in published reports. On the basis of the latest meta-analysis of reports published between 1980 and 2007, the estimated annual incidence of SCD in the United States varies from 180,000 to more 450,000 annually.[3] SCDs account for approximately 50% of all cardiac deaths, and this proportion has remained constant despite the overall decline in cardiovascular death during the last decades.[4,5] Recent decades have shown a steady decline in the total number of cardiac arrests, which is attributed mainly to a decrease in out-of-hospital ventricular fibrillation (VF). Nevertheless, survival after a cardiac arrest remains as low as 5%.[5-8]

Mechanisms of Sudden Cardiac Death

SCD may result from ventricular tachycardia (VT), VF, bradyarrhythmias, or pulseless electrical activity. Before the widespread use of implantable cardioverter-defibrillators (ICDs), data on the final arrhythmia leading to cardiac arrest could only be obtained from studies using Holter recordings, hospital telemetry, or both.[9-13] The largest study to date on SCD episodes occurring while the patients were wearing a Holter monitor was published in 1989 by Bayes de Luna et al.[12] Among 157 subjects, VT degenerating to VF was observed in 62% of cases, torsades de pointes in 13%, and primary VF in 8%. Only 17% of patients died from bradyarrhythmia. Conversely, the proportion of patients with bradyarrhythmia or electromechanical dissociation as a mechanism of SCD, as documented by Liu et al, may be higher in heart failure patients.[13] This observation was later supported by the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) trial, which showed that in heart failure patients, the mechanism of death depends on hemodynamic impairment. Patients with New York Heart Association (NYHA) heart failure class II to III are more likely die suddenly, whereas heart failure progression is responsible for the majority of those in NYHA class IV.[14]

Recent data based on electrocardiograms (ECGs), from implantable loop recorders in patients with prior myocardial infarction (MI) from the Cardiac Arrhythmias and Risk Stratification after Acute Myocardial Infarction (CARISMA) study confirmed that ventricular tachyarrhythmias were associated with SCDs, whereas bradyarrhythmia and electromechanical dissociation were predominantly observed in non-SCD and noncardiac deaths.[15,16] The CARISMA study enrolled 312 patients with a recent acute MI (AMI) and left ventricular ejection fraction (LVEF) less than 40%. Terminal arrhythmias were recognized from loop recorders implanted 5 to 21 days after an AMI. During 2 years of follow-up, 26 patients died: 9 from SCDs, 10 from non-SCD cardiac causes, and 7 from noncardiac causes. Among those with SCD, VF was observed in 6 cases and bradyarrhythmia only in 1 (in 2 cases no rhythm was available for analysis). In contrast to previous Holter-based reports, initiation of VF (visible in 5 cases) was not preceded by VT in any of the cases. These data confirm that primary VF is the main mechanism of death in patients with prior MI and left ventricular dysfunction.

Multi-factorial Etiology of Sudden Cardiac Death: Impact on Risk Stratification

Coronary artery disease (CAD) remains the most common condition associated with SCD and is responsible for approximately 80% of cases.[1] The highest risk of SCD is attributed to cardiac arrest survivors, and these patients are qualified for ICD implantation for secondary prevention of death. Indications for primary prevention of SCD are based on the underlying heart disease that was proven to increase the risk of arrhythmic events. Patients with prior MI and significantly depressed LVEF and those with heart failure or ventricular arrhythmia present with the highest incidence of SCD events.[17,18] Nevertheless, as indicated by Myerburg et al in a review of the population impact of emerging ICD trials, the highest incidence of SCD is observed in survivors of out-of-hospital cardiac death and high-risk post-infarction subgroups, but the highest absolute number of SCD events occurs in large subgroups of patients at a somewhat lower risk, including patients with left ventricular dysfunction, congestive heart failure (CHF), or any prior coronary event (Figure 72-1).

The etiology of SCD is multi-factorial and involves a complex interplay among several elements, including genetic predisposition, cardiac condition, comorbidities, and environmental factors. Such a complex underlying etiology makes risk prediction of "unexpected" SCD events extremely complicated.

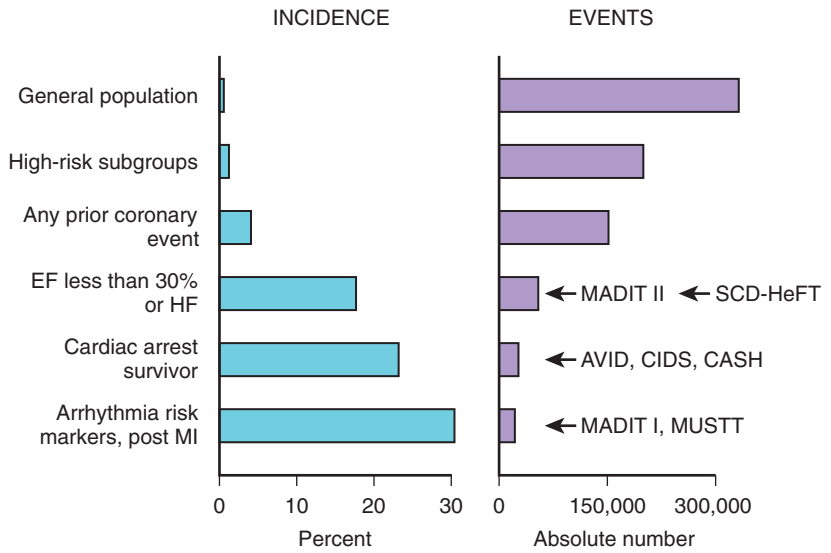

FIGURE 72-1 Absolute numbers of events and event rates of sudden cardiac death (SCD) in the general population and in specific subgroups. The highest incidence of SCD is observed in survivors of out-of-hospital cardiac death and high-risk post-infarction subgroups, but the highest absolute number of SCD events occurs in large subgroups of patients at somewhat lower risk, including patients with left ventricular dysfunction, congestive heart failure, or any prior coronary events. Clinical trials that included specific subgroups are indicated at *right*. *EF*, Ejection fraction; *HF*, heart failure; *MI*, myocardial infarction. *(From Zipes DP, Camm AJ, Borggrefe M, 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,* Circulation *114:e385–e484, 2006.)*

The mechanisms of SCD include VT, VF, bradycardia, asystole, and pulseless electrical activity. Risk prediction is therefore focused mainly on predicting tachyarrhythmias, which can be prevented by ICD therapy. Life-threatening arrhythmias are preceded by a chain of events encompassing the complex interplay among the substrate, triggers, and modulators. Factors known to modulate and trigger arrhythmias include autonomic nervous system imbalance, transient ischemia, metabolic and electrolyte imbalance, transient volume overload of ventricles, and proarrhythmic action of drugs. Malignant arrhythmias are induced and sustained by a series of triggering and modulating events acting on the vulnerable myocardium.[19]

Role of Noninvasive Electrocardiology in Risk Stratification

Even though SCD is defined as being unexpected and frequently occurs as a first clinical event in previously asymptomatic persons, attempts have been made to identify risk markers indicating increased predisposition for arrhythmic events.[20]

Several useful modalities can be used to stratify patients according to risk of arrhythmogenic death. To exert an impact on SCD from an epidemiologically meaningful point of view, prognostic tests need to achieve a high positive predictive accuracy, together with a reasonable degree of sensitivity. Otherwise, the test or the combination of tests would be too specific to have any significant impact on the epidemiologic problem of SCD, simply because these tests yield positive findings only in a small minority of the population. The ideal risk stratifier would identify most of the patients who will have life-threatening arrhythmias and, at the same time, exclude those with arrhythmia-free survival.

Depressed EF that persists for years has been recognized as a major determinant of increased mortality rate, so the assessment of LVEF remains the gold standard in identifying patients who benefit from ICD therapy.[17,21-24] The highest risk of death and SCD is attributed to a subgroup of patients with LVEF less than 30%. In comparison with earlier studies, recent series have suggested that the curve relating death to EF has "shifted to the left," implying that for a given degree of left ventricular dysfunction, the increase in mortality rate is somewhat less than previously reported. Furthermore, the main drawback of EF in risk stratification lies in its low sensitivity and specificity.[25,26]

Noninvasive ECG parameters are believed to reflect the myocardial substrate as well as triggers and modulators potentially contributing to life-threatening arrhythmia risk. Therefore, the combination of ECG markers with low EF may potentially enhance risk stratification. Several ECG markers have been introduced into SCD risk stratification over the past few decades. Most of them have been associated with all-cause mortality and cardiac death. Nevertheless, the association with SCD is unclear, and the results of studies are conflicting.[20,27-29] Detailed descriptions of specific risk stratification methods are available in other chapters in this text that detail these methods.

Electrocardiographic techniques include surface ECG, signal-averaged ECG (SAECG), ambulatory Holter monitoring, exercise tests, and other techniques such as baroreceptor sensitivity assessment. Surface ECG provides data on the underlying rhythm, resting heart rate, QRS duration, conduction abnormalities, QRS fragmentation, Q-T interval duration, and T-wave morphology or specific changes suggestive of primary electrical diseases.[29-31]

SAECG reveals the presence of late potentials reflecting heterogeneity of conduction in the myocardium. The presence of late potentials, prolonged filtered QRS duration, or both in the SAECG of patients with normal QRS duration on standard ECG indicates an increased risk of cardiac events. A broad QRS complex is associated with an increased risk of death, and patients with such conduction disturbances do not benefit from SAECG analyses.[30,31]

Long-term Holter monitoring allows evaluation of heart rate, ventricular ectopy, heart rate variability (HRV), heart rate turbulence (HRT), and dynamicity of repolarization.[20,27-29] Ambulatory Holter monitoring is the most comprehensive tool for identifying and quantifying factors that may contribute to the mechanism of SCD (Figure 72-2). The effects of the autonomic nervous system on the heart could be evaluated by quantifying HRV, illustrating the relationship between the parasympathetic and sympathetic components of this system. HRT complements HRV analysis by

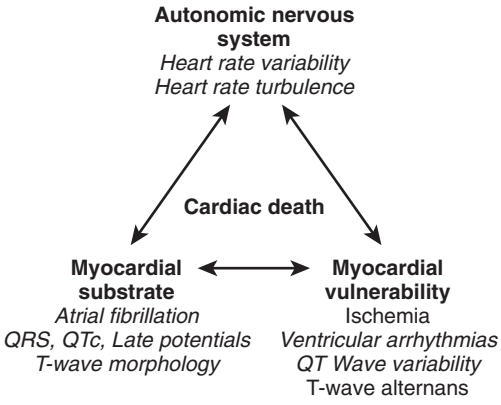

FIGURE 72-2 Factors contributing to cardiac death and respective Holter-derived electrocardiogram parameters. *(From Zareba W, Moss AJ: Noninvasive risk stratification in postinfarction patients with severe left ventricular dysfunction and methodology of the MUSIC II noninvasive electrocardiology substudy,* J Electrocardiol *36[Suppl]:101–108, 2003.)*

providing insight into a baroreflex sensitivity component of central regulation of the cardiovascular system.[28] Abnormalities of the central regulation of the heart are unlikely to cause SCD without an altered myocardial substrate and additional factors increasing the vulnerability of the myocardium to VT. The vulnerability of the myocardium may be expressed as impaired repolarization dynamicity, increased frequency and complexity of ventricular arrhythmias, and transient ischemic ST-T changes.

Exercise tests go beyond evaluating ST-T changes and provide additional information on the risk of SCD based on heart rate behavior and ventricular ectopy during the recovery phase.[32] Microvolt T-wave alternans (TWA), considered to be a reflection of repolarization abnormalities, was originally determined during an exercise test, but numerous recent data support the equal value of TWA assessed by long-term monitoring.[33,34]

Invasive Electrophysiology Study

Testing the inducibility of VT in patients with prior MI has been a standard procedure for a number of years for identifying high-risk patients prone to SCD. Two primary prevention clinical trials—the Multicenter Automatic Defibrillator Implantation Trial (MADIT) and the Multicenter Unsustained Tachycardia Trial (MUSTT)—which enrolled patients with prior MI and depressed LVEF who presented with nonsustained VT (NSVT) and inducibility of ventricular tachyarrhythmias during invasive electrophysiology study (EPS), demonstrated that such a risk stratification algorithm was able to select a subset of patients with prior MI and a very high mortality risk.[21,35] Nevertheless, secondary analysis from MUSTT revealed that despite significant differences in outcome between inducible patients enrolled in the trial and noninducible patients enrolled in a EPS registry, inducibility was found to be of limited use because the 5-year mortality rate in inducible patients was 48% compared with 44% in noninducible patients.[36] Subsequently, MADIT II showed that additional risk stratifiers (including EPS) are not necessary when EF is severely depressed.[22] In fact, in more than 80% of patients randomized to the ICD arm of MADIT II, invasive EPS, in an attempt to induce tachyarrhythmias, was performed at the time of ICD placement. Inducibility of ventricular arrhythmias, observed in 40% of studied patients, was not effective in identifying patients with cardiac events defined as VT, VF, or death.[37] Therefore, MUSTT and MADIT II subanalyses suggested that in patients with substantially depressed left ventricular function, inducibility at EPS should not be considered a useful predictor of outcome. However, inducibility may have much better predictive value in patients with prior MI and an LVEF greater than 30% or less than 35%. Such a hypothesis was confirmed in a study by Cappato et al, who investigated the usefulness of inducibility in 285 survivors of cardiac arrest enrolled in the Cardiac Arrest Study Hamburg (CASH) trial and found that inducibility at EPS was predictive for SCD in patients with LVEF greater than 35% (hazard ratio [HR], 3.0; $P = .006$), whereas it was not useful in patients with lower LVEF (HR, 1.1; $P = .81$).[38]

Inducibility in patients with nonischemic cardiomyopathy has not been considered useful for predicting increased risk of death. However, data from the Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation (DEFINITE) substudy, which evaluated ICD-based inducibility of VT or VF, found that inducibility of either VT or VF was associated with an increased likelihood of subsequent ICD therapy for VT or VF.[39]

Bedside Risk Stratification Models

In risk stratification for SCD or cardiac death, attempts are frequently made to use sophisticated noninvasive or invasive methods reflecting ECG-based electrical myocardial involvement or autonomous nervous system regulation of the cardiovascular system. However, evaluating the risk of death could also be accomplished by using clinical parameters readily available to physicians when assessing patients in hospitals and in outpatient clinics. Retrospective data analyses from the ICD trials MADIT II, MUSTT, and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) yielded risk stratification models based on such clinical variables.[40-42]

The simplest bedside risk stratification model was proposed by the MADIT II investigators, who evaluated five clinical factors: (1) NYHA class higher than class II, (2) age greater than 70 years, (3) blood urea nitrogen level greater than 26 mg/dL, (4) QRS duration greater than 0.12 seconds, and (5) atrial fibrillation (AF). Crude mortality rates in the conventional group were 8% and 28% in patients with zero or one or more risk factors, respectively, and 43% in very high-risk patients, who were defined by a blood urea nitrogen level of 50 mg/dL or more, serum creatinine level of 2.5 mg/dL or more, or both (Figure 72-3). Defibrillator therapy was associated with a 49% reduction in the risk of death ($P < .001$) among patients with one or more risk factors (n = 786), whereas no ICD benefit was identified in patients with no risk factors (n = 345; HR, 0.96; $P = .91$) and in very high-risk patients (n = 60; HR, 1.00; $P > .99$). This model could easily be adopted and could significantly improve low utilization of ICDs for primary prevention of death and SCD in patients with low EF and prior MI.

The MUSTT investigators evaluated 25 variables predicting total mortality and arrhythmic death. The following variables were found to be independently predictive of total mortality: EF, intraventricular conduction defect (IVCD) or left bundle branch block (LBBB), NYHA class II or III, inducible VT, older age, prior coronary artery bypass grafting, AF, and a history of heart failure. On the basis of subsequent analyses, with arrhythmic death as the

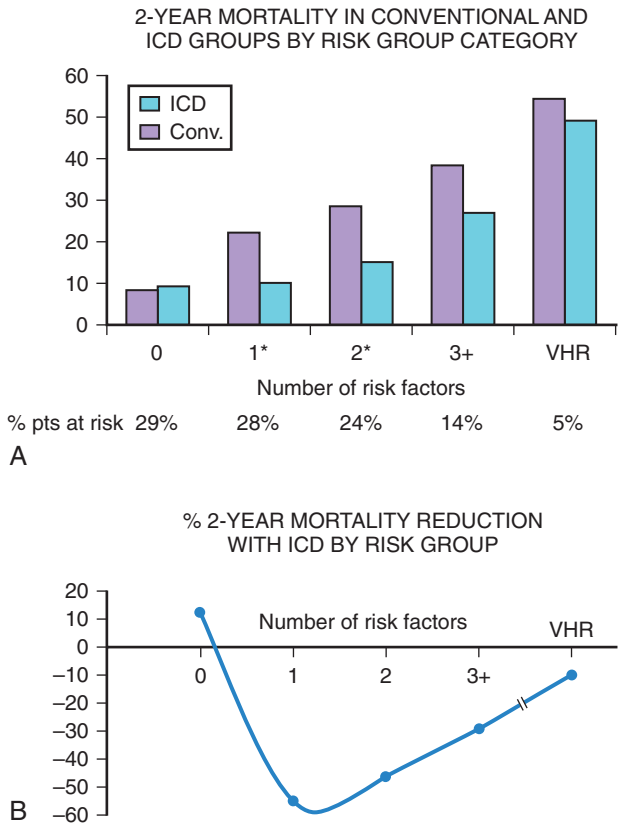

FIGURE 72-3 A, Two-year Kaplan-Meier rates in the implantable cardioverter-defibrillator (ICD) and conventional therapy groups. **B,** The corresponding 2-year mortality rate reduction with an ICD by risk score and in patients with variable heart rate (*VHR*). *(From Goldenberg I, Vyas AK, Hall WJ, et al, for the MADIT-II Investigators: Risk stratification for primary implantation of a cardioverter-defibrillator in patients with ischemic left ventricular dysfunction,* J Am Coll Cardiol *51:288–296, 2008.)*

endpoint, the authors derived a scoring system assigning specific number of points to the following variables:

Inducible VT	17
History of CHF	19
Patient enrolled as inpatient	17
EF ≤20% (for EF values between 20% and 40%, add one point for each EF percentage point >40)	20
EF = 40%	0
NSVT not discovered within 10 days after bypass grafting	17
IVCD or LBBB	10

The score can range from 0 to 100 points, and the risk of total mortality and risk of arrhythmic death increases with an increased number of points. The model demonstrated that patients whose only risk factor is LVEF of 30% or more had a predicted 2-year arrhythmic death risk of less than 5%.

The SCD-HeFT investigators adopted the Seattle Heart Failure Model for predicting mortality and ICD benefit in their study population. The model included age, gender, systolic blood pressure, ischemic origin, NYHA class, LVEF, angiotensin-converting enzyme inhibitor use, angiotensin receptor blocker use, β-blocker use, statin use, furosemide equivalent daily dose in milligrams per kilogram, serum sodium, digoxin use, carvedilol use, and creatinine. This relatively complex model yielded scores categorizing patients in quintile subgroups. ICD treatment decreased the relative risk of SCD by 88% in the lowest risk group versus 24% in the highest risk group (P = .009 for interaction) and decreased the relative risk of total mortality by 54% in the lowest risk group versus no benefit (2%) in the highest risk group (P = .014 for interaction).[41]

The Muerte Subita en Insufficiencia Cardiaca (MUSIC) study was designed to evaluate risk predictors for SCD in patients with mild to moderate CHF (NYHA class II to III). In a cohort of 992 ambulatory patients, a risk score based on 10 variables (prior atherosclerotic vascular event, left atrial size >26 mm/m^2, LVEF ≤35%, AF, LBBB or IVCD, NSVT, frequent ventricular premature beats [VPBs], estimated glomerular filtration rate <60 mL/min/1.73 m^2, hyponatremia ≤138 mEq/L, N-terminal pro–B-type natriuretic peptide >1000 ng/L, and positive troponin) identified ambulatory patients with CHF at high risk of total mortality and SCD during follow-up.[42]

Risk Stratification in Patients with Prior Myocardial Infarction and Ischemic Cardiomyopathy

CAD remains the condition most commonly associated with SCD. Patients with prior AMI are at significant risk of SCD during the first few months after the index event. However, data from patients with AMI and heart failure or depressed EF indicate that during first 3 months, SCD is most frequently caused by recurrent MI or rupture of the ventricle.[43] The risk of SCD from tachyarrhythmia tends to be relatively low during the first few years but increases in later years after MI when remote remodeling of the myocardium takes place. Yap et al, on the basis of a combined analysis of five multi-center trials that enrolled patients with prior MI and LVEF less than 40% or frequent VPBs, documented that in this high-risk subgroup the risk of arrhythmic death is higher than that of nonarrhythmic death for up to 2 years of post-infarction follow-up, with the highest risk during the first 6 months after MI.[44] With time, the risk of arrhythmias decreases, but the risk of death from heart failure persists. Nevertheless, the absolute risk of death from any cause was the highest in the first 6 months after MI and decreased with time. Interestingly, nonarrhythmic death occurred more among females after 6 months. The risk of arrhythmic death was also higher in younger patients.[44]

A variety of clinical factors are related to increased mortality in the post-infarction period. The important ones are age, previous MI, diabetes, smoking, heart failure, hypertension, and depression. Predischarge LVEF is considered the most important risk predictor; however, it is worth re-evaluating the EF a few months after MI and complementing it by additional noninvasive ECG-based tests (which give insight into the structural substrate for arrhythmia and other aspects contributing to increased vulnerability to arrhythmias).

Historically, detecting and quantifying Holter-recorded ventricular arrhythmias was the first ECG-based approach to determine the risk of patients with prior MI and to implement antiarrhythmic therapy.[45] Ventricular arrhythmias are associated with acute ischemia caused by partial or total occlusion of coronary arteries. In patients with ischemic cardiomyopathy,

monomorphic VT may result from re-entry mechanisms in the scarred areas of the myocardium. An association exists between the increased frequency and the complexity of ventricular arrhythmias with cardiac death and SCD. In a classic study by Bigger et al, the occurrence of 10 or more VPBs per hour was associated with an increased mortality rate.[46] Subsequent results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2) trial confirmed that frequent VPBs (>10 per hour) were independently associated with SCD risk in the first 6 months after AMI in the thrombolytic era.[47] Nevertheless, 10 years later, the presence of more than 10 VPBs per hour was associated only with non-SCD but not with SCD in the contemporary post-infarction population treated with modern primary coronary intervention procedures and widely used β-blockers. Conversely, the presence of NSVT was reported as an independent risk marker for SCD in patients with an LVEF less than 35%.[48] It should be stressed that reducing ventricular arrhythmias with pharmacologic agents did not lead to improved survival and, in the case of several drugs, such therapy was associated with worse outcomes.[49] Large day-to-day variabilities in NSVT detected by Holter monitoring further limit the use of this parameter as a risk stratifier. Primary prevention of SCD with ICD therapy was introduced by MADIT and MUSTT in patients with documented NSVT and inducibility of ventricular tachyarrhythmias.[21,35] Nevertheless, after the MADIT II and SCD-HeFT trials, an EF of 30% or less is considered a sufficient risk stratifier without the need for documenting Holter-detected ventricular arrhythmias or inducible VT.[22,24]

As previously discussed, LVEF is the most acceptable measure of changes in the myocardial substrate. However, complementary information about the substrate may be obtained from electrocardiology. The parameters of interest include QRS duration and morphology (conduction disturbances), late potentials, and changes in repolarization duration and morphology. A wide QRS interval, particularly in relation to bundle branch block, has been consistently associated with worse prognosis, indicating increased risk of SCD as well as further deterioration of left ventricular function resulting in pump failure and death.[31] The majority of recent data based on large clinical trials shows consistent association of prolonged QRS duration with all-cause, short-term, and long term mortality. Nevertheless, the association with SCD is not clear. Recent data based on contemporary population of patients with prior MI, the majority of whom were treated with percutaneous coronary intervention (PCI), showed that prolonged QRS (>120 ms) was associated with higher total and cardiac mortality but not with SCD.[50] Discrepancy also exists in terms of QRS duration as a predictor of VT or VF therapy in patients with ischemic cardiomyopathy and ICDs. The Pacing Fast VT Reduces Shock Therapies (PainFREE II) study failed to document any relationship between QRS and VT or VF requiring ICD therapy.[51] In patients from MADIT II with ischemic cardiomyopathy, a greater prolongation of baseline QRS was associated only with a trend toward increased benefit from ICD implantation.[52] Subsequently, post hoc analysis of the MADIT II cohort showed that a prolonged QRS was associated with SCD risk only in the non-ICD arm, not in ICD recipients.[53] It is therefore unclear whether QRS prolongation in the post-infarction cohorts may be considered an independent risk factor for SCD. It is probable that QRS should more likely be considered a surrogate of advanced myocardial disease related to the risk of subsequent events, which are, in turn, related to the development and progression of heart failure, but not as specific for arrhythmic events.

Late potentials refer to low-amplitude signals found at the end of the QRS complex that arise from areas of slow and heterogeneous conduction in a diseased myocardium and may represent and increased risk for subsequent cardiac arrhythmias. In patients with normal QRS duration, the presence of late potentials is a likely risk factor for cardiac events. Various studies in prethrombolytic era documented that abnormal SAECG may predict SCD in patients with prior MI.[53,54] Data from MUSTT demonstrated that filtered QRS duration greater than 114 ms was independently associated with the primary study endpoint (arrhythmic death or cardiac arrest) during a 5-year follow-up.[55] Patients with an abnormal SAECG had a 28% incidence of primary endpoints compared with 17% in those with normal SAECG ($P < .001$). The highest risk was found in a patients presenting with a combination of prolonged filtered QRS duration greater than 114 ms and EF less than 30%. Despite several studies that linked abnormal SAECG to arrhythmic events in patients with prior MI, SAECG is now alternatively used to identify low-risk patients, taking into account its high negative predictive value. Furthermore, it seems that in the reperfusion era with high rate of PCI procedures, late potentials lost their predictive value.[56] An abnormal SAECG recorded in the early post-infarction period has insufficient predictive power, which seems to be overwhelmed by better predictive value of other ECG parameters (including HRT and TWA). However, data indicate that the combination of abnormalities in the SAECG with positive results of the TWA test might be useful in identifying high-risk individuals in the early post-infarction period.[57,58]

Static measures of QT duration and QT dispersion have been, for years, considered to be risk factors in patients with prior MI; however, their predictive value was usually overwhelmed by clinical covariates. Therefore more and more attention is now paid to dynamic measures of repolarization. The most commonly used method to evaluate QT dynamicity is to assess the relationship between the Q-T interval and the preceding R-R intervals expressed by the QT or R-R slope.[29] A steeper slope indicates inappropriate shortening of the Q-T interval at higher heart rate and excessive lengthening of QT during low heart rate—both mechanisms significantly contributing to the risk of arrhythmic events. The dynamicity of the Q-T interval was found to be a potent risk marker of SCD. The Groupe d'Etude du Prognostic de l"Infarctus du Myocarde (GREPI) study demonstrated that a Q-T or R-R interval greater than 0.18 was independently associated with total mortality, with a stronger relationship with sudden cardiac death.[59] An increased number of peaks of prolonged QTc interval—for example, the proportion of QTc intervals above the prespecified threshold (QTc >500 ms)—was described as a marker of life-threatening arrhythmias in patients with prior MI.[60] A Q-T interval influenced by variety of factors may change in terms of duration as well a morphology. The ECG phenomenon consisting of beat-to-beat changes in repolarization duration and morphology appearing without the 2:1 pattern typical for TWA has been termed *QT variability*. These subtle beat-to-beat changes in T-wave amplitude and shape, as well as in QT duration, may be analyzed by several novel computerized ECG methods. These methods enable detection and quantification of microvolt-level changes, which otherwise remain undetected by the naked eye. Increased QT variability predicted arrhythmic events in the MADIT II population.[61] The 2-year risk of VT or VF from Kaplan-Meier curves was twofold higher in patients in the highest quartile compared with those in lower quartiles for QT variability (QTVN) and QT variability index (QTVI) ($P < .05$ for each) (Figure 72-4).

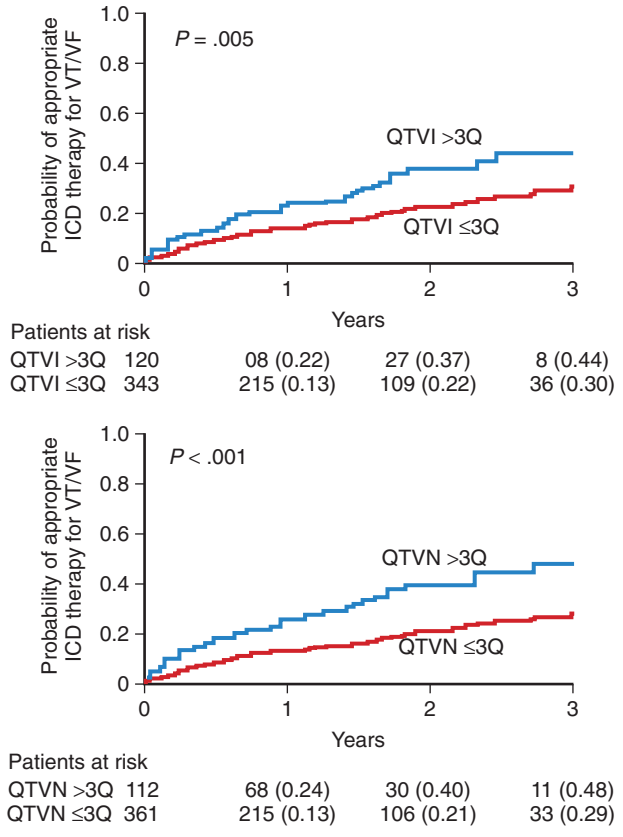

FIGURE 72-4 Cumulative probability of the first appropriate defibrillator therapy for ventricular tachycardia (*VT*) or ventricular fibrillation (*VF*) in patients with QT variability (*QTVN*) in the highest quartile versus lower three quartiles for QT variability index (*QTVI*) (*top*) and QTVN (*bottom*). *ICD*, Implantable cardioverter-defibrillator. *(From Haigney MC, Zareba W, Gentlesk PJ, et al, for the Multicenter Automatic Defibrillator Implantation Trial II investigators: QT interval variability and spontaneous ventricular tachycardia or fibrillation in the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II patients,* J Am Coll Cardiol *44:1481–1487, 2004.)*

In multivariate Cox analysis, adjusted for significant clinical covariates, top-quartile QTVI and QTVN were independently associated with VT or VF (QTVN: HR, 2.18; 95% confidence interval [CI], 1.34 to 3.55; $P = .002$; QTVI: HR, 1.80; 95% CI, 1.09 to 2.95; $P = .021$).

Microvolt TWA (MTWA), which is the presence of 2:1 beat-to-beat changes in the amplitude of the T wave, has been shown to be associated with an increased risk of SCD and serious ventricular tachyarrhythmic events.[62,63] In patients with ischemic cardiomyopathy, assessment of MTWA has been shown to be useful for predicting arrhythmic events. Bloomfield et al reported findings in 177 MADIT II–like patients who were assessed for MTWA and followed up for 2 years.[63] They found that a positive MTWA was associated with a higher mortality rate than that associated with a QRS duration of greater than 120 ms. The actuarial mortality rate was 17.8% in patients with a positive MTWA compared with only 3.8% in MTWA-negative patients. It is noteworthy that most of the studies showed that MTWA carried a high negative predictive value of between 96% and 100%. This indicates that analysis of MTWA may be particularly helpful in avoiding unnecessary ICD implantation in patients with depressed left ventricular function who test negative for MTWA. Currently, MTWA is the only noninvasive ECG technique given class IIa indications for risk stratification, according to guidelines on ventricular arrhythmias and those on noninvasive risk stratification for SCD.[17] Nevertheless, data from the Microvolt T-Wave Alternans Testing for Risk Stratification of Post-Myocardial Infarction Patients (MASTER) and Alternans Before Cardioverter Defibrillator (ABCD) trials indicated that MTWA is not as specific for arrhythmic events as previously believed.[64,65]

Traditional spectral analysis of MTWA requires an elevated and stabilized heart rate achieved by exercise or pacing. Within the past decade, several methods have been proposed to evaluate TWA from ECG recordings. However, the one known as *modified moving average analysis* has been the most extensively studied so far.[66,67] In a small study by Verrier et al, Holter-based detection of TWA was associated with increased risk of arrhythmic events.[68] This first report was further confirmed by findings from the Finnish Cardiovascular Study (FINCAVAS) and Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) trials.[69,70] The Risk Estimation Following Infarction Non-invasive Evaluation (REFINE) study assessed TWA by the traditional spectral method from the exercise stress test as well as from the 20- to 30-minute ECG resting recordings following this stress test. Neither TWA techniques were predictive for the primary endpoint (cardiac death or resuscitated cardiac arrest) when assessed within the first 2 to 4 weeks after MI; however, they were independent risk markers when assessed 3 months after MI. TWA detected by modified moving average techniques was associated with a nearly threefold higher risk of cardiac death or resuscitated cardiac arrest during follow-up. Nevertheless, the best predictive model was provided by complex analysis of autonomic nervous system impairment assessed by HRT and the presence of electrical substrate expressed by TWA. The combination of abnormal Holter TWA and impaired HRT provided the highest HR at 4.18 (95% CI, 2.06 to 8.32; $P = .001$) to predict cardiac death or resuscitated cardiac arrest.[71]

Patients with prior MI are characterized by a scarred diseased myocardial substrate and impaired autonomic nervous tone. A variety of studies have explored the prognostic value of HRV parameters for predicting outcome in these patients.[27,72-74] They have consistently shown that depressed HRV is associated with increased all-cause mortality or death from heart failure. Nevertheless, data on its prognostic significance for predicting SCD or arrhythmic death is limited and conflicting. Evidence for the association between depressed HRV parameters and SCD may be limited because of the difficulty in categorizing the sudden or arrhythmic nature of death but also could be because of a lack of strong evidence for this association. HRV also operates differently in different patient populations according to the disease and its advancement. Similarly, no studies exist that link HRV with EPS inducibility, further indicating that HRV may not be the right approach to identify susceptibility to arrhythmias. The past decade has shown an increased clinical interest in nonlinear dynamics of HRV methods for risk stratification purposes. A few studies have suggested that low levels of α_1, a short-term scaling component of heart rate dynamics, is associated with increased mortality in patients with prior MI.[48,75]

HRT combines the assessment of three risk factors: HRV, PVBs, and baroreflex sensitivity.[28] To date, the prognostic value of HRT has been documented in clinical studies enrolling more than 8000 patients with prior MI.[28,76] Abnormal HRT has been

proven to be an independent risk predictor of all-cause mortality and SCD in patients with prior MI. It is noteworthy that HRT works as a significant risk predictor in patients with an LVEF greater than 35%.[77] The combination of abnormal autonomic nervous tone, reflected by abnormal deceleration capacity (a new parameter describing HRV related to slowing of heart rate), with blunted reactiveness of the autonomic nervous system reflected by impaired HRT, has been called *severe autonomic failure* and has proven to be of certain value in patients with prior MI and EF greater than 35%.[78]

The recently published CARISMA study findings have demonstrated that fatal or near-fatal arrhythmias in patients with prior MI and an LVEF less than 40% can be predicted by numerous risk markers, especially decreased HRV.[15] HRV, HRT, arrhythmias, SAECG, TWA, and programmed electrical stimulation were assessed 1 and 6 weeks after AMI in patients with an EF of 40% or less measured between 3 and 21 days after MI. Of note, outof the 5869 acute MI patients screened in 10 European centers, only 23% presented with an LVEF of 40% or less assessed in the early post-infarction period. These data support the fact that modern treatment has significantly changed the clinical picture of patients with prior MI, and early invasive reperfusion strategies have led to a decreased number of patients with significantly impaired left ventricular function. Of the 312 patients enrolled in the CARISMA study, only 25 (8%) reached a primary endpoint, including 12 cases of symptomatic VT, 8 sudden deaths, 3 resuscitated cardiac arrests, and 2 instances of syncope. The primary endpoint was predicted by abnormal HRV, with the highest HR for left ventricular volume 5.7 or less (HR, 7; 95% CI, 2.4 to 20.3; $P < .001$), QT dispersion greater than 90 ms, SAECG QRS width 120 ms or more, and abnormal turbulence slope assessed at 6 weeks after MI as well as sustained monomorphic VT and sustained VT or VF evoked during programmed electrical stimulation. Neither an EF of 35% or less nor TWA were useful for risk stratification in the study population. Interestingly, HRV and HRT measured early after MI (1 week) were not predictive for arrhythmic event. This observation is consistent with previous results from the REFINE study.[71] Despite strong evidence linking HRV and HRT with an increased risk of arrhythmic death, both are currently classified as class IIb indications for risk stratification in patients with ventricular arrhythmias.

Risk Stratification in Nonischemic Cardiomyopathy

A growing number of patients with nonischemic cardiomyopathy are being seen by cardiologists and are considered for prophylactic ICD therapy. On the basis of the results of the DEFINITE and SCD-HEFT trials, which showed benefit from ICD therapy in patients with nonischemic cardiomyopathy, indications for ICD include nonischemic cardiomyopathy with an EF of 35% or less for ICD therapy.[17]

Identifying patients with nonischemic cardiomyopathy who might benefit from ICD therapy more than other individuals remains a challenge. In contrast to patients with post-infarction cardiomyopathy, in patients with nonischemic cardiomyopathy, most risk stratification modalities were found to be of limited use. Invasive EPS with inducibility of ventricular arrhythmias is not useful as a risk stratification method. Several ECG-based noninvasive techniques have been studied, but the results are conflicting, and their application is therefore controversial.[79]

HRV, which is consistently associated with poor outcome in patients with prior MI, seems to have limited prognostic power in nonischemic patients. Grimm et al observed that neither HRV nor baroreflex sensitivity measures predicted major arrhythmic events in the 242 patients enrolled into the Marburg Cardiomyopathy database.[80] However, an interesting application of HRV analysis was documented by Rashba et al in a subanalysis of the DEFINITE trial.[81] Significant differences in mortality rates were observed between patients categorized according to standard deviation of normal-to-normal interval (SDNN) values. Patients with preserved HRV, defined as an SDNN greater than 113 ms, presented with a 0% mortality rate during a follow-up. It is therefore plausible that HRV may help identify low-risk patients with nonischemic cardiomyopathy.

With regard to repolarization measures, independent prognostic value of QT dynamicity in patients with idiopathic dilated cardiomyopathy was reported by Iacoviello et al, who found that abnormal QT dynamicity was significantly associated with arrhythmic events (VT/VF or SCD) during a mean 39-month follow-up.[82] The combination of steeper QTe slope (>0.19), decreased EF, and NSVT identified the group at the highest risk. It is worth emphasizing that QT or RR identified the higher risk group among patients with a low EF (<35%). The probability of arrhythmic events in patients with an EF less than 35%, NSVT, and increased QT or RR slope was as high as 40% (Figure 72-5). MTWA assessment seems to be of increasing interest in patients with dilated cardiomyopathy. Hohnloser et al studied 137 patients with dilated cardiomyopathy followed up for a mean 14 months. They found that decreased baroreflex sensitivity and the presence of MTWA were the only two significant predictors of arrhythmic events, outperforming other tested parameters such as NSVT, SAECG, EF, and HRV.[83] The T-Wave Alternans in Patients With Heart Failure (ALPHA) study evaluated the prognostic value of MTWA in 446 patients with nonischemic dilated cardiomyopathy with NYHA II to III class heart failure and an EF less than 40%. Study findings showed that an abnormal TWA result was associated with a fourfold higher risk of cardiac death and life-threatening arrhythmias.[84] In contrast, the SCD-HeFT TWA substudy did not demonstrate the usefulness of TWA in predicting life-threatening arrhythmias or ICD shocks.[85] A 2009 meta-analysis on the role of TWA in risk stratification in nonischemic cardiomyopathy based on eight studies with nearly 1500 patients showed that a normal TWA test had a 96% negative predictive value and is useful in identifying low-risk patients who are unlikely to benefit from ICD therapy.[86]

Risk Stratification in Congestive Heart Failure

The occurrence of CHF is increasing among patients with cardiac diseases. The mode of death in patients with CHF depends mainly on the functional NYHA class, with SCD being predominant among patients with less advanced CHF and death from pump failure being predominant among those in NYHA class IV.[14,87]

VPBs can be found in up to 85% of patients with severe heart failure. Even though the relationship between ventricular arrhythmia and SCD is not clear, the majority of trials showed a significant association between the presence of NSVT and cardiac death.[88-90] In the Captopril-Digoxin Multicenter Study, VPB, couplets, and NSVT were univariate predictors of total mortality.[88] The presence of at least two episodes of NSVT was related with

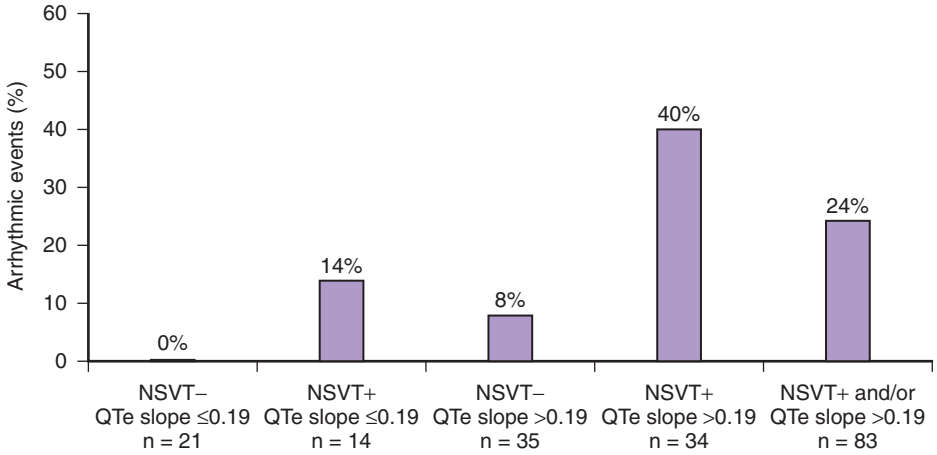

FIGURE 72-5 Probability of arrhythmic events out to 36 months in patients with left ventricular ejection fraction (*LVEF*) <35%, according to the presence or absence of nonsustained ventricular tachycardia (*NSVT*) and QTe slope above or below median value. *(From Iacoviello M, Forleo C, Guida P, et al: Ventricular repolarization dynamicity provides independent prognostic information toward major arrhythmic events in patients with idiopathic dilated cardiomyopathy,* J Am Coll Cardiol *50:225–231, 2007.)*

a threefold increase in total mortality and was an independent predictor of SCD. The Gruppo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA) trial documented that NSVT was associated with increased risk for both all-cause mortality and SCD.[89] Spontaneous sustained VT is infrequent in Holter recordings, but if present, it predicts SCD.[90]

Decreased HRV and resting tachycardia are the common features seen in patients with CHF. The extent of HRV reduction correlates with the advancement of CHF expressed by EF, NYHA class, or brain natriuretic peptide levels.[91] SDNN is the most extensively studied and best-validated HRV parameter. Similar to what was observed in patients with prior MI, reduction in HRV consistently predicts all-cause mortality and heart failure progression. However, it usually fails to predict SCD. In the UK-Heart Study, an SDNN less than 100 ms was associated with death from progressive heart failure but was not related to SCD.[92] With regard to spectral methods, decreased low-frequency (LF) and very-low-frequency (VLF) components are the most frequently reported HRV measures related to death in CHF patients.[93,94] However, different components of spectral analysis are related to different types of death. Decreased nighttime VLF values were related to progressive heart failure, whereas decreased nighttime LF values were associated with SCD.[95]

Data on the predictive value of HRT in patients with cardiomyopathies remain limited. In the Marburg Study, turbulence onset was found to be a significant predictor of transplant-free survival in 242 patients with idiopathic cardiomyopathy.[96] In the UK-Heart Study, abnormal turbulence slope was found to be an independent risk predictor of death from decompensated heart failure.[97] MUSIC findings showed that abnormal HRT was related to an increased risk of death and SCD in patients with mild-to-moderate heart failure, regardless of etiology (ischemic vs. nonischemic). However, consistent with the postulated mechanisms of HRT relating this phenomenon to abnormal baroreflex sensitivity and autonomic imbalance, abnormal HRT showed a trend toward a stronger association with death from heart failure than with SCD.[98]

Risk Stratification in Patients with Preserved Left Ventricular Function

A significant change in the clinical profile of survivors of MI has been seen in recent decades. Post-infarction populations from the 1970s to the 1980s ended up with an EF less than 30% in approximately one third of patients, whereas current data indicate that such values can be found in less than 10% of survivors of MI.[15,26,78] More importantly, aggressive pharmacologic treatments may lead to further positive ventricular remodeling. Progress in the treatment of the acute phase of MI increases the chances of patients surviving and developing heart failure in the future. Therefore the current century has experienced a steady increase in the number of patients with heart failure and preserved EF, who may currently account for up to 40% to 50% of all patients with heart failure.[99] The relative risk of death is lower in patients with preserved left ventricular function than in patients with significant left ventricular impairment, but the absolute number of patients at risk is high.[18,99]

Among patients with stable CAD and preserved EF (>40%) from the Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) study, a simple clinical score that included age, gender, race, current angina, EF, prior revascularization, and diuretic and/or digitalis use, identified patients at risk of SCD. For risk stratification, 2 points were given for age older than 75 years, digitalis use, diuretic use, EF between 40% and 50%, and of non-white race; 1 point was given for male gender, age 65 to 75 years, current angina, and prior revascularization. The incidence of SCD at 4 years of follow-up was 0.8% for patients with a score 0 to 3 points, 2.2% for those with 4 to 6 points, and 10.4% for those with more than 6 points.[100]

With regard to noninvasive ECG risk stratification, data on the prognostic value of these parameters in patients with preserved LVEF is limited and the results are conflicting. Klinhengeben et al documented that in patients with prior MI and an EF greater than 35% treated with PCI for acute coronary syndromes, only patency

of the infarct artery, but not autonomic markers such as baroreflex sensitivity or HRV, was significantly predictive for cardiac death or arrhythmic events.[101] Barthel et al showed that in patients with prior MI and EF greater than 30%, a combination of abnormal HRT with age greater than 65 years and diabetes identified a group of patients at the highest risk of 2-year mortality.[77] Makikalio et al confirmed that in the era of widely used PCI procedures and β-blockers, most of the Holter-based risk markers preserve their prognostic value and were particularly useful in patients with an EF greater than 35%. In a population of 2130 patients treated with coronary revascularization (70%) and/or β-blockers (94%), the incidence of SCD during a 2-year follow-up period was 1.8% in patients with an EF greater than 35% compared with 7.5% in patients with an EF of 35% or less. However, the total number of events was twofold higher in patients with preserved EF (35% vs.17%). Multivariate analysis showed that in patients with relatively preserved EF, SCD was independently predicted by the presence of an abnormal turbulence slope (HR, 4.7), NSVT (HR, 3.5), QRS of 120 ms or greater (HR, 3.2), and detrended fluctuation analysis less than 0.75 (HR, 2.7). Cumulative SCD rate was similar for patients with an EF of 35% or less and for those with an LVEF greater than 35% but with an abnormal turbulence slope.[48]

As documented by Bauer et al among patients with LVEF greater than 30%, the presence of severe autonomic failure identified a group with a 39% mortality rate compared with a 6% mortality rate in patients without such abnormality during a 5-year follow-up. After adjustment for age, diabetes mellitus, history of previous MI, gender, and arrhythmia on Holter monitoring, severe autonomic failure yielded a nearly fivefold higher risk of SCD (HR, 4.6; 95% CI, 3.1 to 7.0; $P < .001$).[78]

Autonomic nervous system measures and the parameters reflecting increased heterogeneity of repolarization have been proven to be useful in the risk stratification. In a Japanese prospective, multi-center study enrolling 1041 patients with prior MI, an EF of 40% or more, a positive MTWA test, and the presence of NSVT on Holter monitoring were significantly associated with serious arrhythmic events on multivariate analysis.[102] The other method of TWA measurement with the modified moving average technique supported the usefulness of TWA test application in a population with preserved EF.[103]

The MUSIC study, which enrolled ambulatory patients with CHF in NYHA class II to III, documented that the risk of death in CHF patients with a relatively preserved EF (>35%) could be stratified by dynamic ECG measures. Patients with heart failure and an LVEF greater than 35% and abnormal ECG parameters had a 3-year mortality rate similar to those with significantly depressed left ventricular function. The scoring system, based on a combination of Holter-based parameters (turbulence slope, QT or RR slope, SDNN), identified patients at high risk of mortality and SCD during a more than 3-year follow-up. Patients with two or more abnormal risk markers were at risk of death (30% 3-year mortality rate) and SCD (12%), similar to death rates observed in patients with an LVEF of 35% or less (Figure 72-6). Interestingly, our study documented that, among patients with CHF with relatively preserved EF, traditional ECG risk markers such as increased heart rate, wide QRS, or frequent VPBs did not play a significant role in risk stratification. It seems that in this population, dynamic—not static—measures play a more important role. This could be explained by the presence of an early autonomic impairment in patients with still relatively preserved LVEF in the early stages of heart failure.[104]

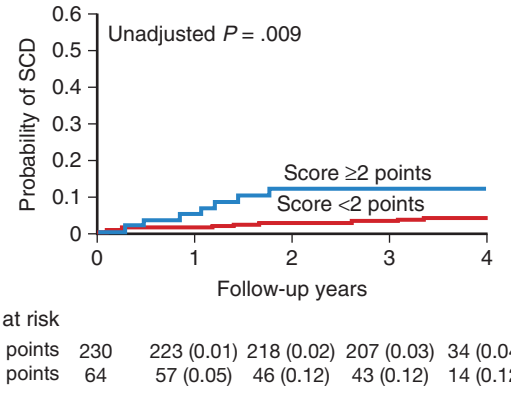

FIGURE 72-6 Cumulative probability of sudden cardiac death (*SCD*) according to risk score in patients with congestive heart failure and ejection fraction >35%. *(From Cygankiewicz I, Zareba W, Vazquez R, et al, MUSIC Investigators: Risk stratification of mortality in patients with heart failure and left ventricular ejection fraction >35%,* Am J Cardiol *103:1003–1010, 2009.)*

Use of such a scoring system may be supported by another study by Watanabe et al, who, in a population of 680 patients with CHF from the Chronic Heart Failure Analyses and Registry in Tokushi District (CHART) study, identified an EF of less than 30%, left ventricular diastolic diameter greater than 60 mm, BNP level greater than 200 pg/mL, diabetes, and NSVT as significant risk predictors for SCD.[105] The CHART patients with an LVEF of 30% or more and 0 to one risk markers were characterized by a very low mortality rate from SCD at 2 years of follow-up (2.8%) compared with 20% if the number of risk factors was three or more.

Ongoing trials will determine whether noninvasive risk markers can serve as indicators for ICD implantation in patients with an LVEF greater than 35% who are currently not covered by ICD implantation guidelines. REFINE will assess the prognostic value of Holter-based TWA and HRT assessment in patients with a history of recent MI and LVEF between 36% and 49%, and the Stratification of Autonomic Regulation for Risk Prediction in Postinfarction Patients with Preserved Left Ventricular Function (ISAR–ICD) study will assess the benefit from ICD therapy in patients stratified based on severe autonomic failure.[106]

Summary

The risk stratification of cardiac death and SCD remains a continuous challenge, especially with the changing nature of cardiovascular diseases altered by more advanced therapies and improved survival of affected patients. Primary prevention of SCD with ICD therapy is still underutilized, with only 30% to 40% of eligible patients receiving devices. Numerous approaches exist that could enhance identification of patients who could benefit (or who may get limited benefit) from ICD therapy, including bedside clinical predictive models, TWA, QT variability, SAECG, HRV, and HRT. Proper use of these techniques with their high negative predictive value may further help risk stratification in daily practice. It is important to emphasize that the risk stratification process is not just a one-time evaluation associated with an index event; it is a continuously repeated assessment of patients whose condition may change over time according to myocardial

substrate, vulnerability to arrhythmia or ischemia, or comorbidities. Increasing attention is being paid to the development of risk stratification algorithms in patients with relatively preserved EF, since this patient population predominates in the number of cases of SCD in society.

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CHAPTER 73

Arrhythmias During Pregnancy

Thomas Adam Burkart and Jamie Beth Conti

Cardiac arrhythmias during pregnancy, although not a routine problem, are not uncommon. Fortunately, life-threatening tachyarrhythmias in women of childbearing age are infrequent; sustained symptomatic bradyarrhythmias in this population are also exceedingly rare. Additionally, most inherent rhythm disorders manifest long before the patient reaches the childbearing age, suggesting that a more aggressive therapeutic approach may be warranted if the individual plans for a future pregnancy.[1] The need to manage arrhythmias in this patient population, however, is likely to become a larger issue as women delay pregnancy until later in life and those with significant congenital heart abnormalities routinely survive into their reproductive years. Few adult cardiologists have had significant exposure to these patients, either in training or in clinical practice. As such, these patients are often approached with a great deal of trepidation, given the recognized pitfall that any management decision on the mother's behalf could potentially adversely affect the health of the unborn child. This need not be the case if straightforward principles of evaluation and management are followed. Most arrhythmias during pregnancy can be safely and adequately managed with conservative therapies that have excellent outcomes for both mother and child.

In general, the approach to the evaluation of arrhythmias in the pregnant patient is similar to that in patients who are not pregnant. However, when deciding on the appropriate therapy, several factors unique to the state of pregnancy must be considered. These factors include the developing fetus; the characteristic hemodynamic changes seen in pregnant women; the effect of antiarrhythmic therapy on labor, delivery, and lactation; and the direct effects of the drugs on the unborn child.

Physiological Changes During Pregnancy

During pregnancy, the mother's cardiovascular system must accommodate significant hemodynamic changes to meet her own needs and those of the developing fetus. Total body water increases by approximately 5 to 8 liters in a normal pregnancy, and even more so in patients with clinical edema. This process begins during the first trimester and continues until mid-pregnancy, at which time total body water levels stabilize and then gradually diminish until the last week of pregnancy.[2] This rise in blood volume results in an approximately 40% increase in cardiac output, significantly increasing the mechanical demands on the maternal heart throughout this period. The increase in cardiac output in early pregnancy is disproportionately greater than the observed increase in heart rate, most likely secondary to the augmentation of stroke volume (Figure 73-1).[3] Peripheral vascular resistance is seen to fall throughout pregnancy in proportion to the rise in total body water, resulting in a decrease in blood pressure in early pregnancy; the blood pressure reaches its nadir by mid-pregnancy and returns to baseline levels at term.

The physiological effects of pregnancy on drug therapy are significant. The observed increase in cardiac output increases renal blood flow by mid-pregnancy by as much as 60% to 80%, resulting in a peak glomerular filtration rate (GFR) that is 50% higher than that before the pregnancy. This GFR level is sustained until the end of pregnancy, resulting in markedly increased metabolism of renally cleared drugs.[3] Changes in gastric motility and secretion affect drug absorption both upward and downward.[4] Additionally, an increased level of progesterone during pregnancy results in the increased metabolism of hepatically cleared drugs.[5] An increased blood volume with the resulting increased volume of distribution may lower the concentration of drugs in the central compartment, increasing their elimination half-life. At the same time, decreases in plasma protein concentration result in less protein binding of susceptible drugs, thus increasing their bioavailability and potential effect.[3,6,7] The combined result of these changes makes careful assessment of clinical drug effect essential, as the measured serum drug concentration may be misleading because of altered protein binding. Total measured serum drug concentration may be low because of decreased protein binding, when, in fact, the drug's active free fraction may have remained unchanged. Thus, although the drug level may appear low, therapeutic efficacy may have been achieved, making increases in drug dosage unnecessary and perhaps dangerous (Figure 73-2).

Principles of Evaluation and Management

There is no place for empirical treatment in pregnant patients.[8] This is the cardinal rule that must be followed in the treatment of patients who are pregnant. Careful documentation, correct diagnosis, and correlation of the arrhythmia, whatever it may be, with symptom severity is vitally important. On the one hand, arrhythmias causing hemodynamic compromise to the mother obviously compromise the fetus via reduced placental blood flow and therefore are of primary concern. On the other hand, patients who complain of palpitations, but in whom no arrhythmia can be documented, have a low likelihood of having a life-threatening arrhythmia. In most cases, no further evaluation is warranted.[9] In patients with minimal or minor symptoms and a structurally normal heart, the conservative principle "less is better" applies.

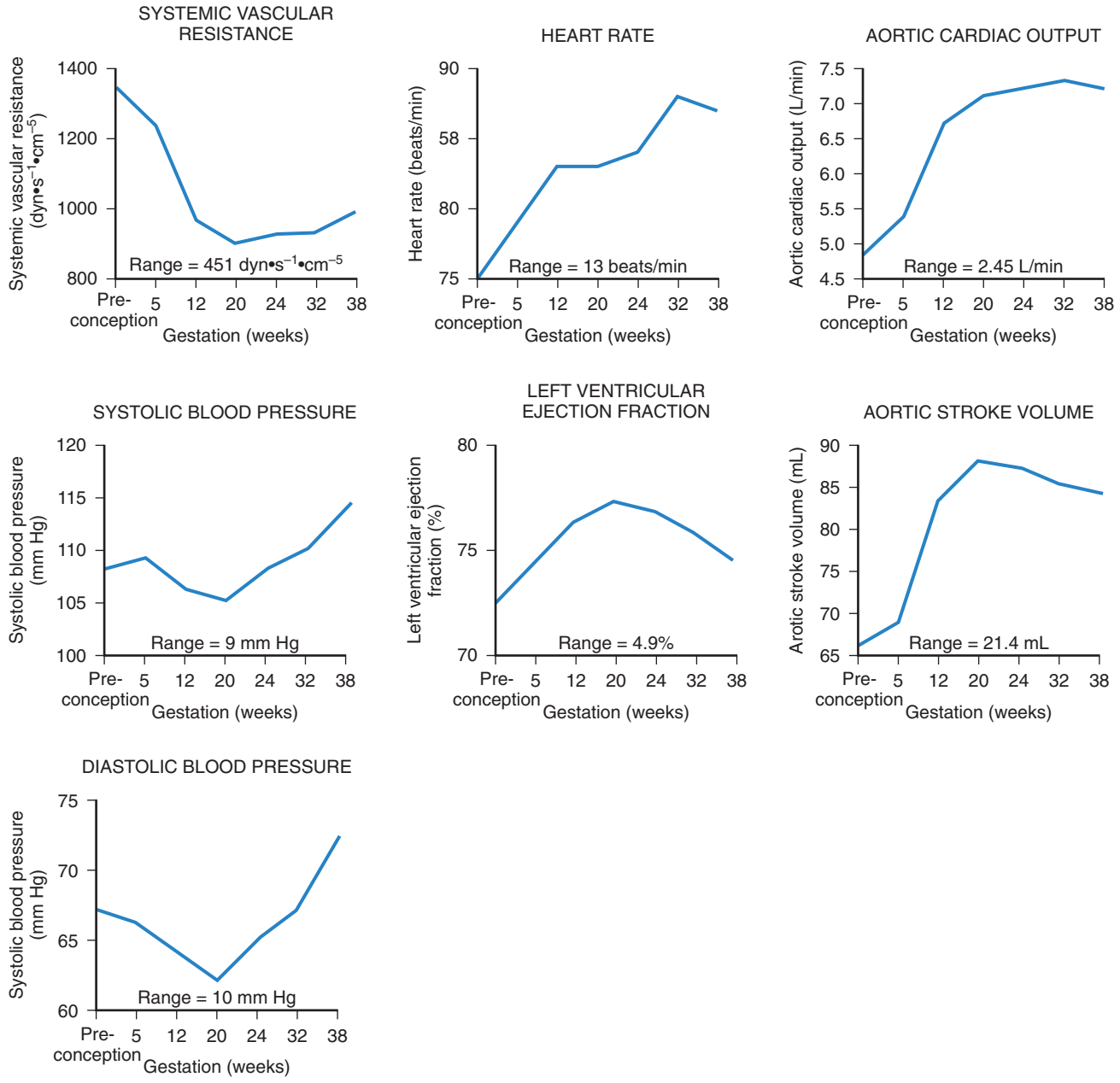


FIGURE 73-1 Cardiocirculatory changes during normal pregnancy. Echocardiographic data show hemodynamic and circulatory changes in 13 women with normal pregnancies. Ranges represent the difference between highest measured value and lowest measured value for each parameter. *Modified form Elkayam U, Gleicher N: Hemodynamics and cardiac function during normal pregnancy and the puerperium. In Elkayam U, Gleicher N, editors*: Cardiac problems in pregnancy, *ed 3, New York, 1988, Wiley Liss, p 4.*

The need for treatment must be clear. Symptom severity should guide clinical judgment as to whether the benefit of therapy outweighs the risks to both mother and fetus.

History

The recorded history should include detailed questioning of onset, length, and degree of symptoms as well as aggravating and alleviating factors. Symptoms of concern for hemodynamic instability include dizziness, syncope, or near-syncope. Precipitants of arrhythmias such as electrolyte imbalances, renal failure, thyrotoxicosis, and gestational diabetes should be considered.[10] Structural heart disease and previously diagnosed tachyarrhythmias are of concern as the women with these conditions are at an increased risk of recurrence or worsening of their arrhythmia throughout the pregnancy. Patients with a history of repaired congenital heart disease will inherently carry the risk of developing scar-related tachyarrhythmias. A new arrhythmia during pregnancy may also be the first manifestation of underlying heart disease.[11-13]

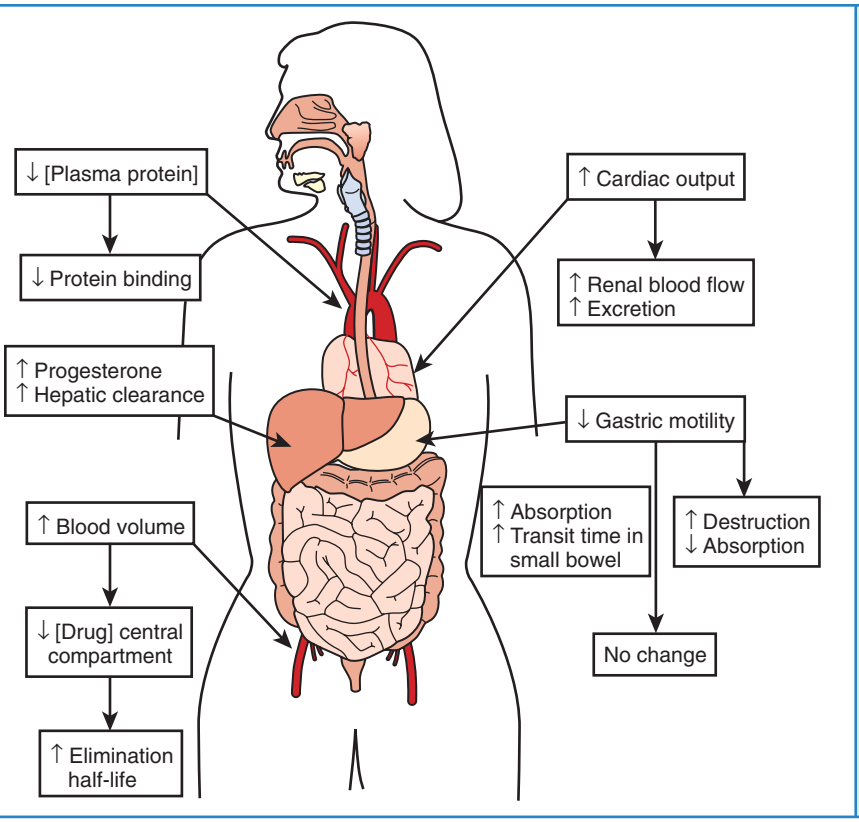


FIGURE 73-2 Schematic drawing representing the physiological changes during pregnancy affecting the absorption, distribution, and elimination of drugs.

Physical Examination

From the cardiovascular standpoint, physical examination of the pregnant patient is essentially identical to that of patients who are not pregnant. Normal findings during pregnancy include a widely split first heart sound, expiratory splitting of the second heart sound late in pregnancy, a soft systolic flow murmur believed to represent increased blood flow across the pulmonic valve, and mild peripheral edema.[14] Findings of specific interest in a patient presenting with an arrhythmia would include murmurs of mitral stenosis, signs consistent with congestive heart failure, and murmurs consistent with congenital heart disease.

Diagnostic Testing

Electrocardiography

The standard 12-lead electrocardiogram (ECG) is, of course, immensely helpful in making the diagnosis if it can be obtained during an arrhythmia episode. A baseline recording may provide clues to the presence of underlying conduction system disease, chamber hypertrophy, ventricular pre-excitation, QT prolongation, and evidence of arrhythmogenic right ventricular dysplasia. The normal ECG during pregnancy may demonstrate a shift in the QRS axis to the left in the frontal plane with a small Q wave with an inverted T wave in lead III (Figure 73-3, *A* and *B*). These are normal changes during pregnancy resulting from a gradual shift in the position of the heart within the thorax.[15]

Ambulatory Monitoring

If symptoms are frequent, 24- or 48-hour Holter monitoring is useful for the identification of arrhythmia and correlation with symptoms. Event monitoring using either a patient-triggered monitored system or one of the newer self-triggering monitoring systems can be used if the episodes are relatively infrequent, sporadic, or otherwise difficult to capture. An implantable loop recorder is of primary value in the documentation of very infrequent, long-term arrhythmia; its implantation is probably unjustified during the 9 months of pregnancy. If no arrhythmia can be documented using noninvasive means, it is unlikely that a life-threatening arrhythmia is present.

Echocardiogram

A transthoracic echocardiogram is of obvious value in ruling out potential congenital or acquired cardiac abnormalities as contributors to the arrhythmia. The authors of this chapter believe that it should be a standard part of any arrhythmia workup, as it is noninvasive and safe and provides a wealth of information regarding the structural and functional integrity of the heart. In any event, it will be necessary to establish the patient's cardiac health before starting any antiarrhythmic treatment that is deemed necessary.

Exercise Treadmill Testing

Exercise testing may be useful in patients with exercise-induced arrhythmias, suspected chronotropic incompetence, or possible underlying ischemic heart disease. Moderate exercise testing

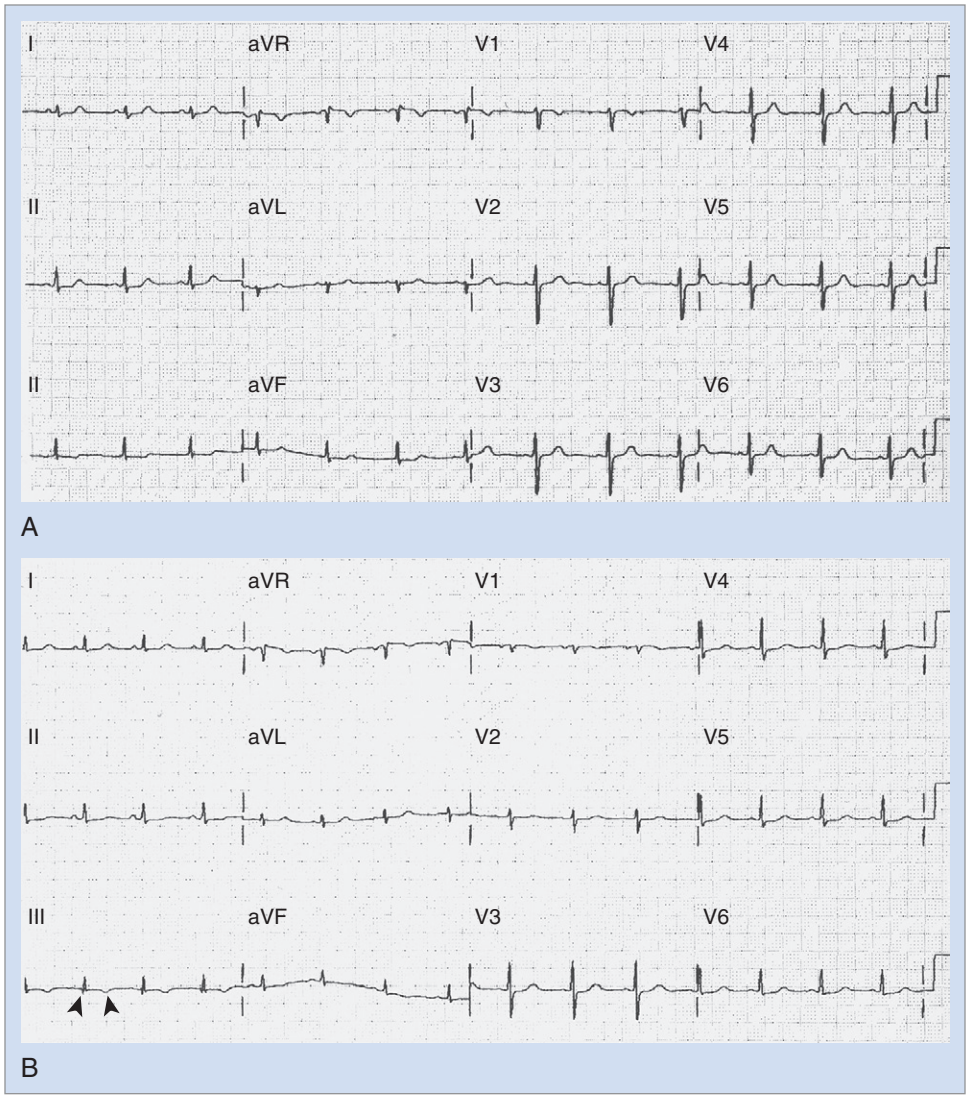


FIGURE 73-3 A, Baseline electrocardiogram (ECG) in a 23-year-old patient before pregnancy. The axis is slightly rightward, with normal T waves seen in lead III. **B,** ECG in the same patient obtained when she was 7 months pregnant. The axis has shifted leftward. A small Q wave and an inverted T wave are seen in lead III (*arrows*).

during pregnancy is not contraindicated but may be impractical in late pregnancy. The patient should be carefully monitored for symptoms, and the exercise test must be stopped if any sign of hemodynamic compromise is detected.

Tilt-Table Testing

This noninvasive procedure is helpful in the diagnosis of orthostatic hypotension, autonomic dysfunction, and neurocardiogenic syncope. It is generally safe during pregnancy and may be of diagnostic value if positional syncope or near-syncope is the main issue. Neurocardiogenic syncope usually improves in most susceptible patients during pregnancy, likely because of the significantly increased intravascular volume associated with this state.

Electrophysiology Study

Although currently electrophysiology studies (EPSs) are routinely performed in the diagnosis and treatment of arrhythmias, the use of fluoroscopy for the positioning of catheters during diagnostic and ablative procedures limits this option during pregnancy.[8] Radiation exposure of the fetus during the first and second trimesters of pregnancy has been linked to congenital malformations and mental retardation.[16] In addition, radiation exposure in utero increases the risk of childhood malignancies, especially leukemia.[17-20] If absolutely necessary, an EPS can be performed, with a lead apron draped over the mother's abdomen; with this approach, good outcomes have been reported in the literature.[21] Using intracardiac echocardiography and an electroanatomic mapping system can (and should) also be used for catheter placement and manipulation to minimize fluoroscopic time if ablation

appears to be the only effective treatment.[22,23] Because of the small, but finite, increased risk of childhood malignancy, routine use of fluoroscopy, even with appropriate shielding, is not recommended.

Cardiac Catheterization

Left heart catheterization performed during pregnancy has been reported infrequently.[24] Although rarely indicated for the evaluation of an arrhythmia, knowledge of the coronary anatomy may be crucial to the management of certain patients such as an individual who has experienced aborted sudden cardiac death (SCD) during pregnancy. As the maternal age increases, the occurrence of acute ischemic events during pregnancy may rise. The same precautions mentioned above should be employed, with radiation exposure minimized as much as possible.

Frequency of Arrhythmias Complicating Pregnancy

Life-threatening arrhythmias during pregnancy are rare. Arrhythmias, when present, most commonly present as symptomatic palpitations, which, in most cases, represent an increased level of background atrial or ventricular ectopic activity. Although no single mechanism has been definitively cited, increased mechanical stress, intravascular volume shifts, elevated hormonal levels, and emotional changes occurring during pregnancy likely account for this increase. As most of these women will have structurally normal hearts, this ectopy is generally well tolerated, should be approached as benign, and can be anticipated to substantially resolve in the postpartum period.[10,25,26]

Women with previously diagnosed tachyarrhythmias are at an increased risk of recurrence of their arrhythmia during pregnancy, possibly initiated by increased ectopic activity serving as a trigger for its onset.[11,12] Patients with no previous history may present for the first time with an arrhythmia for the same reason. Arrhythmias severe enough to require hospitalization, however, are rare. In a recently published paper, 9 years of hospitalizations at a high-volume obstetric service with the admission diagnosis of "arrhythmia" were reviewed.[27] The prevalence of arrhythmia-associated admissions was 166 in 100,000 with an average patient age of 25 years. Sixty percent of arrhythmia admissions comprised a group consisting of patients with sinus tachycardia, sinus bradycardia, and sinus arrhythmia. Premature atrial or ventricular contractions were attributed to 19% of arrhythmia admissions and 14% to supraventricular tachycardia (SVT). Atrial fibrillation (AF) and flutter were counted separately from SVT and comprised only 1% of the arrhythmia admissions. The diagnosis of ventricular tachycardia (VT) or ventricular fibrillation (VF) was made in only 1% of admissions as was atrioventricular (AV) block (Figure 73-4).

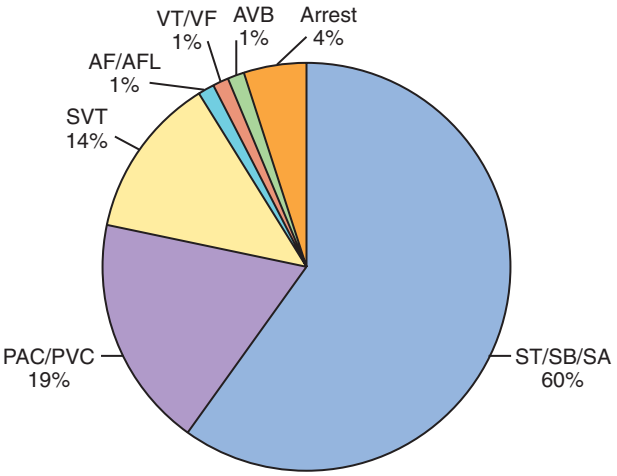


FIGURE 73-4 Distribution of various arrhythmias during pregnancy as expressed as percentage of total arrhythmia occurrence (1992–2000). *AF*, Atrial fibrillation; *AFL*, atrial flutter; *AVB*, atrioventricular block; *PAC*, premature atrial contraction; *PVC*, premature ventricular contraction; *SA*, sinus arrhythmia; *SB*, sinus bradycardia; *ST*, sinus tachycardia; *SVT*, supraventricular tachycardia; *VF*, ventricular fibrillation; *VT*, ventricular tachycardia. *(From 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 *1[11]:539, 2008. Wiley Periodicals, Inc. John Wiley & Sons, Inc.)*

Supraventricular Tachycardia

Sinus tachycardia is a normal response to pregnancy. The risk of paroxysmal SVT is generally equally distributed throughout pregnancy, although a rise in the frequency of onset of new or recurrent PSVT in the second and third trimesters has been reported.[8,12] Several mechanisms have been postulated to explain the increased incidence, including hemodynamic, autonomic, hormonal, and emotional changes occurring in the pregnant patient. Increased mechanical stress, intravascular volume shifts, elevated estrogen levels, and physiological increases in heart rate have all been implicated.[13] AV re-entrant tachycardia—which comprises the pre-excited, Wolff-Parkinson-White (WPW) form of AV reciprocating tachycardia and AV nodal re-entrant tachycardia as well as the non–pre-excited form—is the most common sustained arrhythmia seen in pregnancy and is seen with equal frequency.[28,29] Atrial tachycardia, atrial flutter, and AF are encountered most often in patients with structural heart disease, repaired congenital heart disease, and valvular heart disease.

Ventricular Tachycardia

In 1921, Mackenzie reported that nonsustained ventricular arrhythmias were present in approximately 50% of pregnant women in his study.[30] The recognized causes of recurrent or paroxysmal VT during pregnancy include arrhythmogenic right ventricular dysplasia, long QT syndrome (LQTS), hypertrophic cardiomyopathy, peripartum cardiomyopathy, and, in rare circumstances, coronary artery disease. Patients without organic heart disease who experience nonsustained VT during pregnancy are at a low risk for subsequent morbidity and mortality.[31] Fortunately, very few women during their childbearing years have coronary artery disease, with an even smaller number having re-entrant VT. Multiple cases of sustained VT during pregnancy have been reported. The vast majority of these women

have normal hearts and no history of VT before pregnancy. Some of these patients will invariably be found to have catecholamine-sensitive idiopathic VT.[32,33] Right ventricular outflow tract (RVOT) tachycardia, for example, is often associated with exercise, typically has a left bundle branch block (LBBB) morphology with an inferior axis of depolarization, and is often responsive to β-blocker therapy (see Chapter 45). Onset of such VT during pregnancy with complete resolution after delivery has been reported in the literature.[34] Fascicular VT is also seen in patients with structurally normal hearts. This form of VT generally arises from one of the left ventricular fascicles, most commonly the left posterior fascicle giving a right bundle branch block (RBBB), superiorly directed VT on the 12-lead ECG. This form of VT during pregnancy has also been reported in the literature and is often responsive to calcium channel blockers. Peripartum cardiomyopathy should always be considered with new-onset VT within 6 months of delivery.

Cardiac Arrest

Cardiac arrest during pregnancy is fortunately rare. It is estimated to occur in 1 in 30,000 deliveries as a result of complications occurring during pregnancy, labor, and delivery and in the immediate postpartum period.[35] It is important to recognize that in this patient population, the etiology is often different from that for the general population, including amniotic fluid embolism, pulmonary embolism, hemorrhage, and eclampsia.[36] Table 73-1 lists the most frequent causes of cardiac arrest in pregnancy. Cardiopulmonary resuscitation (CPR) in the pregnant patient will be reviewed later in this chapter.

Arrhythmias in Patients with Previous Tachyarrhythmia and Structural Heart Disease

In women with pre-existing cardiac rhythm disorders, exacerbation of their arrhythmia during pregnancy is common, increasing the risk of fetal complications.[37] In a recently published study, Silversides et al reported on the recurrence rates of arrhythmias during pregnancy in women with known cardiac rhythm disorders.[12] Initially, in sinus rhythm, 44% developed tachyarrhythmia recurrences during the pregnancy or in the early postpartum period. Nearly 50% of the women studied with a prior history of SVT had recurrence of their SVT complicating the pregnancy. AF or atrial flutter occurred in 52% of patients with a prior history of AF or atrial flutter. Almost all of the patients (96%) known to have AF or atrial flutter before their pregnancy had underlying structural heart disease.[12]

Congenital heart disease is a significant risk factor for cardiac arrhythmias and is found increasingly in women of childbearing years. Atrial tachyarrhythmias are frequently encountered, as are ventricular arrhythmias that are associated with such congenital conditions as corrected tetralogy of Fallot, hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia, and congenital LQTS. Silversides et al reported VT complications in 27% of pregnancies in women with a previous history of VT caused by LQTS or structural heart disease.[12]

Table 73-1 Etiology of Cardiac Arrest in Pregnancy

Amniotic fluid embolism
Hemorrhage
Pulmonary embolism
Magnesium sulfate toxicity
Eclampsia
Trauma
Peripartum cardiomyopathy
Epidural anesthesia
Aortic dissection

Use of Drugs in the Management of Arrhythmias

Once the correct diagnosis has been made and arrhythmia has been documented, an accounting of the severity of the patient's symptoms must be undertaken. The reasons for instituting treatment must be clear. Severity of symptoms helps determine whether the risks of therapy outweigh the benefits. The only difference in pregnancy is that the physician must consider the risk/benefit ratio for both the mother and the fetus. An arrhythmia that is hemodynamically compromising to the mother is of major concern because of the resulting compromised blood flow to the placenta. Under normal conditions this will be 6 to 7 L/min during the last trimester. The mother accomplishes this by means of a 15% increase in heart rate and 35% to 40% increase in cardiac output.[36] Pharmacologic therapy should be reserved for patients with hemodynamically unstable arrhythmias, whereas bothersome symptoms in a patient with a normal heart should be treated conservatively with reassurance, if feasible.

If the decision to initiate drug therapy is made, as few drugs at the lowest effective therapeutic doses as possible must be used. Although this is inherently true for the treatment of all patients, it is particularly important in the pregnant patient. This approach exposes the mother and the fetus to the least possible amount of potential toxins. When feasible, drug choice should be limited to those with a history of safe use in pregnancy. The majority of antiarrhythmic drugs are classified as U.S. Food and Drug Administration (FDA) category C—this means that risk cannot be ruled out—as indicated by animal studies that have suggested risk, but no human studies or controlled studies in either humans or animals that suggest risk exists (Table 73-2).[38] Keep in mind that these categories have been criticized as being misleading because they suggest the presence of graded risk as one crosses categories and similar risk among drugs in the same category. This is not accurate, as a wide range of severity of adverse effects exist within classes, and often no distinction can be seen between teratogenic and other toxic effects. For example, if given the choice between a category C drug that is new and one that has a long, safe history of use, the drug with the history of safe use is recommended.[25] Of course, a chance of fetal harm is always present when any antiarrhythmic drug is taken during pregnancy, but in the right situation, the potential benefits should outweigh the potential risk. It is unlikely that comprehensive clinical trials will ever be performed in this patient population, for obvious ethical reasons. The publication of clinical case reports involving the use of these drugs in pregnancy is therefore vitally important.

Table 73-2 U.S. Food and Drug Administration Use-in-Pregnancy Ratings

CATEGORY	INTERPRETATION
A	Controlled studies show no risk. Adequate, well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester of pregnancy.
B	No evidence of risk in humans. Adequate, well-controlled studies in pregnant women have not shown increased risk of fetal abnormalities despite adverse findings in animals, or, in the absence of adequate human studies, animal studies show no fetal risk. The chance of fetal harm is remote but remains a possibility.
C	Risk cannot be ruled out. Adequate, well-controlled human studies are lacking, and animal studies have shown a risk to the fetus or are lacking as well. A chance of fetal harm exists if the drug is administered during pregnancy, but the potential benefits may outweigh the potential risk.
D	Positive evidence of risk. Studies in humans or investigational or postmarketing data have demonstrated fetal risk. Nevertheless, potential benefits from the use of the drug may outweigh the potential risk. For example, the drug may be acceptable if needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective.
X	Contraindicated in pregnancy. Studies in animals or humans or investigational or postmarketing reports have demonstrated positive evidence of fetal abnormalities or risk, which clearly outweighs any possible benefit to the patient.

From the Physicians' desk reference: PDR, *ed 55, Oradell, NJ, 2001, Medical Economics, p 344.*

Effects on the Fetus

The physician must consider the stage of pregnancy before deciding on a drug. The risk of teratogenicity is generally higher during the first trimester; after 8 weeks, organogenesis is complete, and the risk to the fetus is substantially reduced. The occurrence of teratogenic abnormalities depends on the drug the fetus is exposed to, the duration of exposure, and genetic predisposition.[9] To further complicate management, the absorption, distribution, and excretion of drugs are dramatically altered during pregnancy, as previously described, making monitoring of drug levels difficult and therapeutic effects variable. Drug effects at the time of labor and delivery are also of concern and need to be taken into account.[39] In most cases, the method of drug delivery (oral versus intravenous administration) has not been reported to be a significant factor in terms of toxicity. The method of delivery, however, will likely affect the speed and immediate potency of the drug effect and therefore needs to be factored into the decision process.

Lactation and Breastfeeding

Antiarrhythmic drug use during breastfeeding has similar concerns as during pregnancy. Many antiarrhythmic drugs and AV nodal blockers are excreted in breast milk, and thus continued use during breastfeeding must be considered on a case-by-case basis. Both warfarin and heparin are safe for use in nursing mothers who require long-term anticoagulation. Refer to Tables 73-3, 73-4, and 73-5 for current FDA ratings on drug safety during lactation for the most common drugs used to treat arrhythmias.

Table 73-3 Calcium Channel Blocker and Digoxin Therapy During Pregnancy

DRUG	FDA CATEGORY	SAFETY DURING LACTATION
Verapamil	C	S
Diltiazem	C	S
Diltiazem IV	C	NS
Digoxin	C	S

FDA, U.S. Food and Drug Administration; S, generally regarded as safe; maternal medication usually compatible with breastfeeding; IV, intravenous; NS, *generally regarded as not safe and contraindicated or requires cessation of breastfeeding.*

Atrioventricular Nodal Blockers: Adenosine

Although only limited data are available, it appears that *adenosine* has no direct effect on the fetus when fetal monitoring is performed during bolus intravenous (IV) administration.[40,41] Adenosine, which is a purine nucleoside present in all human cells, characteristically depresses AV nodal conduction and sinus node automaticity. These electrophysiological effects have proven useful for the termination of SVT involving the AV node as part of the re-entrant circuit.[42] Because of its rapid onset and short duration of action, it appears to be a safe drug for use during pregnancy, although it remains an FDA category C drug.[43]

Calcium Channel Blockers

Verapamil is a calcium channel blocker with a long history of use in the management of SVT. It crosses the placental barrier and has been reported to affect fetal cardiovascular activity.[44] It is rapidly absorbed but has high first-pass metabolism, with only a small portion excreted unchanged in the urine. Ninety percent of the drug is plasma protein bound. Congenital defects in association with verapamil have not been reported. Verapamil is an FDA category C drug.

Diltiazem is a relatively newer drug than verapamil, so less information on the clinical history of its use in pregnancy is available. Nevertheless, it has been used in the treatment of premature labor without reported congenital abnormalities and thus should be safe for use in arrhythmias.[45] Diltiazem is an FDA category C drug (see Table 73-3).

Digoxin

Digoxin is a cardiac glycoside, which has a long history of use in pregnancy for the management of supraventricular arrhythmias, although it remains classified as an FDA category C drug. Elimination of the drug is predominantly renal. Digoxin crosses the placenta readily, with fetal plasma concentrations similar to maternal values within 30 minutes.[46] These agents have also been administered maternally to manage fetal tachyarrhythmias.[47,48] Digoxin is not teratogenic.

Table 73-4 β-Blocker Therapy During Pregnancy

DRUG	FDA CATEGORY	SAFETY DURING LACTATION	CARDIOSELECTIVITY
Acebutolol	B	S	+
Atenolol	D	S	+
Bisoprolol	C	Unknown	+
Esmolol	C	Unknown	+
Inderal	C	S	–
Labetalol	C	S	–
Lopressor	C	S	+
Metoprolol	C	S	+
Nadolol	C	S	+
Pindolol	B	Unknown	+
Propranolol	C	S	–
Timolol	C	S	–

FDA, *U.S. Food and Drug Administration; S, generally regarded as safe; maternal medication usually compatible with breastfeeding; +, cardioselective drug; –, noncardioselective drug.*

Table 73-5 Antiarrhythmic Drugs During Pregnancy

ANTIARRHYTHMIC DRUG	VAUGHN-WILLIAMS CLASSIFICATION	FDA CATEGORY	SAFETY DURING LACTATION	TRANSPLACENTAL TRANSMISSION
Disopyramide	IA	C	S	Yes
Procainamide*	IA	C	S	Yes
Quinidine	A	C	S	Yes
Lidocaine	IB	B	S	Yes
Mexiletine	IB	C	S	Yes
Flecainide	IC	C	S	Yes
Moricizine†	IC	B	Unknown	Unknown
Propafenone	IC	C	Unknown	Yes
Amiodarone	III	D	NS	Yes
Azimilide†	III	Unknown	Unknown	Unknown
Dofetilide	III	C	Unknown	Unknown
Ibutilide	III	C	Unknown	Unknown
Sotalol	III	B	S	Yes
Dronedarone	III	X	Unknown	Unknown
Adenosine	—	C	Unknown	Unknown

**Commercially available in IV formulation only.*
†No longer commercially available.
FDA, *U.S. Food and Drug Administration; S, generally regarded as safe, and maternal medication usually compatible with breastfeeding;* NS, *generally regarded as unsafe and contraindicated or requires cessation of breastfeeding.*

β-Blockers

β-Blockers have been used extensively in pregnancy. Adverse outcomes with their use, predominantly consisting of fetal bradycardia, hypotonia, neonatal respiratory depression, low birth weight, and hypoglycemia, have been reported.[4,9] The incidence of these adverse outcomes is low. No studies or case reports, to date, implicate any β-blocker in fetal malformations.

Atenolol, however, has recently been reclassified as a category D drug, that is, positive evidence of risk exists, so this drug should not be used in pregnant patients. The risk consists primarily of an increased incidence of reduced birth weight compared with placebo or other β-blockers.[39] If in utero β-blocker use is necessary, it is important to watch for low birth weight and neonatal hypoglycemia in the infant following delivery. Infant blood glucose should be monitored for 24 to 48 hours after delivery, but again, the incidence of these adverse outcomes is low.[4,9]

Acebutolol and pindolol have recently been reclassified by the FDA as category B drugs. This classification designates that no evidence of risk in humans exists. Some data suggest that cardioselective agents (acebutolol) should be used preferentially because they may interfere less with β_2-mediated peripheral vasodilation and uterine relaxation.[49] Propranolol remains a category C drug but has a long history of safe use in pregnancy (see Table 73-4).[50]

Vaughn-Williams Class Drugs

Class IA Antiarrhythmic Drugs

Quinidine

Approximately 70% to 80% of an oral dose of *quinidine* is absorbed from the gastrointestinal (GI) tract, with 80% of the drug bound to plasma proteins. Elimination is predominantly hepatic. Quinidine readily crosses the placental barrier, a property that has been successfully exploited historically to terminate fetal arrhythmias.[51] Of the class IA agents, quinidine has the longest record of safe use during pregnancy. Although isolated cases of adverse effects such as fetal thrombocytopenia and eighth nerve toxicity have been reported, the drug is considered relatively safe.[25] Given its long history of safe use, quinidine is the drug of choice if one elects to use a class IA agent, although it is becoming clinically more difficult to obtain this drug.

Procainamide

Procainamide is 75% to 90% absorbed in the intestines, with 15% of the drug bound to plasma proteins. Elimination is predominantly renal. Although data are limited, procainamide appears to cross the placenta readily and thus has also been used to treat fetal tachyarrhythmias.[52] No adverse fetal outcomes with use of procainamide have been reported, making it an acceptable choice in terminating and managing maternal SVTs. Oral procainamide is no longer clinically available. As it can be administered only intravenously, its use is currently limited to the initial period of arrhythmia management in the hospitalized patient.

Disopyramide

Little published experience in the use of disopryamide in pregnancy is available. It has 60% to 83% absorption in the GI tract and variable protein binding.[4] Elimination is predominantly renal. Although it is not teratogenic, it can cause uterine contractions, which makes this drug less desirable for use during pregnancy than other IA agents.[26]

Class IB Antiarrhythmic Drugs: Lidocaine

Lidocaine is the drug of choice in the initial management of sustained VT and cardiac arrest. It is an FDA category B drug in pregnancy and is believed to be safe to use during lactation. Evidence as to whether or not it alters newborn neurobehavioral responses when administered to the mother during delivery is conflicting.[53]

Class IC Antiarrhythmic Drugs: Flecainide and Propafenone

Flecainide and propafenone both cross the placenta rather easily. Fetal levels of flecainide have been reported to be as high as 86% of maternal levels.[54] Although flecainide is classified as an FDA category C drug, many reports have been made of its safe use during pregnancy with no adverse outcome.[55] Neither of the class IC antiarrhythmic drugs has been reported to be teratogenic. Given the available clinical experience, flecainide is a reasonable choice in patients with structurally normal hearts who require antiarrhythmic therapy.

Class III Antiarrhythmic Drugs

Sotalol

Sotalol has relatively simple pharmacokinetics. It is nearly completely absorbed after oral administration. Approximately 80% to 90% is excreted in urine unchanged, so its use should be avoided in patients with renal insufficiency. It is known to cross the placenta but is the only class I or class III agent to be classified by the FDA as category B.[56] Its use in pregnant patients with no adverse outcome has been reported; however, its quality of prolonging the Q-T interval is well described and must be closely watched for to avoid the risk of torsades de pointes.

Amiodarone

Amiodarone is a highly lipophilic compound that accumulates in multiple body tissues with well-described potential toxic side effects. It accumulates in placental tissue as well, although it achieves fetal concentrations of only 9% to 14% of the maternal serum concentration.[57] It is clearly an effective antiarrhythmic drug in the general population, but its safety profile in pregnancy is poor. Amiodarone appears to have multiple serious adverse effects on the fetus, the most dangerous being neonatal hypothyroidism.[39] (See Table 73-6 for full list of adverse effects.) Whereas amiodarone-induced hypothyroidism is reversible in adults, the newborn infant may suffer irreversible brain damage and seriously compromised respiration caused by a large goiter. Congenital abnormalities in neonates who were exposed to amiodarone have been reported.[58,59] This being said, Strasburger et al reported on

Table 73-6 Reported Adverse Fetal Outcome with Amiodarone Use

Retardation of psychomotor development
Bradycardia
Premature labor
Prolonged Q-T interval
Hypothyroidism
Congenital malformations
Fetal death

the safe and effective use of transplacentally administered (oral) amiodarone for the treatment of drug-refractory fetal tachycardia in 26 fetuses under 36 weeks of gestation.[60] Low rates of associated fetal mortality and excellent efficacy in the treatment of SVT, junctional tachycardia, and VT in the hydropic fetus were also reported.[60] These data suggest that amiodarone may have a role in treating the patient with drug-refractory, symptomatic, and potentially lethal tachyarrhythmias. Nevertheless, this drug carries an FDA category D rating and should be avoided in pregnancy.

Dofetilide

Dofetilide is a relatively new class III agent. It is currently classified as a category C drug by the FDA in human pregnancy, although it has been shown to be teratogenic and toxic in animal fetuses at exposure levels slightly above those expected in humans. As this is a new drug with little clinical experience of its use during pregnancy, the authors do not recommend its use as a first-line agent for the treatment of arrhythmias during pregnancy.[61]

Ibutilide

Ibutilide, a class III antiarrhythmic agent, was approved by the FDA in 1995 for intravenous termination of AF and atrial flutter.[62] It is particularly useful for the termination of AF and atrial flutter in WPW syndrome, as it prolongs accessory pathway refractoriness as well as that of the atrial myocardium and the ventricular myocardium.[63] Published case reports of its safe and successful use in termination of both AF and atrial flutter during pregnancy are now available.[64,65] It undergoes extensive first-pass metabolism in the liver with a half-life of 2 to 12 hours and is clinically effective only in the intravenous form. It can cause significant QT prolongation, thus necessitating cardiac monitoring for at least 4 hours after administration (Figure 73-5). Pretreatment with magnesium sulfate is recommended to reduce the risk of torsades de pointes. The safety of ibutilide in early pregnancy has not been established; however, its use as a one-time agent for the termination of SVT suggests that it has a low risk of teratogenicity and may be a reasonable alternative to external cardioversion, particularly when conscious sedation is deemed undesirable. Ibutilide is an FDA category C drug.

Dronedarone

Dronedarone is a new class III antiarrhythmic developed for the treatment of AF. It is a derivative of amiodarone made by the removal of iodine and the addition of a methane-sulfonyl group.[66] The later change was made to make the drug less lipophilic, shortening its half-life to approximately 24 hours, thus reducing its accumulation in tissue. These changes to amiodarone were made with the intention of producing a drug with electropharmacologic properties similar to those of amiodarone but having a reduced risk of amiodarone-associated thyroid-related disease and pulmonary disease. It has shown some promise in the treatment of paroxysmal and persistent AF and atrial flutter.[67] Currently no data on its use in pregnancy are available, and thus its use cannot be recommended.

Other Cardiac Medications with Possible Antiarrhythmic Effects

Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme (ACE) inhibitors have been shown to have positive effects on atrial and ventricular remodeling and may possibly be beneficial in the suppression of AF.[68] Nevertheless, they are associated with an increased risk of major congenital malformations when taken during the first trimester. ACE inhibitors should be stopped as soon as possible on becoming pregnant and, ideally, in anticipation of pregnancy. They are an FDA category C drug in the first trimester and a category D drug in the second and third trimesters when exposure of the fetus to this class of drug is known to cause fetal abnormalities, especially those related to the kidneys and associated structures.[69]

Fish Oil

Conflicting evidence in the efficacy of omega-3 fatty acids in reducing SCD is currently unresolved.[70,71] Supplements made from fish livers, such as cod liver oil, contain the retinol form of vitamin A and should be avoided completely during pregnancy. Fish oils not derived from fish livers contain high amounts of docosahexaenoic acid (DHA), which is felt to be beneficial to speed of information processing and attention control in infants.[72] At present, no recommendations for the daily intake of DHA by pregnant patients and no indication for its use in arrhythmia suppression exist.

Management of Specific Arrhythmias

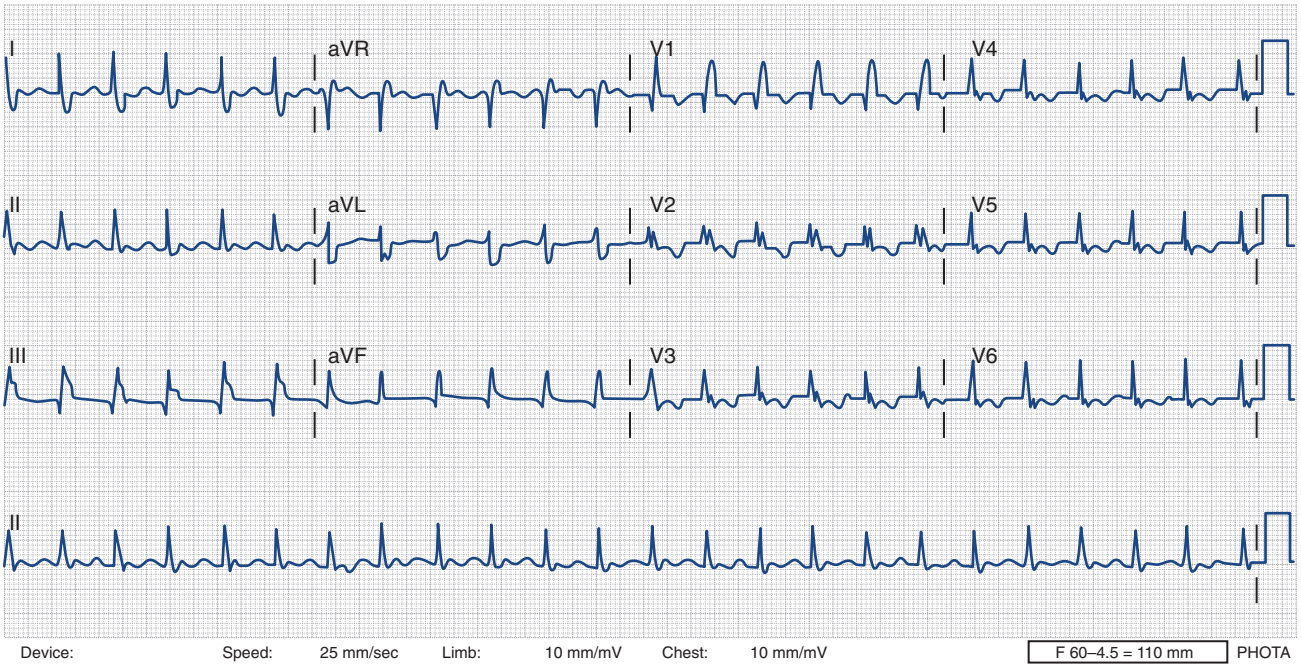
Bradyarrhythmias

Congenital complete heart block is usually diagnosed during childhood; however, some cases are discovered incidentally during pregnancy, particularly in the asymptomatic patient. In general, in the asymptomatic patient, no acute intervention is required during pregnancy. No clear guidelines for the treatment of symptomatic patients in the first and second trimesters exist, but permanent pacemaker implantation, using echocardiographic guidance for lead placement, is probably indicated.[73] In symptomatic women near term, temporary pacing with induction of labor as soon as possible is the procedure of choice.[74] Patients with known congenital third-degree heart block who are considering pregnancy should be referred to a cardiologist for further evaluation. Indications for permanent pacing in these individuals to improve long-term survival have changed on the basis of specific criteria.

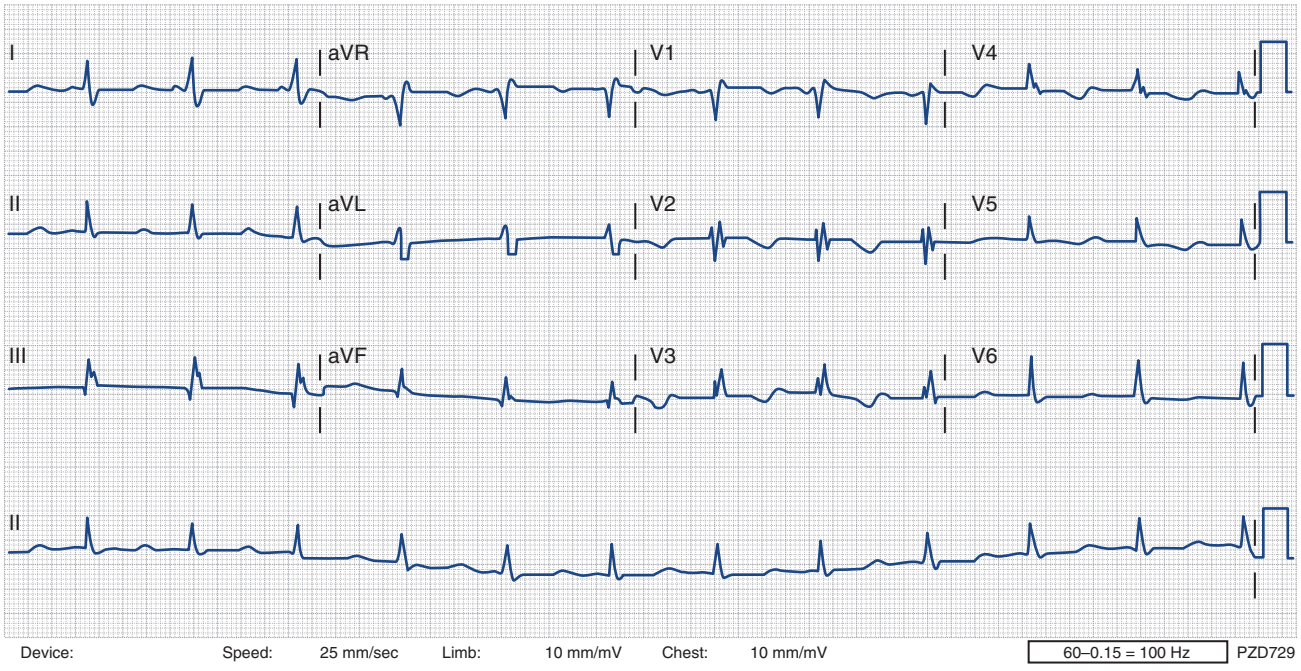
Vasodepressor syncope is one of the most common causes of symptomatic bradycardia in women of childbearing age and may be responsible for more than 20% of unexplained syncope in the general population. Nevertheless, it is rare in pregnancy. Evaluation of the patient with suspected vasovagal syncope may include tilt-table testing, with therapy tailored to the results obtained. Most patients can be simply managed with education about the warning signs of impending syncope and measures to abort the episode. The authors of this chapter stress the importance of not skipping meals, keeping oneself hydrated, and possibly liberalization of dietary salt. Pharmaceutical therapy has mixed results and is probably best avoided in these patients. The use of β-blockers has been advocated in the past but is now falling out of favor because of their poor effect.

Palpitations

Symptomatic palpitations during pregnancy are common and usually represent an increase in "background" atrial, ventricular, and junctional ectopy, likely resulting from increased mechanical



A



B

FIGURE 73-5 A, Baseline 12-lead electrocardiogram (ECG) of patient presenting in atrial flutter with 2:1 atrioventricular conduction (paper speed 25/mm/s). **B,** Twelve-lead ECG immediately following 1-mg IV ibutilide injection and conversion of rhythm back to sinus. Measured QTc: 647 ms.

stress on the heart, intravascular volume shifts, elevated hormonal levels, and emotional changes occurring during pregnancy. Once documented as such, in a patient with a structurally normal heart, reassurance is the best treatment as these arrhythmias are generally benign, and the ectopy is likely to substantially resolve in the postpartum period.[10] If symptoms are severe enough to warrant therapy, a β-blocker is the initial drug of choice.

Supraventricular Tachycardia

AV re-entrant tachycardia (AVRT) with or without pre-excitation on the 12-lead ECG and AV nodal re-entrant tachycardia (AVNRT) are the most common sustained arrhythmias seen during pregnancy. When they are present even before pregnancy, they often recur with increased frequency in the second and third trimesters and may be particularly resistant to treatment.

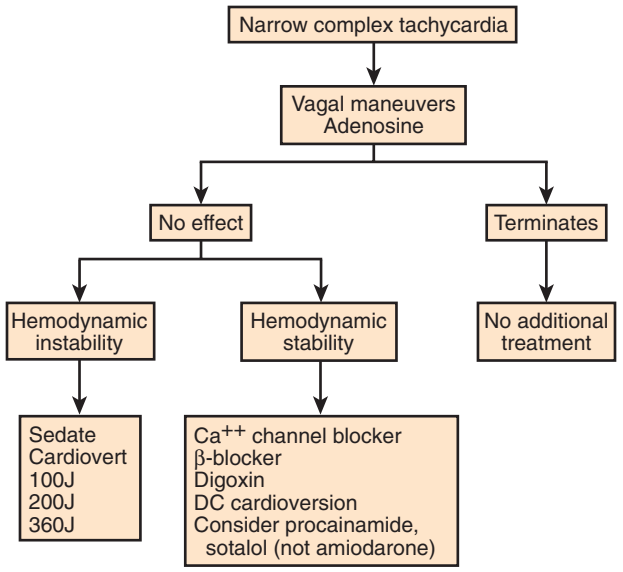


FIGURE 73-6 Proposed algorithm for the management of supraventricular tachycardia in pregnant patients. The algorithm includes the recent changes in Advanced Cardiac Life Support recommendations but excludes the use of amiodarone. *DC*, Direct current.

Pre-existing focal AT may also increase in severity during this time.[11] Atrial flutter and AF are seen less commonly and are most often encountered in patients with underlying structural heart disease. Figure 73-6 outlines a possible treatment algorithm for the acute management of SVT. The mainstay of initial therapy is adenosine for rapid termination. Alternatively, β-blockers or calcium channel blockers can be used for acute termination of SVT and are recommended in the most recent Advanced Cardiac Life Support (ACLS) guidelines as second-line therapy.[75] Procainamide, sotalol, and, to a lesser extent, digoxin are other alternatives. One deviation from the guidelines that should be noted is the use of amiodarone in the SVT algorithm. In pregnant patients, even short-term infusion of amiodarone should be avoided, if possible. Transesophageal overdrive pacing to acutely terminate re-entrant SVT is an older technique, which is infrequently used currently but has proven efficacy. Its desirability for use in pregnancy would be its relative noninvasiveness. Recent case reports of its use during pregnancy and with neonatal SVT are available.[76,77] Electrical cardioversion may be necessary for refractory SVT and is always indicated for hemodynamic instability.[78,79]

Chronic management of these arrhythmias is similar to that in the patient who is not pregnant. If overt pre-excitation is not present on the surface ECG, any of the AV nodal blockers can be used. Verapamil and digoxin should be avoided in the presence of pre-excitation because of their potential to enhance conduction over the accessory pathway. The concern here is with regard to the development of AF and subsequent rapid conduction to the ventricles through the accessory pathway inducing VF. The use of membrane-sensitive antiarrhythmic drugs should be reserved for patients with clearly defined, symptomatic arrhythmias. Flecainide, quinidine, procainamide, and sotalol are included in this group, with sotalol being the drug of choice in the presence of underlying structural heart disease. In the presence of pre-excited AVRT (WPW syndrome), β-blockers are the best choice for initial therapy, with the addition of flecainide or procainamide, if necessary, to impair conduction over the accessory pathway (Figure 73-7).[80,81]

Atrial Fibrillation and Atrial Flutter

AF and atrial flutter are very common arrhythmias in the general population but infrequent in women of childbearing age, except in the presence of underlying heart disease. Ventricular rate control is generally the immediate clinical goal, with verapamil, diltiazem, β-blockers, and digoxin all being acceptable agents in the attempt at achieving it. The risk factors for stroke in AF are at least the same as those in patients who are not pregnant, if not slightly higher because of the hypercoagulable state of pregnancy. If spontaneous conversion to sinus rhythm does not occur, early cardioversion (within 48 hours of the onset) should be performed to avoid the need for anticoagulation. During and immediately after cardioversion, the fetus should be monitored for signs of fetal distress. Cardioversion with up to 300 J has been demonstrated to be safe during pregnancy; however, direct-current cardioversion leading to sustained uterine contraction has been reported in some cases.[82,83] IV ibutilide has also shown promise in the rapid termination of both AF and atrial flutter and may serve as an alternative to direct external current cardioversion in select cases.[64,65] A further alternative is to use one-time high-dose oral flecainide (300 mg) or propafenone (600 mg) to promote conversion to sinus rhythm.[84] If the arrhythmia is recurrent or does not easily convert to sinus rhythm, it is almost always because of underlying heart disease. In the case of refractory AF, the therapeutic goal should be adequate rate control to prevent the hemodynamic compromise of the placental blood supply (ideally <90 beats/min at rest and 140 beats/min with exercise).[8] For the maintenance of sinus rhythm, the same drugs that are acceptable for the treatment of SVT are used for treating AF and atrial flutter. Quinidine, procainamide, flecainide, and sotalol have all been successfully used in this population, and all appear to be relatively safe. See below for recommendations on anticoagulation in the pregnant patient.

Ventricular Tachycardia

As discussed earlier, nonsustained VT during pregnancy is common and generally benign in the setting of a structurally normal heart. Patients without organic heart disease who experience brief nonsustained VT during pregnancy are at low risk for subsequent morbidity and mortality.[31] Withholding drug therapy in this subset of patients, particularly if they are only mildly symptomatic, is reasonable. Idiopathic VT arising from a structurally normal heart is often catecholamine sensitive. In the case of RVOT tachycardia, β-blocker therapy, specifically cardioselective β-blockers, is often effective.[32] Fascicular VT is often responsive to calcium channel blockers.

The risk of sustained VT during pregnancy is low but can occur because of genetic defects (LQTS, hypertrophic cardiomyopathy, right ventricular dysplasia, anomalous coronary artery), peripartum cardiomyopathy, and, less commonly, coronary artery disease. In the presence of hemodynamically unstable VT, immediate direct-current cardioversion is appropriate. If the VT is hemodynamically stable, IV antiarrhythmic drugs can be used. Lidocaine remains the drug of choice in pregnant patients if emergent antiarrhythmic drug therapy is needed, despite recent

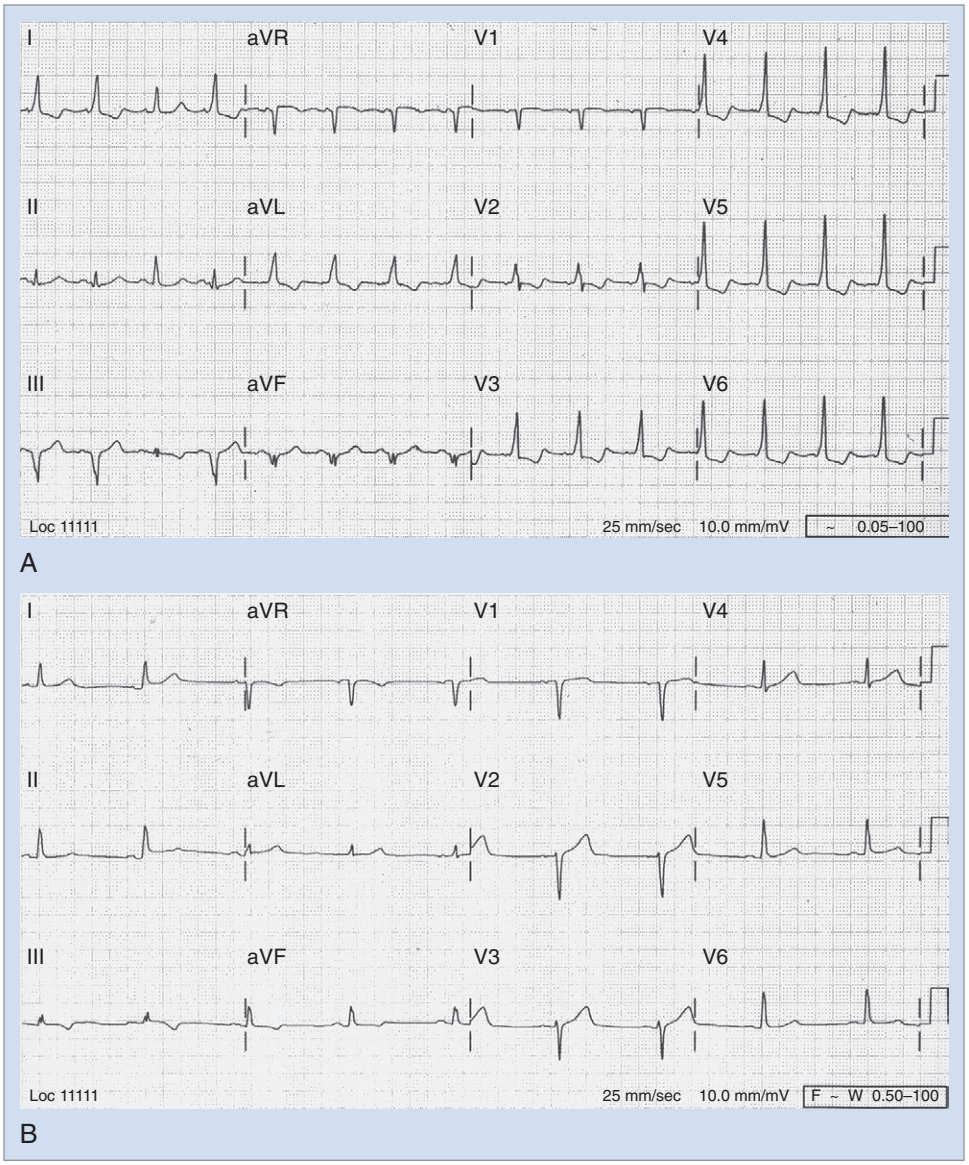


FIGURE 73-7 A, Baseline electrocardiogram (ECG) of a pregnant patient with right-sided accessory pathway, who had intermittent atrial fibrillation requiring therapy. **B,** ECG in the same patient after 2 days of therapy with flecainide. Pre-excitation is no longer seen indicating loss of, or diminished, anterograde conduction down the accessory pathway.

revisions in the ACLS guidelines. Few fetal side effects have been reported with the use of lidocaine, even in early pregnancy and despite significant placental drug transfer.[85,86]

Unfortunately, chronic antiarrhythmic therapy may be unavoidable in the face of sustained or recurrent VT. Most drugs currently used in the suppression of VT are FDA category C category for use in pregnancy. Quinidine, procainamide, and flecainide have all been used in pregnancy for this purpose, with good effect and no adverse fetal outcome.[55,87] Class I antiarrhythmics should be avoided in abnormal hearts because of their proven proarrhythmic effects in this substrate, as in the patient who is not pregnant. Sotalol, however, is an FDA category B drug in pregnancy and remains a good choice in this subgroup of patients so long as renal function is not impaired. The preference of the authors of this chapter for medical therapy after starting a β-blocker would be flecainide in patients with normal hearts and sotalol in patients with structural heart disease. Amiodarone should be avoided in all but the most refractory cases because of its significant adverse fetal effects.

Congenital Long QT Syndrome

A retrospective study of patients with diagnosed LQTS found that the pregnant state was not significantly associated with an increased risk of cardiac events, although the risk did increase in the postpartum period, which suggests that management of these patients should include β-blocker therapy throughout pregnancy and the postpartum period.[88] Syncope is a particularly alarming presentation in these patients and should be interpreted as heralding possible SCD. Patients deemed at high risk may require

hospitalization until after delivery, at which time definitive therapy with an implanted cardioverter defibrillator (ICD) should be performed.[89,90] Telemetric monitoring during labor and delivery is essential, as prolongation of the QTc interval during labor has been described, suggesting the physical and emotional stress during labor might precipitate cardiac arrest in women with LQTS.[91] More recently, Seth et al reported a 2.7-fold increased risk of a cardiac event among women with LQTS during the immediate 9-month postpartum period. Additionally, women with the LQT2 genotype were found to be at a considerably higher risk for cardiac events during this period than those with LQT1 or LQT3 genotypes. β-Blocker therapy was associated with a reduction in cardiac events during the high-risk postpartum period.[92] Of note, successful pregnancy after left stellate ganglionectomy has been reported in a patient with LQTS.[93]

Arrhythmogenic Right Ventricular Dysplasia

Case reports of the management of patients with arrhythmogenic right ventricular dysplasia (ARVD) in pregnancy are scarce. No arrhythmias were reported during pregnancy in those reviewed by the authors of this chapter.[94,95] Sotalol is often used in the management of these patients and could be considered during pregnancy in a patient who demonstrates frequent ventricular ectopy or nonsustained VT. Theoretically, the management of these patients should be the same as that of those who are not pregnant, with the caveat that ablation of the VT substrate should be considered following delivery, possibly in conjunction with ICD implantation.

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) during pregnancy is fairly well described in the literature.[96-98] The physiological changes that are most devastating for patients with HCM, particularly those with an obstructive component, are peripheral vasodilatation and a reduction in preload. Pregnancy characteristically causes an increase in intravascular volume and a decrease in systemic vascular resistance. Thus, a vast majority of patients with this abnormality do quite well during pregnancy, although maternal and fetal death from ventricular arrhythmias associated with HCM have been reported.[97] Aortocaval compression during late-term pregnancy or large blood loss during delivery can compromise cardiac preload, thereby precipitating hemodynamic collapse and impeding successful resuscitation.

Implantable Cardioverter-Defibrillator

Implantable cardioverter-defibrillators (ICDs) are now the mainstay of the treatment of life-threatening ventricular arrhythmias. Guidelines for their use in primary and secondary prevention of SCD in the ischemic and nonischemic patient based on multiple large, randomized, prospective clinical trials have been published.[99,100] Having an ICD is not a contraindication to becoming pregnant and may, in fact, simplify patient management by decreasing the reliance on suppressive drug therapy until proven absolutely necessary (i.e., the patient experiences an appropriate shock).[101] In rare circumstances, it may be desirable to implant an ICD during the pregnancy, in which case lead placement should be accomplished with echocardiographic guidance to prevent radiation exposure to the fetus, or it should be performed under traditional fluoroscopic guidance with appropriate shielding of the fetus, if device implantation is attempted during later-term pregnancy when lesser risk to the fetus from such exposure is present. Pregnancy does not increase the risk of major ICD-related complications or result in a higher number of ICD discharges.[101] Wearable external defibrillator harnesses are now commercially available. They do not yet have FDA approval for use during pregnancy but would seem to be a logical alternative as a bridge to permanent ICD implantation for the duration of the pregnancy. Unpublished documentation of the successful use of LifeVest (ZOLL LifeCor; Pittsburgh, PA) for termination of VT caused by LQTS in a pregnant patient (ZOLL Corporation, personal communication) exists.

Cardiopulmonary Resuscitation in the Pregnant Patient

Cardiac arrest in the pregnant patient is complicated by several physiological factors, particularly in late-term pregnancy. Until the fetus becomes viable, at approximately 25 weeks, CPR should be performed as in the patient who is not pregnant. After 25 weeks, the presence of the increasing mass in the abdomen results in aortocaval obstruction and reduced venous return and forward blood flow with chest compression. This can occur as early as 20 weeks into the pregnancy. At term, the vena cava is completely occluded in 90% of supine pregnant patients.[102] Thus, one of the most important steps that must be taken before initiating CPR in a noticeably pregnant patient is to displace the uterus to decrease aortocaval compression. One method is to place a wedge or rolled towel under the patient`s right hip to tip the uterus toward her left hip creating a tilt of at least 15 degrees. As anything more may decrease the effectiveness of chest compressions, the degree of pelvic tilt should be no more than 30 degrees. An alternative is manual displacement of the uterus during two-person CPR, with one rescuer on the patient's left side using both arms to pull the uterus toward the left while the second performs chest compressions (Figure 73-8).[103,104]

Resting oxygen demand increases 20% during pregnancy to meet the requirements of the mother and the growing fetus. In addition, mothers experience a 20% decrease in lung functional residual capacity because of upward pressure on the diaphragm and lungs by the gravid uterus. The diaphragm is displaced upward by 1½ to 2 inches, and the anteroposterior chest diameter will increase slightly to maximize lung capacity, which leads to decreased chest compliance. As a result, pregnant patients become hypoxic much more quickly. These changes make it difficult to provide adequate oxygenation and circulation with standard CPR. Consequently, chest compressions require increased force and are generally performed higher on the chest than usual to accommodate for the shift in the abdominal contents toward the head. Early intubation should be strongly considered to maximize oxygenation and minimize the risk for aspiration of gastric contents during CPR, which is significantly increased in these patients.[105]

The most recent ACLS guidelines list amiodarone as the drug of choice in cases of refractory VF. In pregnancy, patients should receive lidocaine or procainamide first if defibrillation is unsuccessful. However, if the fetus is not yet viable and the death of the mother is imminent because of refractory VF, amiodarone would certainly be worth a try. After 25 weeks, cesarean section to save the fetus should be seriously considered within 5 minutes of arrest. It may facilitate the successful resuscitation of the mother

as well.[8] Neonatal and obstetric personnel should be involved early in the resuscitation effort.

The literature documents success with no adverse effect to the mother or fetus with energies as high as 300 J if defibrillation is performed.[81] The risk of inducing a fetal arrhythmia is small, primarily because only a fraction of the total energy reaches the fetal heart.[106] Some case reports, however, have described sustained uterine contraction causing fetal distress and necessitating emergency cesarean section when direct-current cardioversion is used.[82]

Anticoagulation Therapy in Pregnancy

Anticoagulation should be instituted in the presence of AF in patients with significant risk factors for embolic stroke (diabetes, hypertension, congestive heart failure, previous stroke, rheumatic heart disease) and should be maintained throughout pregnancy. Warfarin, the standard means of long-term anticoagulation in the general population, is, unfortunately, an FDA category X drug and cannot be used in pregnancy. The drug passes the placental barrier and may lead to spontaneous abortion, fetal hemorrhage, mental retardation, and birth malformations, particularly when used during the first trimester.[107] High-dose subcutaneous heparin has been used as a substitute, particularly in the first trimester of pregnancy, as its large molecular weight prevents placental transfer. It should be discontinued at the onset of labor or 24 hours before the induction of labor. (See Table 73-7 for the advantages and disadvantages of heparin and warfarin.) Enoxaparin is a low-molecular-weight heparin (LMWH) and is classified as an FDA category B drug in pregnancy. A recent shift has occurred in practice, as many physicians are now using enoxaparin almost exclusively during pregnancy with no reported adverse effects to the pregnancy or the fetus. This shift in practice can be attributed to several factors, including the more favorable pharmacokinetic profile of the drug, its lower risk of heparin-induced thrombocytopenia, and ease of administration. To date, no evidence of teratogenicity exists.[108,109] A recent consensus report suggests that enough data are available to support the safe and effective use of LMWH in the patient with a nonmechanical heart valve for the prevention and treatment of thromboembolism and the prevention of adverse obstetric complications during a high-risk pregnancy.[110] Protocols for the use of this drug during pregnancy have been published.[106]

The prevention of maternal mechanical valve thromboses presents a difficult dilemma. Unfortunately, enoxaparin is not fully effective in preventing mechanical heart valve thrombosis, thus committing the mother to continuous IV heparin infusion or warfarin throughout the pregnancy.[110] The use of warfarin during pregnancy has been reported and has been limited to those patients with mechanical heart valves from weeks 13 through the middle of the third trimester.[108] Limited data are available to support this practice (see Table 73-7).

Labor and Delivery

During labor, cardiac output and blood pressure increase and continue to increase in the immediate period following delivery. Within the first hour following delivery, cardiac output begins to fall, returning to baseline levels by 2 weeks after delivery. SVTs occurring in the peripartum period can be managed as previously

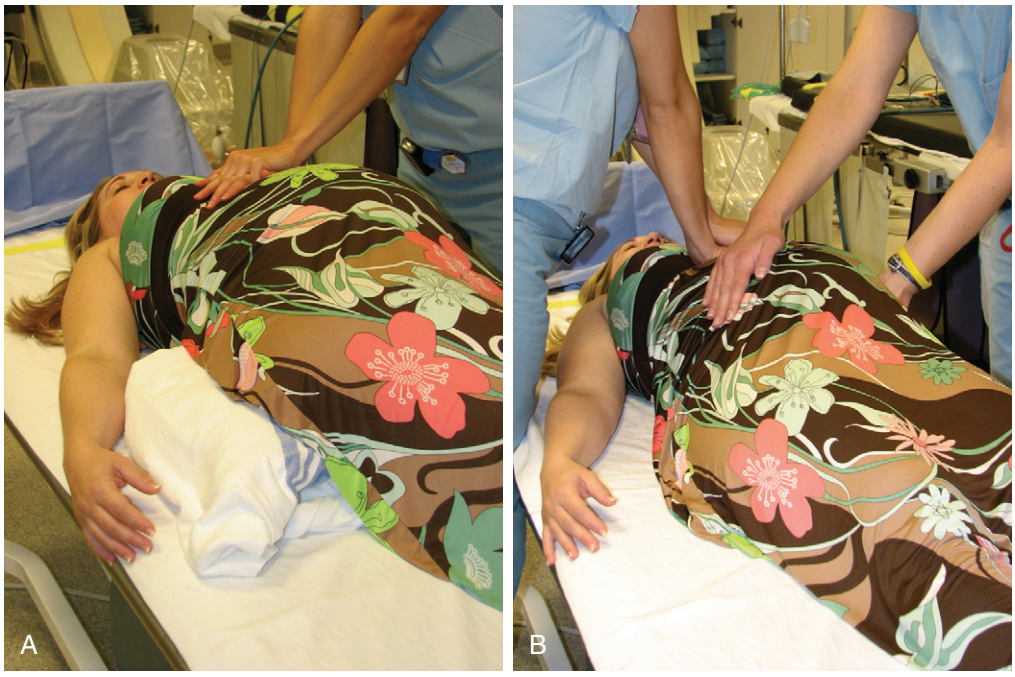


FIGURE 73-8 A, Facilitation of effective chest compressions during cardiopulmonary resuscitation (CPR) in late-term pregnancy. Placement of a wedge or rolled towel under patient's right hip to tip the uterus toward her left hip resulting in a tilt of at least 15 degrees to relieve aortocaval compression by the uterus. **B,** Manual displacement of the uterus during two-person CPR, with one rescuer on the patient's left side using both arms to pull the uterus toward the left, off the aorta and the inferior vena cava.

described. If the arrhythmia proves to be difficult to manage or fetal compromise is a concern, cesarean section may be advantageous. Adenosine remains a safe, rapid means of terminating re-entrant SVTs by using the AV node. Patients with underlying heart disease should have continuous cardiac monitoring during labor and delivery, even if no previous arrhythmia has been documented, as the stress of labor may provoke arrhythmia onset.[111]

Complete heart block occurring during labor and delivery is uncommon but has been described in the literature.[111] Treatment of sudden complete heart block during labor and delivery is limited to those patients who become hemodynamically unstable. The best approach would be the placement of a temporary transvenous pacing wire under echocardiographic guidance.[74]

When to Hospitalize a Patient

The indications for hospitalization of a pregnant patient for arrhythmia management are similar to those of the patient who is not pregnant. In most cases, pregnant patients should be hospitalized for the initiation of antiarrhythmic therapy; the possible exception would be class 1C antiarrhythmic drugs to control supraventricular arrhythmias. Patients do not need to be hospitalized for the evaluation of palpitations or for hemodynamically stable supraventricular arrhythmias that are self-terminating or that terminate easily with vagal maneuvers. Patients suffering cardiac arrest, sustained or symptomatic VT, and hemodynamically unstable SVT should be hospitalized while undergoing evaluation and implementation of therapy.

Table 73-7 Anticoagulant Therapy in Pregnancy

AGENT	ADVANTAGES	DISADVANTAGES
Heparin	Does not cross the placenta	Must be administered parenterally
	Easily and rapidly reversed	Maternal osteopenia
	Short half-life	Maternal thrombocytopenia
	Safe with breastfeeding	Maternal mechanical valve thrombosis
		Risk of systemic infection with continuous intravenous infusion
Warfarin	Highest efficacy for preventing thromboembolic events	Crosses the placenta
	Safe with breastfeeding	Cannot be easily or rapidly reversed
		Teratogenic during the first trimester
		Increased risk of hemorrhage during labor and delivery
Enoxaparin	Lower incidence of osteopenia or osteoporosis with long-term use	Maternal valve thrombosis
	Lower incidence of heparin-induced thrombocytopenia	
	Favorable pharmacokinetics	

Management of the Patient After the Pregnancy

In the case of arrhythmias that are treatable by an ablative procedure (AVNRT, AVRT, WPW, AT, RVOT VT, fascicular tachycardia, etc.), every effort should be made to address the problem early after delivery. The patient's symptoms are likely to improve following delivery, but it should be stressed to the patient that the substrate for the return of the arrhythmia remains unchanged. Whether or not future pregnancies are planned, EPS and catheter ablation should be seriously considered. The patient with congenital complete heart block should be evaluated for pacemaker implantation, particularly if management issues were present during the last pregnancy. In the case of VT related to structural or genetic abnormalities, an EPS should be sought with the aim of ICD implantation for indications of either primary or secondary prevention, particularly for the patient with LQT2.

Summary

Arrhythmias during pregnancy are not uncommon. Most are benign and require no intervention. Documentation and correct diagnosis of the arrhythmia are paramount before initiating any form of pharmacologic or device therapy. If symptoms warrant therapy, drugs with the most historical use in pregnancy must be chosen; the least number of drugs possible at the lowest effective dose should be used. It must be kept in mind that in the hemodynamically unstable patient with tachycardia, early external cardioversion is generally safe during pregnancy. Symptomatic arrhythmias during pregnancy can be safely managed both pharmacologically and nonpharmacologically with rare exceptions.

Acknowledgment

The authors thank David Frohnapple, MD, for his contributions to this chapter.

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CHAPTER 74

Assessment and Treatment of Fetal Arrhythmias

Janette F. Strasburger and Bettina F. Cuneo

The assessment and management of the human fetus with an arrhythmia is an area of medicine that presents many complexities. Because the fetus is hidden within an environment that is accessible only through remote means, direct knowledge of the condition and stability of the fetus is often in question. Current noninvasive and safe methods for fetal assessment, largely dominated by echocardiography, are limited and need to be expanded. The arrhythmias that are being treated are only those that are known at present. Potentially diagnosable and treatable intrauterine electrophysiological conditions may exist entirely hidden from the scope of perinatal medicine as it is practiced today.[1-6] Many arrhythmias can be diagnosed by pulsed Doppler, tissue Doppler, and M-mode echocardiographic assessment of the atrioventricular (AV) relationship; however, the ventricular and atrial rate echo techniques do not measure the electrophysiological activity of the fetal heart but, rather, the mechanical consequences of that activity.[7] Even the most sophisticated echocardiographic techniques cannot measure cardiac intervals (PR, QRS, QT duration) or repolarization characteristics. Nor is it possible to evaluate the fetus continuously over time, such as is done with ambulatory electrocardiography (ECG) monitoring. Despite these shortcomings, with the application of newer technologies such as fetal electrocardiography (fECG) and fetal magnetocardiography (fMCG) and more evolved echocardiographic techniques such as tissue Doppler, current understanding of arrhythmia mechanisms and the natural history of arrhythmia disturbances in the fetus has greatly expanded.[8-15] Hidden fetal arrhythmias may contribute to the high rate of intrauterine fetal demise, unexplained nonimmune hydrops, and prematurity to a greater extent than has been appreciated. This chapter will focus on what is known at present about the assessment and treatment of fetal arrhythmias. It is divided into sections covering bradycardias, tachycardias, ectopy, diagnostic techniques, and management of the high-risk fetus.

Electrophysiological Diagnostic Techniques

Fetal Echocardiography

Fetal echocardiography provides many of the views necessary to risk-stratify patients with fetal arrhythmias; however, it is limited by the fact that it measures mechanical events only, and this can overestimate the P-R interval while underestimating the severity of fetal disease related to acquired and congenital depolarization or repolarization abnormalities. Echocardiography also can provide individual rates for atrial or ventricular rhythms; however, trending of these rates over time and catching rapid changes in rate and rhythm are difficult with echocardiography. Until techniques used below become more available, echocardiography remains a mainstay of diagnosis. Many excellent reviews have been written describing techniques for echocardiographic assessment of fetal arrhythmias.[16-21]

Fetal Magnetocardiography and Electrocardiography

Many experts believe fMCG to be the most reliable method for the full analysis of fetal arrhythmias because it can provide real-time telemetry as well as signal-averaged waveform (see Figure 74-13).[2-6,10,12,22-32] While these technologies are not readily available in most institutions, current biotechnology development projects funded by the National Institutes of Health (NIH) will likely bring fMCG to common use within the next 3 to 5 years. Several fECG devices are available on the market worldwide. The ECG devices can provide up to 24 hours of rhythm recordings and a signal-averaged ECG waveform (provided the rhythm is stable). Acquisition success using the device is variable, and during the period from 26 to 36 weeks, when vernix is present, electrical insulation of the fetus leads to a poor signal-to-noise ratio. In this setting, the echocardiograms, nonstress testing, and biophysical profiles are usually used, but abnormalities seen in any one of these three may lead to early delivery. The addition of fECG or fMCG might reduce the need for some early deliveries by providing reassuring heart rate reactivity trends, Q-T intervals, and QRS durations.

Fetal Bradycardias

The standard obstetric definition of *fetal bradycardia* is a sustained (>10 minutes) fetal heart rate (FHR) of less than 110 beats/min with the usual heart rate ranging between 110 and 180 beats/min. However, as gestation progresses, basal FHR decreases significantly—from a mean and range of 141 beats/min (135 to 147 beats/min) at less than 32 weeks, to 137 beats/min (130 to 144 beats/min) at 37 to 40 weeks.[33] Thus, the absolute value of the FHR cannot be deemed normal without considering gestational age. For example, a basal FHR of 125 beats/min at 32 weeks is in the tenth percentile, while the same rate at 25 weeks is well below the first percentile. The "low" FHR early in gestation, which does not meet the classic definition of bradycardia and

Table 74-1 Findings in Fetal Bradycardia

ARRHYTHMIA	A RATE (BEATS/MIN)	A-A INTERVAL	AV RELATION	V RATE (BEATS/MIN)	V-V INTERVAL	INCIDENCE*	CLINICAL RELEVANCE AND OUTCOME
Sinoatrial bradycardia	75–110	Regular	1:2	75–110	Regular	+	Depends on cause
Atrial bigeminy, blocked	Normal	Regular irregular	2:1	65–90	Regular	+	Minor, transient
2:1 AV block	Normal	Regular	2:1	60–75	Regular	Rare	Major, may progress
Complete block	Slow-normal	Regular	Disassociated	35–80	Regular	++	Major, irreversible

A, *Atrial;* AV, *atrioventricular;* V, *ventricular.*
*++, *Detected in 1/1000 pregnancies;* +, *detected in 1/10,000 to 1/100,000 pregnancies;* rare, *affects <1/100,000 pregnancies.*
From Jaeggi ET, Friedberg MK: Diagnosis and management of fetal bradyarrhythmias, Pacing Clin Electrophysiol *31(Suppl 1):S50–S53, 2008.*

"normalizes" in later gestation, has been seen in fetuses with long QT syndrome (LQTS).

The most prevalent mechanisms of bradycardia in the fetus are sinus bradycardia, blocked atrial bigeminy, and AV block. The echocardiographic presentation, incidence, and relevance of the different mechanisms of bradycardia are shown in Table 74-1. In studies, approximately 70% of fetuses with bradycardia referred to either fMCG or echocardiography had AV block, 10% to 20% had blocked atrial bigeminy, and 10% to 20% had sinus bradycardia. Of those with sinus bradycardia evaluated by fMCG, 40% had LQTS (Cuneo, AHA November 2009, unpublished data).[34]

Sinus Bradycardia

The hallmark of *sinus bradycardia* is a slow heart rate with 1:1 AV conduction. Technically, it cannot be determined from echocardiography if the atrial impulse originates in the sinus node or from an ectopic atrial pacemaker. In the setting of heterotaxy syndromes (left and right atrial isomerism), congenital abnormalities of location and number of atrial pacemakers result in bradycardia that can persist throughout gestation. By fECG or fMCG, discordance between the predominant direction of P and QRS may be found with low atrial rhythms.

Sinus bradycardia can also be secondary to inflammation, fibrosis, and damage to a developmentally normal sinus node caused by viruses or maternal Sjögren's antibodies.[35] An extreme form of sinus node fibrosis, that is, complete replacement of normal atrial tissue with fibrotic cells, was reported in a fetus presenting with atrial standstill and bradycardia with a junctional escape rhythm.[34] However, the most common cause of sinus bradycardia with a structurally normal or abnormal heart is vagally mediated bradycardia from fetal head or umbilical cord compression. If undue pressure is placed on the maternal abdomen by the transducer during ultrasound studies, transient but rather profound bradycardia can occur, but it disappears immediately when the pressure is relieved. Persistent sinus bradycardia can indicate fetal distress from hypoxia caused by placental insufficiency or cord compression. Other causes of sinus bradycardia are fetal hypothyroidism, central nervous system (CNS) abnormalities, intrauterine growth restriction, and maternal treatment with β-blockers.[36]

Fetal sinus bradycardia has also been reported in congenital sick sinus syndrome and, in the absence of AV conduction system disease, in fetuses with maternal Sjögren (SSA/Ro, SSB/La) antibodies.[37,38] The causative role of a sodium channelopathy in both diseases is supported (1) by the demonstration of sinus node dysfunction in fetal hearts perfused in vitro with anti–52-kD SSA antibodies from mothers whose children developed AV block and (2) by the fact that recessive mutations in the sodium channel gene *SCNA* are found in congenital sick sinus syndrome.[37,39]

Persistent bradycardia, a marker in infants and children younger than 3 years for congenital LQTS, is also the most common presentation in fetuses with LQTS.[40,41] After 30 weeks' gestation, the fetal heart rate over time can be reactive or nonreactive during nonstress tests (Figure 74-1). Numerous mutations in the genes coding critical ion channel subunits have been reported to cause congenital LQTS, but 60% of affected individuals will have mutations in five genes coding critical ion channel subunits. The etiology of the bradycardia is purported to be either an autonomic imbalance with deficient sympathetic activity or a pathologic mutation reducing the activity of a G-protein mandatory for the coupling of β-adrenergic and sinus node receptors.[42] Thus, signal transduction at the sinus node is impaired, which, in turn, affects the functioning of the pacemaker current, I_f.[43]

It has been reported that neonates with sinus bradycardia are more likely to have *KCNQ1* mutations (LQTS1), while those who manifest 2:1 second-degree AV block are more likely to have *HERG* mutations (LQTS2).[44] Further recognition and characterization of fetal LQTS is necessary to determine if the genotype can be predicted on the basis of clinical presentation before birth.

Long QT Syndrome

While LQTS is not always associated with fetal bradycardia, this is the most common fetal presentation. In addition to sinus bradycardia, congenital LQTS can also manifest as intermittent or persistent torsades de pointes (TdP), second-degree AV block, or both. All manifestations of congenital LQTS, including T-wave alternans, have been described by fMCG (Figures 74-2 to 74-5).[1,6,45] The more widespread use of noninvasive recording may enhance the ability to identify individuals with de novo mutations associated with fetal arrhythmias, especially fetal bradycardia, as well as to recognize the presence or absence of Q-T abnormalities in pregnancies of affected family members.[1,2,28] The normative data for Q-T intervals in utero as well as in the preterm infant have recently been reported.[46] Values for term infants have been previously reported and corrected Q-T intervals greater than 0.48 seconds at birth have been associated with a 41-fold increase in

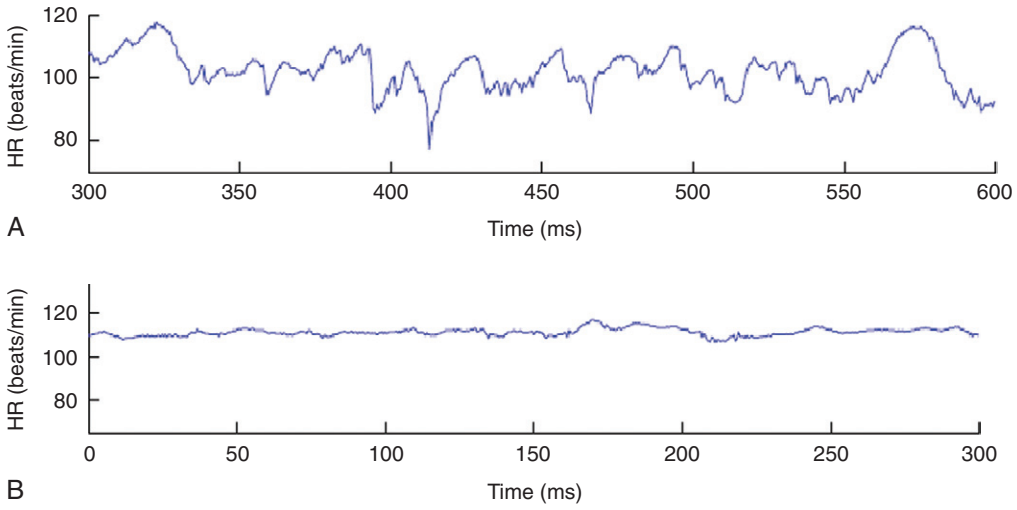

FIGURE 74-1 Different patterns of heart rate (*HR*) variability in two fetuses at 34 weeks of gestation with congenital long QT syndrome and sinus bradycardia. Although the baseline fetal HRs are similar, **A** demonstrates normal variability and reactivity, whereas the tracing in **B** is nonreactive.

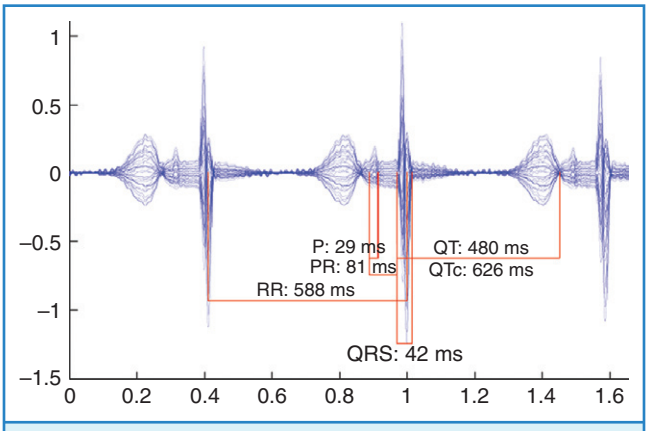

FIGURE 74-2 Fetal magnetocardiography signal-averaged "butterfly plot," demonstrating cardiac intervals in a fetus with congenital long QT syndrome. The corrected Q-T interval was 626 ms.

the incidence of sudden infant death syndrome.[40,47] Preliminary data suggest that a QTc of more than 580 ms before birth correlates with the presentation of TdP and 2:1 second-degree AV block either prenatally or postnatally (Cuneo, AHA November 2009, unpublished data).

It is important to consider a diagnosis of congenital LQTS using the same criteria applied to a child or a young adult, recognizing that established normative data for LQTS are based on only a very limited number of fetuses. Further, Zhao and colleagues recognized that the rate dependence of the Q-T interval on cycle length is much stronger in the fetus than in children of other ages.[5] The mother should be questioned for a history of stillbirths at whatever gestational age, as fetal loss may be associated with familial mutations.[48] The cardiac registry, which is composed mostly of patients with LQTS type 1 (LQTS1), did not find a higher association with miscarriage, but this may have been caused by bias introduced by the inclusion of extended families and LQTS1. If the specific familial mutation is known, prenatal genetic diagnosis of at-risk fetuses is possible from genomic deoxyribonucleic acid (DNA) extracted from cultured amniocytes.[49]

Blocked Atrial Bigeminy

A common cause of bradycardia in the fetus is blocked atrial bigeminy, or nonconducted premature atrial contractions. Occasionally, at first, the fetus will have atrial ectopy and an irregular rate, but at other times a persistent bradycardia will be present. Typically, the rate detected is lower than that in sinus bradycardia but faster than that in complete AV block (see Table 74-1).[26] During blocked atrial bigeminy, a normally conducted atrial contraction is followed by a premature atrial contraction, which finds the AV node refractory and unable to conduct the impulse. Thus, every other atrial contraction is conducted (see Figure 74-5). This rhythm can persist for many weeks or for only a few hours. The management of blocked atrial contractions is the same as that of atrial ectopy: weekly or biweekly fetal heart rate auscultation to ensure that supraventricular tachycardia (SVT) has not developed. Isolated blocked atrial bigeminy does not require antiarrhythmic treatment in utero. Like atrial ectopy, blocked atrial bigeminy can be associated with SVT. The incidence of associated SVT is about 0.5% to 3%.[50] The most important point to keep in mind about blocked atrial bigeminy is that it should not be mistaken for either sinus bradycardia caused by fetal distress, resulting in an unnecessary emergency cesarean section, or AV block, which has a very different prognosis and management protocol.[51,52]

Atrioventricular Block

Diagnosis and Etiology

Fetal AV block is secondary to either a congenitally malformed conduction system associated with complex structural cardiac defects or immune or infectious damage to a morphologically normal conduction system.[53,54] The hallmark of high-grade

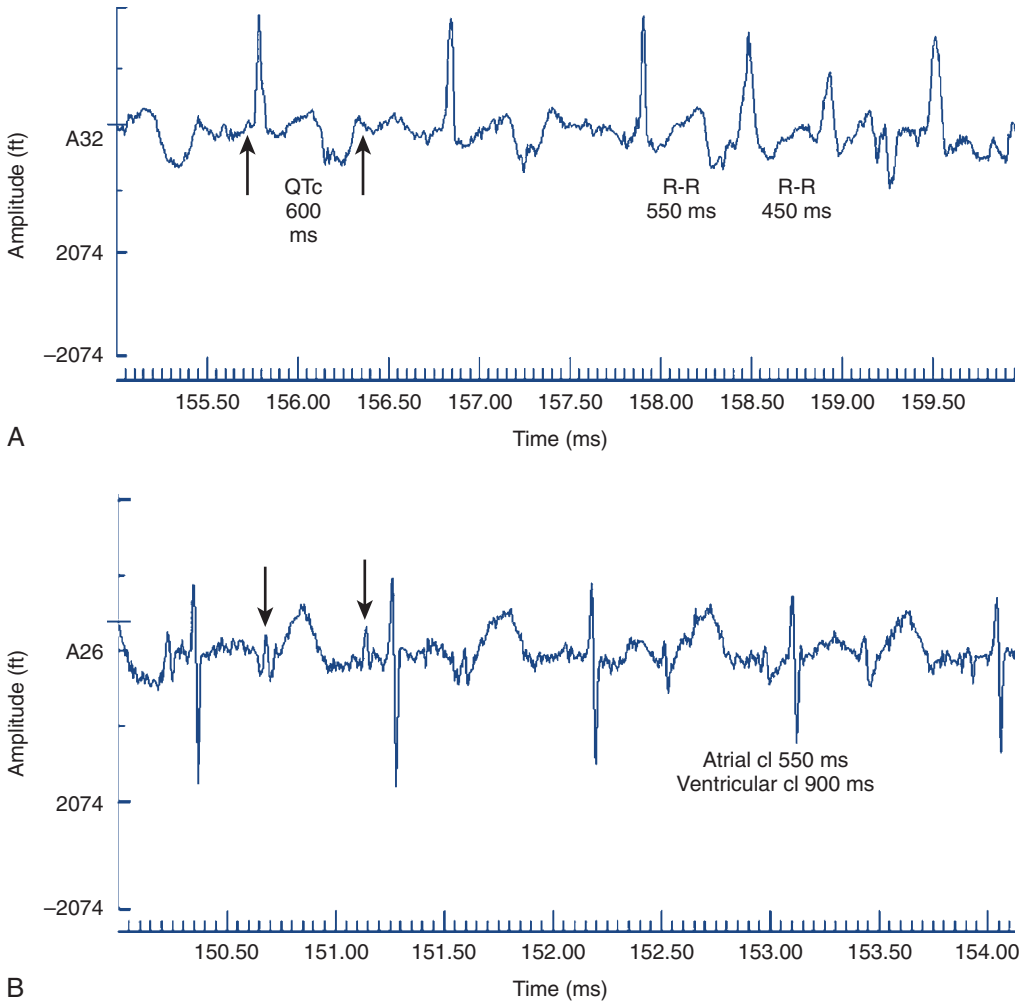

FIGURE 74-3 Fetal magnetocardiography rhythm strip showing sinus bradycardia, the onset of torsades de pointes (**A**), and 2:1 second-degree atrioventricular block (**B**) in a 32-week-old fetus with congenital torsades de pointes. The QTc interval (*arrows*) is 600 ms.

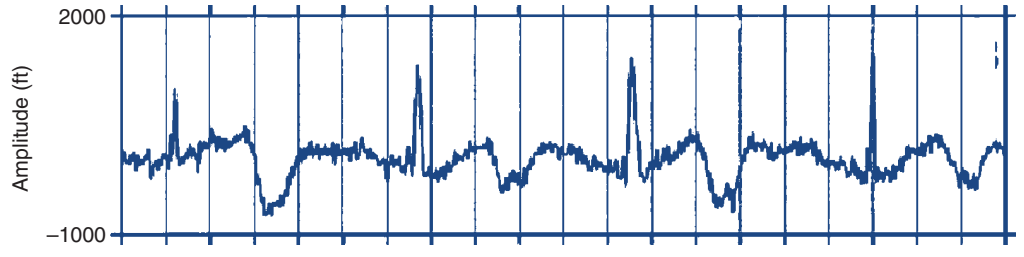

FIGURE 74-4 Rhythm strip showing macroscopic T-wave alternans during sinus bradycardia in the 32-week-old fetus with congenital long QT syndrome type 3 described in Figure 74-3.

(second-degree or third-degree) AV block is an atrial rate more regular and faster than the ventricular rate, ventricular bradycardia, and AV dissociation. AV block can be suspected during fetal heart rate auscultation as either an irregular rhythm (type 1 or intermittent type 2, second-degree AV block) or as bradycardia (type 2, second-degree AV block with 2:1 conduction, or third-degree AV block), and confirmed by M-mode or pulsed Doppler echocardiography (see below). Fetal heart rate auscultation cannot detect first-degree AV block; rather, this can be diagnosed on the basis of a prolonged mechanical P-R interval (>150 ms) measured by simultaneous mitral inflow and aortic outflow pulsed Doppler or simultaneous interrogation of the superior vena cava (SVC) and the aorta from the so-called *three-chamber view* (Figure 74-6).[7,55]

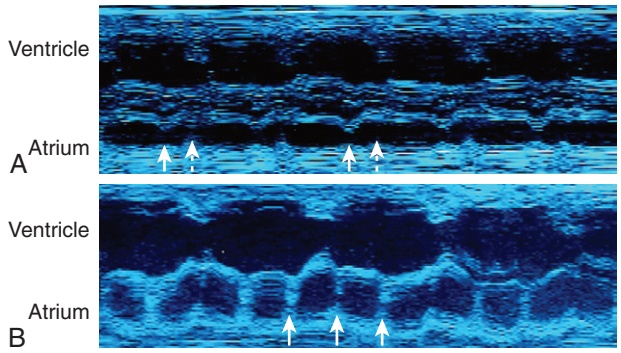

FIGURE 74-5 Simultaneous ventricular (*top*) and atrial (*bottom*) M-mode during blocked atrial bigeminy (**A**) and complete atrioventricular (AV) block (**B**). In **A,** a premature atrial contraction (*dashed arrow*) following a conducted atrial contraction (*arrow*) finds the AV node refractory and is not conducted, so no ventricular deflection is present. Thus, every other atrial contraction results in ventricular contraction. In **B,** the atrial rate is regular and the AV relationship is dissociated, resulting in bradycardia.

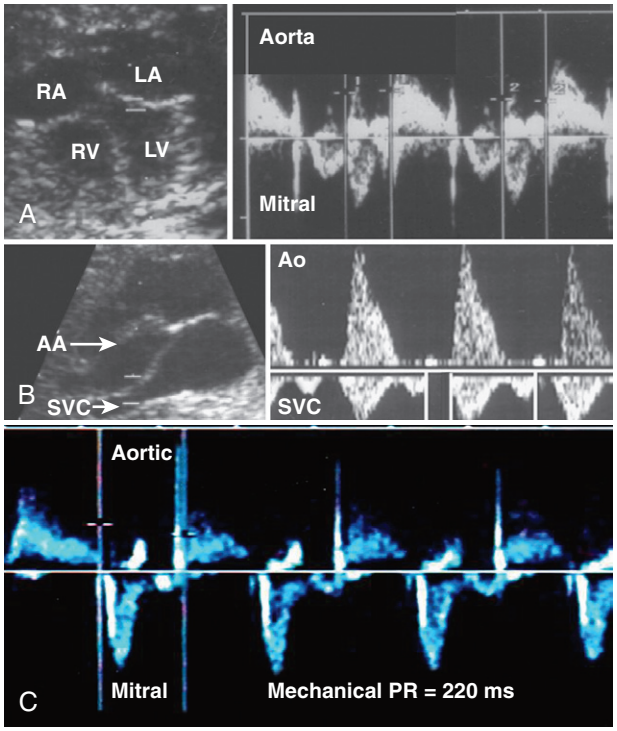

FIGURE 74-6 The pulsed-Doppler–derived mechanical P-R interval in sinus rhythm and first-degree atrioventricular (AV) block. **A,** The two-dimensional, "four-chamber" image of fetal heart demonstrating the position of the cursor between of the mitral valve and the aortic valve. Next to this image is the pulsed-Doppler image of a normal (<150 ms) mechanical P-R interval, measured from the onset of the mitral A wave (reflecting atrial contraction) to the onset of the aortic pulse (reflecting ventricular contraction). **B,** The two-dimensional great vessel view showing the position of the cursor between the superior vena cava (*SVC*) and the ascending aorta (*AA*), followed by the pulsed-Doppler image of the normal mechanical P-R interval from the onset of the SVC retrograde flow (reflecting atrial contraction) to the onset of the aortic pulse. **C,** Doppler image of a prolonged (220 ms) mechanical P-R interval or first-degree AV block. E and A waves have fused, which is common in very prolonged measurements. It is unrelated to fetal heart rate. The P-R interval on the electrocardiogram after birth was also 220 ms. *RA,* Right atrium; *LA,* left atrium; *RV,* right ventricle; *LV,* left ventricle; *Ao,* aorta.

Using either technique, type 1, second-degree AV block can be distinguished from second-degree AV block with 2:1 conduction, and third-degree AV block (Figure 74-7).

Atrioventricular Block with a Congenitally Malformed Conduction System

Congenital cardiac defects associated with AV block include left atrial isomerism (LAI) and congenitally corrected transposition of the great vessels. Both can be readily diagnosed by two-dimensional fetal echocardiography. LAI—also known as *polysplenia*, left isomerism, and bilateral left-sidedness—includes paired left-sided viscera and absent right-sided viscera and is part of the syndrome known as *heterotaxy*. Heterotaxy (Greek for *unusual arrangement*) includes cardiac, vascular, and visceral abnormalities. In LAI, levocardia and a midline liver typically are present. The cardiac defects typically consist of the following:

1. Bilateral left atrial appendages
2. Systemic venous abnormalities, including bilateral superior vena cava (SVC) and interrupted inferior vena cava (IVC), with azygous continuation to the SVC
3. Complete AV septal defect
4. Common atrium
5. Partial anomalous pulmonary venous return
6. AV block caused by a congenitally malformed conduction system

The cardiac defects are complex because embryologically the right and left chambers are malaligned with the inflow and outflow portions of the heart. Because of this, a discontinuity between the AV node and the conduction system exists. The discontinuity of the conduction system results in AV block. The AV block has been reported to progress from second degree to third degree during gestation, but this has not been corroborated by fECG or fMCG. In a recent large series of 35 cases of heterotaxy diagnosed over a 10-year period, AV block was seen in 12 (55%) of 22.[56] Of fetuses diagnosed with AV septal defects, approximately 20% will have LAI, and of those diagnosed with AV block, approximately 50% will have LAI.[56,57]

In addition to the complex structural cardiac defects and the conduction system abnormalities, the myocardium in LAI has an unusual spongiform texture, similar to ventricular noncompaction (VNC). VNC can be identified echocardiographically in the left ventricular (LV) apex and mid-portion as numerous excessively prominent trabeculations with deep intertrabecular recesses that communicate with the ventricular cavity. This primary myocardial abnormality results in abnormal systolic and diastolic function.[58]

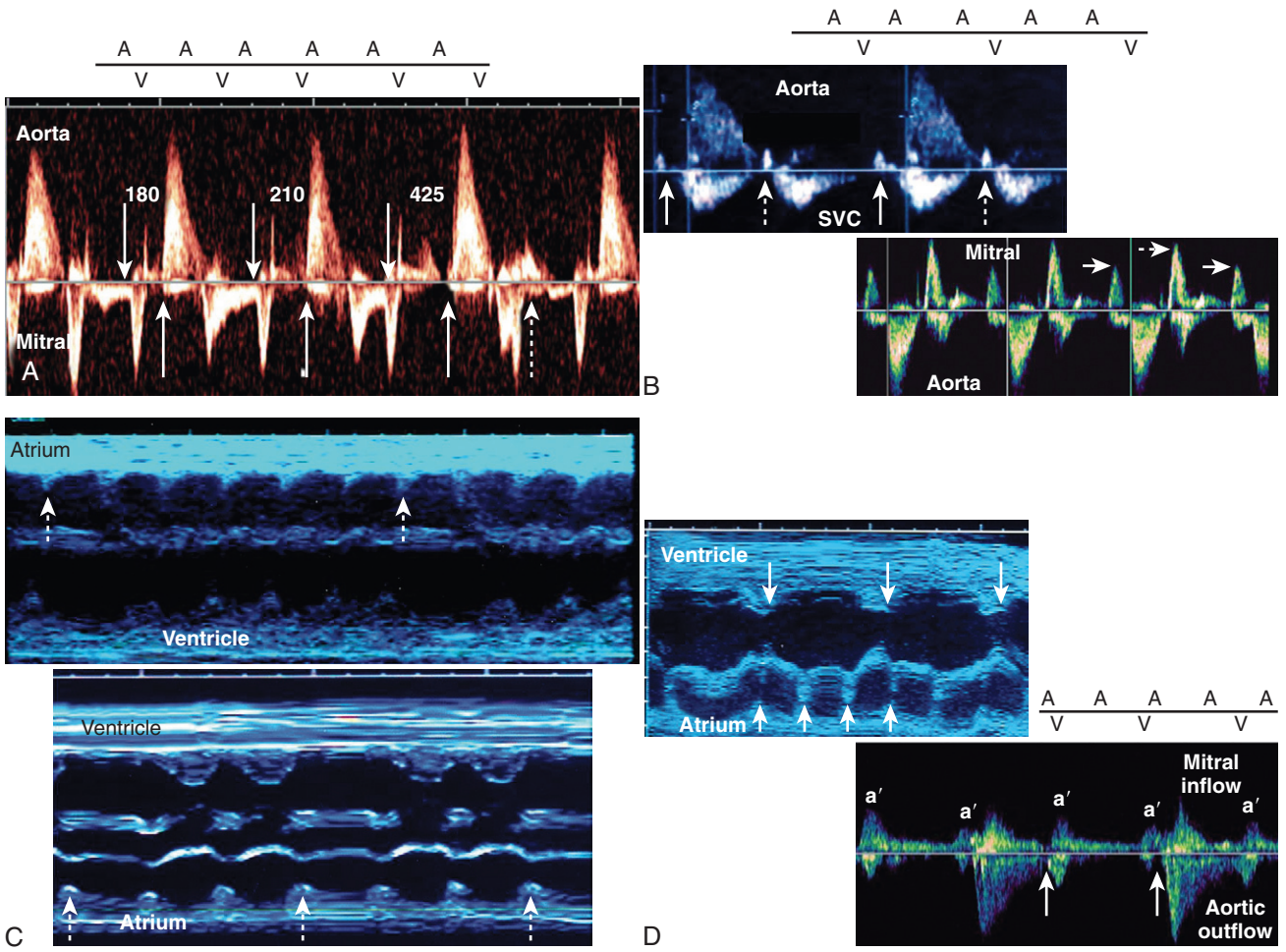

FIGURE 74-7 Atrioventricular (AV) ladder diagram, pulsed-Doppler, and M-mode examples of second-degree and third-degree AV block. **A,** Mobitz 1, second-degree AV block. The mechanical P-R interval (*numbers*) increases from 180 to 425 ms. The following atrial beat is not conducted (*dashed arrow*). **B,** Mobitz 2, second-degree AV block with 2:1 AV conduction demonstrated by pulsed-Doppler interrogation of mitral inflow and aortic outflow (*top tracing*) and the superior vena cava (*SVC*) and aorta (*bottom tracing*). Conducted atrial beats (*solid arrows*) are followed by nonconducted beats (*dashed arrows*). The *a-a* interval does not vary, and the P-R interval does not lengthen before the nonconducted beat. **C,** M modes of second-degree AV block. *Top:* Either type 1 or type 2 second-degree AV block. *Bottom:* Type 2 second-degree AV block. This was proven by fetal magnetocardiography. **D,** Third-degree AV block. Note the AV dissociation, a regular atrial rate, and a slow and regular ventricular rate. The mechanical P-R interval varies in the pulsed-Doppler tracing (*arrows*) because of the AV dissociation.

The prognostic factors for prenatal survival have been evaluated in several studies. In a series of 31 fetuses, 22 pregnancies were interrupted and 3 fetuses died in utero.[59] Of the 6 live-born infants, 2 survived. Five hydropic and 3 non-hydropic fetuses were given transplacental sympathomimetic therapy, which successfully augmented the fetal heart rate (FHR) but did not improve the hydropic fetuses. Interestingly, the atrial rate and not the ventricular rate predicted the development of hydrops with lower atrial rates having a worse prognosis (but neither the ventricular rate nor the atrial rate was associated with outcome in this series). Hydrops and cardiomegaly were associated with a poor outcome: Every fetus with a cardiothoracic (CT) ratio of more than 61% died. In another large series, hydrops and a low ventricular rate (<60 beats/min) were associated with a poor prognosis.[60] Of 11 fetuses with LAI in continued pregnancies, only 1 survived to 1 year, despite in utero sympathomimetic therapy. A third study again demonstrated that the findings of AV block and anomalous pulmonary venous connections had the highest association and postnatal death in fetuses diagnosed with single-ventricle physiology.[61]

Prenatal diagnosis has not been shown by any study to make a difference in outcome (except for elective termination of pregnancy). The outcome of LAI and AV block is bleak: Even with in utero terbutaline treatment to augment ventricular rate and prompt pacing in the newborn period, the postnatal mortality in most series exceeded 50%.[56,57,59-66] In the United States, terbutaline is generally the β-sympathomimetic of choice because it is available for oral as well as parenteral administration. Salbutamol can be administered only by the inhalation or oral route.

In contrast to extensive data on the fetal presentation and outcome of LAI and AV block, only limited data on AV block and congenitally corrected transposition of the great vessels are available. These data suggest that AV block is not a common presentation of congenitally corrected transposition. Additionally, once detected, the in utero survival is high: Of 17 reported cases

detected in utero, all survived the prenatal period, and only 1 died during epicardial pacemaker implantation.[5,59,60,67-69]

Atrioventricular Block with a Structurally Normal Conduction System

The other major category of AV block that develops during fetal life occurs in a structurally normal conduction system. In the vast majority, the block is secondary to immune-mediated inflammation and fibrosis of the fetal conduction system from maternal SSA (Ro) antibodies, SSB (La) antibodies, or both.[35,70-72] These antibodies cross the placenta and result in AV block in 2% to 3% of lupus pregnancies. If a previous child has been affected, the incidence increases 10-fold.[71] A developmental susceptibility to the immune-mediated effects on the conduction system appears to exist in the fetus: AV block is generally not seen before 18 weeks, and onset is rare after 28 weeks. This appears to be related to the timing during which immunoglobulin G (IgG) antibodies cross the placenta. About 50% of all cases develop in mothers who are asymptomatic and unaware that they carry the SSA antibodies, SSB antibodies, or both.[73]

In addition to AV conduction disease, patchy areas of echogenicity (by echocardiography) seen in the ventricular endocardium, in the chordae of the AV valves, and in the atrial septum and free walls can be seen with or without AV block. Histologically, these areas represent endocardial fibroelastosis (EFE), which may be a precursor to dilated cardiomyopathy, the most dreaded sequela of immune-mediated fetal cardiac disease. Dilated cardiomyopathy has a high mortality rate without transplantation. Endocardial fibrosis and dilated cardiomyopathy can develop with or without conduction system disease.[74-78] Other manifestations of SSA-mediated or SSB-mediated cardiac disease include sinus node dysfunction, bundle branch block, and a late-onset rupture of the AV valve chordae.[38,79]

The diagnosis of fetal SSA-mediated or SSB-mediated AV block is made on the basis of an increased titer of maternal SSA or SSB antibodies. Prospective evaluation of pregnancies complicated by maternal SSA or SSB antibodies using weekly echocardiographic measurement of the mechanical P-R interval has not successfully identified an orderly progression in the fetus, from first-degree through second-degree to third-degree AV block. Rather, as one study showed, third-degree AV block with ventricular dysfunction developed in less than 1 week, and first-degree AV block identified in the third trimester did not progress.[80] Rein and colleagues recently reported that first-degree AV block could be reversed if recognized.[81] Similarly, progression from second-degree AV block to third-degree AV block did not occur in fetuses evaluated longitudinally by fMCG (see Figure 74-13).[5] Thus, it seems that the clinical phenotype of SSA-mediated or SSB-mediated disease varies from normal rhythm followed by sudden progression over a few hours to severe conduction system and myocardial disease and to a more indolent course. Either mild low-grade conduction system disease is seen or, as some believe, slow progressive conduction disease.[81]

If AV block is detected in the fetus and the maternal SSA or SSB antibody titers are negative, a channelopathy may be the cause. Both *NKX2.5* mutation and *SCN5A* mutation have been linked to progressive AV block. Other clinical manifestations of these mutations include cardiomyopathy (Lenegre-Lev disease, caused by *SCN5A* mutation) and congenital heart disease. Questioning the family may elucidate a history of congenital heart disease, conduction system disease, sudden death, or cardiomyopathy in first-degree relatives of the fetus.[82-85]

The electrophysiological characteristics and in utero history of AV block have been elucidated by fMCG in a large study of 28 fetuses.[5] About 30% of fetuses had other complex and unsuspected arrhythmias, including ventricular tachycardia (VT) and junctional ectopic tachycardia (JET). JET occurred in the mid-second trimester and decreased in rate and duration as gestation progressed. VT occurred at any time during gestation. Isolated ventricular ectopy and atrial ectopy were also common and seen in 70% of fetuses.

Although it is generally assumed that during fetal AV block the ventricular rate is monotonous, two distinct patterns of FHR acceleration exist. In a study, the first, a nonreactive pattern (Figure 74-8, *A*), was seen in fetuses who were paced as neonates on the basis of standard recommendations.[86] The second, a reactive pattern of acceleration (Figure 74-8, *B*), predicted freedom from pacing for at least 4 months after birth. Additional information about patterns of acceleration in AV block was detected by fMCG evaluation of fetuses with low ventricular rates augmented by terbutaline.[87] In this study, heart rate patterns of acceleration differed based on the etiology (associated with LAI, or SSA-mediated or SSB-mediated damage) of the AV block.

Unsuspected repolarization abnormalities have also been identified by fMCG in a high proportion of fetuses with conduction system disease, including prolonged QTc interval and T-wave alternans. QTc interval prolongation has been identified in a much higher proportion of fetuses than in newborns with isoimmune disease.[6]

Treatment and Outcome of SSA-Mediated or SSB-Mediated Atrioventricular Block

Fetal survival and 1-year survival of patients with AV block diagnosed in utero has greatly improved over the last 20 years (Table 74-2).[69,88-94] Improved survival can probably be attributed to a combination of factors, including earlier identification of at-risk fetuses and more vigilant follow-up during pregnancy. In addition, the improvements in perinatal care of high-risk fetuses have allowed many without risk factors for intrauterine demise to be managed to term or nearly to term despite very low FHRs. The benefits of transplacental pharmacologic treatment have not been proven in a prospective randomized trial. Treatment options include β-agonists such as terbutaline to augment the fetal ventricular rate; dexamethasone, a fluorinated steroid, which crosses the placenta and appears to reduce inflammation; and intravenous immunoglobulin (IVIG), which decreases the amount of circulating maternal antibodies.[95-99] In anecdotal experience, IVIG was given to fetuses with severe EFE or cardiac dysfunction who did not respond to fluorinated steroids.[33] The ability of IVIG to prevent progression in at-risk pregnancies is also under study; however, outcomes have been mixed, with better outcomes seen in those receiving higher doses or more frequent doses. Its use for prophylaxis remains unproven as yet.[70,71] Risks to the mother and the fetus are mainly from exposure to blood products. Terbutaline appears to be well tolerated, with no serious sequelae in most mothers and fetuses.[87]

In utero treatment of AV block, with fluorinated steroids remains controversial. It has been reported to attenuate both myocardial and conduction system sequelae, but not in a consistent fashion.[6,7,31] No evidence indicates that dexamethasone treatment will restore normal conduction in the face of third-degree AV block. However, some studies have reported that dexamethasone reverses or stabilizes incomplete block: Askanese and colleagues

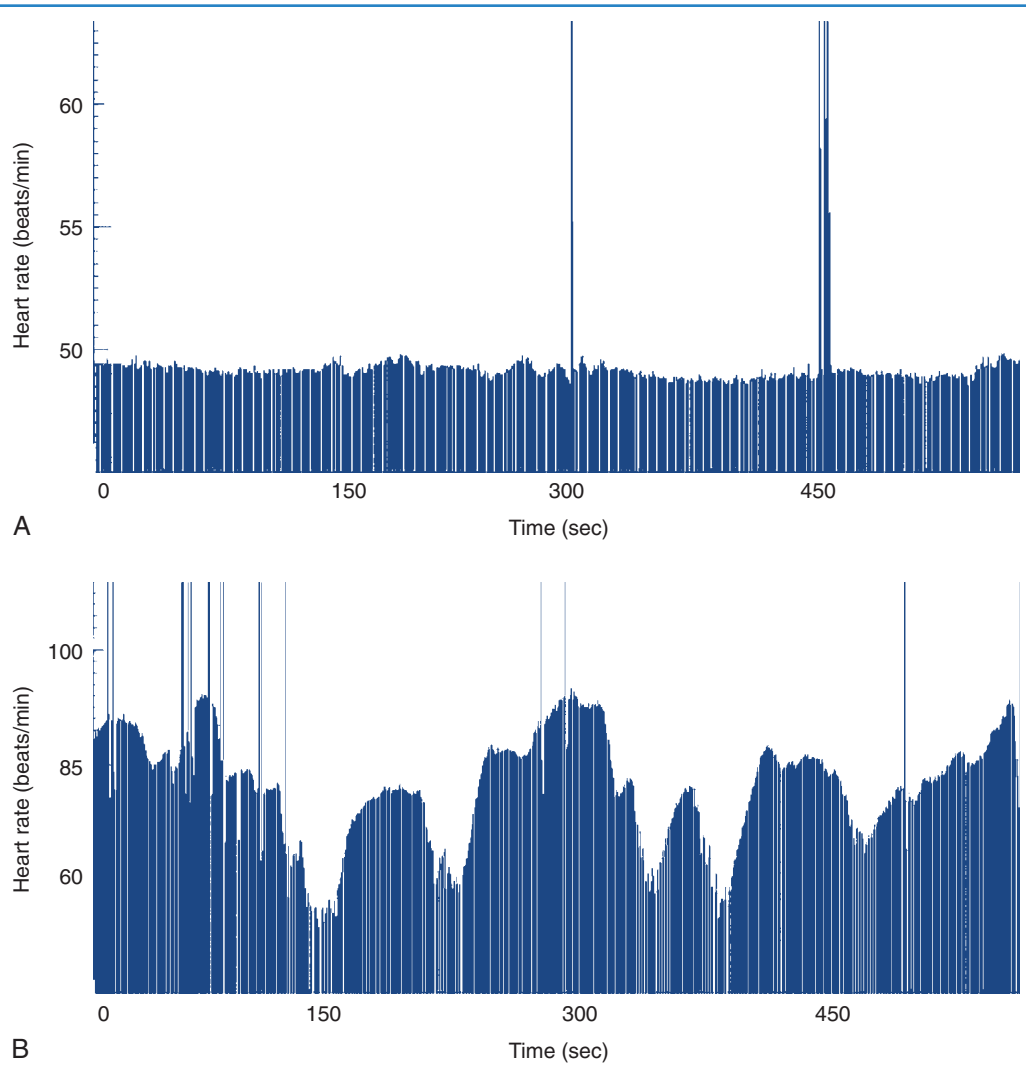

FIGURE 74-8 Fetal heart rat patterns of acceleration in third-degree atrioventricular block. Heart rate (*y-axis*) and time in seconds (*x-axis*) are shown. Each *line* is an individual R-R interval. Lines off the top of the scale are premature beats. **A,** A nonreactive pattern, which predicted the need for neonatal pacing. **B,** A reactive pattern, which predicted freedom from pacing until after 4 months of age.

Table 74-2 Outcome of SSA-/SSB-Mediated Fetal Atrioventricular Block

STUDY PERIOD	LEAD AUTHOR	N	% TREATED WITH DEXAMETHAZONE	% TREATED WITH TERBUTALINE	LIVE-BORN (%)	1-YEAR SURVIVAL (%)
1980–1993	Groves	36	9	3	75	67
1988–2006	Lopes	32	0	—	93	90
1990–1996	Rosenthal	26	27	7	—	77
1990–1996	Jaeggi	16	29	7	80	47
1996–2008	Lee	30	97	43	100	93
1997–2003	Jaeggi	21	95	43	89	86
1997–2004	Rosenthal	14	0	7	—	93

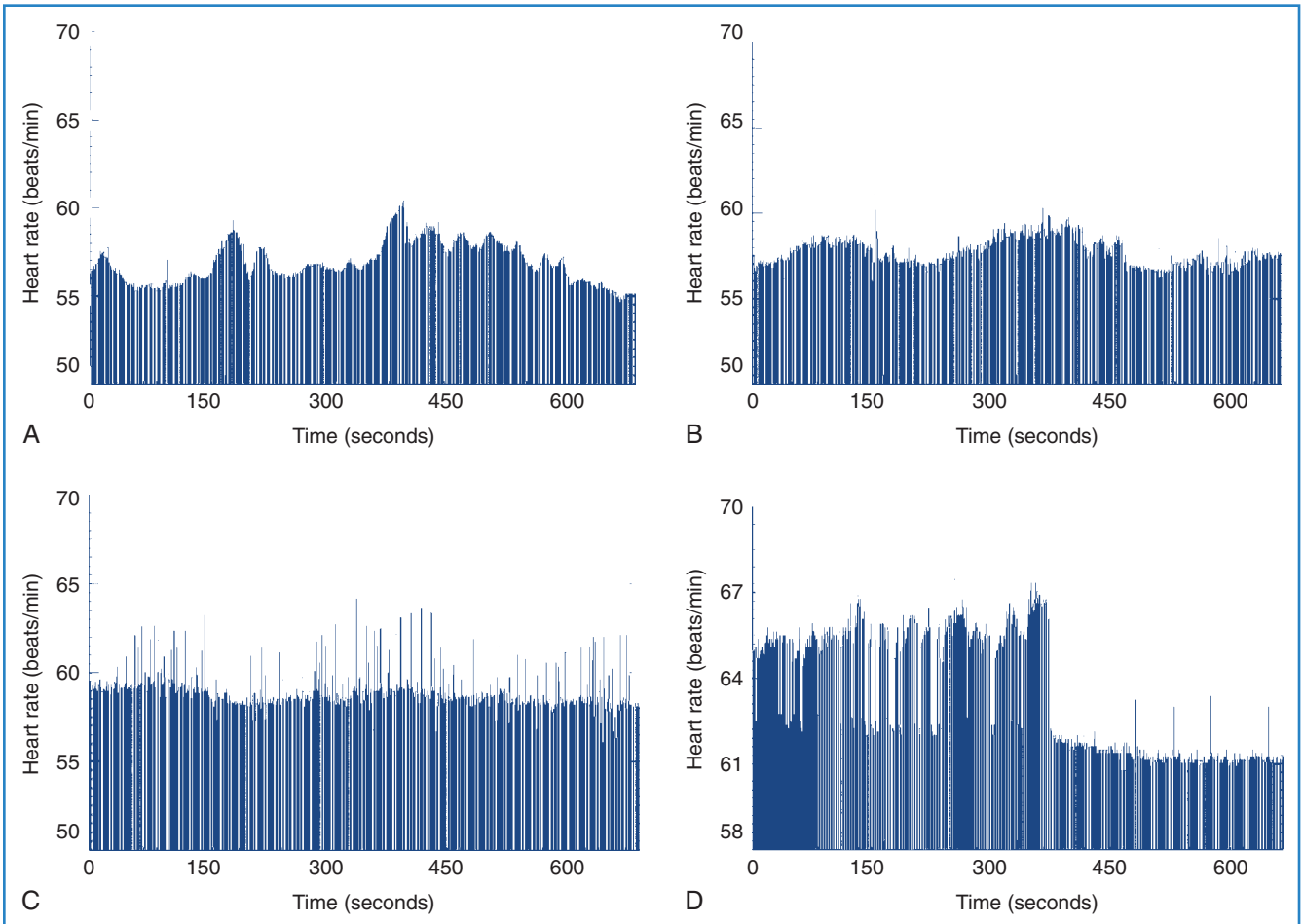

FIGURE 74-9 Fetal heart rate patterns of acceleration in third-degree atrioventricular (AV) block at baseline and on terbutaline to augment ventricular rate. Heart rate (*y-axis*) and time in seconds (*x-axis*) are shown. Each *line* is an individual R-R interval. **A,** Immune-mediated AV block at baseline. **B,** After maternal treatment with terbutaline; gestational age is 24 weeks. **C,** AV block with left atrial isomerism at baseline. **D,** After maternal treatment with terbutaline; gestational age is 30 weeks.

reported two fetuses with second-degree AV block treated in utero with dexamethasone and had normal ECGs at birth.[100] Rein reported regression of first-degree AV block in six patients.[81]

Dexamethasone is known to stabilize sodium channels and has modulated conduction system disease associated with a single mutation in the *SCN5A* coding region.[32,33,101]

Thus, anti-inflammatory treatment may stabilize an ongoing disease process and modulate the final expression of disease. However, because the side effects of fluorinated steroids on the mother and the developing fetus are potentially significant, the risks and benefits of treatment should be discussed in depth with the family, and the treatment duration should be as short as possible. For example, weaning the dose of dexamethasone after 30 weeks of gestation appears to limit the incidence of neonatal hypoaldeosteronism, while cardiac disease does not progress.

Preliminary results suggest that the morbidity of treatment in this population may not be as severe as previously thought; thus, one approach has been to start dexamethasone treatment soon after diagnosis, adding terbutaline if the ventricular rate falls to 55 or fewer beats/min.[87,102,103] IVIG may be given if myocardial disease worsens despite dexamethasone or if additional electrophysiological abnormalities such as sinus node dysfunction or atrial flutter appear[21,72,104] More data will be necessary to determine the optimal management with the least mortality and to determine if and how in utero therapy improves the long-term outcome of this high-risk population.

Fetal Tachycardia

Supraventricular Tachycardia

Morbidity and Mortality

Despite three decades of treatment, fetal SVT remains a rare but significant cause of intrauterine fetal nonimmune hydrops, premature delivery, and perinatal morbidity and mortality. The primary reasons are (1) inability to detect SVT until after the onset of hydrops (35% to 57% of cases); (2) inability to recognize the difference between SVT and other rarer forms of fetal tachycardia, which leads to less effective or even inappropriate treatment regimens; (3) poor response to transplacental therapy (7% without hydrops, 7% to 40% with hydrops, depending on the drug and route of treatment); (4) perinatal decision-making or interventional techniques leading to preterm delivery (25%); (5)

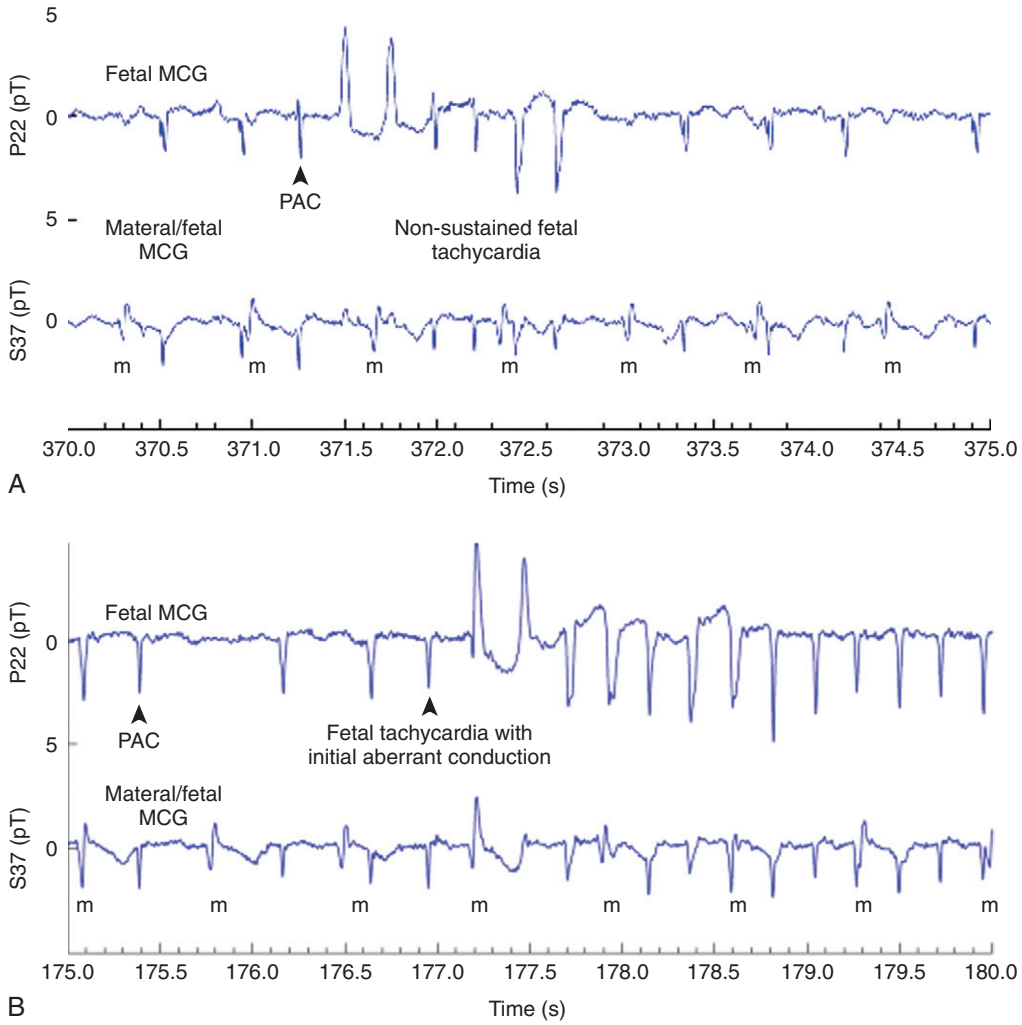

FIGURE 74-10 Nonsustained (**A**) and sustained (**B**) fetal re-entrant supraventricular tachycardia initiated by premature atrial contractions (*PAC*) (*arrows*). The tachycardia exhibits aberrancy near its initiation, in this case both left and right bundle branch block of differing coupling intervals. Such subtle changes would not be easily recognized with echocardiography alone. *MCG*, Magnetocardiography; *m*, maternal.

intracordal techniques that lead to fetal demise (up to 50% of hydropic fetuses in one series)[105]; and (6) complications of hydrops fetalis and prematurity in the neonatal period (25% to 40% of those with severe nonimmune hydrops).[7,105-118]

Diagnosis-driven treatment strategies hold the greatest potential for altering these high morbidity and mortality rates. fMCG and fECG can provide a definitive diagnosis but as yet are not readily available.[12,31,119,120] The difference between narrow-QRS and wide-QRS tachycardia can be determined after about 18 weeks of gestation by fMCG, with full assessment of the P wave in tachycardia after about 24 weeks. Many consider fMCG to have the ability to provide the best clarity in fetal arrhythmias (Figure 74-10). fECG currently can be performed using devices that signal average, that is, if the rhythm is regular, P and QRS waves can sometimes be defined.[9,119,120] P waves may be too small to resolve, and if the rhythm is irregular, signal averaging is not possible. Echocardiography provides the next-best method for fetal tachycardia diagnosis, and many reports have outlined these techniques.[20,121-125] The critical element is the determination of the relationship of the atrial contraction pattern to the ventricular contraction pattern. The V-A interval can be estimated using either the flow patterns in the SVC-aorta or in the pulmonary artery/pulmonary vein.[16,21,121,126]

Brief tachyarrhythmias may be underdetected by ultrasound alone. Zhao and colleagues found nonsustained tachyarrhythmias in 30% of fetuses with congenital AV block, none of whom were felt to have had any tachyarrhythmias at referral.[5] Current nonstress testing is also not sufficient for monitoring deviations from normal heart rate ranges because the equipment halves the heart rate above 240 beats/min.

Management of Pregnancy Complicated by Fetal Tachycardia

Cuneo and colleagues have outlined management strategies for nonsustained fetal reciprocating tachycardia.[127,128] For the fetus near term (>35 weeks), delivery should be considered rather than maternal medication, provided that treatment is considered necessary. For those with tachycardia less than 50% of the time, or at rates greater than 220 beats/min, observation may be the requirement. Expectant monitoring twice weekly or more often with frequent echocardiography, observing for signs of hydrops, may be the safest approach. Even in immature fetuses

with heart rates less than 220 beats/min, close observation without treatment may be considered, provided that the fetuses have only intermittent tachycardia, normal ventricular function, and no hydrops. In the authors' center, at-home hand-held Doppler monitoring is prescribed to ensure that nonsustained SVT is not becoming sustained SVT. This is a transition that can develop more frequently in the fetus less than 24 weeks' gestational age with heart rates greater than 220 beats/min. For the immature fetus with rates greater than 220 beats/min, gestational age less than 35 weeks, with sustained tachycardia on in-hospital fetal monitoring (with or without hydrops), pharmacologic treatment is indicated, although the risk/benefit ratio for the mother must always be acceptable when any pharmacologic treatment is considered.

Treatment can take the form of transplacental transfer via administration of antiarrhythmic drugs to the mother or direct intramuscular or intracordal administration to the fetus. These two forms of drug treatment are reserved only for fetuses with hydrops and should be performed in conjunction with maternal transplacental therapy. In the authors' center, intramuscular digoxin is often administered during the maternal loading with digoxin. The dose used has been 88 μg/kg dry fetal weight, repeated every 12 hours for either three total doses or until fetal conversion, whichever comes sooner.[113] Transplacental transfer of most drugs is significantly reduced with hydrops. Intracordal administration has been associated with a higher mortality when used repeatedly.[21,105] While intracordal treatment with agents such as adenosine is a tempting option, it is not effective in maintaining sinus rhythm in fetal SVT and is not worth the risk of cord access in the authors' experience.

Ineffectiveness of transplacental therapy is largely because of the use of the oral route instead of the intravenous route for the administration of digoxin, subtherapeutic dosing, and early discontinuation. With most antiarrhythmic drugs, relatively high doses must be used during the second and third trimesters, since the maternal circulating blood volume and renal clearance are both increased. Although women are known to require larger doses of some medications because of the high circulating blood volume, protein binding, and other factors that may contribute to maternal side effects, adequate systematic study of the pharmacokinetics, pharmacodynamics, and even a registry of early and late side effects has not been performed despite at least three decades of treatment for fetal tachycardia. Serious maternal adverse effects appear to have been rare in most reported series, and most side effects have resolved with discontinuation of therapy.[116,129,130] Examples of serious side effects have included thyroid dysfunction (amiodarone) and thrombocytopenia (quinidine, amiodarone). Fetal complications that have been encountered are usually drug specific.[131,132] Table 74-3 provides the most common adverse effects of antiarrhythmic agents.

Table 74-3 Fetal Tachycardial Treatment Series

	HANSMANN ET AL	OUDIJK ET AL	SIMPSON ET AL	FROHN-MULDER ET AL	VAN ENGELEN ET AL	ALLAN ET AL	SONNESON ET AL	JUNIAK ET AL	STRASBURGER ET AL
Year published	1991	2000	1998	1995	1994	1991	1998	2003	2004
Patients	60	20	110	35	34	14	14	25	24
% HF	35	40	39	37	44	100	57	100	93
SVT (# pts)	54	10	105	35	25	12	14	21	15
% of SVT HF patients converted	50	60	66	59	82	100	60	93	93
AFL (# pts)	6	10	22	0	9	2	0	4	9
% HF patients converted AFL		80	0	0	?	85	71	33	33
% Direct therapy	21 (IV)	0?	3 (IV)	?	?	0?	0	0?	86 (IM)
% HF, mortality*	T 20%, D 46%	30	T 27%, D 50%	46	13	8	14	12	0
Digoxin (# pts)	14+/45–	0	40+/28–	13+/6–	11+/4–	2	14	9	23–
Verapamil (# pts)	37 (+/–?)	0	24+/4–	0	0	0	0	0	0
Flecainide (# pts)	1–	0	20+/5–	7+/4–	9+	14+	0	7+/3–	0
Sotalol (# pts)	0	16+/4–		0	0	0	10+/4–	2–	0
Amiodarone (# pts)	1+/1–	0		0	0	0	0	7+/4–	12+ SVT, 3+/6– AF
Multi-drug (# pts)	2+/1–	0	23+/11–	5–	8+/2–	0	0	0	3+ SVT
Total	59	20	110	35	34	14	14	25	24

AFL, *Atrial flutter;* D, *direct;* HF, *hydrops fetalis;* SVT, *supraventricular tachycardia;* T, *transplacental.*
**Mortality is expressed only as mortality for the hydropic group.*
From Strasburger JF: Prenatal diagnosis of fetal arrhythmias, Clin Perinatol *32:891–921, 2005.*

Table 74-4 Fetal Transplacental Drugs: Therapeutic and Toxic Effects

DRUG	DOSE RANGE	THERAPEUTIC LEVEL AND EFFECT	TOXICITY
Digoxin (PO, IV)	LD: 1200 μg/24 hours IV MD: 375–750 μg/day PO divided BID	0.7–2.0 ng/mL Nausea+, fatigue+, sinus bradycardia+, first-degree AV block, rare nocturnal Wenchebach AV block	Nausea/vomiting+++, sinus bradycardia or AV block+++, proarrhythmia
Flecainide (PO)	100–300 mg/day divided q8h PO	0.2–1.0 μg/mL Mild IVCD, headache	Visual CNS symptoms; bundle branch block; maternal, fetal, neonatal, proarrhythmia
Amiodarone (PO)	LD: 1800–2400 mg/day divided q6h × 48 h MD: 200–600 mg/day	0.7–2.8 μg/mL Sinus bradycardia maternal/fetal, first-degree AV block, P and QRS widening	Nausea/vomiting+++, maternal/fetal thyroid dysfunction, photosensitivity rash, thrombocytopenia, bundle branch block, proarrhythmia, fetal TdP in LQTS fetuses
Sotalol (PO)	160–480 mg/day divided BID or q8h	NA Bradycardia, first-degree AV block, P and QRS widening	Nausea/vomiting, dizziness, fatigue, bundle branch block, maternal/fetal pro-arrhythmia
Lidocaine	1–1.5 mg/kg IV followed by infusion of 1–3 mg/min	1.5–5 μg/mL	CNS symptoms
Propranolol (PO)	60–320 mg/day divided q6h	25–140 ng/mL Bradycardia	Fatigue, bradycardia+++, hypotension
Magnesium sulfate (IV)	2–4 g IV followed by 1–2 g/h	1.5–3 mmol/L	Fatigue, CNS symptoms STOP if loss of patellar reflex at levels of 3.5–5 mmol/L; cardiac arrhythmias at high levels
Procainamide (PO, IV)	LD: 500–600 mg over 20 min IV MD: 2–6 mg/min IV PO: Initially 1250 mg, followed in 1 hour by 750 mg, then 250–1000 mg q3–6h	4–10 μg/mL	Nausea/vomiting, hypotension, proarrhythmic blood dyscrasias

PO, *Oral;* IV, *intravenous;* LD, *low dose;* MD, *medium dose;* BID, *twice per day;* AV, *atrioventricular;* IVCD, *intraventricular conduction defect;* CNS, *central nervous system;* TdP, *torsades de pointes;* LQTS, *long QT syndrome.*

In many centers, digoxin is used as first-line maternal therapy because of its relatively safe profile, its longstanding use during pregnancy, as well as its ease of use. In the past, it was used for congestive heart failure related to rheumatic heart disease. In some European countries, flecainide is currently used as primary therapy, even in the absence of hydrops (Oudijk, personal communication).[112]

The choice of second-line anti-arrhythmic therapy in transplacental management of fetal tachyarrhythmias is still controversial. Flecainide, sotalol, and amiodarone have all been used as second-line therapy. (Table 74-4).[21,112,116,118,127,130,133,134] In the presence of ventricular dysfunction and hydrops, intramuscular digoxin and amiodarone appear to have the least mortality associated with their use; however, amiodarone is currently a class D drug in the second and third trimester because of its maternal side effects.[133] Unfortunately, large multicenter clinical trials of antiarrhythmic agents have not been conducted in fetal arrhythmia care; therefore, treatments remain somewhat arbitrary. Further, it is unclear whether the fetal deaths in these cases are, indeed, related to the drugs, to the modes of administration of the drugs, to the timing of treatment in the disease course, to the combinations of drugs, or to other factors. Recently, the authors' group has used maternal nutritional treatments to reduce the potential for maternal and fetal QT prolongation, which can accompany antiarrhythmic treatments with these drugs and can also accompany hypocalcemia, hypomagnesemia, and vitamin D deficiency, all of which are not uncommon during pregnancy.

Prematurity and delivery by cesarian section are common in fetal SVT, as is placental insufficiency in the later weeks of pregnancy. Patients cared for in tertiary centers with experience in maternal and fetal medication management have a lower risk of premature delivery and cesarian delivery.[111] Maternal nonstress testing or biophysical profile assessment is advisable once to twice weekly after 32 weeks of pregnancy to evaluate for placental insufficiency. Attention should be paid to maternal weight gain, which may be low during treatment because of appetite suppression.

Postnatal Management

Following fetal tachycardia, many newborns will be free of SVT. In one series, only about 50% required postnatal treatment.[111] This is likely caused by accessory AV connections resolving as part of the normal developmental process.[135] The infant can undergo in-patient monitoring for 48 hours without medications, and if no spontaneous recurrence is seen, trans-esophageal pacing can be used to determine whether treatment is required. Some centers will arbitrarily continue treating the infant for several months after fetal tachycardia because of the infant's limited ability to

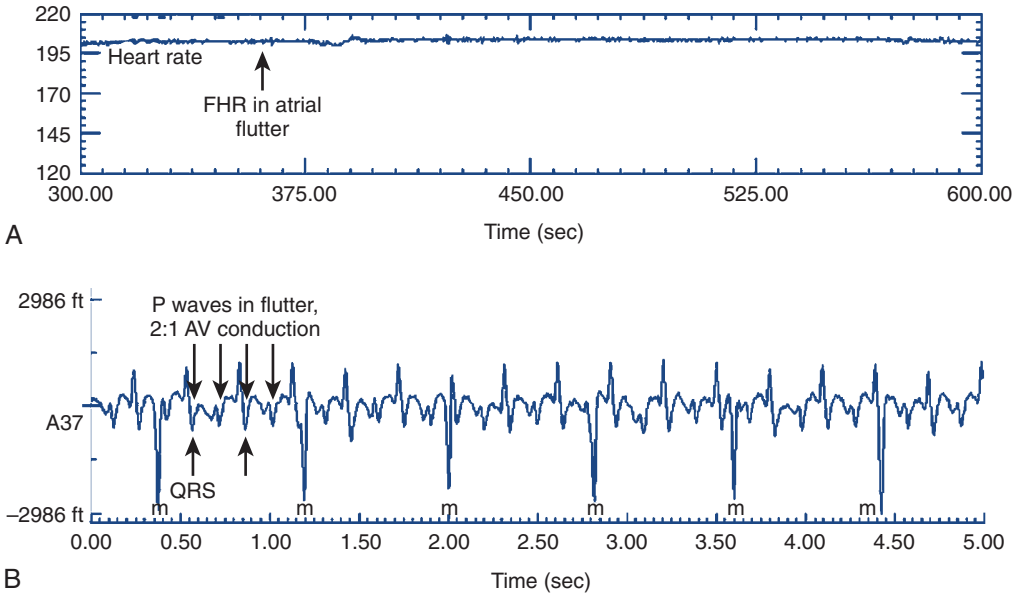

FIGURE 74-11 Atrial flutter at a ventricular rate of 184 to 200 beats/min in a 32-week-old fetus. Flutter was sustained for more than 3 weeks. QRS is abnormally wide, P waves are large, and conduction is 2:1. QRS aberrancy was likely related to class III antiarrhythmic agent administration. *FHR*, Fetal heart rate.

respond with recognizable symptoms before cardiovascular collapse. Hydrops in utero appears to be more associated with left-sided accessory AV connections than with right-sided or septal connections.[111,136]

Atrial Flutter

While re-entrant SVT is the most common mechanism of fetal tachycardia, atrial flutter accounts for about 30% of fetal tachycardias.[52,58,112,116,129,137] It usually is associated with heart rates of 200 to 220 beats/min in 2:1 AV block (Figure 74-11). Atrial rates are usually 375 to 500 beats/min. Most atrial flutter is associated with re-entrant accessory pathways and AV re-entrant SVT (70%).[111,138,139] Atrial flutter can be seen also with myocarditis, structural heart disease, SSA isoimmunization, and heart block but is most often isolated.[21,38] It is treated with sotalol or digoxin.[112,137] In Oudijk's study, sotalol was shown to be effective in converting 80% of fetuses with atrial flutter without mortality.[112] Amiodarone can slow the atrial flutter but generally has not converted it to sinus rhythm.[116] Postnatally, trans-esophageal pacing or synchronized cardioversion is usually effective in restoring sinus rhythm. Brief asystole is occasionally seen with the conversion, often related to residual drug effects. Asystole can be treated with brief temporary atrial pacing if a trans-esophageal lead is in place or with atropine. It is important to be prepared for this potential at the time of cardioversion.

Rare Forms of Fetal Tachycardia

Ventricular Tachycardia

VT has been observed in association with the early and late decompensatory phases of AV block, with cardiac tumors such as rhabdomyoma or septal fibroma, with acute myocarditis, and with hereditary ion channelopathies.[1,2,5,6,23,38,52,112,140-142] Two principal manifestations are observed: (1) a very rapid TdP or (2) slower monomorphic VT. The echocardiogram usually shows significant ventricular dysfunction and AV valve regurgitation. VT is usually intermittent, but hydrops is common even when the rate is relatively slow. Retrograde ventriculoatrial (VA) block results in atrial dissociation in most cases, and this can be a differentiating feature echocardiographically.[143]

In addition, ion channelopathies such as LQTS may present in utero with bradycardia, often early (<20 weeks). When tachyarrhythmia and bradyarrhythmia coexist, LQTS has been the dominant diagnosis.[144,145] Therefore, fMCG can be quite useful for antiarrhythmic selection. If the tachycardia is related to isoimmunization or to myocarditis, fluorinated corticosteroids such as betamethasone or dexamethasone may be effective in converting the VT.[5,38] Magnesium administered to the mother should be considered as first-line treatment for fetal VT.[1,146,147] Maternal propranolol, intravenous lidocaine, and oral mexiletine have all been used, but only lidocaine and propranolol have been effective for VT.[1,146,147]

Accelerated Ventricular Rhythm

In a slow and more benign form of VT, the accelerated rhythm competes with sinus rhythm at rates that are less than 220 beats/min and often quite similar to the sinus rate. This arrhythmia often occurs later in gestation. As in infancy, accelerated ventricular rhythm generally does not require prenatal treatment and is not usually associated with hydrops or significant ventricular dysfunction.

Junctional Ectopic Tachycardia

JET is commonly associated with SSA isoimmunization in the fetus and the neonate.[5,23,148] It can be treated with steroids as in the case of VT, or if it is sustained, it can be treated with

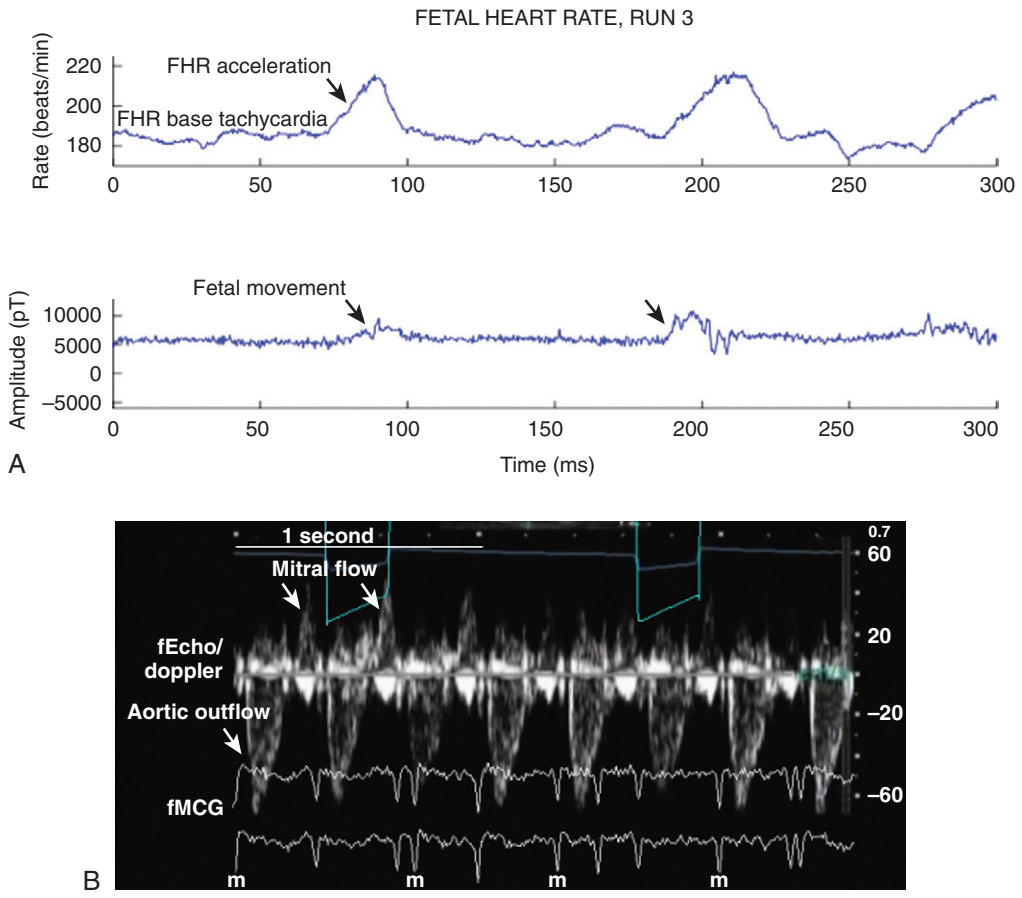

FIGURE 74-12 Atrial ectopic tachycardia often presents with mild tachycardia and heart rates that vary with fetal activity. **A,** Baseline fetal tachycardia at approximately 187 beats/min, with accelerations to 218 beats/min. The P-R interval is often prolonged in atrial ectopic tachycardia. **B,** In this 29-week-old fetus, the combined fetal magnetocardiography (*fMCG*) and echo Doppler demonstrates *e* and *a* wave overlap (mitral inflow) and mechanical P-R interval longer than the R-P interval with a heart rate of approximately 187 beats/min. This new fetal electromechanical technique allows the assessment of timing of activation of Doppler relative to fMCG.

antiarrhythmic agents. Little published experience exists with regard to prenatal treatment of JET, largely because without fMCG, the condition cannot be distinguished easily from VT. This tachycardia is usually slower than SVT, but as with VT, it can be associated with valvular regurgitation, ventricular dysfunction, or hydrops fetalis. Progression to AV block is occasionally seen, and when JET is nonsustained, it is often accompanied by complete AV block.

Atrial Ectopic Tachycardia

Atrial ectopic tachycardia (AET) has been observed in utero. In most cases, the conduction is mostly 1:1 with rates less than 220 beats/min the majority of time (Figure 74-12). Hence, either treatment is not required, or treatment with digoxin is customary when ventricular dysfunction is present.[16,123] Rarely, hydrops has developed, and in this setting, second-line agents have slowed the ventricular rate.[116]

Multi-focal Atrial Tachycardia

Chaotic atrial tachycardia is rare and is usually seen within the last few weeks of pregnancy.[149] Often, it extends into the neonatal period and is relatively difficult to suppress completely.[150,151] β-Blockers are usually used in the neonatal period, but digoxin is usually all that is required for treatment in utero. Many cases are, however, left untreated in utero.

Sinus Tachycardia

When sinus tachycardia is persistently present, it is usually 180 to 190 beats/min and is associated with infection, medication use, hyperthyroidism, or thyroid antibody in the mother. Only the underlying cause is usually treated.[16,52]

Ectopy in the Fetus

Fetal ectopy occurs in 1% to 3% of all pregnancies and, in general, has been reported to be a relatively benign condition. Atrial ectopy is 10-fold more common than ventricular ectopy. Studies by Cuneo, however, suggested that as many as 2% of pregnancies with fetal ectopy have associated P-R interval prolongation, which, in itself, has been associated with LQTS, fetal or neonatal atrial flutter, and second-degree AV block.[152] A mechanical P-R interval should be determined in any echocardiography

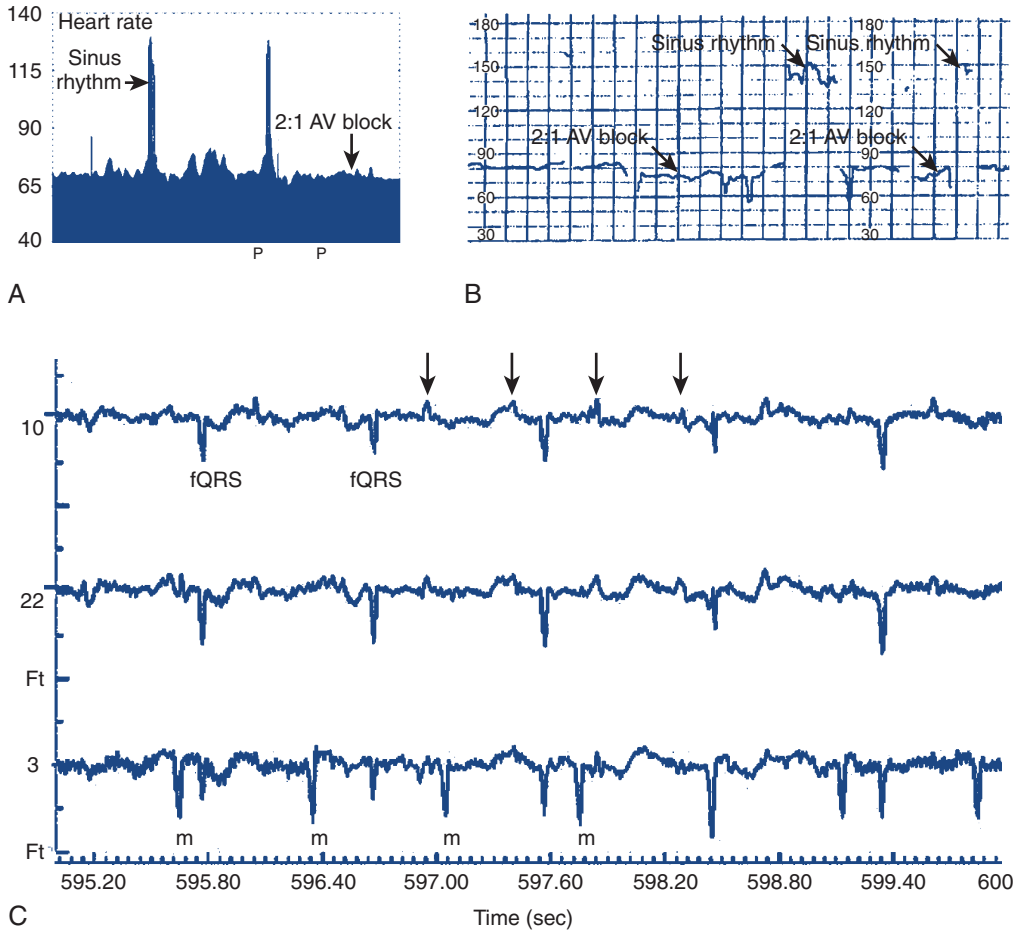

FIGURE 74-13 Fetal second-degree atrioventricular (*AV*) block in a 30-week-old fetus exposed to SSA/SSB antibody displayed using fetal magnetocardiography 5-minute heart rate trend (**A**), fetal nonstress testing at 38 weeks (**B**), and fMCG rhythm strip (**C**). Note the slight improvement in amount of sinus rhythm at 38 weeks. P waves are marked with an *arrow*. *fQRS,* Fetal QRS; *m*, maternal QRS complexes.

performed for fetal ectopy, and if mechanical P-R interval is prolonged, SSA and SSB antibodies should be assessed. Blocked atrial bigeminy (discussed in the section on bradycardia) is often associated with very early premature ectopic beats with a fixed coupling interval. Medication is not required to treat either premature atrial complexes (PACs) or for blocked atrial bigeminy.

Management of High-Risk Fetal Populations

It has long been recognized that pregnant patients with systemic lupus erythematosus and maternal hypertension, primigravidas older than 40 years, those with diabetes, those with congenital heart disease, and those who have experienced a prior fetal loss have a higher than acceptable incidence of stillbirths. Fetuses with structural heart defects and other birth defects such as gastroschesis also have higher stillbirth rates. The exact etiology of fetal deaths in many of these cases has not been determined, but placental insufficiency is a common counterpart to the fetal demise.[46,153-159] Recently, fMCG documentation of the transition of the fetus from a healthy state to one of recognized severe adverse conduction system disease has supported that fetal deaths may, in part, be related to primary or secondary cardiac disease.[2,5,6,38,160] Electrophysiological screening of pregnant patients at risk for fetal demise may improve early disease detection. Recently, in a study by Serra and colleagues, new nomograms for fetal heart rates and bradycardia were developed.[33] The use of new gestation-based parameters for inappropriately low heart rates could potentially enhance early detection of LQTS, where fetal bradycardia is a common presentation.[3,40,143,161] Before 24 weeks, heart rates less than 130 beats/min may actually be abnormal. The relationship of fetal bradycardia to LQTS certainly exists; however, the number of fetuses within this range with conduction abnormalities will need to be determined. If heart rates have been inappropriately low during fetal life, it may be advisable to screen the infants for LQTS with an fECG at 3 days to 3 weeks of age.

Innovative fetal diagnostics and bio-instrumentation, along with well-planned fetal treatment protocols, are necessary to move fetal cardiovascular care forward from its present state. Inclusion of pregnant women as subjects in research and post-marketing assessment of antiarrhythmic drugs used in pregnancy are needed so that the best care can be provided to pregnant women and their fetuses.

A team approach to treatment involving pediatric cardiologists or electrophysiologists and perinatologists is needed, given the

complex fundamental knowledge of arrhythmias and pharmacology required to ideally manage tachyarrhythmia or bradyarrhythmia. Therapeutic measures such as transplacental or direct fetal drug therapy, when implemented, impact the entire maternal-fetal-placental unit. Because fetal tachyarrhythmias are rare, only published case series, rather than randomized clinical trials, have so far outlined treatment. Complex communication structures are common in fetal arrhythmia management, and, in particular, attention must be paid to patient/caregiver communication and physician/physician communication. Follow-up of laboratory testing and medications prescribed for the pregnant patient and delivery and neonatal planning are important. Funding models must be developed that allow the study of such issues as breastfeeding after prenatal drug treatment, the safest long-term strategy for determining the need for treatment of the infant at birth, and long-term follow-up of both pregnant women and fetuses exposed to medications.

SUMMARY

In summary, what is known about fetal arrhythmias is superseded by what is not known. Enhancement of imaging modalities in diagnostic assessment will likely improve prenatal detection of disease and allow diagnosis-specific treatment. Superconducting quantum interference devices (known as *SQUID*), magnetometers, atomic magnetometry, and new processing algorithms for fECG will bring the monitoring modalities, so commonly used to diagnose patients at other ages, to the care of the human fetus within the next decade. The progress in fetal arrhythmia diagnosis over the past decade has accelerated, largely because of interdisciplinary research teams that include bioengineers and medical physicists on the basic science end and medical teams from pediatric and adult cardiology or electrophysiology and obstetrics on the medical end. Despite this, the prenatal period is one of the most significant periods of loss of human life. Over the past five decades, decline in the rate of fetal mortality has been only modest and much slower for the fetus than for the mother, the neonate, or the infant. Greater focus on the fetus will likely lead to dramatic reductions in fetal mortality and improved care.

All references cited in this chapter are available online at expertconsult.com.

CHAPTER 75

Evaluation and Management of Arrhythmias in the Pediatric Population

Victoria L. Vetter and Larry A. Rhodes

Appropriate evaluation and management of arrhythmias in pediatric patients require an understanding of the presentation, clinical correlations, and unique responses of children to the various potential treatments. The primary focus of this review of arrhythmias in the pediatric population is on arrhythmias that are seen more frequently or behave differently in children than how they do in adults. For arrythmias that have shared characteristics, we refer you to the excellent chapters in this text dealing with each specific rhythm disturbance.

Supraventricular Tachycardia

General Presentation and Evaluation

Supraventricular tachycardias (SVTs), which are arrhythmias that originate above the ventricles and involve the atria, the atrioventricular (AV) node, or the accessory bypass tracts, represent the most common tachycardias seen in infants and children, with an incidence of 1 in 250 to 1000 in the United States.[1] SVTs are classified by identifying those components of the heart that are involved in maintaining the tachycardia. SVTs include *primary atrial tachycardias* (those in which the AV node and the ventricles are not involved), *AV reciprocating tachycardias* (those that involve both the atrium and the ventricle), and *AV nodal re-entrant tachycardias* (those that do not involve the atria as part of the circuit). The presentation of the pediatric patient with SVT varies from palpitations to signs of marked cardiac failure. This variability is related to the patient's age at presentation and his or her ability to communicate symptoms, the duration and rate of the tachycardia, as well as the mechanism of SVT. Parents of infants with SVT occasionally note changes in feeding habits and irritability as symptoms. Symptoms in those old enough to voice complaints include palpitations (noted as skipped or rapid heart beats, or as "heart beeping"), chest pain, shortness of breath, fatigue, dizziness, and syncope.

The evaluation of pediatric patients includes a 12- or 15-lead electrocardiogram (ECG), which may show Wolff-Parkinson-White (WPW) syndrome or other abnormalities such as an ectopic atrial rhythm. While the ECG is often normal when SVT is not present, an ECG during SVT can be very helpful in distinguishing the mechanism of the tachycardia. A recent study suggested that leads V1 and III were the most helpful in this diagnosis.[2] Twenty-four-hour ambulatory (Holter) monitoring is useful to screen for occult arrhythmias or to assess heart rate ranges and variability if the patient is having frequent symptoms (i.e., on a daily basis). Transtelephonic event monitors are often helpful in those with fleeting symptoms, allowing the patient or parent to record symptoms as they occur with simultaneous ECG recordings. Exercise tolerance testing is useful in those with palpitations or symptoms associated with activities. More invasive testing such as a transesophageal or intracardiac electrophysiological study (EPS) is used to induce arrhythmia and determine the particular mechanism and often as a prelude to catheter ablation.

Mechanisms

Three primary mechanisms are involved in SVT: (1) enhanced automaticity, (2) triggered automaticity, and (3) re-entry. Automaticity is the ability of cardiac myocytes to spontaneously depolarize, which leads to myocardial contractions. Sinus and AV nodes are the primary sites of automaticity in the heart. Enhanced automaticity occurs when myocytes outside the sinus or the AV node depolarize spontaneously, which leads to atrial or ventricular ectopic beats or SVT and to ventricular tachycardias (VTs) when repetitive ventricular ectopic beats occur.[3]

Tachycardias arising secondary to enhanced automaticity have characteristics that are distinct from those of re-entry. They are highly catecholamine sensitive, with warm-up and cool-down phases. This leads to variable rates during the tachycardia. These tachycardias are not inducible with programmed stimulation, nor are they terminated with overdrive pacing or with direct-current cardioversion. Automatic tachycardias can arise from all areas of the heart, with those from the atria referred to as *ectopic atrial tachycardia*, those from the AV junction as *junctional ectopic tachycardia*, and those from the ventricles as *automatic VT*.

Triggered automaticity results from spontaneous myocardial contractions that occur secondary to oscillations during repolarization reaching threshold and leading to a depolarization.[4,5] These oscillations are referred to as *after-depolarizations*. Arrhythmias arising from triggered automaticity have characteristics shared by both enhanced automaticity and re-entry. They are highly catecholamine sensitive and have warm-up and cool-down phases with a wide variation in heart rate, similar to other forms of automaticity. They can be induced and terminated with pacing maneuvers and respond to direct-current cardioversion, as do re-entrant arrhythmias. Triggered automaticity is thought to play a role in the arrhythmias seen in digoxin toxicity.[6]

Re-entry occurs when a wavefront of electrical activation travels through tissue for a distance and then re-enters the original tissue and propagates through the circuit again. Re-entrant SVT is the most common type of tachycardia seen in pediatrics.

To have a re-entrant circuit, at least two pathways with distinct conduction properties and refractory periods must be present. The sequence of events in a re-entrant circuit is as follows. A stimulus encounters two distinct pathways, with one pathway refractory to conduction (the pathway with the longer refractory period) and one ready for conduction (the pathway with the shorter refractory period). The impulse is conducted along the pathway, with the shorter refractory period having enough conduction delay to allow the first pathway to recover and to conduct the impulse back to the original site of entry into the circuit. The impulse then re-enters the original pathway and transverses the circuit again. Re-entry can occur in the sinus node, the atrial tissue, the AV node, and the ventricular tissue or between the atrium and the ventricle. Those re-entry circuits between the atrium and the ventricle involve specialized conduction tissue referred to as *accessory pathways*. In AV nodal re-entrant tachycardia (AVNRT), the accessory pathway is in the AV node or in the AV nodal region. Moe and colleagues initially described the evidence of dual AV node physiology in 1956.[7] Re-entry tachycardias have characteristics that are distinct from those seen in automatic tachycardias. They often have sudden onset and termination, with patients frequently feeling that they have been "switched" on and off. The tachycardia is regular, with little variation in rate. Re-entry tachycardias often respond to vagal maneuvers by slowing or terminating the tachycardia. These tachycardias are easily induced and terminated with pacing protocols ranging from single premature stimuli to burst pacing or by direct-current cardioversion.

Specific Mechanisms in Children

The most common specific mechanism of SVT in children, representing 75% to 90% of arrhythmias in children without other cardiac conditions, is re-entry through an accessory pathway between the atrium and the ventricle or within the AV node.[8,9] Over two thirds of these pathways are concealed, and one third are manifested as WPW or other forms of pre-excitation. AV nodal re-entry represents around 15% of pediatric SVTs, most commonly seen in adolescents, with up to one third of SVTs presenting in adolescence, the cause being AVNRT.[9,10] Automatic atrial ectopic tachycardia represents 10% to 18% of SVTs in children. Atrial flutter and atrial fibrillation (AF) are responsible for 10% and 40% in non-postoperative and postoperative children, respectively, and junctional ectopic tachycardia responsible for less than 1% in non-postoperative patients.

Atrioventricular Reciprocating Tachycardias

Presentation and Treatment

Some variability exists in the presentation of *AV reciprocating tachycardia* in childhood. This may relate more to the age of the patient than to the specific type of tachycardia. For this reason, the presentation and treatment of pediatric patients with AV nodal re-entry, concealed bypass tract, and WPW re-entrant tachycardia are combined in the following overview, with emphasis on the different age-related presentations and treatment strategies.

Tachycardia may be seen as early as during fetal development. The diagnosis of fetal SVT may be made by auscultation of the baby's heart rate during maternal examination and is confirmed by fetal ultrasonography or fetal magnetocardiography.[11] See Chapter 76 for detailed information on these arrhythmias.

It has been reported that 50% to 60% of SVTs in children present in the first year of life, with accessory pathway–mediated re-entrant tachycardia being the most common mechanism.[12,13] The heart rate in infants with SVT is usually 220 to 320 beats/min. Neonates and infants with tachycardia are often very ill, presenting with congestive heart failure, which occurs if the tachycardia has been present for more than 48 to 72 hours before the patient receives medical care. This occurs because of the infant's inability to communicate and the family's lack of awareness that the child could have a significant medical condition. Parents may note that the infant is acting somewhat different from normal, is more irritable, or is not eating well. This is often interpreted as colic or some other "normal" childhood problem. At presentation, these babies often are acidotic from decreased cardiac output and may need aggressive resuscitation, including artificial ventilation and rapid termination of the tachycardia. Intravenous (IV) adenosine is effective in the acute termination of SVT in this population, but IV access is often difficult in a 3- to 4-kg baby with congestive heart failure. It has been suggested that in the treatment of infants, the starting doses of adenosine should be higher than those generally recommended as the average effective dose in infants, which is around 200 μg/kg.[14] If IV access is not possible, transesophageal overdrive pacing has proven to be effective. Once the rhythm is restored to normal and the cardiac function has begun to recover, IV access becomes easier, and IV medications can be administered. If the infant is hemodynamically compromised and the rhythm cannot be medically converted, electrical synchronized cardioversion is indicated.

Medications for the acute treatment of SVT are shown in Table 75-1. Digoxin is a first-line medication used in the treatment of SVT in infants with decreased myocardial performance. It is contraindicated as a chronic treatment in patients with WPW syndrome but can be used acutely in those with decreased ventricular function with careful monitoring. The authors of this chapters do not discharge patients with WPW syndrome on digoxin because of its potential effect to enhance conduction of atrial impulses to the ventricle but switch them to another medication once the cardiac function has normalized. Other IV medications used acutely to treat SVT include β-blockers such as esmolol, amiodarone, and procainamide. These medications must be used with caution because of their negative inotropic effects, which can lead to worsening of cardiac function. The use of IV calcium channel blockers is contraindicated in infants and children younger than 1 year because as sudden death has been reported in some cases.[15,16] In a long-term study from Sweden, the SVT was managed with a single drug in 62% of patients.[17]

Prognosis

While the majority of SVTs will resolve around 1 to 2 years of age, one third will recur by adolescence. Recurrence is only 10% for AVRT secondary to concealed accessory pathway but more than 31% if a WPW pattern persists.[17]

Presentation in Older Children

After the peak of presentation in the first year of life, the other two common ages of presentation are early childhood (6 to 8 years of age) and adolescence.[12,18] SVT in children is predominantly caused by concealed or manifested accessory pathways (WPW)

Table 75-1 Pharmacologic Agents for Acute Treatment of Supraventricular Tachycardia

AGENT	INITIAL TREATMENT (IV)
Adenosine	50–100 μg/kg, increase by 50-μg/kg increments Every 2 min to 400 μg/kg or 12 mg maximal dose
Amiodarone	IV: 5 mg/kg over 1 hour, followed by IV bolus of 2.5 mg/kg q4–6h
Digoxin	Dose is age dependent Give in 3 doses (½ TDD, ¼ TDD, ¼ TDD) Preterm infant: 10–20 μg/kg TDD Term newborn to adolescent: 30–40 μg/kg TDD oral to maximal TDD of 1–1.5 mg (IV 3/4 PO) Oral maintenance: 10 μg/kg/day q12h
Esmolol	IV Load: 200–500 μg/kg/min over 2–4 min. May increase in 50–100 μg/kg/min increments (maximum dose = 1000 μg/kg/min) Maintenance infusion: 50–200 μg/kg/min
Phenylephrine	100 μg/kg bolus 10 μg/kg/min infusion
Procainamide	5 mg/g over 5–10 min or 10–15 mg/kg over 30–45 min 20–100 μg/kg/min infusion
Propranolol	0.05–0.1 mg/kg over 5 min q6h
Verapamil	0.05–0.30 mg/kg over 3–5 min Maximal dose: 10 mg

IV, *Intravenous;* TDD, *total digitalizing dose.*

throughout early childhood, with the proportion of patients with AVNRT increasing with age.[8] The heart rate in older children is generally in the range of 160 to 280 beats/min. Older children often present with palpitations or dizziness. It is not uncommon to hear a 3- or 4-year-old complain that the heart is "beeping" too fast. These patients are generally not in SVT long enough to develop congestive heart failure, as seen in infants, because they can communicate to their caregivers that they are experiencing something abnormal or unusual. With the exception of those with WPW syndrome with rapid conduction down their accessory pathway during an atrial tachycardia, patients rarely present with syncope during SVT.

Treatment

The long-term treatment of infants with AV reciprocating tachycardia includes the use of oral preparations of the medications listed in Table 75-2, with digoxin or propranolol/β-blocker medications being the most commonly used agents. During initiation of therapy with oral antiarrhythmics in infants, the authors of this chapter monitor the patients in the hospital for at least five half-lives of the medication, allowing a steady state to be reached, watching for side effects, and educating the family about administering the medication and recognizing the tachycardia. The family can also be taught about simple vagal mechanisms to interrupt the tachycardia. When starting therapy with oral β-blockers in infants and young children, the patient must be monitored for hypoglycemia and the caregivers must know how to recognize the symptoms of hypoglycemia. The authors of this chapter ask the family to notify medical personnel if their child is not tolerating the medication or if side effects occur. It is not the authors' practice to discharge patients with heart rate monitors. Families can assess their children for recurrent SVT without resorting to continuous monitoring. Most infants are treated with oral medications for 10 to 12 months, with the dosage adjusted on the basis of weight gain. At 10 months to 1 year of age, if no recurrences of the SVT have occurred, the patient will be weaned from the medication unless the WPW pattern is still present on the ECG. Approximately one third of all patients who develop SVT in the first 3 months of life will outgrow it by 1 year of age.[12,18,19,20]

The short- and long-term medical management of children and adolescents is similar to that of infants. The exception is that catheter ablation becomes more of a therapeutic option around 4 to 5 years of age and is more commonly used after 8 years of age. Ablation can and has been performed in younger children, but the overall consensus is that it should only be used for patients 4 years of age or younger who have medically refractory arrhythmias, as the risks of the procedure are higher under 4 years of age.[21,22] See Chapter 78 for detailed information on catheter ablation in children.

Parents should be reassured regarding the generally benign nature of these arrhythmias. Parents should be taught about vagal maneuvers that can be used to interrupt the tachycardia, including applying ice or cold to the face, inducing gagging, breath holding, Valsalva maneuver, and performing a headstand or handstand. Schools should have emergency plans in place regarding whom to contact and what symptoms should prompt a call for emergency help, such as when a student faints and is unresponsive or seems to be experiencing a cardiac arrest.

Concealed Bypass Tachycardia

Concealed bypass tachycardias are tachycardias in which unidirectional conduction in an accessory pathway is present. The re-entrant circuit uses the AV node for antegrade conduction and the accessory pathway for retrograde conduction. In these pathways, the conduction is only from the ventricle to the atrium (retrograde), with no antegrade conduction. No indication of the accessory pathway is seen on a resting ECG. These accessory pathways can occur anywhere along the AV groove, either on the right side or on the left side of the heart or in the septal region. These tachycardias are seen throughout all phases of childhood. Patients can present with concealed bypass tract tachycardias in the neonatal period as well as throughout adolescence. The tachycardia may resolve spontaneously in children when it results from this mechanism in the first year, whereas it is not likely in those with presentation after 2 years of age.

Persistent Junctional Reciprocating Tachycardia

Persistent junctional reciprocating tachycardia (PJRT) is a specific form of AV re-entrant tachycardia using a concealed accessory pathway that is generally located in the posterior septal region. These pathways have long refractory periods with slow retrograde conduction, resulting in a long P-R interval with negative P waves in leads II, III, and aVF. PJRT tends to be an incessant arrhythmia and can be refractory to single-drug therapy. It is frequently confused with ectopic atrial tachycardia (especially those arising from the low right atrium) secondary to ECG findings and is resistant to treatment.

Table 75-2 Chronic Antiarrhythmic Agents for Supraventricular and Ventricular Tachycardia

ARRHYTHMIA	AGENT	DOSE (ORAL)	LEVEL
SVT	Digoxin	Dose is age dependent Give in 3 doses (½ TDD, ¼ TDD, ¼ TDD) Preterm infant: 10–20 μg/kg TDD Term newborn to adolescent: oral to maximal TDD of 1–1.5 mg (IV ¾ PO)	1–2.5 ng/mL 30–40 μg/kg TDD Oral maintenance: 10 μg/kg/day q12h
	Verapamil	2–8 mg/kg/day tid	100–300 ng/mL
VT	Phenytoin	Loading dose: 10–20 mg/kg/day q12h × 2 days Maintenance: 5–10 mg/kg/day q12h	10–20 μg/mL
	Mexiletine	5–15 mg/kg/day q8h	0.5–2.0 μg/mL
SVT or VT	Propranolol	0.5–2 mg/kg/dose q6h	50–100 μg/L
	Nadolol	0.25 mg/kg/dose q12h	0.03–0.13 μg/mL
	Atenolol	0.5–1 mg/kg/day q24h	
	Procainamide	20–100 mg/kg/day q4–6h	PA: 4–10 mg/L; NAPA = 4–8 mg/L
	Quinidine	20–60 mg/kg/day q6–8h	2–5 mg/L
	Disopyramide	5–15 mg/kg/day q6h	2–4 μg/mL
	Flecainide	50–200 mg/m^2/day or 3–6 mg/kg/day q12h	0.2–1.0 mg/L
	Amiodarone	Loading dose:10–20 mg/kg/day q12h × 7 days Maintenance: 5–10 mg/kg/dose q24h	RT_3 < 90 ng/dL
	Sotalol	2–8 mg/kg/day q12h	

IV, *Intravenous;* NAPA, N-*acetylprocainamide;* PA, *procainamide;* RT_3, *reverse* T_3*;* SVT, *supraventricular tachycardia;* TDD, *total digitalizing dose;* VT, *ventricular tachycardia.*

Wolff-Parkinson-White Syndrome

Presentation

WPW syndrome in children is very similar to that in adults. This syndrome involves an accessory pathway between the atrium and the ventricle that usually has bi-directional conduction properties. The reported incidence of WPW syndrome ranges from 1 to 4 per 1000 live births.[23] Of all patients who present with WPW syndrome in childhood, one fifth to one third will have associated cardiac abnormalities. The most common congenital lesions include Ebstein's anomaly of the tricuspid valve and L-transposition of the great arteries.[18] Patients with WPW syndrome present any time from fetal life through adolescence. The patients who present during fetal life and early infancy present with re-entrant SVT. Children and adolescents also present with re-entrant SVT but can occasionally present with atrial fibrillation (AF) with rapid conduction down the accessory pathway. Approximately 10% of children will present with an antidromic tachycardia that uses the accessory pathway as the antegrade limb, with approximately half of these patients having multiple accessory pathways.[24] A number of asymptomatic patients are noted to have the pattern of WPW syndrome on ECGs obtained for other reasons. Sudden death can be the first manifestation of WPW, leading some authors to suggest that risk stratification, including an EPS, should be done for all patients with WPW beyond infancy and early childhood.[25] The presence of a short refractory period or multiple pathways increases the risk of a subsequent life-threatening event, and catheter ablation is advised.[26] Occasionally, an infant presents with a narrow-complex tachycardia with no evidence of a WPW pattern on a baseline ECG, but pre-excitation becomes obvious when the patient is treated with a medication (e.g., digoxin) that slows AV nodal conduction.

Treatment

In the young adolescent or older child who presents with WPW syndrome, the authors of this chapter offer catheter ablation as a first-line therapeutic option. In their practice, in children with known WPW syndrome older than 6 to 8 years of age, the accessory pathway conduction or the refractory period of the accessory pathway is routinely assessed by using exercise testing, esophageal pacing, intracardiac EPS, or combinations of these methods. When given the option, many patients who are old enough to decide or their caregivers agree to an intracardiac EPS so that a catheter ablation procedure can be performed and the WPW addressed definitively. The treatment strategies for patients with WPW syndrome vary on the basis of the patient's age and symptoms at the time of presentation. The mainstay of treatment in infants and young children with WPW has been the use of antiarrhythmic medications. The authors refrain from the use of digoxin or calcium channel blockers in patients with WPW because conduction down the accessory pathway may be enhanced, along with blockade of the conduction through the AV node. This is thought to lead to an increased risk of rapid conduction of AF or premature atrial contractions through the accessory pathway. The authors recommend β-blockers as a first-line therapy unless a contraindication such as severe reactive airway disease is present. When β-blocker therapy is contraindicated or fails to control the tachycardia, the authors use other medications such as flecainide, amiodarone, or sotalol. Occasionally, a neonate with WPW syndrome presents with significant signs of cardiac decompensation and cardiogenic shock. In those circumstances, to improve ventricular function as well as to suppress the tachycardia, the authors use digoxin while the patient is still in the hospital. The patient is always converted from digoxin to another antiarrhythmic medication before being discharged.

A special consideration in the pediatric population is the patient who presents with asymptomatic WPW syndrome following an ECG obtained for some other indication such as chest pain or for a school physical examination. The authors recommend that patients older than 6 to 8 years of age have the evaluation mentioned above to assess whether they have rapid conduction down their accessory pathways. Generally, these patients are taken to the electrophysiology laboratory to measure their minimum cycle length of pre-excitation both with atrial pacing and during AF. A minimum cycle length of pre-excitation of less than 220 ms is used during AF as a marker that the patient may have a significant risk of sudden death. This is based on studies performed by Bromberg et al and Paul et al, which demonstrated that these values are helpful, though not fully predictive of cardiac arrest and syncope.[27,28] Additional studies by Pappone and Santinelli show an increased risk for sudden death with WPW with short accessory pathway effective refractory periods and with multiple pathways and recommend that catheter ablation be performed.[26,29,30]

Activity Recommendations

Activity restriction is generally not required in individuals with controlled SVT. If WPW is present, risk stratification with EPS and possible catheter ablation are recommended before participation in any activity, according to the Bethesda Guidelines.[31]

Atrioventricular Nodal Re-entrant Tachycardia

In AVNRT the re-entry circuit is the region of the AV node. AVNRT occurs more commonly in young adults and adolescents than in younger children. It is infrequently seen in patients during the neonatal period. The classic finding on an ECG is a tachycardia with very short R-P interval or no visible P wave. This is secondary to the fact that the retrograde limb of the pathway conducts very rapidly from the ventricle to the atrium. Treatment is aimed at the AV node, with the most commonly used drugs in older children being digoxin, β-blockers, and calcium channel blockers.

Primary Atrial Tachycardia

Ectopic Atrial Tachycardia

Ectopic atrial tachycardia (EAT), or *automatic atrial tachycardia*, is an arrhythmia arising from both atria with inappropriately fast atrial rates. This tachycardia represents approximately 10% of the SVT seen in the overall population.[32] The heart rates seen in EAT vary on the basis of the patient's age and catecholamine state during the tachycardia. The heart rates in automatic atrial tachycardias will be inappropriately fast for the patient's level of activity and are generally in the 130 to 250 beats/min range. In general, the rates are not as fast as those seen in re-entrant tachycardias. The pulse rate may not be reflective of the atrial rate because of variable atrial conduction through the AV node.

Tachycardias arising from foci of increased automaticity can be found in all areas of the atria. The automatic foci are more likely to be located in certain areas than in others. In the right atrium, the foci are frequently found in the right atrial appendage, and in the left atrium, they are often mapped to the orifices of the pulmonary veins.[33-35]

Presentation

EAT is not seen frequently in young infants, but the overall incidence of automatic atrial tachycardia reported by Gillette was 18% of all SVT seen in children.[36] EATs usually have a "warm-up" phase in which the heart rate will gradually increase to its maximum rate. During termination, it will "cool down" with a gradual slowing of the rate and become indistinguishable from that of sinus rhythm. This gradual increase in heart rate and termination, which is markedly different from the sudden onset and termination seen in re-entrant SVT, makes it difficult for the patient to recognize the tachycardia. Failure to perceive the arrhythmia and its incessant nature can lead to significant depression of myocardial function, which results in a tachycardia-mediated cardiomyopathy. Many patients with EAT present with signs of congestive heart failure with decreased left ventricular (LV) contractility, AV valve regurgitation, and atrial dilation.[37] If the tachycardia is not treated aggressively, the myocardial function can continue to decline, resulting in an irreversible cardiomyopathy. Resolution of the cardiomyopathy can take 6 to 12 months after the tachycardia has been terminated.

Evaluation

ECGs in patients with an EAT generally show a P-wave axis distinct from sinus rhythm. When the focus arises from the left atrium, the P wave is negative in lead I; those with the focus in the low right atrium show a negative P-wave axis in lead aVF and a positive P wave in lead I. Occasionally, the focus is in an area close to the sinus node or in the high right atrium with the P-wave axis similar to sinus tachycardia (0 to 90 degrees in the frontal plane). This can lead to a delay in diagnosis and institution of therapy, when the rhythm is thought to be sinus tachycardia. EAT, as well as other primary atrial tachycardias, can show variable degrees of AV conduction on ECG and Holter monitoring, which is often helpful in establishing the diagnosis. Figure 75-1 represents an ECG of a patient with EAT.

Holter monitoring is helpful in establishing the diagnosis and in determining the frequency of EAT. A careful review of the patient's diary of activities along with the corresponding heart rates allows the determination of inappropriate elevation of heart rate. The overall average heart rate over 24 hours provides an indication of the amount of time the patient is in SVT. Special attention should be given to the heart rate during sleep. These noninvasive evaluations may be the only way to assess the patient with EAT. Exercise testing is frequently not useful in evaluating EAT because as the sinus heart rate increases, the automatic focus is suppressed. In most cases, EAT cannot be induced in the cardiac catheterization laboratory using conventional pacing protocols but may be induced by rapid atrial pacing of the heart (if triggered automaticity is the mechanism) or by isoproterenol infusion.

A patient with EAT should have a complete echocardiographic evaluation to rule out congenital heart disease, especially the types that could lead to an abnormal sinus node (and therefore abnormal P-wave axis), such as heterotaxy syndrome. A careful assessment of ventricular function, as well as the presence of AV valve regurgitation, should be performed. This evaluation should be done as a baseline study, before medical intervention, to document the progression of the disease or the possible deterioration of ventricular function secondary to the negative inotropic properties of the medical management or to inadequate control of the tachycardia.

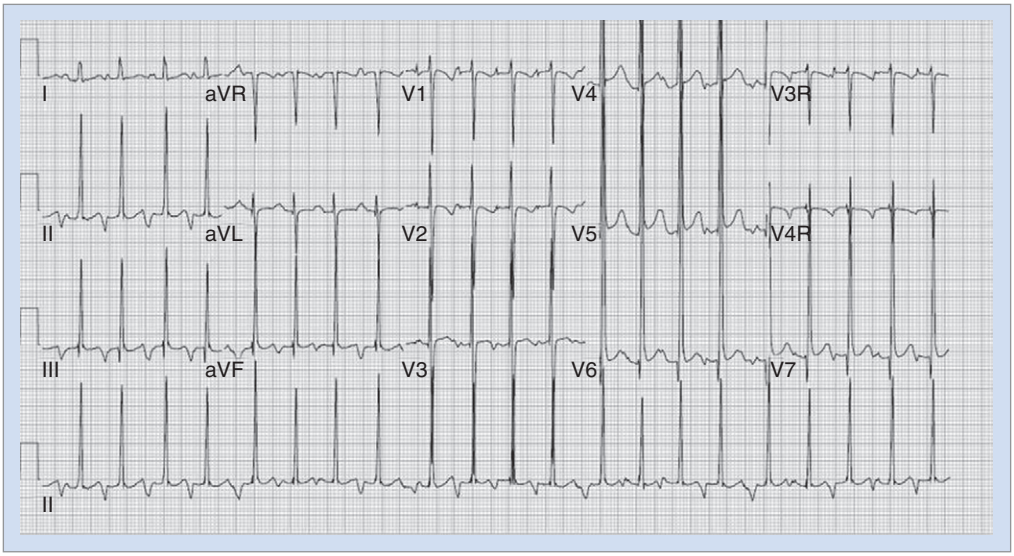

FIGURE 75-1 Electrocardiogram of ectopic atrial tachycardia in a 10-year-old. Note atrial rhythm originating from a low right atrial focus.

Treatment

The medical management of EAT may be problematic, as complete control of the tachycardia is difficult to attain. Two strategies are used in the treatment of EAT. One strategy is an attempt to slow the ventricular rate by slowing conduction through the AV node. The primary medication used in this effort is digoxin, which slows the conduction through the AV node by enhancement of vagal activity. Digoxin is a positive inotropic agent and helps improve ventricular performance. Calcium channel blockers can increase AV block but are negative inotropes and should be used with caution. Medications that have the potential to slow the tachycardia include β-blockers and class I and class III antiarrhythmics. β-Blockers have the potential to slow the tachycardia by blocking the effect of catecholamines on the ectopic focus. Class IC medications such as flecainide and propafenone have shown some success in the management of EAT.[38,39] Amiodarone and sotalol (class III) have been used with modest success by slowing conduction throughout the myocardium as well as by slowing AV conduction.[40-42] Class IA antiarrhythmic medications such as procainamide decrease automaticity, prolong refractoriness, and slow conduction velocity.[43,44] All of these medications have the potential to decrease myocardial performance and must be used with caution in patients with decreased LV function. Similarly, the side effects must be carefully monitored. The second strategy, nonpharmacologic methods of treatment, is gaining increasing interest because of the difficulty in the medical management of EAT and the sequelae of uncontrolled tachycardia. These procedures include surgical ablation procedures, which have reasonable success rates but require an open chest procedure, frequently including cardiac bypass.[45,46] Catheter ablation, using radiofrequency or cryothermal energy, has become the treatment of choice for patients with poorly controlled EAT.[35,34,47] Certain technical aspects may make catheter ablation of EAT challenging. It is difficult to induce EAT. If the arrhythmia does not occur spontaneously, it cannot be mapped and ablated in the electrophysiology laboratory. EAT is considerably catecholamine sensitive. It is not uncommon for the tachycardia to "go to sleep" when the patient does, making sedation an issue in the laboratory. See Chapter 78 for information on ablation.

Multifocal Atrial Tachycardia or Chaotic Atrial Tachycardia

Multifocal atrial tachycardia (MAT), or *chaotic atrial tachycardia* (CAT), is a primary atrial tachycardia arising from multiple areas of enhanced automaticity in the atria. By definition, the tachycardia must have at least three distinct P-wave morphologies to be considered a MAT. These tachycardias are similar to other primary atrial tachycardias in that there may be variable conduction from the atrium to the ventricle. MAT is occasionally confused with AF in that multiple P-wave morphologies and variable P-R and R-R intervals are present. The most common presentation occurs in the newborn, with a large percentage resolving spontaneously over time.[48]

Presentation and Management

MAT is similar to EAT in that patients frequently present with signs and symptoms of congestive heart failure, which are often very difficult to treat. The management strategies are similar to those used in the treatment of EAT (i.e., slowing AV conduction or suppressing the focus of the tachycardia). In the chapter authors' experience, a combination of medications is required to control the rate. This aggressive treatment strategy will often slow the underlying rhythm to the point that the patient may require the use of a pacemaker. Because of the multiple foci, catheter ablation has not been very useful. Mapping the ectopic foci is difficult because the site of activation changes constantly. Although these tachycardias are very difficult to manage, many spontaneously resolve by school age.

Yeager et al reported a 17% incidence of sudden death in patients with MAT.[49] Two of these deaths were thought to be bradycardia mediated. The bradycardia that is encountered may be related to the aggressive medical therapy required to control the rapid heart rates.

Atrial Flutter

Atrial flutter is a re-entry circuit confined to the atria. Although atrial flutter is seen fairly commonly in adults with structurally normal hearts, the majority of atrial flutter seen in the pediatric population occurs in patients with congenital heart disease. In "classic" atrial flutter, typical ECG findings include negative flutter waves in the inferior leads (II, III, and aVF) instead of P waves, with atrial rates of 250 to 450 beats/min. This type of atrial flutter usually involves the isthmus between the inferior vena cava and the tricuspid valve as part of its circuit through the atrium.

Neonates present with atrial flutter in utero, at the time of birth, or shortly thereafter. In most cases, the patient has a structurally normal heart, although congenital heart disease may be present. Atrial flutter represents 15% to 50% of all fetal SVTs, often resulting in fetal hydrops (a form of congestive heart failure).[50-52] Treatment with sotalol has been effective in 80% of fetuses with atrial flutter.[53] See Chapter 76 for additional information on fetal atrial arrhythmias.

Atrial flutter seen in the newborn presents most commonly in the first month of life, often within 2 days of birth. A report of 50 cases indicated that heart failure was present in 20% of these infants. The atrial rate range was 340 to 580 beats/min.[54] Twenty-two percent developed additional atrial or supraventricular arrhythmias during the follow-up. AF is generally converted to sinus rhythm with medication, transesophageal pacing, or direct current cardioversion. In the remainder of these patients, recurrence is rare.

Patients with congenital heart disease may develop atrial flutter before or following surgical interventions. This is most commonly seen in those lesions with extensive atrial surgery or prior postoperative atrial dilation. The multiple atrial flutter circuits seen after surgery for congenital heart defects results in slower rates and unusual flutter wave axis and morphology. These different "flutter" characteristics have led many experts to refer to this as *intra-atrial re-entry tachycardia* rather than as atrial flutter. Refer to Chapter 80 for additional information on atrial flutter in association with congenital heart disease.

Presentation

The presentation of patients with atrial flutter is variable, with symptoms ranging from episodes of syncope to no symptoms at all. Symptoms are related to the ventricular rate during the tachycardia and the underlying health of the myocardium. The heart rate is secondary to the AV conduction of the atrial impulses to the ventricles. In patients with brisk AV conduction, the atrial flutter can be conducted in a 1:1 or 2:1 ratio, depending on the flutter rate. This rapid AV conduction can lead to dizziness, syncope, or sudden death, especially in patients with poorly functioning ventricles and little myocardial reserve. If variable AV conduction is present, the patient will occasionally complain of palpitations.

Patients may present with decreased exercise tolerance or the complaint of feeling unwell. This is most likely secondary to the loss of AV synchrony and the loss of the atrial contraction.

Treatment

Before attempting to convert atrial flutter, the presence of atrial thrombi should be ruled out to prevent emboli with conversion of the rhythm. The most effective means to evaluate intracardiac thrombi is a transesophageal echocardiogram. An associated congenital heart defect such an undiagnosed atrial septal defect can be ruled out at the same time. Acute treatment of atrial flutter includes the use of IV medications, overdrive pacing, or direct-current cardioversion. Medications that have been used include those from class IA such as procainamide, class IC (propafenone), and class III (amiodarone, sotalol). Before using these medications, rapid AV nodal conduction should be blocked with medication such as digoxin to slow AV nodal conduction. Digoxin, which is the first-line medication used in the chronic treatment of atrial flutter, works by slowing the conduction through the AV node, preventing rapid ventricular rates, or preventing the initiation of atrial flutter. Frequently, digoxin alone will not control atrial flutter in these patients. Other medications such as class IA agents (procainamide, quinidine, and disopyramide) have been used. These medications have potential deleterious side effects. Each has the propensity to prolong the Q-T interval and can be proarrhythmic with the development of torsades de pointes. Disopyramide is a potent negative inotrope, which may be detrimental to the patient with marginal ventricular function. Class IC medications such as flecainide and propafenone have been used, but they have negative inotropic properties. Class III medications (amiodarone and sotalol) have had varying degrees of success in the management of patients with chronic atrial flutter. These medications have the benefit of slowing conduction through the AV node. Sotalol, which has β-blocking properties, can be a significant negative inotropic agent. As the use of any of these medications can lead to the development of significant bradycardia, patients should be monitored closely for sinus bradycardia, sinus arrest, or junctional escape rhythms. Pacemakers can be used in those patients who develop symptomatic bradycardia.

In patients with recurrent atrial flutter who are beyond early childhood, catheter ablation is an effective treatment with success in 91%.[55] See Chapter 78 for details.

Atrial Fibrillation

AF is a primary atrial tachycardia that involves a number of micro–re-entry circuits in the atrial tissue. AF is thought to arise primarily from the left atrium and the pulmonary veins. It is seen much more commonly in adults with acquired heart disease than in the pediatric population. It is a very common arrhythmia following rheumatic mitral valve disease and in patients with poor LV function. The classic finding of AF is a patient with an atrial rate of 350 to 400 beats/min with a very irregular ventricular rate, secondary to the variable conduction through the AV node.

A population of adolescents with structurally normal hearts presents with idiopathic AF. Most of these patients will not experience recurrences once the rhythm is converted, but some will have recurrences and require anticoagulation to protect them from the development of thromboembolic phenomena, along with antiarrhythmics to control the arrhythmia.

In patients with atrial flutter and AF, the ECG after conversion should be carefully evaluated to rule out ST-segment changes associated with Brugada syndrome because of the association of these arrythmias with Brugada.

AF has been studied in individuals with WPW syndrome. Inducible AF has been associated with spontaneous clinical AF in 73% and subsequent ventricular fibrillation in 27%.[29] Additional studies of subjects with WPW syndrome reported that AVRT degenerated to AF in 51% and to AF with rapid ventricular response in 34%.[56]

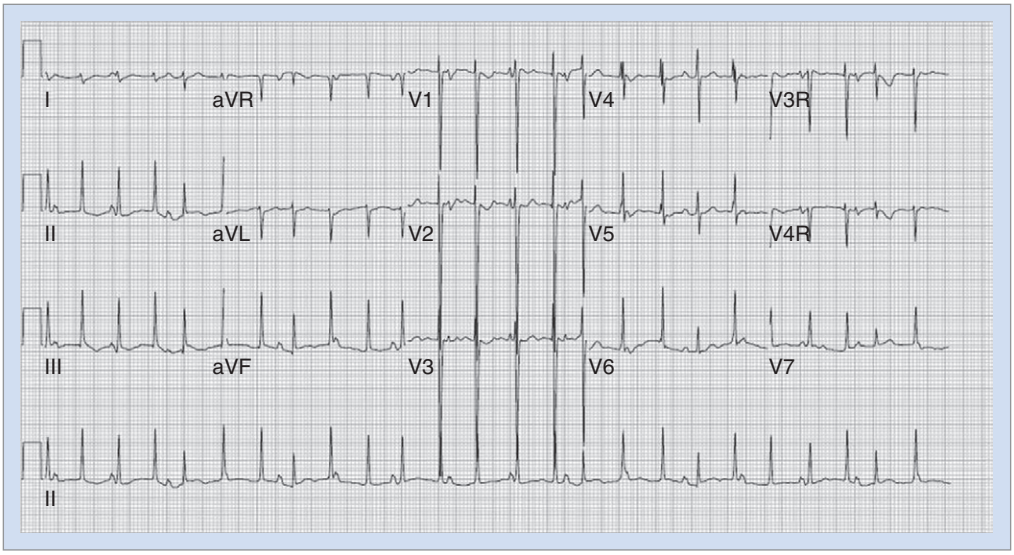

FIGURE 75-2 Electrocardiogram of junctional ectopic tachycardia. Note narrow-complex tachycardia with atrioventricular dissociation. The ventricular rate is 240 beats/min, and the atrial rate is 120 to 140 beats/min.

Junctional Ectopic Tachycardia

Junctional ectopic tachycardia (JET) is an automatic tachycardia that arises from the AV junction. Two distinct types of JET are seen in childhood. The first is a familial form that occurs in early infancy and may be associated with congenital heart defects in up to 50% of patients.[57] The second type is seen in the early postoperative period following repair of congenital heart disease (see Chapter 80).[58] In both forms, the tachycardia appears to be secondary to enhanced automaticity. In those patients who present with the familial type of JET, the heart rates will range from 180 to 240 beats/min. The ECG findings in JET show a tachycardia with a ventricular rate that is faster than the atrial rate, with a narrow QRS complex similar to that seen in the patient's normal sinus rhythm. The ECG findings of JET are shown in Figure 75-2. Rarely, patients with JET develop rate-related aberrancy, and some postoperative patients have a pre-existing bundle branch block that will lead to a wide-complex tachycardia. If the QRS is wide, the diagnosis of VT must be considered and ruled out by comparison with the QRS in normal sinus rhythm or by pacing the atrium faster than the ventricular rate to demonstrate conduction through the His-Purkinje system with persistent wide-complex QRS morphology.

JET tends to be faster and more incessant when it manifests before 6 months of age.[59] Patients with JET can present with signs and symptoms of congestive heart failure secondary to the persistently elevated heart rate. Sudden death has been reported in this patient population.[59,60]

Treatment

Treatment strategies for the familial form of JET include digoxin to slow the rhythm and provide inotropic support. Digoxin alone may not be sufficient to manage this arrhythmia, and the addition of a class IA, class IC, class II, or class III antiarrhythmic agent may be required. It has been the chapter authors' experience that a combination of these medications is required to control the tachycardia. Class III agents such as IV amiodarone are quickly added to treat individuals who have rapid rates and poor ventricular function, while carefully monitoring blood pressure and cardiac output. The amount of antiarrhythmic medication needed to control the rate to prevent decompensation of cardiac function may suppress the sinus node considerably, necessitating a pacemaker. Amiodarone appears to be the most effective agent in the largest group reported with a 60% success rate. Patients with JET have been treated with catheter ablation with a 80% to 85% success rate but with a risk of AV block, which has led to the more recent recommendations of the use of cryothermal energy (see Chapter 78).[61,62] Because of the proximity of the AV node and His bundle to the area of enhanced automaticity that is responsible for JET, catheter ablation in this setting carries a relatively high risk of causing complete heart block. It is possible that, over time, the junctional rate will slow to a point that the patient could be weaned from the chronic medications. Refer to Chapter 80 for additional information on postoperative JET.

Ventricular Arrhythmias

Ventricular arrhythmias include premature ventricular contractions (PVCs), couplets, nonsustained ventricular tachycardia (NS-VT), sustained VT, and ventricular fibrillation (VF). PVCs may be seen in 15% of normal newborns, one third of normal adolescents, and two thirds of adolescents and adults with repaired congenital heart disease.[63] PVCs may occur without identifiable cause in children and are often benign. PVCs may be associated with acute or more chronic conditions. A marked difference in prognosis for PVCs is seen between children with normal hearts and those with abnormal hearts, so investigation of children with PVCs for associated conditions should be undertaken.

Evaluation

An echocardiogram should be obtained to look at associated factors and conditions, including structural abnormalities such

as hypertrophic cardiomyopathy and abnormalities in cardiac function that might accompany myocarditis or dilated cardiomyopathy. Rarely, cardiac tumors such as rhabdomyomas are identified, or noncompaction of the ventricular myocardium is seen. The evaluation should include a standard ECG on which the QTc (corrected Q-T interval) is carefully measured manually. A 24-hour Holter monitor will determine the amount and complexity of the ectopy. In the presence of a normal heart, less than 20% ectopy usually does not interfere with cardiac function and can be monitored. More than 30% ectopy may result in ventricular dysfunction over time. Patients with this degree of ectopy may have underlying cardiac disease that was not initially diagnosed. Magnetic resonance imaging (MRI) may be indicated if *arrhythmogenic right ventricular cardiomyopathy/dysplasia* (ARVC) is suspected. In patients with more frequent PVCs, an exercise stress test should be performed. Generally, suppression of PVCs during exercise is a positive finding, whereas an increase in ventricular arrhythmia with exercise is not. Prolongation of the corrected Q-T interval, especially in the recovery phase, may be seen in patients with long QT syndrome (LQTS). An EPS would rarely be indicated, unless symptoms suggest more complex arrhythmias or the PVCs are associated with conditions that might predispose the patient to VT or VF.

Prognosis

Long-term follow-up suggests that PVCs and VT disappear over time in 37% to 65% of patients with normal hearts.[64] Sudden death is rare in children with PVCs with otherwise normal health, but a few cases have been reported in the literature. In children with abnormal hearts, PVCs may be precursors of more serious arrhythmias, especially if they are complex-multiform, coupled, or associated with VT.

Clinical Signs and Symptoms

Children with PVCs are frequently asymptomatic and unaware of their arrhythmias, especially if they are younger than 5 years. Older children may complain of a skipped or hard beat or a fluttering in their chest. Some children perceive PVCs as painful.

Treatment

PVCs do not need intervention unless they are frequent enough to interfere with cardiac output, are closely coupled, or frequently fall on the T wave in patients judged to be vulnerable to such occurrences (e.g., those with LQTS). PVCs associated with heart disease such as myocarditis, cardiomyopathy, or congenital heart disease may require further investigation and treatment, especially if they are frequent or occur in runs resulting in hemodynamic instability. Treatment for PVCs is discussed along with treatment for VT below.

Ventricular Tachycardia

As with PVCs, VT occurs in both acute and chronic situations. Ventricular arrhythmias are less common than supraventricular arrhythmias in children but appear to be occurring more frequently in recent years or are being recognized to a greater extent. An increase in VT in patients after congenital heart surgery is seen, as survival after complex surgery has increased (see Chapter 80).[65] Improved methods of surveillance and diagnosis of arrhythmias have made it possible to recognize various etiologies of VT in children, with the most common being congenital LQTS, cathecholaminergic polymorphic ventricular tachycardia (CPVT), hypertrophic and dilated cardiomyopathies, ARVC, myocarditis, abnormal foci or circuits in structurally normal hearts, and idiopathic etiologies.

Electrocardiographic Manifestations

The electrocardiographic diagnosis of VT is made most easily in the presence of a wide QRS tachycardia with AV dissociation. Many children have ventriculoatrial (VA) conduction with relatively rapid 1:1 retrograde VA conduction, and AV dissociation may not occur. VT must be differentiated from all other forms of wide QRS tachycardias, including SVT with bundle branch aberrancy; antidromic SVT using an accessory AV connection; SVT using a nodoventricular, nodofascicular, or atriofascicular connection; or atrial flutter with aberrant conduction. Although other mechanisms of wide QRS tachycardia have been described, until proven otherwise, a wide QRS tachycardia in a child must be considered to be VT. It must be remembered that the normal QRS duration in infants and young children is 40 to 80 ms, so a wide QRS in an infant might only be slightly longer than 80 ms. The rates of VT in pediatrics vary from 120 to 300 beats/min. The T-wave vector is divergent from the QRS vector, but opposite polarity will not occur in every lead. Left bundle branch block (LBBB) is the most common morphology, but right bundle branch block (RBBB) or alternating RBBB and LBBB may occur. The presence of PVCs during sinus rhythm with the same configuration as VT is a suggestive sign of the ventricular origin of the arrhythmia. AV dissociation is suggestive of VT, but 1:1 VA conduction is common, especially in young children. Fusion beats are commonly noted at the onset or termination of the VT, which may be sustained (>30 consecutive complexes) or nonsustained (3 to 30 consecutive complexes).

Further differentiation is made according to the morphology, with VT being described as monomorphic or polymorphic. Two types of polymorphic VT have been described, torsades de pointes and bi-directional VT (Figure 75-3). Torsades de pointes is associated with LQTS and so named because of its twisting, undulating nature. Bi-directional VT, with beat-to-beat variation in the QRS axis on ECG, has been associated with digoxin toxicity, familial hyperkalemic paralysis, or CPVT.[66]

Etiology of Ventricular Tachycardia

Causes of acute VT not associated with congenital heart defects are shown in Box 75-1. These most common causes include metabolic and electrolyte abnormalities; infectious processes such as myocarditis, which may cause LV microaneurysms[67]; human immunodeficiency virus (HIV) infections[68]; blunt cardiac trauma, including commotio cordis[69-71]; coronary ischemia, especially in association with Kawasaki disease; and drugs such as caffeine, inhalation anesthetics, and recreational drugs, including amphetamines and cocaine.

The causes of chronic or recurrent VT include congenital heart disease, both preoperatively and postoperatively; acquired heart diseases; metabolic disorders, including disorders of fatty acid metabolism[72]; neuromuscular disorders such as Duchenne's muscular dystrophy; cardiomyopathies, including ARVC; hypertrophic cardiomyopathy (HCM); tumors and infiltrates; left

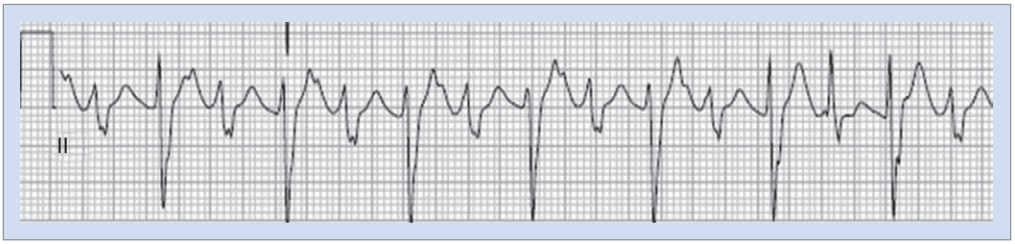

FIGURE 75-3 Electrocardiogram of bi-directional ventricular tachycardia. Note the two distinctly different wide QRS morphologies.

Box 75-1 Etiology of Acute Ventricular Tachycardia

DRUGS/TOXINS
General anesthetics
Antiarrhythmics
Caffeine
Nicotine
Sympathomimetics/catecholamine infusions
Psychotropic agents: tricyclic antidepressants/phenothiazines
Cocaine
Digoxin toxicity

METABOLIC
Hypoxia
Acidosis
Hypoglycemia
Hypocalcemia

TRAUMA
Blunt: Cardiac contusion
Thoracic surgery
Cardiac catheters

MYOCARDIAL ISCHEMIA
Abnormal coronaries/infarction
Kawasaki disease

HYPERLIPIDEMIA

INFECTIOUS
Myocarditis
Pericarditis
Rheumatic fever

IDIOPATHIC

ventricular noncompaction (LVNC), VT originating in both the right ventricle and the left ventricle, associated with structurally normal hearts; VT associated with LQTS; and other primary electrophysiological abnormalities such as Brugada syndrome and CPVT. A detailed list is provided in Table 75-3. While failure to identify a specific cause for VT in children is not unusual, persistence in evaluations often identifies the pathology in patients initially thought to have an unidentifiable etiology.[73-77]

Mechanism of Ventricular Tachycardia

VT has been reported to result from re-entry, triggered automaticity, and abnormal automaticity. An EPS is helpful in differentiating these mechanisms. The mechanisms of VT in children include re-entry in 60% and abnormal automaticity in 40%.[78] Re-entry is most often the mechanism in patients with congenital heart disease after surgical repairs, related to re-entry circuits that

Table 75-3 Etiology of Chronic Ventricular Tachycardia

Congenital Heart Disease	Ebstein anomaly Tetralogy of Fallot, absent PV leaflets Aortic valve disease, AI/AS Mitral valve prolapse Hypertrophic cardiomyopathy/IHSS Coronary artery anomalies Eisenmenger syndrome, pulmonary hypertension
Postoperative CHD	Tetralogy of Fallot, DORV Ventricular septal defects AV canal defects Aortic valve disease, stenosis, and insufficiency Single ventricle complexes status post–Fontan repair D-TGA status post–intra-atrial repair
Acquired heart disease	Rheumatic heart disease Lyme disease Myocarditis Kawasaki disease
Cardiomyopathies	Hypertrophic RV cardiomyopathy/dysplasia Dilated cardiomyopathy Postviral Connective tissue disease: SLE Marfan syndrome Muscular dystrophy, Friedrich ataxia
Tumors and infiltrates	Rhabdomyoma Hemosiderosis: Thalassemia, sickle cell disease Oncocytic cardiomyopathy Leukemia
Idiopathic/structurally normal heart	RV outflow tract VT LV septal VT/fascicular tachycardia
Primary arrhythmias	LQTS Congenital complete heart block Familial VT
Other	Myocardial ischemia/infarction

AI, Aortic insufficiency; AS, *aortic stenosis;* AV, *atrioventricular;* CHD, *congenital heart disease;* DORV, *double outlet left ventricle;* D-TGA, *D-transposition of the great arteries;* IHSS, *idiopathic hypertrophic subaortic stenosis;* LQTS, *long QT syndrome;* LV, *left ventricular;* PV, *pulmonary valve;* RV, *right ventricular;* SLE, *systemic lupus erythematosus;* VT, *ventricular tachycardia.*

develop around suture lines and ventriculotomy scars. Triggered automaticity is thought to be the mechanism in CPVT.

Clinical Correlations

Presentation of patients with VT varies and depends, to a large extent, on the underlying etiology and clinical status with regard to myocardial function and structure. In one study of patients with VT with structurally normal hearts, presentation was most common in infancy (48%), with 58% being younger than 6 months.[73] Associated findings were heart failure in 30%, hemodynamic compromise or collapse in 23%, and in utero diagnosis in 18%. Diagnosis was incidental in 30%. No specific etiology was found in 50%, with cardiomyopathy or myocarditis (20%) being the most common etiology identified.

Clinical Signs and Symptoms

The type and degree of symptoms appear to be rate related, with symptoms being most common in patients with rates greater than 150 beats/min. Except for those patients with underlying cardiac disease or ventricular dysfunction, patients with VT have symptoms similar to those of SVT, with the severity of symptoms relating more to the rate than to the mechanism of tachycardia. Symptoms include dyspnea, shortness of breath, chest or abdominal pain, palpitations, dizziness, syncope, and cardiac arrest or sudden death. Older children may exhibit exercise intolerance or easy fatigability. Infants may feed poorly and be irritable or lethargic. Patients with VT and heart disease usually have symptoms, whereas only one third with normal hearts and VT have symptoms. The type of symptom relates to both the tachycardia rate and the underlying state of the myocardium. Sudden death occurs most commonly in the presence of an abnormal heart but has also been reported in patients with normal hearts.[74,79,80] Children younger than 5 years or those in incessant tachycardia may not have a perception of a fast heart rate or be able to accurately express what they are feeling. Signs include palpitations, sensation of a rapid heart rate, tachypnea, or hypotension with accompanying pallor and diaphoresis as well as signs of congestive heart failure. Although VT usually has a sudden onset, it may occur during exercise and be difficult to perceive. It may gradually "warm up" or increase in rate.

Specific Associated Conditions

Accelerated Ventricular Rhythm

An accelerated ventricular rhythm is a rhythm originating from the ventricle with all the characteristics of VT but with a rate that is only slightly more rapid than the underlying sinus rhythm, usually less than 120 beats/min. It is often seen in children with normal hearts. This arrhythmia is not uncommon in neonates and has been reported in two patients with fetal tachycardia. It is self-limited, resolving in 2 weeks to 3 months after birth.[81] These early ventricular arrhythmias are probably related to developmental factors associated with the autonomic nervous system. In older children, these arrhythmias may be related to unidentified viral infections with myocarditis that affects only the conduction system. This arrhythmia is seen around puberty and probably relates to autonomic and hormonally mediated factors. In addition, accelerated ventricular rhythms have been reported in association with metabolic abnormalities, medication, ARVC, and myocardial infarction.[82] In pediatric patients, this arrhythmia is generally thought to be benign, even in the occasional patient who has congenital heart disease.[82,83] It has been suggested that those rhythm disturbances arising from the right ventricular outflow tract (RVOT) may be a marker for future development of ARVC in some patients.[82-84]

Idiopathic Ventricular Tachycardia

VT in the absence of underlying heart or known genetic disease is unusual in childhood. Of that population, 27% present in infancy, with the mean age of presentation being 5 years.[85] Severe heart failure was uncommon but did occur in 12%, with 36% having some evidence of LV dysfunction. Resolution can be expected in two thirds of patients over time. The most favorable prognosis is in patients with right ventricular tachycardia and in infants.

Evaluation and Treatment

Evaluation should include ECG, 24-hour Holter monitoring, and exercise stress testing in patients older than 5 years of age, who can cooperate during the procedures. These patients generally require no therapy but should be monitored because an occasional patient will have acceleration of their VT to a much higher rate and develop symptoms. Treatment of this arrhythmia and restriction of activity is not required in the majority of patients, especially those with normal hearts.

Arrhythmogenic Right Ventricular Cardiomyopathy

An unusual cause of VT known as *arrhythmogenic right ventricular cardiomyopathy* or *arrhythmogenic right ventricular dysplasia* (ARVD) was first described in 1978.[86] The VT has a LBBB pattern in most instances. One pediatric series reported ARVC in 30% of its patients with VT and an apparently normal heart, although it is much less common in most other pediatric series. ARVC is a familial form of right ventricular (RV) cardiomyopathy associated with sudden death.[87] It has an autosomal dominant genetic pattern with variable penetrance and variable expression. The pathologic lesion involves massive replacement of the RV wall by fibrous tissue, fatty tissue, or both. Focal myocardial changes may be present and include necrosis, degeneration, or hypertrophy and chronic inflammatory infiltrates. This is a progressive process that starts with the epicardium or midmyocardium and extends to become transmural. Although many cases are familial, sporadic cases have been reported as well. ARVC has not been commonly reported in young patients, as it usually presents in the second to fourth decade, with a male predominance, but should be considered in previously healthy children or adolescents who present with VT.

Evaluation

Patients who are suspected of having this condition should have an ECG, echocardiogram, and MRI. Because of the localized nature of this condition, echocardiography may not be diagnostic. MRI may be more helpful by demonstrating thinning of the RV myocardium replaced by fatty tissue or showing localized areas of hypokinesis in the infundibulum, free wall, or RV apex, accompanied by RV dilation and decreased contractility. LV free wall and septal involvement in this process has been noted.[88] Although the above findings have been helpful in making the diagnosis in adults, standard MRI criteria applied to 81 pediatric patients suspected of having ARVD provided a low diagnostic yield.[89] Other potential

diagnostic modalities include exercise testing, contrast ventriculography, signal-averaged ECG, and single photon emission computed tomography (SPECT) analysis.[90-96] Research on genetic identification is still under way. Immunohistochemical analysis of myocardial biopsies has demonstrated reduced levels of plakoglobin at intercalated discs in patients with ARVC and not in other forms of heart-muscle disease.[97] This may prove helpful in establishing a diagnosis of ARVC. Currently, no single gold standard exists, and the best strategy consists of combining information from several diagnostic tests.[89] Children in affected families should be evaluated by using ECGs, 24-hour Holter monitors, echocardiograms, and MRIs.[77,98]

Treatment and Follow-Up

Variable medical therapies, including β-blockers and sotalol, have been suggested for patients with frequent, symptomatic, or potentially life-threatening ventricular arrhythmias. Automatic implantable cardioverter-defibrillators (ICDs) have been used and can be life saving in these patients.[99,100] Extensive surgical procedures, including a complete electrical disconnection of the RV free wall, have been reported.[101] The prognosis and clinical course reported in these patients have been quite variable. Continued surveillance with periodic Holter monitoring and exercise stress testing are important in the follow-up of this patient group, as the incidence of serious arrhythmias increases with age.

Long QT Syndrome

Congenital LQTS is an inherited condition characterized by syncope, seizures, and sudden death, associated in most individuals with a prolongation of the Q-T interval on the ECG.[102] An example of the ECG in LQTS is shown in Figure 75-4. In addition to the prolongation of the QTc, these patients often have bizarre or notched T-wave morphology with prominent U waves or T-wave alternans. They develop life-threatening VT, known as *torsades de pointes*, or VF. This syndrome includes Jervell and Lange-Nielson syndrome (JLNS), described in 1957, associated with congenital deafness caused by an autosomal recessive inheritance and Romano-Ward syndrome, described in 1963 and 1964, demonstrating autosomal dominant inheritance, without hearing deficit.[103-105]

The prevalence of the disorder is estimated to be 1:2000 to 1:10,000.[106-108] This condition has variable expression and penetrance within families, leading to a spectrum of severely affected members with repeated cardiac events and arrest to those with the identical mutation but who are totally asymptomatic.[109]

In 1993, statistics from a group of 287 children were compiled from a number of medical centers.[110] The initial presentation was cardiac arrest (9%), syncope (26%), seizures (10%), presyncope, or palpitations (6%). Sixty-seven percent with symptoms had exercise-related symptoms. Thirty-nine percent were identified because of family history or the identification of other family members with the syndrome. Thirty-nine percent of the patients were asymptomatic at presentation; of these, 4% experienced sudden death compared with 8% overall. The strongest predictors of sudden death were QTc longer than 0.60 seconds and noncompliance with taking recommended medication.

Bradycardia is commonly seen in these patients, and some may develop or present with second-degree AV block. This is more common in neonates who may have second-degree or third-degree AV block, but it may be seen in older children, especially during exercise.[111]

One series reported sudden death occurring in 73% without treatment, and others have reported sudden death in 21% of symptomatic patients in the first year after presenting with syncope.[112,113]

Diagnosis and Evaluation

The diagnosis of this syndrome is made from a variety of criteria. Schwartz et al provided some criteria and suggested a scale for identifying these patients by categorizing them into high-risk, intermediate-risk, or low-risk groups.[114] All criteria involve measurement of the Q-T interval and taking a careful history of syncope, seizures, and arrhythmias in the patients and their

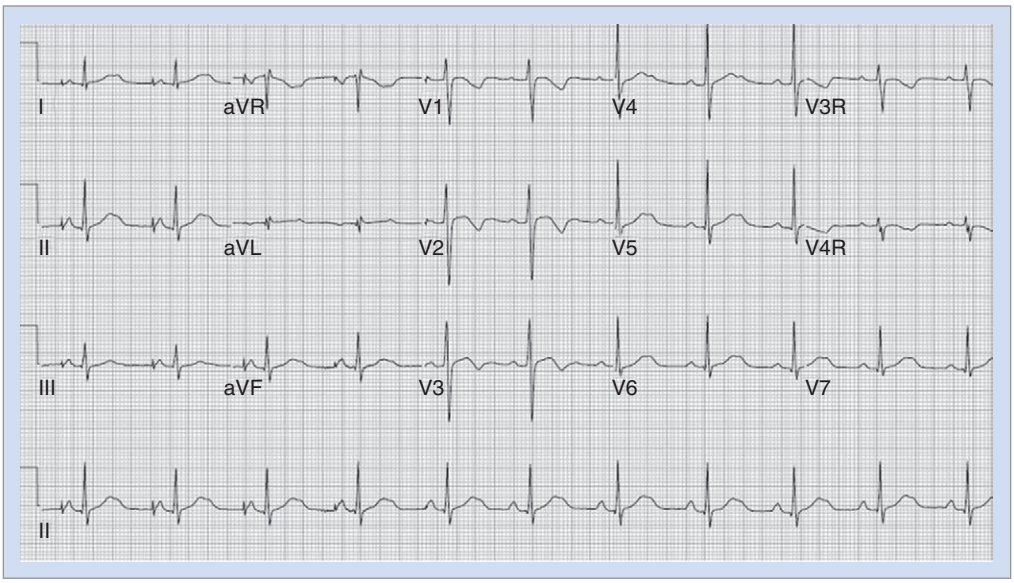

FIGURE 75-4 Electrocardiogram of patient with long QT syndrome. The QTc measures 490 ms. Note the long, notched T waves.

families. Commonly, a complete history may reveal syncope or seizures associated with exercise or emotional stress or a family history of sudden death in young relatives, including unexplained automobile accidents or drowning.

Additional studies such as 24-hour monitoring and exercise stress testing may provide helpful information in the form of significantly prolonged Q-T intervals, especially during recovery from exercise, or the occurrence of polymorphic ventricular arrhythmias during or after exercise. The use of provocative tests such as isoproterenol or epinephrine infusions can identify some subclinical cases, especially LQT1 with a prolongation or paradoxical response in these individuals.[115,116]

A high level of suspicion is needed to diagnose LQTS. Any patient who presents with syncope during or immediately after exercise or with VT, especially of the polymorphic or torsades de pointes type, or in association with physical or emotional stress should have an ECG, with determination of QTc intervals. Evaluation of a resting ECG may not be sufficient as more than 10% to 15% of gene carriers may have normal ECGs.[117] A more worrisome study by Priori showed an even lower penetrance of the gene in Italian families, with probands initially thought to have sporadic occurrences of LQTS. Genetic studies revealed multiple family members who were genetic carriers but with normal ECGs.[118] ECGs should be obtained in all family members of identified individuals with LQTS. When genetic mutations are identified, this can be used to screen family members more specifically.

Since a variety of drugs can prolong the QTc, a careful history of medication use should be obtained during the evaluation. Those with prolonged QTc with medication often are subclinical LQT cases or have single nucleotide polymorphisms for LQTS genes.

Clinical Implications of Molecular Genetics

The molecular genetic understanding of LQTS began in 1991.[119] Many other genetic discoveries have resulted in the current and rapidly expanding knowledge of the etiology of LQTS.[120-125] Genetic studies have identified repeated mutations in at least 12 genes that encode for proteins that modulate the ion channels, primarily potassium or sodium channels, causing LQTS by altering cardiac repolarization and increasing the risk for ventricular arrhythmias. Mutations in a few other genes have been found in only isolated individuals. It is estimated that 25% of the gene mutations have not yet been identified. The mutations are primarily in the coding regions of the genes. These mutations result in a decrease in repolarizing potassium currents prolonging repolarization or in late entry of sodium or calcium into the cardiac cell prolonging depolarization or repolarization. Both of these mechanisms prolong the Q-T interval. These genes that involve sodium and potassium currents include *KCNQ1*(I_{Ks}), *KCNH2*(I_{Kr}), *minK*, and *MiRP1*, and *SCN5A* and represent LOT1, 2, 5, 6, and 3, respectively.[122-127] Syndromic LQT genetic disorders include LQT7, otherwise known as *Andersen-Tawil syndrome*, associated with skeletal malformations and periodic paralysis, caused by mutations in the *KCNJ2* gene with reduced Kir2.1 currents and LQT8, or *Timothy syndrome*, associated with syndactyly, and mutations in the *CACNA1C* gene with increase in the $Ca_v1.2$ current. LQT9 is associated with mutations in the *cavelolin-3* gene, and LQT10 is caused by a mutation in the *SCN4B* gene, both with late increases in sodium currents. Other mutations have been found in the *ankyrin-B* gene causing malfunction in a cytoskeletal membrane adapter (LQT4). LQT11 is associated with mutations in *AKAP9* and LQT12 with mutations in *SNTA1.* In addition to these genes that affect ionic channels altering the repolarization phase of the cardiac action potential and resulting in the development of ventricular arrhythmias, an imbalance or oversensitivity of the myocardium to sympathetic stimulation appears to play a role in the development of ventricular arrhythmias. The trigger for arrhythmia in the LQTS is believed to be spontaneous secondary depolarizations that arise during or just following the prolonged plateau phase of action potentials, early after-depolarizations (EADs). Increased sympathetic tone may increase EADs, with these spontaneous repolarizations triggering a sustained arrhythmia. The implications of the location of the mutations, coding type, and the resulting biophysical malfunction has been well described for LQT1 mutations.[128] Mutations located in the transmembrane portion of the ion channel protein and the degree of channel malfunction independently affect the clinical course of the individual.

Specific Genetic Defects

KvLQT1 *(LQT1) and* MinK *(LQT5)*

The *KCNQ1* gene encodes the voltage-gated potassium channel α-subunits.[126,129] *MinK (KCNE1)* encodes a much smaller potassium channel β-subunit. *MinK* subunits assemble with *KCNQ1* subunits to form cardiac I_{Ks} channels.[124,130,131] Abnormalities of either or both of these genes inhibit channel function and prolong repolarization by affecting I_{Ks} by a greater than 50% reduction in channel function, which is a dominant-negative effect. Other mutations may reduce repolarizing potassium currents by causing trafficking defects and interfering with the transport of the subunits to the cell membrane, resulting in an up to 50% reduction in channel function (haplo-insufficiency). Current evidence suggests that more than 40% of affected LQTS families have *KCNQ1* mutation.[132] Approximately 5% of mutations identified to date have involved *minK*.[132,133] It has been reported that a homozygous mutation of *KCNQ1* or *minK* causes JLNS.[134,135] Both *KCNQ1* and *minK* are expressed in the inner ear. Homozygous mutations of *KCNQ1* or *minK* have no functional I_{Ks} channels. This leads to inadequate endolymph production and deterioration of the organ of Corti with neural deafness.[136]

KCNH2 *(LQT2) and* MiRP1 *(LQT6)*

In 1994, Jiang et al identified the human ether-a-go-go-related (*HERG*) gene, now referred to as *KCNH2*.[127] These mutations represent 45% of the total number of LQTS mutations found to date. This gene encodes for the α-subunits that form the cardiac potassium channel delayed rectifier I_{Kr} channel, the second of two channels responsible for the termination of the plateau phase of the action potential.[137,138] These mutations result in decreased outward potassium current, preventing termination of the plateau phase of the action potential. *KCNH2* subunits assemble with the *MiRP1* (*minK*-related protein1), also known as *KCNE2*, to form cardiac I_{Kr} channels.[125] *MiRP1* mutations represent 2% of the identified LQTS mutations. Multiple drugs are known to prolong the Q-T interval and potentially induce arrhythmias. The structure of *KCNH2* channels appears to be predisposed to blockage by multiple drugs, making this the channel most commonly blocked by drugs.[139]

SCN5A *(LQT3)*

Jiang et al reported an additional group of LQTS families with mutations in the human cardiac sodium channel gene that encodes the subunit of sodium channel responsible for initiating cardiac action potentials.[122,140,141] Gain of function mutations,

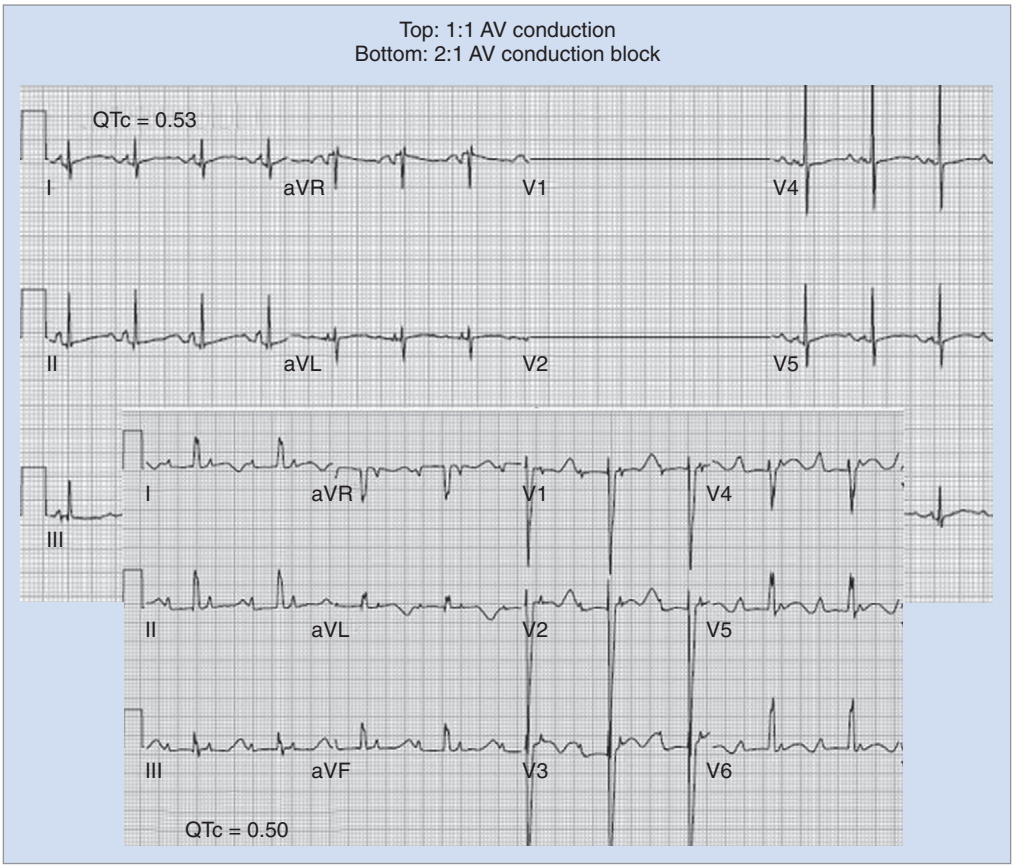

FIGURE 75-5 Electrocardiogram of patient with long QT syndrome and paroxysmal 2:1 atrioventricular *(AV)* block. Note the prolonged QTc of 0.50 seconds.

especially in the inactivation gate between domains III and IV of the sodium channel, have been reported with abnormal gain of function, resulting in continued inward sodium current prolonging the action potential and predisposing to ventricular arrhythmias.[133,142]

Special Considerations in Long QT Syndrome

Vincent's study in 1992 indicated that some patients may be genetic carriers for this syndrome without significant prolongation of the Q-T interval.[117] Some noncarriers (15%) have abnormal prolongation of the Q-T interval above 0.44 seconds. A QTc of more than 0.47 seconds had a 100% positive predictive value in gene carriers. Above 0.47 seconds, no false-positives were seen in this study. Only 6% of gene carriers had a QTc of less than 0.44 seconds.[117] These genetic tests may make it possible to identify more specifically many patients with LQTS. Priori identified families with only a 25% penetrance, and 33% of family members considered to be unaffected on clinical grounds were found to be gene carriers.[118]

Another interesting association that has come from the International Registry relates to the association of asthma and LQTS. The occurrence of asthma in LQTS patients increases with QTc duration. Asthma comorbidity in LQTS patients is associated with an increased risk of cardiac events. This risk is diminished after initiation of β-blocker therapy.[144]

A special group of LQTS patients are newborns. Studies have suggested that sinus bradycardia is more likely associated with LQT1 and 2:1 AV block with LQT2 or LQT3.[145,146] 2:1 AV block has been associated with a high mortality rate,[145,147] but more recent studies show this can be moderated.[147a] An example of 2:1 AV block in association with LQTS is shown in Figure 75-5.

Jervell Lange-Nielsen Syndrome

JLNS is the general descriptor applied to LQTS associated with a hearing deficit. It is caused by homozygous or compound heterozygous mutations in the *KCNQ1* or *KCNE1* genes, resulting in a reduced I_K current and associated sensorineural deafness.[134,148] Most (85% to 93%) of these patients experience cardiac events, and 50% are symptomatic by age 3 years.[149] Events are generally triggered by emotions or exercise. Many have events despite β-blocker therapy, and early consideration of defibrillators has been advised.

Gene-Specific Clinical Correlations

ST-T wave changes have been associated with specific genetic mutations, as shown in Figure 75-6. Because of an overlap, the specificity of this finding is limited.[150,151] The influence of genotype on clinical course is being elucidated.[150] The frequency of cardiac events is higher among subjects with LQT1 (63%) or LQT2 (46%) than among patients with LQT3 (18%). The likelihood of dying during a cardiac event is higher among patients with LQT3 (20%)

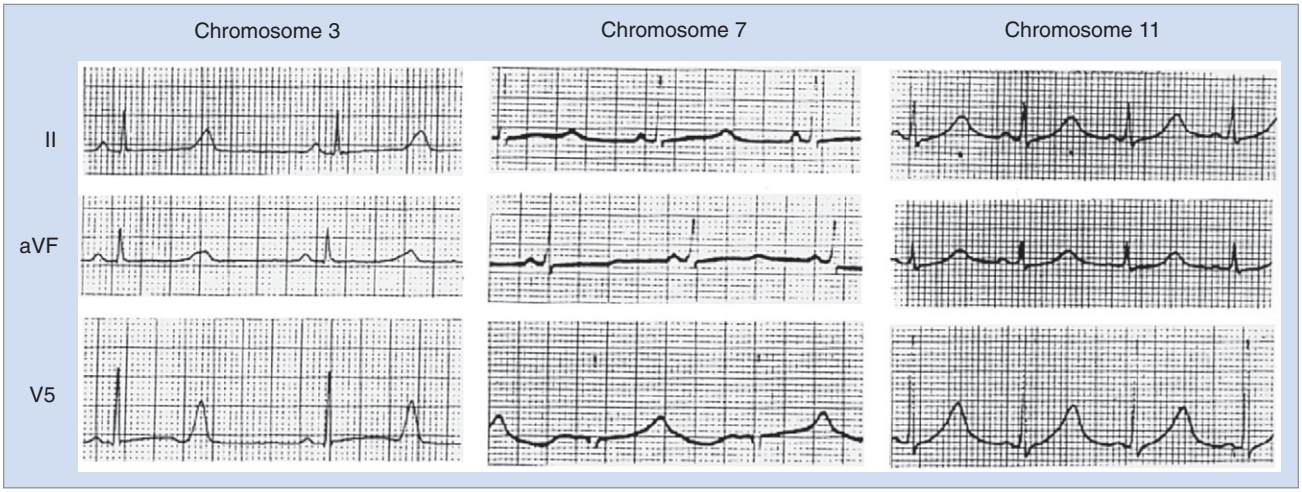

FIGURE 75-6 Electrocardiographic recordings from leads II, aVF, and V5 in three patients with long QT syndrome, linked to chromosomes 3, 7, and 11. The patient with chromosome 3 linkage has late-onset T waves with a QTc of 570 ms. The patient with chromosome 7 linkage has low-amplitude T waves and a QTc of 583 ms. The patient with chromosome 11 linkage has early-onset broad T waves with a QTc of 573 ms. *(From Moss AJ, Zareba W, Benhorin J, et al: ECG-T wave patterns in genetically distinct forms of the hereditary long QT syndrome,* Circulation *92:2931, 1995.)*

than among patients with LQT1 or LQT2 (4%). Cardiac events in patients with LQT1 occur frequently during exercise (62%), especially swimming.[152-154] Only 3% occurred during sleep. Among patients with LQT1, around 53% experience the first event by age 15 years, with 86% becoming symptomatic by 20 years of age. The probability of a cardiac event increases during adolescence in all three of the major genotypes (LQT1, LQT2, and LQT3), with the risk being higher in males before puberty and higher in females after puberty. In those with LQT2, symptoms are most commonly triggered by emotions (43%) or auditory stimuli (26%). While some events do occur with exercise (37%), more occur during rest (49%) or sleep (29%). The average age of first manifestation of symptoms is 16 years. Pregnancy increases the risk, particularly in women with LQT2, for up to 9 months after delivery. In those with LQT3, symptoms are less commonly triggered by exercise (13%) and occur primarily at rest (39%). The median age of presentation is 16 years. The percentage of patients who are free of recurrence with β-blocker therapy is higher, and the death rate is lower among patients with LQT1 (81% and 4%, respectively) than among those with LQT2 (59% and 4%) and LQT3 (50% and 17%).[152] Patients with LQT3 have more cardiac events at rest or during sleep, whereas patients with LQT2 experience more events during exercise or stress. LQT2 events are more likely to be stimulated by loud noises.[155]

Risk Factors for Long QT Syndrome

High-risk factors for patients with LQTS include a QTc greater than 0.50 seconds to greater than 0.53 seconds, aborted cardiac arrest, torsades de pointes or complex ventricular arrhythmia, recent syncope (>2 times in past 2 years), male gender and ages 10 to 12 years, and noncompliance with prescribed LQTS medications. While younger males with LQT1 have the highest risk, no gender difference exists between young individuals with LQT2 and those with LQT3. In adulthood, a higher risk of cardiac events is present in females than in males with LQT1 and LQT2. The risks of lethal events are highest in males with LQT3 (19% risk) and females with LQT3 (18% risk), higher in males with LQT1 and LQT2 (5% and 6% risk, respectively) than in females with LQT1 and LQT2 (2% risk for either). Additionally, risks are higher in individuals with a QTc greater than 0.53 seconds, in individuals with recent syncope (within 2 years), and in individuals with frequent syncope (>2 times).[152,156] The location of the mutation in LQT2 imparts higher risk to those with pore region mutations, whereas the site of the mutation appears to have less impact in LQT1.[157] A study evaluating the risks of aborted cardiac arrest and sudden cardiac death in children found that a QTc greater than 0.50 seconds and syncope in males and syncope in females conferred the greatest risks.[157]

The probability of a first cardiac event before the age of 40 years and before therapy can be classified as high-risk, intermediate-risk, and low-risk by the characteristics illustrated in Figure 75-7.[158] In LQT1 and LQT2, the risk of dying during a cardiac event is 4%, with the risk of death being 4% overall. In LQT3, the risk of dying is 17%, with the risk of dying during an event being 20%.

Sudden Infant Death Syndrome

Schwartz reported on ECGs on 34,442 Italian babies on days 3 or 4 of life; 24 subsequently died because of sudden infant death syndrome (SIDS) and 12 had prolongation of the Q-T interval greater than 0.44 seconds.[159] Additional reports have confirmed *SCNA5* and *HERG* mutations in a few babies who died from SIDS.[133-135] Postmortem molecular studies in infants and children with autopsy-negative sudden unexplained death found that 10% to 30% had genetic mutations for one of the electrical conditions associated with SCA.[160]

Evaluation and Diagnosis of LQTS

Diagnosis is made by taking a careful history of the affected individual's episodes as well as a complete family history to identify sudden unexplained death, syncopal episodes in family members, unusual seizure disorders, or hearing deficits. All patients suspected of LQTS should have a standard ECG with careful QTc

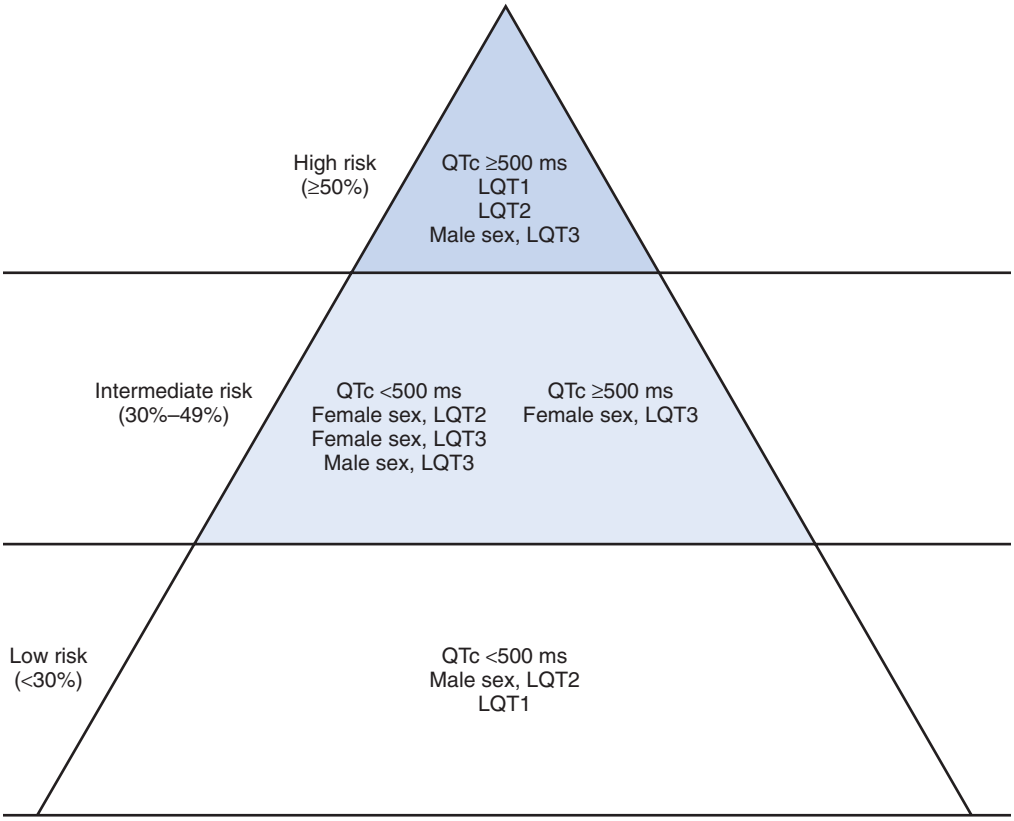

FIGURE 75-7 Risk stratification by gender, genotype and QTc. *(From Prior SG, Schwartz PJ, Napolitano C, et al: Risk stratification in the long-QT syndrome,* N Engl J Med *348:1866–1873, 2003.)*

measurement, 24-hour Holter monitoring, and exercise stress testing, as appropriate for age. The chapter authors do not routinely use other provocative testing such as isoproterenol or epinephrine infusions, reserving it instead for isolated cases with a high index of suspicion but negative testing otherwise.

Careful evaluation of the ECG and 24-hour Holter monitoring is essential. The QTc is measured manually by using Bazett's formula.[161] The longest Q-T interval in any lead is divided by the square root of the preceding R-R interval. The measurement should be made manually and calculated, as computerized values are frequently incorrect. The authors consider a value greater than 0.46 seconds in any lead in children as abnormal on the resting or exercise ECG. Although a number of methods have been proposed for calculating the QTc in the presence of sinus arrhythmia, the authors make every attempt to record an ECG not in sinus arrhythmia.[162] In addition to the Q-T interval, each lead of a standard 12- or 15-lead ECG should be evaluated for abnormal T-wave morphology and ST morphology. As different filters are used on the Holter monitor, the authors consider a value greater than 0.50 seconds as abnormal. In addition to Q-T interval prolongation, the Holter monitor may be helpful in illustrating T-wave abnormalities, R-on-T phenomenon, short runs of nonsustained VT, sustained VT, or torsades de pointes.

Provocative testing should include exercise stress testing in children who are able to exercise. Exercise will generally obliterate sinus arrhythmia; a strip can be obtained and a reasonable QTc calculation made. The recovery period with heart rates around 120 to 130 beats/min seems to demonstrate the greatest degree of QTc prolongation in many patients. Exercise may uncover abnormal T waves, polymorphic PVCs, or VT. If suspicion for LQTS is high and other testing has not been definitive, isoproterenol or epinephrine infusion may help identify LQTS. During these provocative tests, T-wave abnormalities may occur in addition to QTc prolongation or the development of ventricular arrhythmias.[157]

Efforts to identify patients at high risk for syncope and sudden death continue. High-risk ECG markers have included a QTc greater than 0.53 seconds, T-wave alternans, and QTc dispersion.[163,164] Dispersion of the Q-T interval has been correlated with high risk in patients with LQTS.[163,165,166] QT dispersion, which indicates heterogeneity of repolarization, could predispose to the development of torsades de pointes. In Priori's study, patients not responding to β-blockers had a significantly higher dispersion of repolarization than did responders.[163] In Shah's study, patients with LQTS at high risk for developing critical ventricular arrhythmias had a QT or JT dispersion more than 55 ms.[166] Little information is available on microvolt T-wave alternans in patients with LQTS, although visible T-wave alternans is known to be a high-risk factor.

Treatment

Emergent treatment of these patients includes lidocaine and cardioversion. Magnesium may be used to treat torsades de pointes.[167,168] Intravenous propranolol and phenytoin have also been successfully used in these patients.[169] Class I agents, which are known to prolong the Q-T interval in normal patients, should be avoided in patients with LQTS. This is felt to be related to QTc

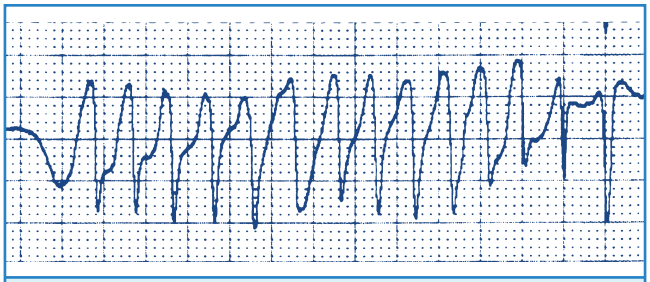

FIGURE 75-8 Electrocardiogram rhythm strip of torsades des pointes from a patient with long QT syndrome. This ventricular rhythm is rapid, irregular, and polymorphic.

prolongation with associated bradycardia, ventricular arrhythmias, or both. Temporary pacing and removal of the offending agent are effective measures in this situation. Sudden death is secondary to the ventricular arrhythmias (torsades de pointes) of the type shown in Figure 75-8, which frequently degenerate to VF. The standard long-term treatment in this condition is the use of β-blockers. Those most commonly used are propranolol and nadolol. Some authors have suggested long-acting propranolol or atenolol. A concern about once-daily dosing relates to the lowest levels of the medication being present in the early morning hours, a particularly high-risk time for some patients. Therefore, we suggest twice-daily dosing at least in this group of patients. One study did suggest a less-than-favorable result with atenolol.[170] In patients with compliance issues, once-daily β-blocker would be preferable to no medication. The dose of β-blocker required is variable and is usually greater per kilogram in younger patients. Most teenagers only require 10 to 20 mg of nadolol twice daily. The authors titrate the appropriate dose on the basis of the heart rate response to maximal exercise testing, aiming for a blunted maximal heart rate response of 150 to 160 beats/min on therapy. The prevalence of sudden death decreases from more than 50% to 1% to 2% with β-blockers.[171,172] Other series indicate that β-blockers are not protective in every segment of this population and are most effective in patients with LOT1.[173] While β-blockers are less effective in LQT2 and even less in LQT3, as no harm has been proven with this regimen, the authors continue to use them in all patients, with ICD backup when indicated clinically. The authors have added mexiletine to the therapeutic regimen of many of their patients with LQT3. Their patients are followed up yearly or twice yearly with exercise stress tests and Holter monitoring to establish the adequacy of treatment, the development of significant ventricular arrhythmias, or both. Patients who do not respond to β-blockers may be treated with mexiletine, phenytoin, or pacing. Rarely, other antiarrhythmics may be used, but those known to prolong the Q-T interval should be avoided. Potassium therapy may be helpful, especially in patients with LQT2, in which case potassium should be maintained above 4 mmol/L.

Left cervico-thoracic sympathetic denervation (LCSD) is a controversial treatment with variable success but may be useful in individuals whose condition is refractory to drug or ICD therapy.[174-177] Permanent pacing, often in association with an ICD, has been shown to be an effective adjunctive treatment in these patients, especially those with severe bradycardia either from the syndrome itself or from the β-blocker therapy.[178,179] The rate of the pacing should be at least 10% to 20% higher than the sinus rate and in severe cases should control the rhythm as much of the time as possible. Pauses should be avoided. Episodes of torsades de pointes may be reduced or eliminated with this treatment. In patients known to have had a cardiac arrest or frequent or significant syncope associated with ventricular arrhythmias, the chapter authors recommend the implantation of an automatic ICD. These devices can recognize VT or VF according to programmed criteria and provide a series of shocks to convert the patient's rhythm to normal (sinus rhythm). Some devices can provide backup pacing, but at present, these are not appropriate for continuous higher rate pacing, as the battery is depleted prematurely. The sizes of the devices led to limited use in smaller children, but improved technology now allows even small children to benefit from this technology. This is not a therapy to be undertaken lightly at this time, as the need for constant follow-up and inappropriate discharges from the device can significantly affect a child's life and lifestyle.[180] Groh reported on 35 patients with LQTS who had ICDs and were followed up for a mean of 31 months.[94] The major indication was aborting of sudden death. Sixty percent of patients had at least one appropriate discharge in the follow-up period. Two patients had multiple discharges and required additional therapies. None of the patients died. These results were similar to those reported earlier by Silka.[181]

A greater understanding of the molecular mechanisms of LQTS has prompted a number of studies to identify more specific or gene-directed therapies.[182] The sodium channel blocker mexiletine has been used in some patients.[183] The Q-T interval was noted to decrease with mexiletine treatment in patients with LQT3. Sato et al had reported using a potassium channel opener, nicorandil, in a patient with LQTS.[184] Trials are under way with potassium supplementation and spironolactone. An LCSD has been recommended in patients with recurrent cardiac events and repeated appropriate ICD discharges. The benefit of this is still being debated.

It is generally recommended that competitive athletic activities be avoided by patients with LQTS. With regard to those with documented LQTS and symptoms or arrhythmias, the chapter authors would certainly agree with this recommendation. However, as more "carriers" or asymptomatic patients who have only a prolonged Q-T interval, no arrhythmias, and no family history of sudden death or ventricular arrhythmias are being identified, individual exercise and sports participation recommendations may be made. The most important aspect of the care of these patients is continued surveillance. This is true for young family members who appear to have normal Q-T intervals on initial evaluation. The authors have seen the Q-T interval change with age and would recommend periodic ECGs and appropriate 24-hour and exercise ECG in children and adolescent members of families with LQTS who have initial negative results of evaluation unless genetic testing has definitively ruled out LQTS.

In the past, it was considered that adults were at extremely low risk and did not need medication, but this has been shown to be incorrect. Therapy is now recommended in most adults, especially in those who have had symptoms throughout their lives.[185,186] It is recommended that patients with LQTS avoid caffeine, adrenergic stimulants such as epinephrine, and over-the-counter stimulants such as decongestants. Medications that prolong the Q-T interval should be avoided. A list of these medications can be found at the website www.qtdrugs.org.

Short QT Syndrome

In 2000, Gussak reported a familial short Q-T interval associated with AF. Subsequent reports associated a short Q-T interval with

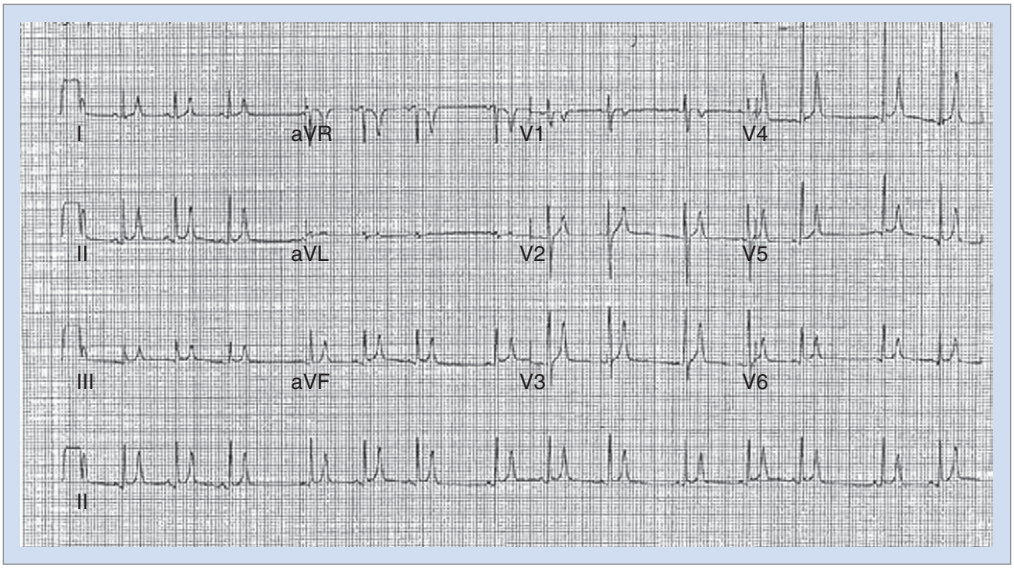

FIGURE 75-9 Electrocardiogram of patient with short QT syndrome. Note the short QTc of 0.27 seconds and peaked T waves.

sudden death. In 2004, Brugada found mutations in *KCNH2*.[187] Short QT syndrome (SQTS) is diagnosed by a short Q-T interval of less than 0.32 seconds or QTc less than 0.34 seconds associated with AF, syncope, and sudden death. Additionally, tall symmetric T waves are present, as illustrated in Figure 75-9. Five forms of SQTS have been found with mutations in *KCNH2*, *KCNQ1*, and *KCNJ2* predominantly resulting in gain of function and shortened repolarization. Additional mutations in the *CACNB2B* and *CACN1C* genes encoding the subunits of cardiac L-type calcium channels have been reported. ICD implantation has been recommended as the treatment.[187-189] Quinidine has been suggested as an effective therapy, particularly in the young.[190]

Brugada Syndrome

The association of an ECG pattern of RBBB and ST segment elevation in ECG leads V1 to V3 with sudden death, which was reported in 1992, has been labeled *Brugada syndrome*.[191] Patients die during sleep, which is presumed to occur secondary to VF. The average age of diagnosis is 44 years, although this condition has been reported in a 2-day-old and linked to SIDS.[192,193] The syndrome is both sporadic and inherited, with an autosomal dominant mode. A mutation of *SCNA5* causes loss of function with slowing of conduction velocity.[194] Mutations in the *SCN5A* gene leading to loss of function account for approximately 18% to 30% of Brugada syndrome cases.[192,195] A newly identified gene called *glycerol-3-phosphate dehydrogenase 1-like gene (GPD1L)*, which results in a partial reduction of I_{Na}, has been associated with the syndrome.[196] The syndrome occurs most commonly in males (3:1) and Asians. Presentation in childhood is uncommon, with a series of 30 children finding symptoms in only one third, most identified during a family evaluation.[197,198] Fever was the most common precipitating factor. Patients with unexplained syncope or aborted sudden death or a family history of these occurrences should be evaluated for this condition. More recent reports indicate that approximately 20% of patients with Brugada syndrome develop supraventricular arrhythmias.[198a] A meta-analysis by Gehi suggested that a prior history of syncope or aborted sudden cardiac death, male gender, and a spontaneous typical type I Brugada ECG (coved ST-segment elevation >2 mm) are predictors of high risk.[198b]

Evaluation and Treatment

Patients with this condition have normal Q-T intervals, ST-segment elevation with a "coved" appearance, RV conduction delay, and a propensity for sudden death. Sodium channel blocking agents such as procainamide or flecainide have been used to unmask this condition.[197,199] Placement of the precordial leads several intercostal spaces higher than usual may unmask the condition as well. In children, the condition also may be unmasked by fever; vagotonic agents or events; or medications, including tricyclics or β-blockers; and recreational drugs such as cocaine.[192,198] Antiarrhythmics have not decreased the incidence of sudden death in these patients, and implanted defibrillators are often recommended, although this remains controversial, as does the use of inducible VT in the electrophysiology laboratory.[192,195,200,201] Some evidence exists that quinidine may be effective in children too young for ICD implantation who present with potentially threatening symptoms.[202]

Cathecholaminergic Polymorphic Ventricular Tachycardia

Cathecholaminergic polymorphic ventricular tachycardia (CPVT) is a genetic disorder associated with stress-induced, bi-directional VT that may degenerate into VF and result in sudden death. This condition usually occurs in childhood, adolescence, or young adulthood, with an estimated prevalence of 1:10,000.[203] Reports of mutation in the cardiac ryanodine receptor gene *RyR2* with autosomal dominant inheritance have been found in 70% of families with catecholamine-induced VT.[204] Abnormalities of this gene would result in an abnormality of intracellular calcium handling, which leads to calcium overload and tachyarrhythmias. An autosomal recessive form of CPVT has been reported to be associated with mutations in the *CASQ2* gene, which encodes calsequestrin,

a protein that is the major calcium (Ca^{++}) reservoir within the sarcoplasmic reticulum.[205] Mutations can be identified in 50% to 70% of cases.[206] The proposed mechanism is triggered automaticity. The initial symptom is usually syncope triggered by emotional or physical stress. The mean age of onset is between 7 and 9 years.[206] Approximately 30% have a positive family history of syncope or sudden death. Over 70% also have supraventricular arrhythmias.[203] Patients with CPVT frequently have associated sinus node dysfunction and inducible atrial tachyarrhythmias, which indicates that the pathogenesis of CPVT is associated with not only the ventricular myocardium but also with broad regions of the heart, including the sinus node and atrial muscle.[207]

Evaluation and Treatment

Evaluation should include ECG, Holter monitoring, and exercise stress testing, with periodic surveillance testing in affected individuals. The resting ECG is normal, but the characteristic bi-directional or polymorphic PVCs or VT is seen with exercise on stress testing or Holter monitoring. Sinus bradycardia is common.

Treatment includes β-blockers and ICD implantation in patients who have had significant symptomatic episodes or have threatening arrhythmias seen on Holter monitoring or exercise stress tests.[203] Verapamil has been proposed as an additional therapeutic agent.[208] Left cardiac sympathetic denervation (LCSD) has been suggested for refractory cases.[209]

Myocarditis

Patients with myocarditis present another special problem. Of patients with ventricular ectopy, 14% to 50% have been shown to have histologic evidence of myocarditis.[210,211] The most common causes of viral myocarditis include coxsackie A and B viruses and adenovirus. A large number of these patients present with ventricular arrhythmias, usually single PVCs or nonsustained VT and only mild or no impairment of ventricular function.

Evaluation and Treatment

Resting ECGs may show ST-T wave changes or low-voltage QRS in addition to PVCs or VT. 24-hour Holter monitoring will indicate the extent and complexity of the arrhythmia. In a hospitalized patient, telemetry monitoring may pick up runs of sustained or nonsustained VT or periods of AV block.

Steroid therapy has been beneficial in some patients.[212] The use of IV immunoglobulin may help in the recovery of LV function and improve survival in the first year after presentation in these patients.[213] In instances of simple ventricular arrhythmias, no treatment may be needed. Patients with more complex or frequent arrhythmias may need treatment. The chapter authors have used β-blockers or mexiletine successfully in these patients. Some patients have slow rates from sinus node dysfunction or AV block and develop rapid ventricular arrhythmias as the heart rate slows. Temporary pacing may be necessary in these patients and may result in the control of the ventricular arrhythmia without the use of pharmacologic agents. When ventricular arrhythmias in these patients are potentially life threatening or impair ventricular function, immediate treatment may be needed. Often, these patients with diminished myocardial function require inotropic support to maintain cardiac output. Although each patient has unique sensitivities, a supportive agent with the least arrhythmogenic characteristics should be chosen, if possible. For example, dobutamine is usually less arrhythmogenic than dopamine, which, in turn, is less arrhythmogenic than epinephrine or isoproterenol. Ventricular arrhythmias may occur in patients with myocarditis and associated complete heart block and slow escape rhythms. In these instances, an increase in the heart rate with a temporary transvenous pacemaker may be all that is needed to control the ventricular arrhythmia. In general, pressor agents should not be used just to increase the heart rate because of their arrhythmogenic potential in this subset of patients.

Postoperative Ventricular Tachycardia

With few exceptions, patients who undergo intracardiac surgery risk the development of postoperative arrhythmias and conduction defects.[214] A history of previous surgery on the ventricle or previous elevation of LV pressure before surgery is seen in most patients with VT after surgery for congenital heart disease. Most of the instances of sudden death in these postoperative patients are seen after repair of aortic stenosis, coarctation, transposition of the great arteries, or tetralogy of Fallot.[215]

Evaluation

All postoperative patients, especially those noted earlier to be at the highest risk, should have periodic follow-up (usually yearly) with standard ECGs. Holter monitoring should be performed every 2 to 3 years in those without known arrhythmias and every year in those with identified arrhythmias. Those being treated for arrhythmias may need more frequent monitoring. Patients with arrhythmias on Holter monitoring who are old enough to exercise should perform an exercise stress test. Those with complex arrhythmias (nonsustained VT, polymorphic PVCs, or polymorphic VT) or monomorphic VT should undergo further testing. This would include an EPS and possible catheter ablation as described in Chapter 76. The EPS has been used to evaluate the propensity of these patients to develop VT, evaluate the efficacy of specific pharmacologic therapies, and locate the site of origin of the arrhythmia in patients who are candidates for ablative therapy.[216-218]

Management and Treatment of Patients with Postoperative Ventricular Tachycardia

Because of their high incidence in postoperative patients, the precise role of ventricular arrhythmias in the occurrence of sudden death is unclear. It is known that after repair of tetralogy of Fallot, exercise stress testing or Holter monitoring will uncover a 25% to 70% incidence of ventricular arrhythmias. In 1985, Garson reported that treatment of more than 10 PVCs per hour on Holter monitoring decreased the incidence of sudden death in their study population.[218a] In contrast, Sullivan and others have reported no increase in the incidence of sudden death by not treating similar patients.[219] A definitive conclusion is still pending as no large controlled study of these patients has been performed yet. The presence of frequent or complex ventricular ectopy probably identifies a high-risk group, but at present, the ability to further identify patients at highest risk is limited. It appears that patients with QRS duration above 180 ms and severe pulmonary regurgitation represent the high-risk group. The best time for valve replacement in children has not yet been determined.

Although no complete agreement as to the indications for treatment exists, the chapter authors have adopted a policy of treating patients with clinical episodes of VT or with symptoms and inducible VT. They generally treat patients with complex ventricular arrhythmias and abnormal hemodynamics or patients with significant symptoms, abnormal hemodynamics, or both. We use the EPS to determine the efficacy of specific drug

regimens or the need for ICD implantation in patients with ineffective drug therapy or hemodynamic deterioration.

Treatment can include a combination of pharmacologic agents, radiofrequency ablation, surgical repair, and ablation or implantation of a pacemaker or an ICD. The most commonly used drug regimens include β-blockers, mexiletine, or class IA or IC agents. In the 1970s, phenytoin was found to be an effective drug in this population, but mexiletine is more commonly used at present. Amiodarone has been found to be an effective drug in some patients with refractory disease. Recently, surgical or catheter ablation has been used effectively in these patients. ICDs are used in patients who have had syncopal events or aborted sudden death or those in whom unstable VT or VF is induced in the electrophysiology laboratory.

Ventricular Tachycardia and Tumors

An association is known to exist between VT and cardiac rhabdomyomas. An incessant form of VT has been reported in infants and young children secondary to myocardial hamartomas. These patients can be treated successfully with surgical ablation.[220] The chapter authors have found that aggressive medical management, including combination drug therapy, may be used to control this type of VT. These tumors and rhabdomyomas may regress over time. A more diffuse infiltrative type of disease known as *histiocytoid* or *oncocytic cardiomyopathy of infancy* is known to manifest as incessant VT in infancy and is usually fatal.[221] Any patient with a diagnosis of tuberous sclerosis, which is known to be associated with cardiac rhabdomyoma, should have an ECG and echocardiogram done. If tumors are noted, 24-hour Holter monitoring is necessary.

Ventricular Tachycardia and Mitral Valve Prolapse

In adults, the incidence of sudden death associated with mitral valve prolapse (MVP) is 1.4%.[222] Sudden death has been reported in children and adolescents, especially in athletes with MVP.[223] The sudden death is proposed to be secondary to ventricular arrhythmias.[224] One study found MVP in 25% of patients with idiopathic VT. On follow-up, sudden death did not occur in any patient.[224a] Twenty-four-hour monitoring has revealed PVCs or more complex ventricular arrhythmias in as many as 46% of children with MVP.[225] Twenty-three percent of these arrhythmias were considered life threatening. Exercise stress testing revealed serious ventricular arrhythmias in 20% of patients. β-Blockers have been the drugs of choice for the control of these arrhythmias. The incidence of these events was 0.32% per year. Predictors of adverse outcome included an enlarged left ventricle or left atrium, MVP with thickened mitral leaflets, or cardiovascular symptoms.[225]

Although no large or long-term follow-up studies have been performed in pediatric patients with MVP, studies in relatively young adults have been performed and have shown a small but significant risk. Four hundred four U.S. Air Force aviators with a diagnosis of MVP were followed up for a mean of 8.6 years and evaluated for "suddenly incapacitating events" described as sudden cardiac death, syncope, pre-syncope, and cerebral ischemic episodes.[225a]

Left Ventricular Aneurysms

Aneurysms or diverticula of the left ventricle have been reported in children, especially newborns, and may be associated with ventricular arrhythmias. Treatment is determined by the clinical condition of the patient. Many of these diverticula will regress over time.[226]

Ventricular Tachycardia and Cardiomyopathies

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy is the most common inherited cardiovascular disorder affecting 1 in 500 individuals in the general population.[227,228] A high incidence of sudden death is seen in children with *hypertrophic cardiomyopathy* (HCM), also known as *idiopathic hypertrophic subaortic stenosis* (IHSS), which is presumed secondary to ventricular arrhythmias.[229-232] HCM is the most common cause of sudden death in young competitive athletes.[229,233] The clinical manifestations are a result of cellular disarray, fibrosis, and hypertrophy of the myocyte leading to diastolic dysfunction, myocardial ischemia, and arrhythmias.[234,235]

Clinical Correlations

A family history of ventricular arrhythmias leading to sudden death, including nonsustained VT on 24-hour Holter monitors, previous syncope, extensive generalized hypertrophy, or ventricular systolic or diastolic dysfunction, may identify a high-risk population.[232] Asymptomatic VT on Holter monitoring may or may not be predictive.[236] Abnormal blood pressure response to exercise may predict sudden death. Exercise stress testing may uncover ST-segment depression or an abnormal systolic blood pressure response, including a small difference between peak and resting systolic blood pressure. Predictors of sudden cardiac death include higher left ventricular outflow tract (LVOT) pressure gradient at rest and failure of systolic blood pressure to increase during exercise testing.[237] Two events that predict subsequent sudden death include a combination of inducible sustained VT at EPS and a history of cardiac arrest or syncope.[235] A multi-center study evaluating 1511 consecutive patients with HCM demonstrated a relative risk of sudden death of 1.78 in patients with unexplained syncope and 0.91 with neurally mediated syncope compared with patients without syncope. A fivefold increased risk was seen in patients with unexplained syncope within 6 months of their initial evaluation. Of the 1511 subjects, 147 were younger than 18 years of age. During 6.5 years of follow-up, 15 sudden deaths occurred, that is, an incidence of 15.7 per 1000 person-years. Seven of the 147 patients had experienced unexplained syncope before their initial evaluation, with 3 dying suddenly. In those with syncope, the mortality rate was 120 per 1000 person-years compared with 13 per 1000 person-years in those without unexplained syncope.[236] More than one third of patients who experience syncope with VT/VF or resuscitated VF will die within 7 years from sudden cardiac death or progressive heart failure.[237] Unfortunately, many high-risk patients will not have inducible VT at EPS but may still be at high risk. It has been suggested that fractionation of electrograms with programmed stimulation may be a marker for high-risk patients.[238] Recent studies suggest that myocardial bridging of the left anterior descending coronary arteries may cause myocardial ischemia in children with HCM.[239] The primary problem with regard to treatment is the divergence of opinion regarding the bridging or compression of branches from LV hypertrophy.[240]

HCM is a genetic disease caused by mutations in contractile sarcomeric proteins. The penetrance is often incomplete and 20% to 30% of adults with these gene mutations do not express the phenotype.[241] It is hoped that the recent genetic identification of

HCM mutations will increase understanding and help identify high-risk patients.[240] The first gene identified for HCM is the β-myosin heavy chain MHC located on the long arm of chromosome 14.[242] The MHC gene (*MyHC*) is responsible for 35% of familial HCM.[243] Multiple other genes that code the proteins of the sarcomere have been found to be responsible for HCM. These include the gene of cardiac T-troponin (*cTnT*),[241] the gene of α-tropomyosin, and the gene of binding protein C (*MyBP-C*).[244] Specific mutations have been reported to be associated with a higher incidence of sudden death, but this is not fully agreed upon.[242]

Evaluation

All family members and identified patients should be monitored with periodic ECGs and echocardiograms. ECG findings have been identified as major criteria in the diagnosis of hypertrophic cardiomyopathy, including left ventricular overload, deep Q waves more than 40 ms in the LV inferior lateral wall, and T-wave inversion 3 mm or more in V3 to V6, L1, and aVL and 5 mm or more in L2, L3, and aVF (Figure 75-10).[244] In identified patients, yearly Holter monitoring should be performed. Exercise stress testing should be performed in those who are of an appropriate age. EPS should be performed in those who have had syncope, documented complex arrhythmias, or symptoms suggesting ventricular arrhythmias. It has been noted that atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are elevated up to 5 and 85 times the normal levels, respectively, in patients with HCM.[245] These values may be useful in the initial evaluation as well as follow-up in those with a diagnosis of HCM.

Treatment

Treatment includes antiarrhythmic therapy, "pacemakers," myotomy or myectomy, and ICDs.[170,246-251] Maron reported a retrospective multi-center study of efficacy of ICDs in preventing sudden death in 128 patients with HCM who were judged to be at higher risk for sudden death and had ICDs implanted. Twenty-three percent had appropriate shocks or anti-tachycardia pacing, and 7% had inappropriate shocks per year. In those in whom secondary prevention was provided after cardiac arrest or VT, 11% had appropriate activation. The interval between implantation and the first appropriate discharge was substantially prolonged by 4 to 9 years in six patients. The defibrillators were highly effective in terminating life-threatening ventricular arrhythmias.[251a] The recommendations of the 36th Bethesda Conference are that athletes with a diagnosis of HCM or probable HCM abstain from competitive sports and vigorous training, with the exception of low-intensity activities.[252]

Dilated Cardiomyopathy

The most common etiology of dilated cardiomyopathy (DCM) in children is idiopathic,[253] but other causes include antecedent myocarditis, familial or genetic associations, and immune regulatory abnormalities.[253-256] The prognosis for children with DCM is poor, and the reported mortality has been estimated at 24% to 50%. In a study of 62 children and adolescents (followed up for 3.9 to 4.5 years), 50% died, 16% recovered, 27% had residual decreased LV function, and 7% underwent orthotopic heart transplantation.[257] In another study of 41 children followed up for a median of 2.5 years, 30% died, 32% recovered, and 38%survived with decreased LV function.[258] Mortality rates at follow-up were 24% at 1 year and 29% at 5 years. Poorer prognosis was associated with clinical severity at presentation, lower mean shortening fraction, and severe arrhythmias.[258] Little information is available on risk stratification in children with dilated cardiomyopathy.

Clinical Correlations

In adults, a variety of high-risk factors have been suggested, including the presence of ventricular arrhythmia, LV end-diastolic diameter of more than 70 mm, and nonsustained VT on Holter monitoring. Low ejection fraction of less than 30% and nonsustained VT are high-risk factors as well.[253]

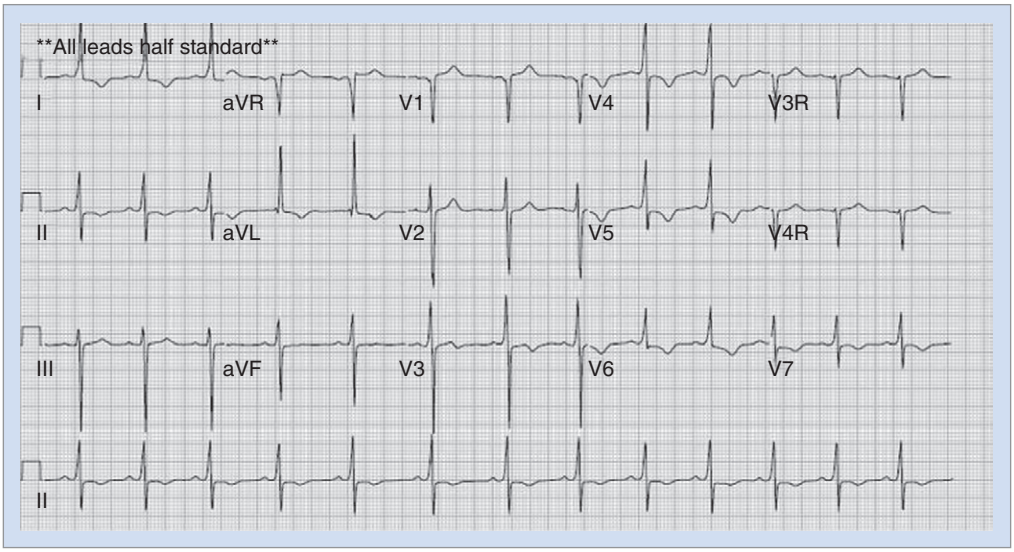

FIGURE 75-10 Electrocardiogram of patient with hypertrophic cardiomyopathy. Note the deep S in V1, tall R in V5 and V6, and T-wave inversion in V4 to V7. All leads are half standard.

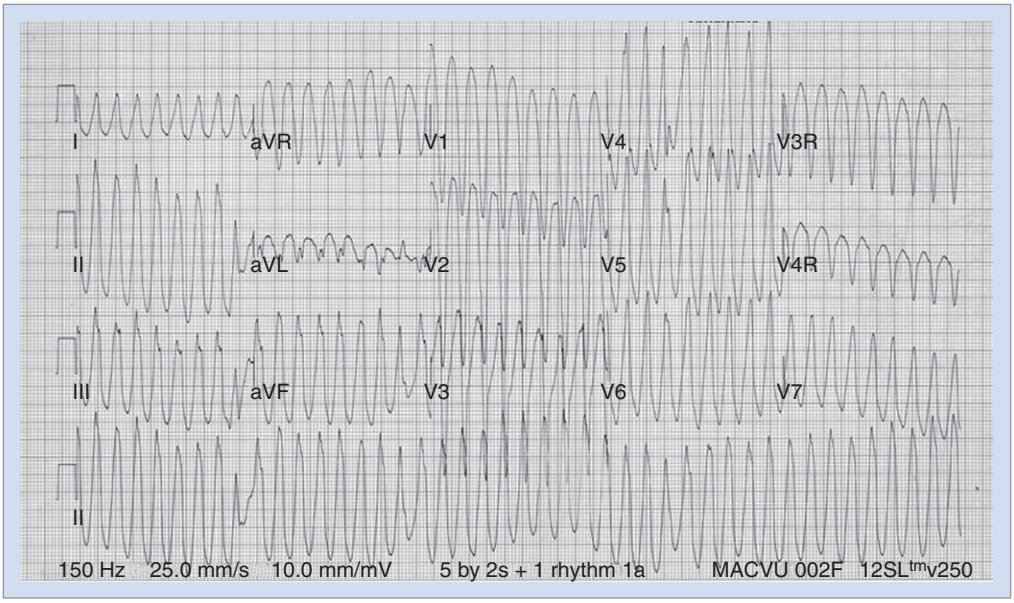

FIGURE 75-11 Electrocardiogram in patient with ventricular tachycardia origination in the right ventricular outflow tract. Note the QRS morphology with left bundle branch block pattern and left-axis deviation.

Treatment

Treatment includes antiarrhythmic therapy, biventricular pacing, and implantable ICDs. Ten percent of patients will require heart transplantation. In the past decade, a number of pediatric studies have looked at the effect of β-blocker therapy in the treatment of pediatric patients with dilated cardiomyopathy.[260-262] These studies have primarily evaluated the safety and effectiveness of carvedilol in this population. Each of these has demonstrated a significant improvement in systemic ventricular function as assessed by shortening, ejection fraction, or both. Carvedilol was added to other standard therapeutic modalities in each of these studies. The use of carvedilol, other β-blockers, or both in patients who develop significant arrhythmias may result in an interaction with other antiarrhythmics such as amiodarone.

Biventricular pacing has been reported recently as a successful treatment modality in adults with symptomatic drug-refractory heart failure secondary to dilated cardiomyopathy and associated interventricular conduction delay.[263,264] Several electrophysiologists are recommending a combination of biventricular pacing, implantable ICDs, or both for adults.[251,265] The usefulness of biventricular pacing in pediatric patients with a dilated cardiomyopathy, interventricular conduction delays, ventricular asynchrony, and congestive heart failure has not been studied in large clinical trials but may be a new treatment option for these patients. Several large multi-center trials of biventricular pacing are ongoing, including trials to evaluate the effects of biventricular pacing on ventricular arrhythmias.[263,264,266] Although early results in adults are encouraging, many questions still remain to be answered.

Ventricular Tachycardia and Structurally Normal Hearts

Two sites have been associated with VT and structurally normal hearts. The first is located in the right ventricular outflow tract (RVOT), usually in the anterior portion, most commonly anteroseptal, but also in the anterolateral and anterior regions.[267] The morphology of VT on ECG is LBBB, most commonly with an inferior axis but also with a superior or rightward axis (Figure 75-11). An RBBB pattern with superior or rightward axis is also seen. Both sustained and nonsustained VT are seen clinically. It has been suggested that RVOT tachycardias may resolve over time. However, Drago reported biopsies positive for acute myocarditis, ARVD fatty infiltration, and other histologic abnormalities in 67% of patients without obvious heart disease and RVOT tachycardia.[269] The tachycardia may be induced as nonsustained or sustained VT by programmed electrical stimulation and isoproterenol in 40% to 80% of selected patients. Pacemapping can help identify the specific site of VT in the RVOT.

The second form of VT in patients without heart disease originates from the left ventricle, most commonly in the septum in the mid-to-inferior position. The morphology of the VT is generally RBBB with left axis deviation (Figure 75-12). It can be induced in a similar fashion to VT in the RVOT. These VTs are often sensitive to verapamil. VT from the basal aspect of the superior LV septum can appear as repetitive monomorphic VT, revealing a dominant R-wave pattern in V1, an inferior axis, and a precordial R-wave transition at or before lead V2.[270] These VTs may be responsive to verapamil or adenosine, which suggests a triggered mechanism.[271] Some LV VTs originate in the LVOT with an LBBB pattern.

Evaluation

Holter monitoring and exercise stress testing should be used to evaluate patients with these arrhythmias. An EPS may be necessary to identify the site of the tachycardia if catheter ablation is being considered.

Treatment

Antiarrhythmic therapy may be appropriate in many of these patients, especially in those who are not yet adolescents. Some of

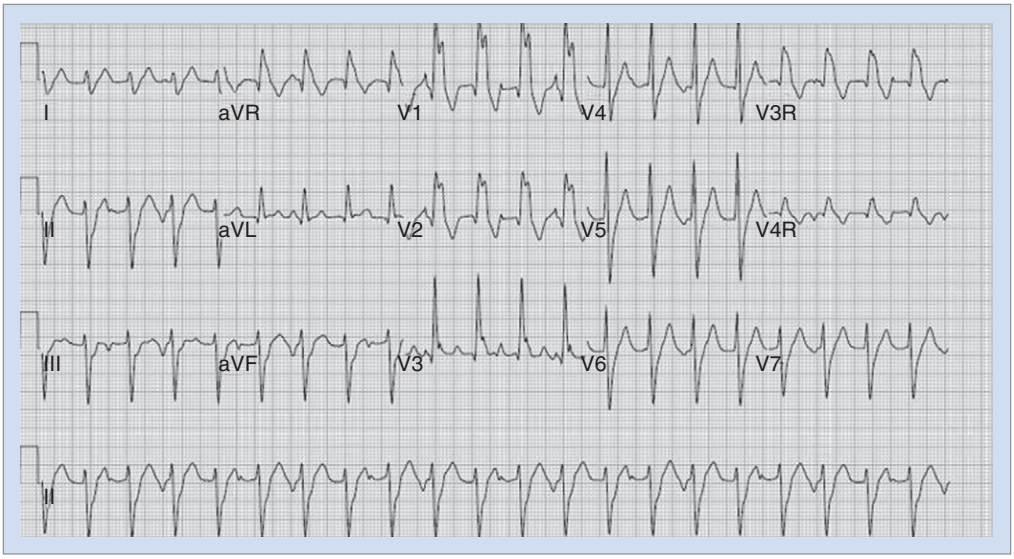

FIGURE 75-12 Electrocardiogram in patient with left ventricular septal or fascicular ventricular tachycardia. Note the QRS morphology with right bundle branch block with a rate of 160 beats/min and left-axis deviation.

the RVOT tachycardias will resolve, and conservative therapy may be appropriate in those with slower VT that is easily controlled with medication. VT in the RVOT may respond to β-blockers or mexiletine. LV tachycardia may respond to β-blockers or verapamil.

Both forms of VT are amenable to treatment with catheter ablation.[259-261,270] Those with an LBBB pattern, inferior axis, and early precordial transition may be ablated from the left or noncoronary aortic sinus of Valsalva.[262] For LV septal VTs, ablation at the pre-Purkinje potential recording site during VT seems to be most successful.[272]

RV tachycardia may be ablated using standard entrainment, pacemapping, or noncontact mapping, including electro-anatomic mapping techniques. A higher success rate has been seen in the treatment of RV tachycardias.

Acute Treatment of Ventricular Tachycardia

VT should be treated emergently unless the rate is slow and the patient is clinically stable. If an extracardiac cause such as an electrolyte abnormality or acidosis has been identified, the underlying abnormality should be corrected. The correction usually results in the conversion of the ventricular arrhythmia to sinus rhythm. In patients with cardiac compromise, IV lidocaine at 1 mg/kg should be given immediately. If the lidocaine is effective, a continuous infusion of lidocaine at 10 to 50 μg/kg should be started to maintain an adequate level of lidocaine. Lidocaine levels should be monitored carefully to prevent toxicity. Although lidocaine has proven to be a safe and effective medication in the treatment of VT, current advanced cardiac life support (ACLS) protocols also recommend the use of IV amiodarone in this population.

Synchronized cardioversion at 2 to 5 watt-sec/kg should be performed if the lidocaine does not result in immediate conversion or if an IV site is not available. The energy requirements in biphasic cardioversion and defibrillation are less than those in monophasic cardioversion and defibrillation. Current ACLS recommendations call for no reduction in the energy delivered during cardioversion or defibrillation.

Procainamide IV has been used to treat acute episodes of VT. Because of the associated negative inotropic effects, patients must be monitored very carefully during the infusion. More recently, amiodarone has been shown to be effective for VT when given intravenously. Other drugs used in acute therapy are listed in Table 75-4. Rapid ventricular pacing may be used to convert the rhythm to sinus if pharmacologic therapy fails or is contraindicated.

Long-Term Treatment of Ventricular Tachycardia

Once the arrhythmia has been converted, choice of an appropriate long-term regimen is essential to maintaining the stability of the patient. The drugs most commonly used are listed in Table 75-1. If lidocaine has been successful, it may be continued until adequate levels of a chronic regimen have been reached or the acute causative agent is no longer present. When switching to mexiletine, the lidocaine should be gradually weaned as the mexiletine is initiated to prevent the combined toxicity of these two drugs, as their side effects are similar. Propranolol or other β-blockers are especially effective in patients whose arrhythmia is sensitive to adrenergic stimuli.[274] Class I agents and amiodarone are effective in more refractory cases.[274,275] A combination of amiodarone and propranolol has been effective in infants and children.[276]

As sudden death occurs in up to 30% of patients with VT and congenital heart defects, these patients should be placed on a long-term regimen. This type of arrhythmia is poorly tolerated by patients in the immediate postoperative period, but the arrhythmia generally responds to lidocaine or IV amiodarone and to correction of other underlying hemodynamic and metabolic abnormalities. Studies have shown that patients with early postoperative VT are likely to develop this arrhythmia in the late postoperative period, so long-term therapy is often recommended. The patient who presents months to years after surgery also requires long-term therapy. A thorough investigation is

Table 75-4 Acute Treatment of Ventricular Tachycardia

INITIAL TREATMENT	DOSAGE	LEVEL
Lidocaine	1-2 mg/kg IV bolus q5-15 min	1.5-5.0 mg/L
	IV infusion: 20-50 μg/kg/min	
Cardioversion	1-5 watt-sec/kg; double if ineffective	
SECONDARY TREATMENT	**IV DOSAGE**	**LEVEL**
Amiodarone	5 mg/kg over 1 hour, followed by 2.5 mg/kg IV bolus q4-6 h	
Magnesium	0.25 mEq/kg over 1 min, followed by 1 mEq/kg over 5 hours to achieve Mg^{++} level of 3-4 mg/dL	
Phenytoin	3-5 mg/kg over 5 min, not to exceed 1 mg/kg/min	10-20 μg/mL
Procainamide	5 mg/kg over 5-10 min or 15 mg/kg over 30-45 min	NAPA: 4-10 mg/L
	Infusion: 20-100 μg/kg/min	PA: 4-8 mg/L
Propranolol	0.05-0.1 mg/kg over 5 min q6h	

NAPA, N-*acetylprocainamide;* PA, *procainamide.*

needed to rule out underlying hemodynamic abnormalities, as VT is tolerated less well by this group of patients. Residual or new hemodynamic lesions may be contributing to the arrhythmia. Mexiletine has been shown to be an effective long-term drug in patients after tetralogy of Fallot repair, as is the β-blocker class of drugs.[261] Class I agents as well as amiodarone may be effective in refractory cases. The EPS may be a helpful guide to medical therapy.[216,217] In cases refractory to drug therapy, the EPS can determine the site of origin of the tachycardia and direct treatment by surgical or catheter ablation. Patients with life-threatening episodes or those not responding to medical or ablative therapy may require ICDs. See Chapter 80 for more details.

Electrophysiological Study of Ventricular Tachycardia

Specific indications for the performance of EPS in children with VT are included in Box 75-2. Intracardiac recordings during VT show the absence of His-bundle deflections consistently preceding ventricular depolarizations. Atrial capture at rates more rapid than the tachycardia normalizes the QRS complex. One of the most significant differences between adults and children is the mechanism responsible for VT.[78] In adults, more than 90% have inducible VT. In children, only 30% to 60% have inducible or re-entrant VT, and the rest have triggered or automatic VT. Inducible re-entrant VT in children is more commonly associated with structural heart disease.

Catheter Ablation of Ventricular Tachycardia

In the pediatric population, the categories of VT that are amenable to catheter ablation include those in structurally normal hearts that originate primarily in the RVOT or in the left ventricle, especially in the mid-to-inferior septum. The other category of patients who may have VT that is amenable to catheter ablation are those who have postoperative VT, particularly in the RVOT, commonly those with tetralogy of Fallot.[217] Scarring from right ventriculotomy or infundibular resection allows a zone of slow conduction producing the substrate for re-entry.

Box 75-2 Indications for EPS in Ventricular Tachycardia

INDICATIONS FOR EPS

1. Documented VT >150 beats/min or wide QRS tachycardia, except in association with acute metabolic or electrolyte abnormalities, myocarditis, or long QT syndrome; value of EPS in cardiomyopathies has not been determined but may be helpful in selected cases
2. Nonsustained VT or complex premature ventricular depolarizations in a patient with an abnormal heart
3. Suspected VT in the presence of syncope or cardiac arrest of unknown etiology
4. Symptoms suggestive of VT in vulnerable patient with an abnormal heart (e.g., postoperative tetralogy of Fallot)
5. Follow-up of patient with inducible, documented VT to test efficacy of long-term medication
6. For catheter ablation in selected patients
7. For evaluation of inducible VF in patients with Brugada syndrome

EPS, *Electrophysiological study;* VT, *ventricular tachycardia;* VF, *ventricular fibrillation.*

Prognosis of Ventricular Tachycardia

The prognosis of VT depends on the underlying condition. Reviews of VT in children have reported a high incidence of death: 10% to 47%.[65] The higher incidence occurs in those patients with underlying structural or postoperative heart disease and poor hemodynamic results. Sudden death has been reported in patients with normal hearts at an incidence of 6% to 8%.[277]

In the absence of structural heart disease, especially in the neonate or young child, spontaneous resolution of VT may occur. The outlook for infants and children with VT is excellent if the VT can be controlled with treatment.[73]

Sinus Node Dysfunction

Sinus node dysfunction is uncommon in the pediatric patient. Patients can present with significant bradycardia with long pauses secondary to sinus arrest, with chronotropic incompetence

leading to exercise intolerance. Infrequent presentations include intermittent periods of tachycardia and bradycardia (sick sinus syndrome). Etiologies of sinus node dysfunction include congenital defects of the sinus node, traumatic damage to the sinus node or its blood supply, inflammatory processes, or idiopathic causes. Relatively hemodynamically insignificant congenital heart abnormalities can lead to sinus node dysfunction, such as the absence of the right superior vena cava with persistent left superior vena cava or other abnormalities in the venous drainage to the heart (heterotaxy syndromes). In some instances, the patient may present with signs and symptoms consistent with sinus node dysfunction wherein the sinus node is normal but the autonomic input to the sinus node is abnormal.

Presentation

The pediatric patient with sinus node dysfunction may present with symptoms of fatigue and decreased exercise tolerance, dizziness, syncope, or palpitations. Some patients are completely asymptomatic, and the sinus node abnormality is noted on screening for other cardiac abnormalities. Occasionally, infants and toddlers present with a history consistent with breath-holding spells that progress to frank syncope. These episodes are often brought on by a noxious stimulus such as pain, scolding, or frustration over not getting his or her way. Persistent crying proceeds to syncope. In evaluating these children, the chapter authors have found that these events are often secondary to periods of prolonged sinus arrest lasting as long as 15 to 20 seconds. It appears that these periods of asystole are likely secondary to increased vagal tone and not related to abnormalities in the sinus node.

Evaluation

The workup of a patient with suspected sinus node dysfunction should include an ECG to determine if the underlying rhythm is sinus. If the rhythm is atrially derived with a P-wave axis not between 0 and 90 degrees, further evaluation to rule out congenital heart diseases should be performed. Patients should also undergo 24-hour Holter monitoring to document low and high rates to evaluate heart rate variability and to look for significant periods of bradycardia or long pauses and for default to secondary pacers such as ectopic atrial, junctional, or ventricular rhythms. If the patient is old enough (generally 5 years of age or older), an exercise tolerance test should be performed to evaluate chronotropic competence. Occasionally, patients undergo intracardiac electrophysiological evaluation to access sinus node function. In the authors' laboratory, sinus node function is evaluated by using sinus node recovery times with the patient at a baseline state as well as on isoproterenol, with or without atropine. Sinus node recovery times are helpful in determining if a primary defect exists in the sinus node versus an autonomic etiology for the bradycardia. It is the authors' impression that these electrophysiological parameters should be used in combination with other testing modalities such as exercise stress testing and 24-hour Holter monitoring.

Treatment

Treatment of sinus node dysfunction is reserved for symptomatic patients and not based on heart rate alone. Therapy should be initiated if the patient has dizziness, decreased exercise tolerance, arrhythmias, syncope, or signs of increased heart size as seen on chest radiograph or echocardiogram. If asymptomatic, the patient should be monitored without therapy.

Pacemakers are the mainstay of therapy for patients with significant sinus node dysfunction. Attempts have been made to use pharmacologic agents such as caffeine, β-sympathomimetics (e.g., theophylline), and oral vagolytic agents such as glycopyrrolate or atropine. These interventions generally have proven to be ineffective or only partially effective in treating significant bradycardia, with the potential for being proarrhythmic in a population that may be at an increased risk of tachyarrhythmias. In patients with hypervagotonia, the authors have had some positive results with the oral administration of the IV formulation of atropine, while avoiding significant side effects.

Although pacemakers have been used with great success in pediatrics, certain issues are unique to this population.[278] See Chapter 79 for more detailed information.

Atrioventricular Block

Abnormalities of AV conduction are uncommon in children, but they do occur. Etiologies include congenital abnormalities, inflammatory processes, and trauma. Occasionally, no distinct etiology can be identified, and the block may be related to increased vagal tone.

First-Degree and Second-Degree Atrioventricular Block

First-degree and second-degree heart block may be congenital or acquired. Acquired etiologies include traumatic damage associated with surgery for congenital heart defects and inflammatory processes such as rheumatic heart disease or Lyme carditis. The EPS in pediatric patients has generally localized the delay to the AV node.[269] Delay in the His-Purkinje system with prolongation of the H-V interval may be more significant, indicating a predisposition to the development of complete heart block.[279,280] Patients with first-degree and second-degree AV block are generally asymptomatic unless the ventricular rate is significantly decreased. It is not uncommon to see first-degree and Mobitz I AV block during 24-hour Holter monitoring in teenagers, especially during sleep. The low heart rates are especially significant in patients with compromised myocardial function, and thus the cardiac output may be insufficient to meet the patient's needs.

Evaluation

Patients with first-degree and second-degree AV block should have 24-hour Holter monitoring to determine the longest pause and the lowest rate. The tracing should also be evaluated for periods of higher grade AV block. Exercise stress testing should be used to determine the maximal heart rate and to look for potential ventricular arrhythmias.

Treatment

If a higher rate is needed, pharmacologic agents such as atropine may be helpful, especially if the block is in the AV node and partially mediated by vagal influences. Isoproterenol may increase the heart rate by increasing the rate of the escape pacemaker. As mentioned earlier, oral medications such as caffeine, theophylline, and antivagolytics are often not very useful in changing the heart rate or AV conduction. Acutely, temporary transcutaneous or

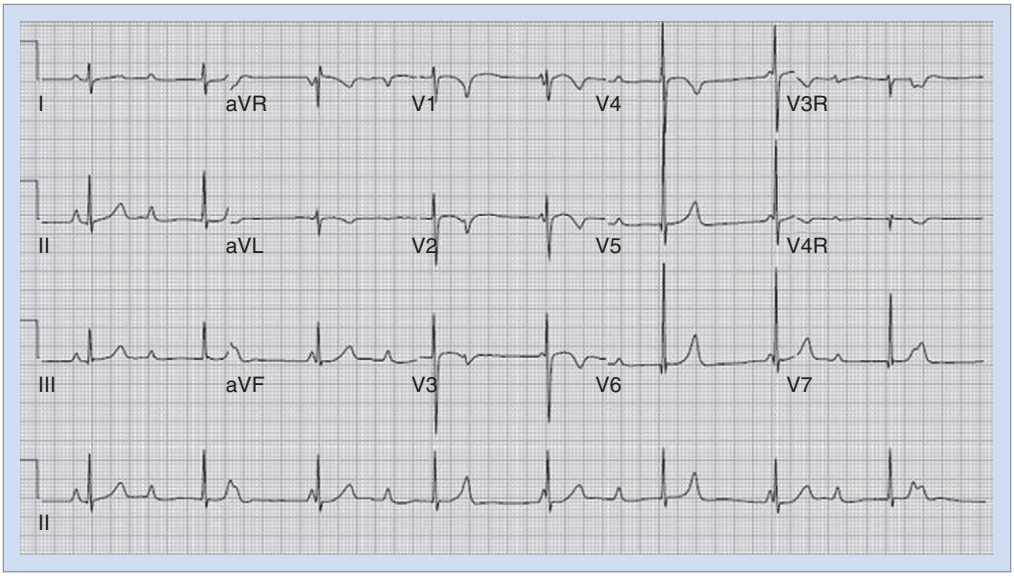

FIGURE 75-13 Electrocardiogram findings in association with complete heart block. The atrial rate is 75 beats/min, and the ventricular rate is 50 beats/min with atrioventricular dissociation. QRS is narrow, indicating a high junctional escape focus.

transvenous pacing may be necessary. For persistent symptomatic or high-grade AV block, permanent pacing may be needed. In some patients with second-degree AV block, progression to complete AV block may occur.[279,280]

Complete Heart Block

Complete heart block is the most common cause of significant bradycardia in children. The ventricular rate is usually 40 to 80 beats/min, depending on the patient's age. The QRS morphology and heart rate are related to the location of the escape pacemaker. The higher the origin of the pacemaker within the AV conduction system, the faster is the ventricular rate and the narrower the QRS complex (Figure 75-13). Wider QRS escape complexes usually originate from the His bundle or below. The usual rate in the neonate is 60 to 80 beats/min.

Complete heart block may be either congenital or acquired and occurs in 1 per 20,000 live births. The same causes of acquired heart block that cause second-degree AV block discussed earlier can cause complete heart block. In a series of 599 patients with congenital complete heart block, followed up for more than 10 years, 92% survival was seen in patients without associated structural heart disease.[281] The greatest risk of mortality was during the first weeks of life, especially in those delivered prematurely secondary to fetal hydrops, with half of the deaths occurring during the first year. The highest risk was indicated by associated cardiac anomalies, cardiomegaly, ventricular bradycardia less than 55 beats/min, and atrial tachycardia greater than 140 beats/min in infants.

A strong association has been noted with connective tissue disease in the mother and congenital complete heart block. The prevalence has been reported to be as high as 85% in mothers of affected infants.[282,283] Only one half of these affected mothers are symptomatic, whereas the other half, although asymptomatic, are serologically positive. A mother with systemic lupus erythematosus has a 1:20 risk of having a child with complete heart block if she is anti-Ro positive.[284] Maternal immunoglobulin G antibodies to soluble tissue ribonucleoprotein antigens, found in the cytoplasm or nucleus of human cells (anti-Ro:SS-A and anti-La:SS-B), cross the placenta after 12 to 16 weeks of gestation. This results in an inflammatory response in the fetal heart, particularly in the conduction system, leading to the destruction of the AV node.[285-287]

Buyon demonstrated an increased risk when the maternal antibodies target specific portions of the ribonuclear complex, particularly the 48-kd La (SS-B), the 52-kd Ro (SS-A), and the 60-kd Ro (SS-A). The highest risk was reactivity to both the 48-kd La (SS-B) and the 52-kd Ro (SS-A) components.[288] Because of this immunologic factor, dexamethasone and plasmapheresis have been recommended as effective treatments for the mother of an affected fetus.[288,289] Although the heart block has not been shown to resolve with these treatments, the clinical course of the fetus has improved, with decreased pleuro-pericardial effusions and other signs of fetal hydrops.

Presentation

Some cases will be diagnosed in utero because of low fetal heart rates, which usually develop after the seventeenth week of gestation. Fetal echocardiography may show fetal hydrops in 15% to 61%, with a higher incidence being seen in association with structural heart disease, especially AV valve regurgitation. The survival with hydrops is less than 10% unless the fetus can be delivered immediately. Even with early delivery, these infants are often very ill and difficult to manage and require an aggressive team approach by neonatologists, cardiologists, and cardiothoracic surgeons. With this aggressive management, the outlook is relatively good if the fetal heart rate is more than 55 beats/min and if no structural heart disease is present.

Structural heart disease is present in one third to one fourth of infants with congenital heart block. The associated congenital heart defects most commonly include those with L-transposition of the great arteries (L-TGA) (physiologically

corrected transposition) or the heterotaxy syndromes. With associated heart disease, mortality in the first year has been reported to be 29% in one study.[281] Complex postoperative congenital heart lesions or those with an unusual course of the AV conduction system may develop postoperative block.[291] After ventricular septal defect repair, the presence of RBBB and left anterior hemiblock is 7% to 17%, with a 1% incidence of complete heart block.[292] Complete heart block has been reported to occur as late as 14 years after surgical repair.[293] Complete heart block occurs more commonly after repair of AV canal defects, probably because of the unusual course of the conduction system in these lesions, and may be seen in up to 7% of patients.[294] Physiologically corrected L-TGA is associated with AV conduction disturbances ranging from first-degree to complete heart block in 30% to 60% of patients.

These conduction disturbances may be present at birth, develop insidiously, or occur during or after the surgical correction of associated defects. The AV bundle and conduction system have been found to cross the pulmonary outflow tract and descend along the anterior rim of the ventricular septal defect or along the right margin of the foramen ovale between the main and outflow chambers in a single ventricle with an outflow chamber. Careful attention to these facts and intraoperative mapping have decreased the incidence of this form of postoperative block.

When low fetal heart rates are noted, fetal echocardiography should be performed. Signs of cardiac decompensation include evidence of fetal hydrops with pleural or pericardial effusions or ascites. Cardiac function may be decreased, and tricuspid regurgitation is often present.

In a study of patients with congenital heart block who were followed up for more than 30 years, only 10% did not require a pacemaker, and a 20% incidence of sudden death was noted. Mitral regurgitation and prolonged QTc were poor prognostic findings. Pacemakers were recommended even in asymptomatic adults.[295]

Evaluation and Treatment

Twenty-four-hour Holter monitoring may be used to determine the average heart rate, heart rate ranges, QRS duration, Q-T intervals, and the presence of ventricular arrhythmias or long pauses.

Although many infants with congenital complete heart block are asymptomatic at birth, others show findings typical of congestive heart failure and require treatment. A subset may develop severe congestive heart failure and cardiovascular collapse. These distressed infants may require intubation and ventilation, treatment of acidosis, and catecholamine support of heart rate and blood pressure.

In emergencies, immediate transthoracic pacing can be accomplished. The transcutaneous pacemaker may be effective in short-term emergency situations but should be replaced with another pacing method as soon as possible. Placement of a temporary transvenous pacemaker, either through the umbilical vein or the femoral vein under direct fluoroscopic observation, is preferred. Although infants with rates less than 50 beats/min or slightly higher rates and associated congenital heart defects or cardiomyopathies may require pacing, this decision should not be made on the basis of heart rate alone. Older children with congenital heart block may develop evidence of exercise intolerance, easy fatigability, or syncope. Not all patients with congenital complete heart block need a pacemaker, and many do not require one until they reach an older age.[295]

Pacemakers may be placed because of associated ventricular arrhythmias, either during sleep or exercise, easy fatigability or exercise intolerance, syncope, or presyncope.[296-298] Other indicators for pacing that have been associated with sudden death include severe bradycardia, ventricular ectopy especially with exercise, prolonged pauses, increased QRS width, prolongation of QTc, and a junctional recovery time of more than 3 seconds.[299,300] Another important indicator for pacer placement is cardiac enlargement shown by chest x-ray or echocardiogram. With cardiac output being the product of heart rate and stroke volume, the LV will dilate, indicating that the heart rate is not adequate to meet the metabolic demand.

The acquired heart block associated with inflammatory disease such as viral myocarditis, Lyme disease, or rheumatic fever may be transient and require only temporary pacing.

With postoperative heart block, temporary pacing is usually performed 7 to 10 days after surgery. Permanent pacing should be performed if sinus rhythm does not return because of the high incidence of sudden death in this group of postoperative patients if they are not paced.[301] As the return of sinus rhythm does not ensure that heart block will not recur at a later time, close follow-up is indicated.

Abnormalities in intraventricular conduction may be congenital or acquired. Congenital RBBB may be inherited or found in association with Ebstein's anomaly of the tricuspid valve.[302,303] Children with Kearns-Sayre syndrome are likely to develop RBBB that progresses to complete heart block.[304] Prophylactic placement of a pacemaker is recommended in this group of patients to prevent sudden death. Postoperative RBBB is common after repair of many cardiac anomalies and is either central or peripheral.[305,306]

Treatment of Bradycardia

Acute medical therapy consists of atropine (0.02 to 0.04 mg/kg IV) or isoproterenol (0.01 to 2.0 µg/kg/min). Temporary atrial pacing may be performed by the transcutaneous, esophageal, or intracardiac routes. If AV conduction is not intact, the ventricle must be paced using transcutaneous or intracardiac pacing. Long-term medical therapy is rarely indicated, and persistent symptomatic bradycardia should be treated by permanent pacing.

Implantable Pacemakers

The use of permanent pacemakers in children was first reported in the early 1960s and predated many recent advances in lead and generator technology.[307-310] These advances, including programmability and miniaturization, have significantly increased pacemaker use in the pediatric population.[311-314] See Chapter 79 for more detailed information on the use of pacemakers in children.

Conclusion

Arrhythmias in children are complex and variable with differences in presentation noted over time as developmental changes are manifested. Evaluation must be adjusted to accommodate the fleeting and evolving nature of many arrhythmias in this population. Similarly, the choice of treatment requires the understanding of the unique responses of the young to therapies with medications and devices.

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CHAPTER 76

Use of Ablation to Treat Arrhythmias in Children and Patients with Congenital Heart Disease

Maully Shah and Ramesh Iyer

Over the past two decades, transcatheter ablation (CA) of cardiac arrhythmias has emerged as definitive therapy for many forms of tachyarrhythmias in children. This is true for children with structurally normal hearts as well as for those with congenital heart disease (CHD). Advances in surgical techniques for CHD palliation and repair have improved long-term survival, but arrhythmias continue to be a source of morbidity and mortality in this population. This chapter will discuss catheter ablation in children with CHD and those without CHD.

Transcatheter Ablation of Arrhythmias in Children with Structurally Normal Hearts

Arrhythmia mechanisms in children are similar to those seen in adults, but with differences in frequency and arrhythmia burden that may have an impact on approach and management. Other important differences include more fragile tissues, especially in small children, smaller cardiac chambers and coronary arteries, and shorter distance between the coronary sinus and the compact atrioventricular (AV) node. In addition, the developing heart appears to have the potential for spontaneous resolution of some arrhythmias, which should always be considered prior to attempting CA.

Supraventricular tachycardia (SVT) accounts for the majority of childhood arrhythmias. Re-entrant tachycardia secondary to accessory pathways (APs) is responsible for 75% of SVTs in children with AV nodal re-entrant tachycardia and primary atrial tachycardia accounting for the rest.[1] Ventricular tachycardia is rare (only 5% of all tachycardias).[2]

The overall acute success for AP ablation is 91%, with higher success for left-sided pathways (96%) versus septal pathways (87%) and right free wall pathways (86%).[3,4] These results may be even better with the lower risk of complications such as heart block in the present era since the advent of three-dimensional mapping and cryo ablation. The risk of major complications in the Pediatric Electrophysiology Registry comprising 4651 procedures was 3.2% and included AV block, perforation, pericardial effusion, brachial plexus injury because of arm position, emboli, and pnemothorax.[4,5-7] Body weight of 15 kg or less correlated with a higher complication rate in one study.[4] The overall death rate was 0.15%, which was similar to that reported for adult ablations.[3]

Indications for radiofrequency (RF) ablation for cardiac arrhythmias in children are as follows:[5]

Class I

- Wolff-Parkinson-White (WPW) syndrome following aborted sudden cardiac death
- WPW syndrome, syncope, atrial fibrillation (AF) with pre-excited resting rate (RR) less than 250 ms or
- Accessory pathway effective refractory period (APERP) less than 250 ms
- Chronic or recurrent SVT with ventricular dysfunction
- Recurrent ventricular tachycardia, hemodynamic compromise, amenable to CA

Class IIA

- Recurrent/symptomatic SVT refractory to medical management more than 4 years of age
- Chronic or incessant SVT with normal ventricular function
- Palpitations with SVT at electrophysiology study (EPS)

Class IIB

- Asymptomatic WPW syndrome more than 5 years of age; risks/benefits of arrhythmia and ablation explained to family
- SVT more than 5 years; replace effective antiarrhythmic medications
- SVT less than 5 years; ineffective antiarrhythmic medications or side effects
- VT one episode, hemodynamic compromise, amenable to CA

Class III

- Asymptomatic WPW syndrome less than 5 years of age
- SVT less than 5 years, effective antiarrhythmic medications
- Nonsustained VT, no hemodynamic compromise
- Nonsustained SVT, minimally symptomatic

Procedural Implications

The ablation procedure, including catheter placement, programmed electrical stimulation, and recording and analysis of electrograms, is similar to that in adults. Standard CA includes

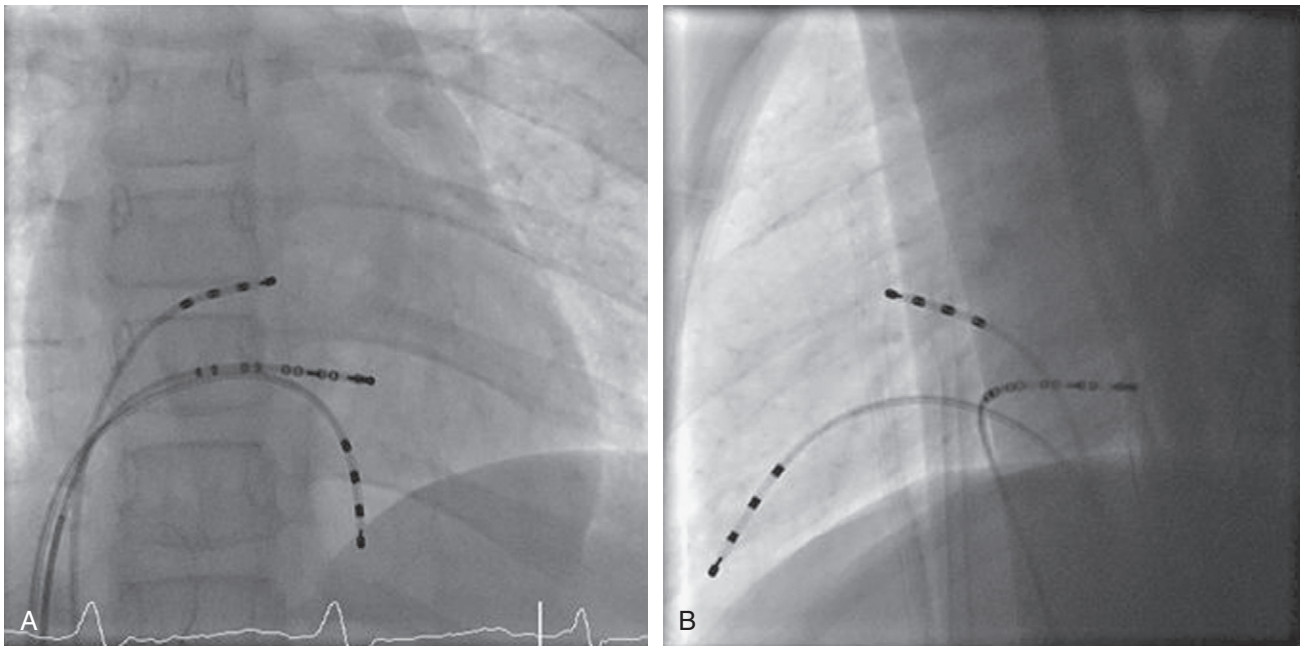


FIGURE 76-1 Fluoroscopic image of catheters in the His bundle, coronary sinus, and right ventricular apex positions. **A,** Right anterior oblique view. **B,** Left anterior oblique view.

placement of a multiple-polar (octapolar or decapolar) catheter in the coronary sinus from either the right internal jugular vein or the femoral vein and quadripolar catheters in the His bundle and right ventricular apex positions (Figure 76-1). Programmed electrical stimulation (PES) and pacing maneuvers are performed from the atrium and the ventricle to identify the location and characteristics of the AP (such as effective refractory period [ERP]) and inducibility of different arrhythmias. The procedure can be modified by using smaller caliber and fewer catheters in younger patients without compromising the procedure. This can be accomplished by the occasional use of an esophageal electrode for atrial stimulation and recording to replace an intracardiac catheter or by the use of His–right ventricular apex (RVA) multiple-polar catheter to obtain both RVA and His-bundle signals with a single catheter. Attention must be paid to the procedure, anesthesia duration, and fluoroscopy times, as younger patients are more susceptible to radiation effects. Ideally, pediatric interventional electrophysiology laboratories need to be specifically equipped with bi-plane, low-dose-rate pulsed fluoroscopy, and special shielding techniques. Availability of pediatric cardiac anesthesiologists, pediatric interventional cardiologists, and specially trained pediatric nursing personnel are essential to the safety and success of electrophysiology procedures in children.

Sedation and Anesthesia

In children older than 10 years of age who are not overly anxious or resistant to intravenous (IV) sedatives, conscious sedation and careful monitoring may be used. General anesthesia, with or without endotracheal intubation, may be necessary in children younger than 10 years or when comorbid pulmonary, neurologic, or hemodynamically significant structural heart disease coexist.[5] Deeper sedation with general anesthesia as well as "breath holding" apnea techniques may be preferred if a para-Hisian septal pathway is suspected to minimize catheter instability related to respiratory motion.[5] When no anesthesiologist is present, a nurse with sedation experience is crucial for close monitoring of the airway and vital signs and to avoid sedation overdose, especially during long procedures.

Ablation Energy Source

In the current era, RF energy or cryothermal (cryo) energy is used to interrupt abnormal pathways and ablate ectopic foci. The developing myocardium has the potential for the growth of lesions over time after application of RF energy, but no long-term follow-up studies are available to understand the implications. This potential should be considered when RF ablation is used in young children. Cryo energy application is preferred if the target is near the sinoatrial (SA) node, AV node, or His bundle to prevent damage to these areas of specialized conduction tissue that could result in SA node dysfunction or permanent heart block. Cryo ablation is preferred for ablation inside the coronary sinus as RF energy delivery in this region can result in blood coagulation, inadequate energy delivery, coronary artery injury, or perforation. Long-term recurrence risk of arrhythmia after cryo ablation, which may be as high as 10% to 20%, can be diminished by accurate mapping and requiring stringent time to success of less than 15 seconds after the onset of a cryo lesion before proceeding with a complete lesion.[7]

Approach to Ablation of Accessory Pathways

The approach to the ablation of APs depends on whether the pathway is concealed or manifest (in WPW syndrome) (Figure 76-2). Subjects with WPW syndrome should have the antegrade

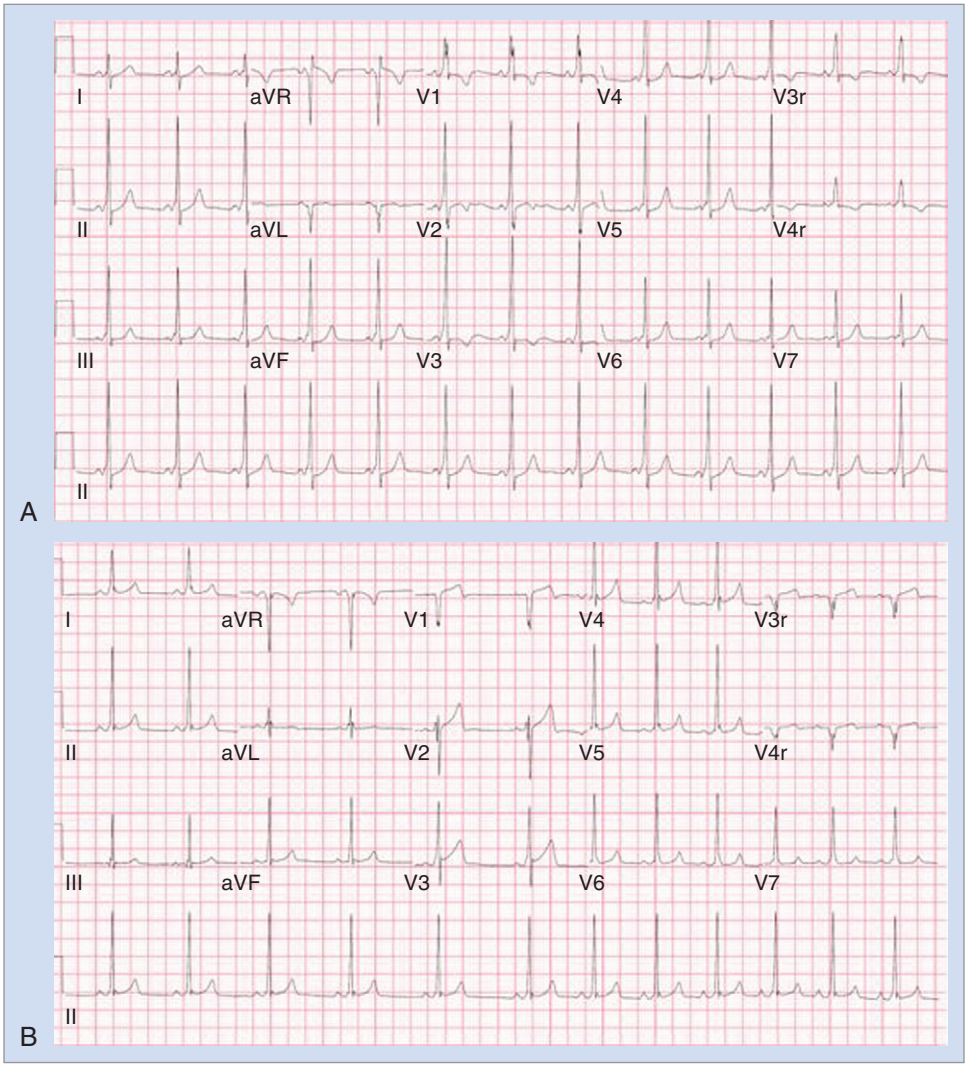
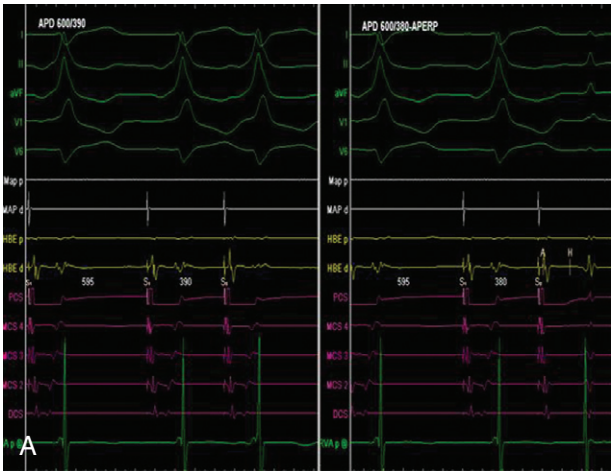


FIGURE 76-2 Fifteen-lead electrocardiograms showing Wolff-Parkinson-White syndrome. **A,** Left-sided accessory pathway. **B,** Right-sided accessory pathway.

ERP and the shortest pre-excited R-R interval in AF determined. Indicators of high-risk AP include an ERP of less than 250 ms (Figure 76-3, *A*), the shortest pre-excited R-R interval of less than 220 ms, or the presence of multiple pathways.[8–10] More recent studies have reported on a follow-up of 184 asymptomatic patients with WPW syndrome over 57 months (mean age, 10 years); 19 subjects (almost 10%) developed life-threatening arrhythmias, which makes a case for risk stratifying all patients with WPW syndrome at some point during the clinical course of their disease (Figure 76-3, *B*).[11] Mapping of APs can be performed either during sinus rhythm with overt pre-excitation (Figure 76-4), during ventricular pacing by observing retrograde atrial conduction (Figure 76-5), or by observing retrograde atrial activation during SVT (Figure 76-6). If retrograde AP conduction is mapped during ventricular pacing, it must be ensured that fusion with retrograde AV nodal–His-Purkinje conduction, which is quite robust in children, does not occur.[12] This can be confirmed with the administration of a bolus of IV adenosine during ventricular pacing, which blocks the retrograde AV nodal conduction but not the retrograde AP conduction. Additionally, other pacing maneuvers such as ventricular PES with single extrastimuli will eliminate retrograde AV nodal conduction. Rarely, children can have adenosine-sensitive antegrade or retrograde conducting APs.

Approximately 60% of all APs are located on the left AV groove.[12] Access to the left atrium is achieved by the trans-septal technique using a trans-septal puncture kit (which includes the sheath, the dilator, and the needle) with the assistance of bi-plane fluoroscopy, pressure monitoring, and contrast injection (Figure 76-7). Rarely, transesophageal echocardiogram (TEE) or intracardiac echocardiogram (ICE) may be helpful in the presence of complex heart disease. Heparinization is essential for ablation of left-sided pathways once trans-septal access is obtained; activated clotting time should be maintained above 250 seconds with heparin infusion or bolus doses for the duration of the procedure. In some pediatric laboratories, a retrograde trans-aortic technique is preferred for left-sided pathways (Figure 76-8) with established safety[13]; the presence of aortic valve disease or younger age (<5 years) may be relative contraindications to this approach because of the risk of damage to the aortic valve from the maneuvering of the ablation catheter.

In cases with a left-sided AP, mapping is improved by placing a multiple-electrode catheter in the coronary sinus for initial



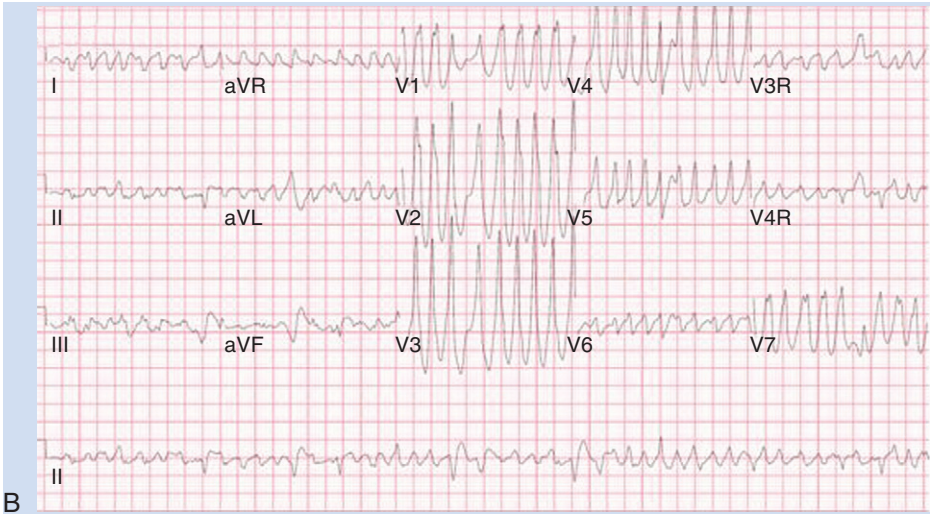


FIGURE 76-3 **A,** Demonstration of accessory pathway effective refractory period with programmed electrical stimulation. *Right panel* shows an accessory pathway effective refractory period of 380 ms. **B,** Fifteen-lead electrocardiogram showing atrial fibrillation and rapid one-on-one ventricular conduction in a patient with Wolff-Parkinson-White syndrome.

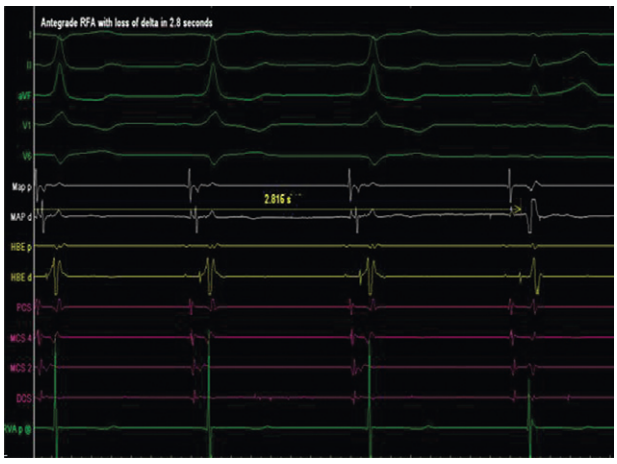


FIGURE 76-4 Sinus rhythm mapping of left-sided accessory pathway in Wolff-Parkinson-White syndrome, showing successful signal and loss of pathway conduction with radiofrequency.

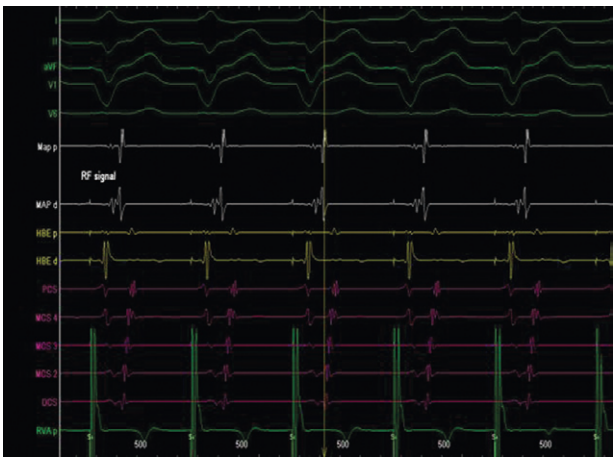


FIGURE 76-5 Mapping during ventricular pacing of left-sided accessory pathway in Wolff-Parkinson-White syndrome, showing successful signal.

pathway localization. Access to right-sided pathways, although straightforward from an access standpoint, may be technically challenging. The lower success rate of right AP ablation is related to mapping error and poor catheter stabilization. The tricuspid valve (TV) has a larger circumference than the mitral valve and differs with respect to the angle at which the valve attaches to the annulus. In addition, the absence of a reference catheter in an annular venous structure (such as the coronary sinus) increases mapping errors. The right coronary artery (RCA) runs along the ventricular aspect of the right epicardial AV groove and has a constant anatomic relation to the right AV annulus, regardless of the location of valve attachment. RCA mapping with various catheters has been used for pathway localization in selected patients in some EP laboratories (Figure 76-9). The efficacy and safety of this technique using a multiple-polar 2F microcatheter in a select group of children has been reported.[14] Despite accurate mapping of the right AV annulus, the procedure is often confounded by catheter instability. It is often necessary to use a long sheath with specially directed curves that orient the catheter tip toward the right AV groove. Additionally, cryo ablation, by virtue of catheter adherence to the AV groove during a lesion, may be advantageous. This may be specifically helpful in right-sided anteroseptal and midseptal APs. In these locations, accurate mapping with minimal catheter movement is important to avoid any injury to collateral structures such as the His bundle (Figures 76-10 and 76-11). Catheter mapping from the right internal jugular approach is sometimes more helpful than the traditional femoral approach because of the angle of approach to the AV groove.

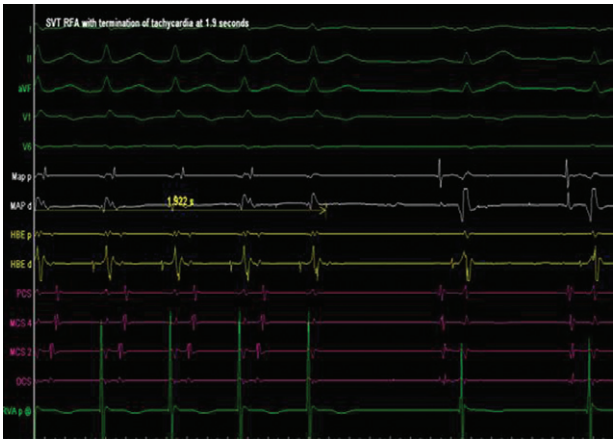


FIGURE 76-6 Supraventricular tachycardia (SVT) mapping of left-sided accessory pathway in Wolff-Parkinson-White syndrome, showing successful signal and loss of pathway conduction during SVT with radiofrequency.

Approximately 5% to 10% of the patients may have multiple pathways or multiple SVT mechanisms.[9] Post-ablation EP testing includes repeat programmed electrical stimulation to exclude the presence of multiple pathways or confirm the recovery of the recently ablated AP. After a presumed successful ablation, adenosine confirms the absence of antegrade or retrograde AP conduction. Isoproterenol is used to provide adrenergic

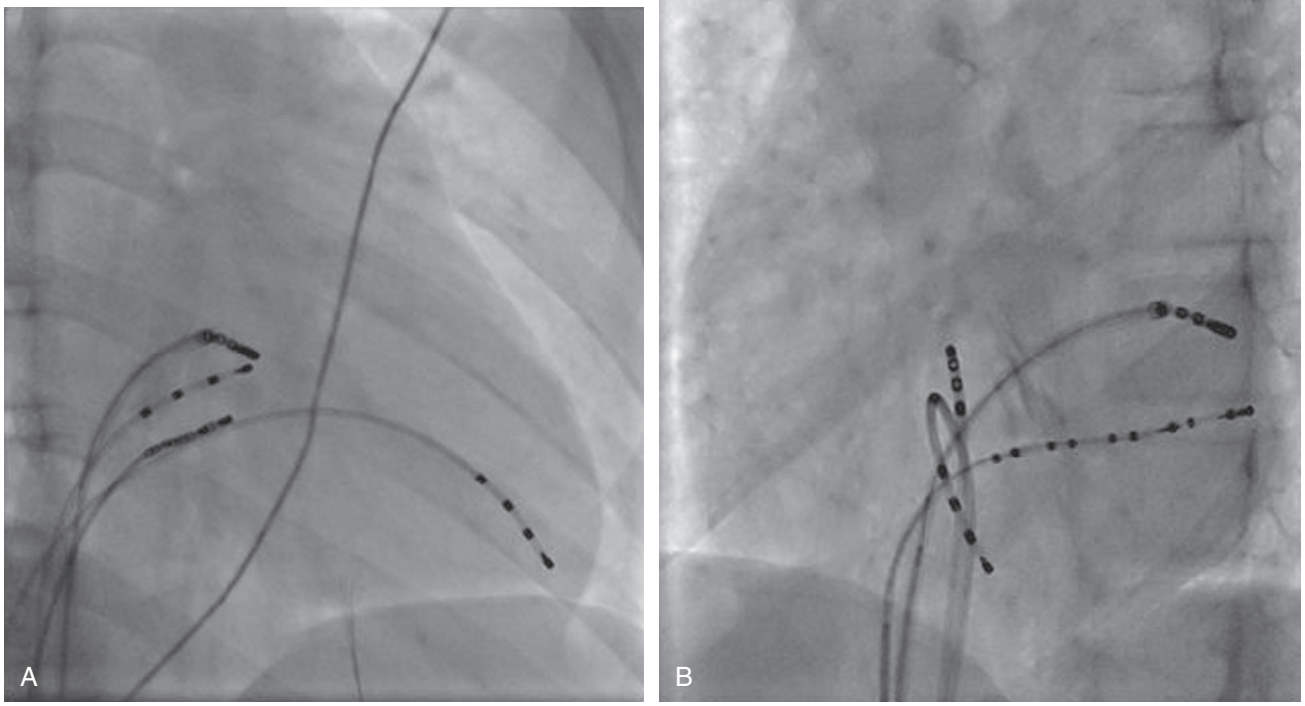


FIGURE 76-7 Fluoroscopic image of catheters in the His bundle, coronary sinus, right ventricular apex positions, and trans-septal sheath with radiofrequency catheter in left atrium. **A,** Right anterior oblique view. **B,** Left anterior oblique view.

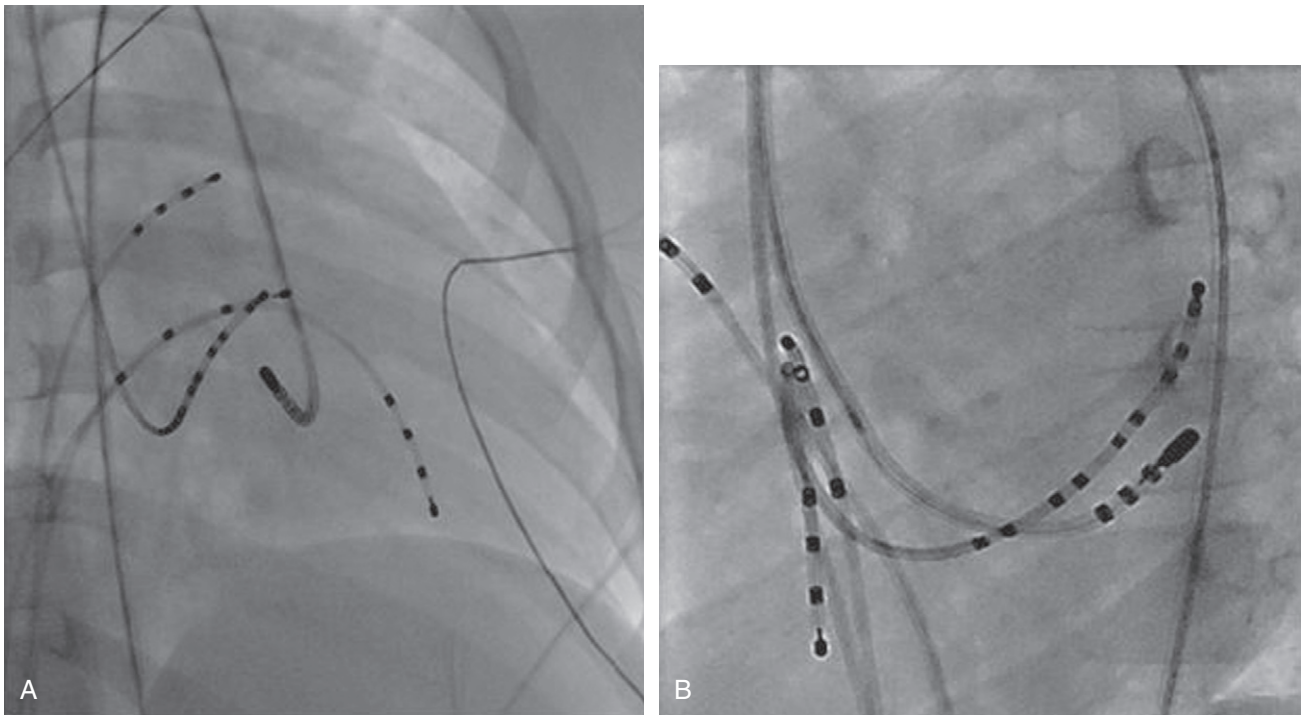


FIGURE 76-8 Fluoroscopic image of catheters in the His bundle, coronary sinus, right ventricular apex positions, and trans-aortic retrograde radiofrequency catheter approach. **A,** Right anterior oblique view. **B,** Left anterior oblique view.

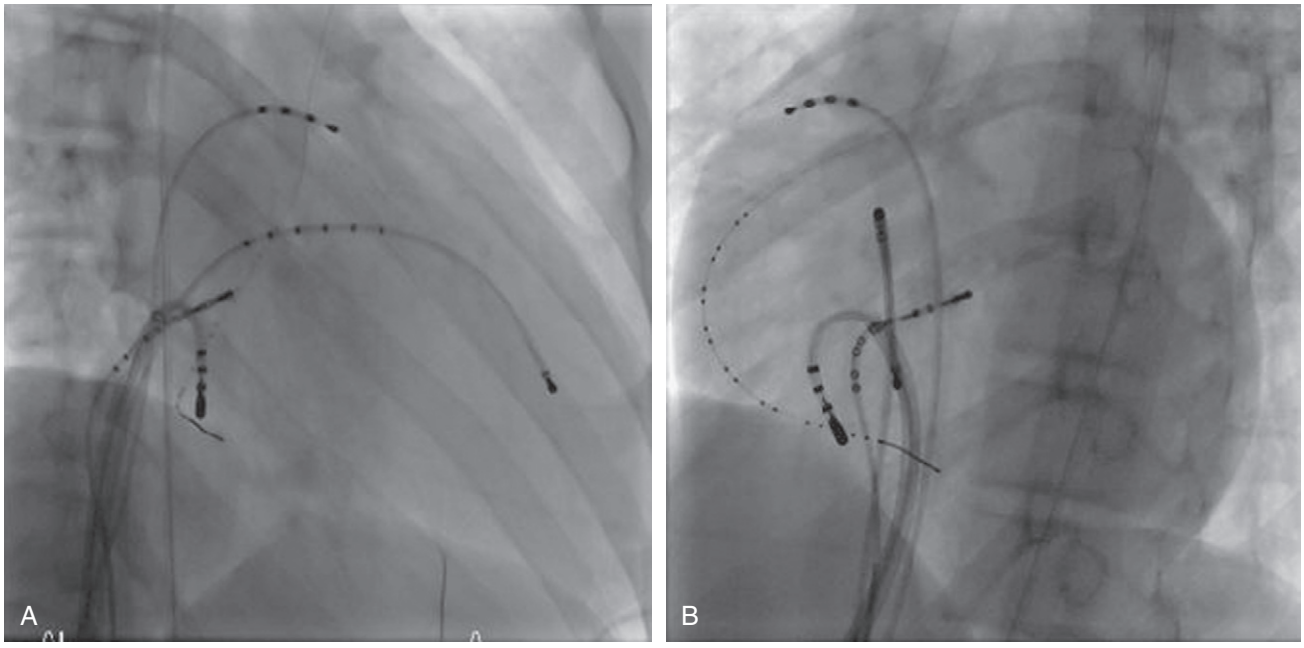


FIGURE 76-9 Fluoroscopic image of catheters in the His bundle, coronary sinus, right ventricular apex positions, and 2F multiple-polar catheter in the right coronary artery. **A,** Right anterior oblique view. **B,** Left anterior oblique view.

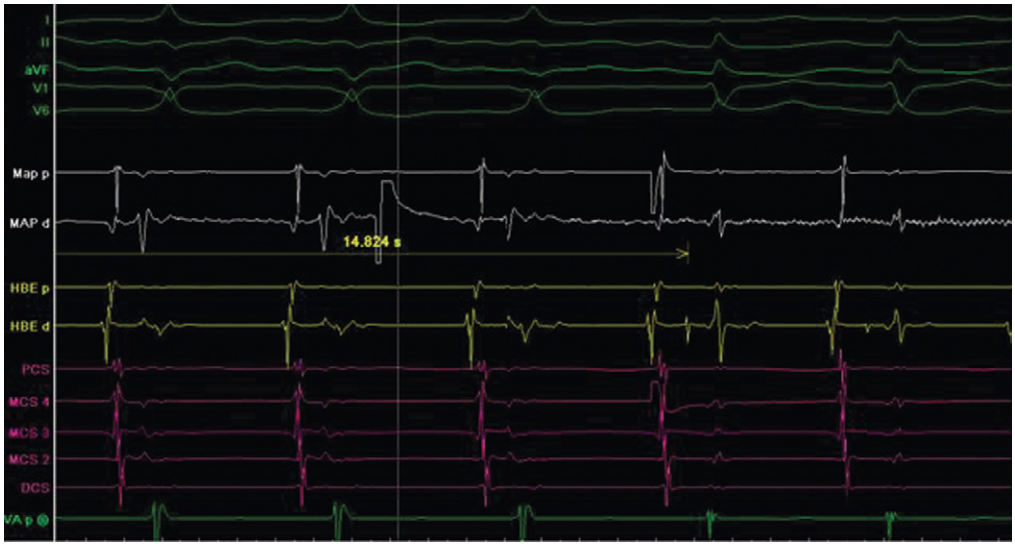


FIGURE 76-10 Balanced signals in right anteroseptal atrioventricular groove showing successful signal and loss of pre-excitation in 14.8 seconds with the onset of cryothermal ablation.

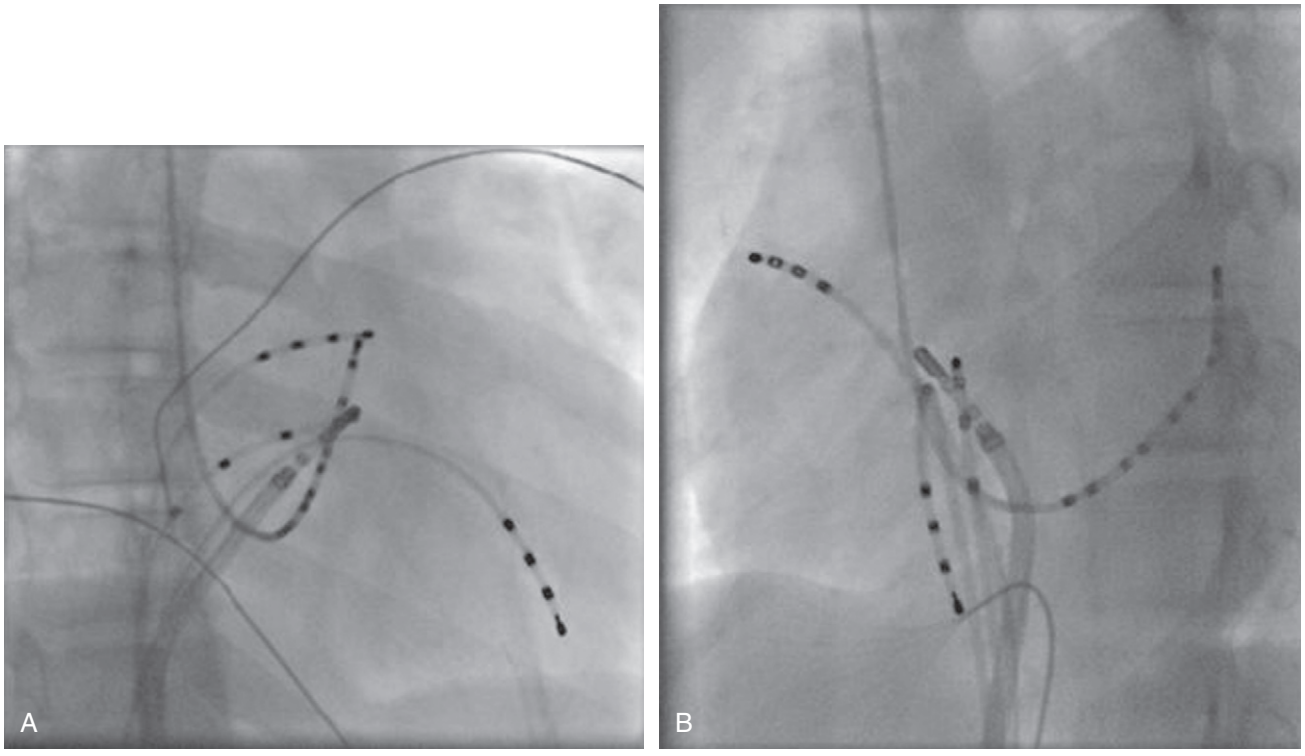


FIGURE 76-11 Fluoroscopic image showing use of long sheaths for stabilization of cryo catheter in the right anteroseptal region. **A,** Right anterior oblique view. **B,** Left anterior oblique view.

stimulation during programmed electrical stimulation to indicate lack of inducibility of SVT. This protocol is used during the "waiting period" after ablation to confirm a successful ablation with noninduction of SVT and absence of residual or additional APs. The "waiting period" after the successful lesion may vary from 30 to 60 minutes.

Ablation for Atrioventricular Nodal Re-entry Tachycardia

AV nodal re-entry tachycardia (AVNRT) is infrequent in infants and young children, but its incidence increases with age.[1] Although

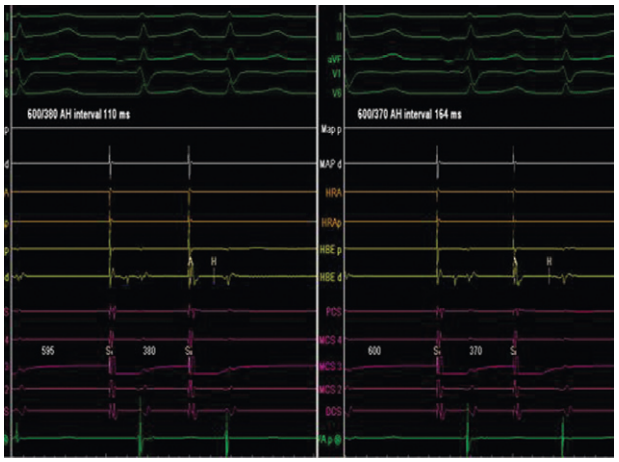


FIGURE 76-12 Demonstration of dual atrioventricular node physiology by programmed electrical stimulation. *Left,* A-H interval 110 ms. *Right,* A-H interval of 164 ms with a 10-ms decrement to the S2 interval.

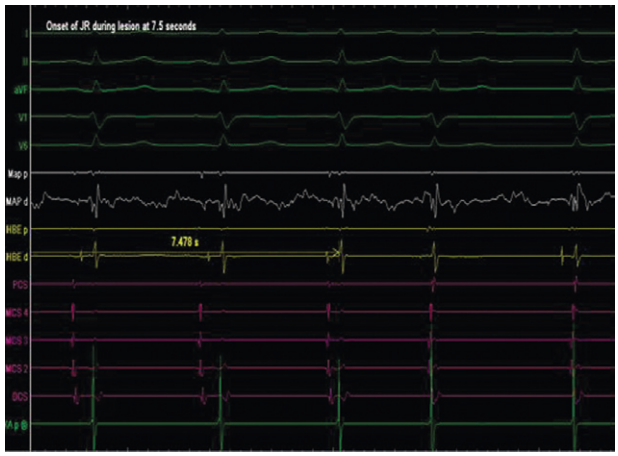


FIGURE 76-13 Evidence of junctional rhythm with intact ventriculoatrial conduction with radiofrequency application in the slow pathway region.

the mechanism of AVNRT induction is similar in children and adults, the same definition of dual AV node physiology—that is, 50-ms increase in the atrium to His (A-H) with a 10-ms decrease in atrium-to-atrium (A-A) extrastimulus (Figure 76-12)—may not be applicable to the pediatric population; typical and atypical AVNRT may be induced without clear-cut evidence of dual AV node physiology. Slow pathway elimination or modification is performed by RF or cryo energy delivery to the area of slow conduction in the triangle of Koch. Although the dimensions of the triangle of Koch are relatively constant in adults of different sizes, the area increases with growth in children. In children with a body weight less than 20 kg, the area is 50 mm^2 or less.[15] This small dimension, along with the proximity of the AV node and His bundle region, should be considered carefully when applying RF energy in small children with AVNRT. With RF application in the slow pathway region, accelerated junctional rhythm is observed. Care needs to be taken to preserve fast pathway conduction (by either atrial pacing or by watching the ventriculoatrial [VA] conduction in junctional rhythm) (Figure 76-13). Successful elimination of AVNRT can be achieved with a 95% success rate and a low recurrence risk by using RF energy. Optimal temperatures during RF ablation should not exceed 55° C and often 45° to 48° C is sufficient.[16]

Radiofrequency Ablation Versus Cryothermal Ablation

With the advent of cryo technology, more operators are choosing cryo ablation over RF ablation as the first line of approach to avoid AV block. Success and recurrence risks have been reported to be similar in both procedures, but procedure time may be longer in cryo ablation.[17] More recent studies have shown overall lower success rate of 83% with cryo ablation with a 6-mm catheter tip in comparison with the standard RF ablation success rate of 93%.[7] In addition, this study compared the use of 6-mm cryo catheters for cryo ablation with RF ablation and found a 0.7% incidence of heart block with RF ablation, no heart block with cryo ablation, and no difference in procedure or fluoroscopy times. The use of 8-mm tip cryo catheters has also been shown to be effective, with 91% acute success with a 2.8% long-term recurrence risk[18]; a 6.5% incidence of transient AV block with complete recovery was seen in all subjects, and pacemaker implantation was not needed in any. Cryo lesions are usually placed in the slow pathway location in a sinus or paced rhythm while monitoring the antegrade fast pathway conduction; junctional rhythm is usually not seen, in contrast to slow pathway modifications with RF energy. Because the cryo ablation catheter is stable, an EPS (using PES) for a slow pathway can be performed during placement of the lesion to assess the efficacy of the cryo ablation.

Ablation for Ectopic Atrial Tachycardia

Ectopic atrial tachycardia (EAT) is an uncommon arrhythmia accounting for 5% to 20% of all SVTs.[19] The tachycardia may be incessant and result in tachycardia-induced cardiomyopathy. In younger patients (<1 year), conventional drug therapy is attempted, but in older patients, catheter ablation is often preferred, especially if the tachycardia is incessant. A small percentage of patients may have spontaneous resolution of their tachycardia over time.[12] PES is often of little help, as the SVT is often focal and automatic; however, it may respond to catecholamines. EATs can be left sided or right sided in origin (Figures 76-14 and 76-15) and sometimes can have a triggered mechanism. Use of conventional mapping with complementary three-dimensional systems, such as contact and noncontact mapping, is often helpful in decreasing fluoroscopy and procedure times and in increasing chances of ablation success.[20] Depending on the cycle length and location of the EAT, mapping (Figures 76-16 and 76-17) and entrainment maneuvers (Figure 76-18) are performed before using RF ablation or cryo ablation. In the pediatric population, some of these ectopic tachycardias may be sensitive to sedation and anesthesia and may be noninducible because of suppression of the automatic focus by the sedation or the anesthetic. This may make mapping difficult in the very young, in whom conscious sedation may not be an option. Multiple P-wave morphologies and multiple foci may be present, which necessitates careful mapping in both atria

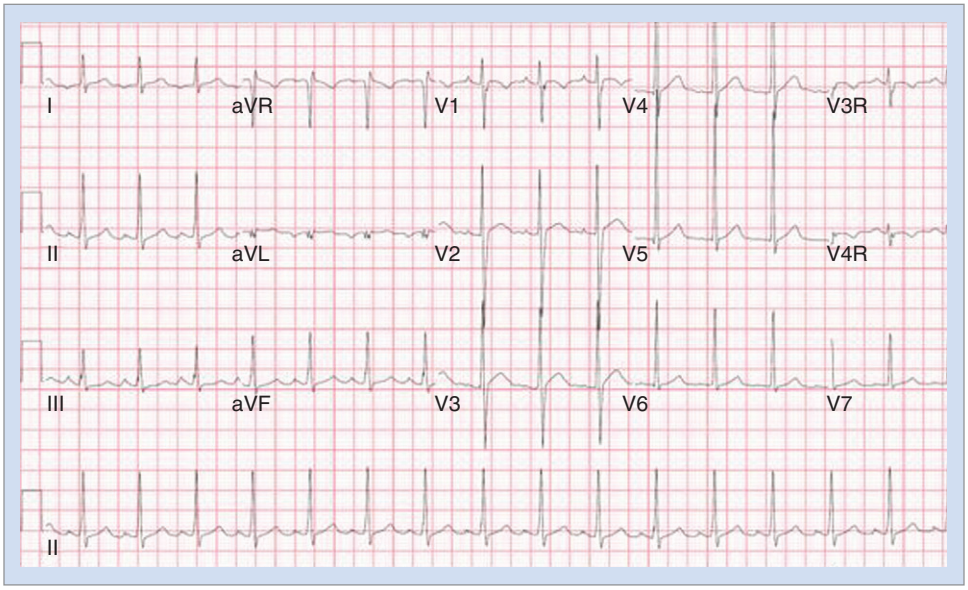


FIGURE 76-14 Fifteen-lead electrocardiogram showing left-sided ectopic atrial tachycardia from the right pulmonary vein. Positive P waves are seen in leads V1, 2, 3, and aVF, and negative P waves are seen in leads V1 and AVL.

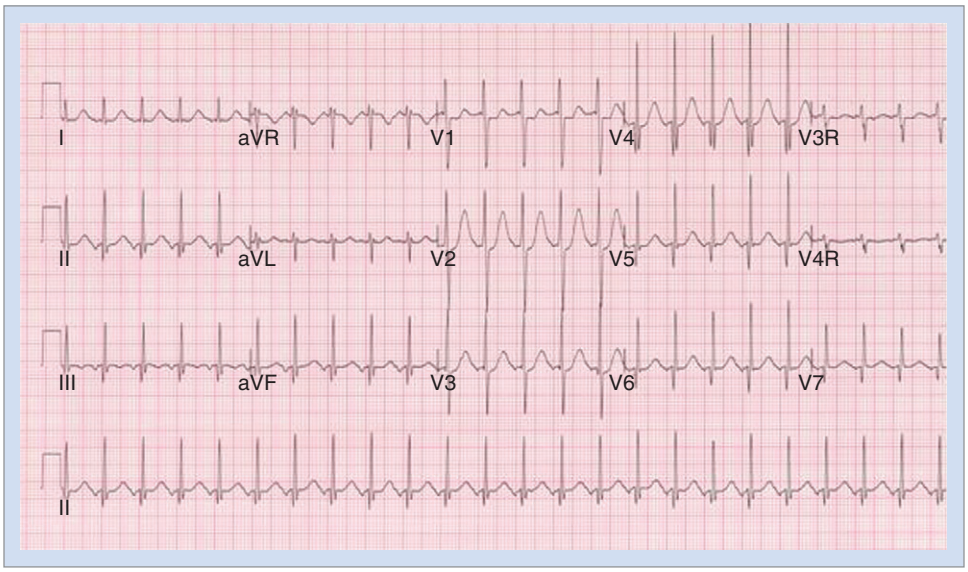


FIGURE 76-15 Fifteen-lead electrocardiogram showing right-sided ectopic atrial tachycardia from the mouth of the coronary sinus. P waves are isoelectric in lead V1, positive in lead aVL, and negative in leads 2, 3, and aVF.

before ablation is performed. Some of the secondary ectopic foci will become apparent after ablation of the initial clinical tachycardia.

Junctional Ectopic Tachycardia

Junctional ectopic tachycardia (JET) is an automatic tachycardia arising from the AV node or the His bundle, which can be seen either as a congenital (Figure 76-19) or as a postoperative form. Congenital JET may present early in life (in the first year of life, shortly after birth) and is often familial in 50% of the cases, and the etiology is unclear.[21] Some pathology reports have shown inflammatory changes at the crest of the ventricular septum, and others have linked it to anti-SSA and anti-SSB antibodies.[22,23] In contrast, the postoperative form is seen in the immediate postoperative period after repair of ventricular septal defect (VSD) or of complex CHD such as palliation of tetralogy of Fallot, AV canal, and single ventricle and transposition of the great artery.[19] Treatment of congenital JET initially usually consists of medical therapy with amiodarone in combination with digoxin, β-blockers, or flecanide. If the tachycardia is incessant with associated hemodynamic compromise, cryo or RF ablation is an option. Because RF has a high risk of causing AV block, cryo ablation is the preferred choice. Mapping is performed during tachycardia, and the region of interest is the anterior septum near the bundle of

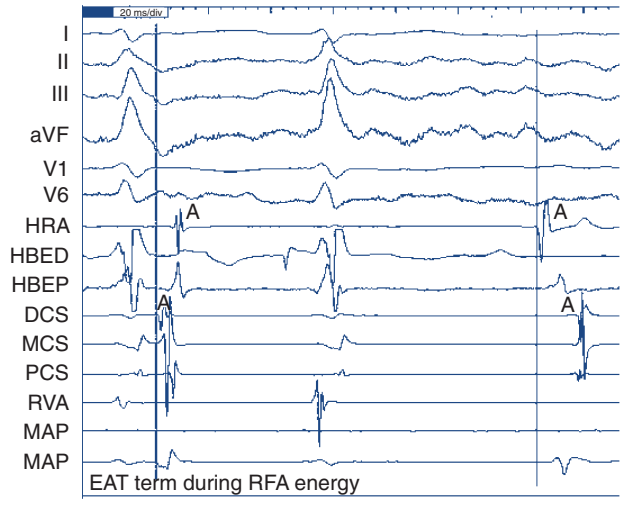


FIGURE 76-16 Intracardiac electrograms showing mapping and successful radiofrequency ablation (*RFA*) of left lower pulmonary vein ectopic atrial tachycardia.

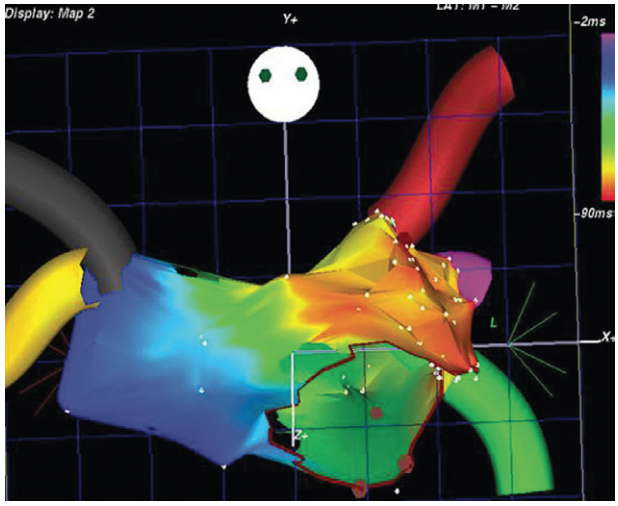


FIGURE 76-17 CARTO (Biosense Webster Inc., Diamond Bar, CA) activation map showing earliest activation in left lower pulmonary vein region of ectopic atrial tachycardia.

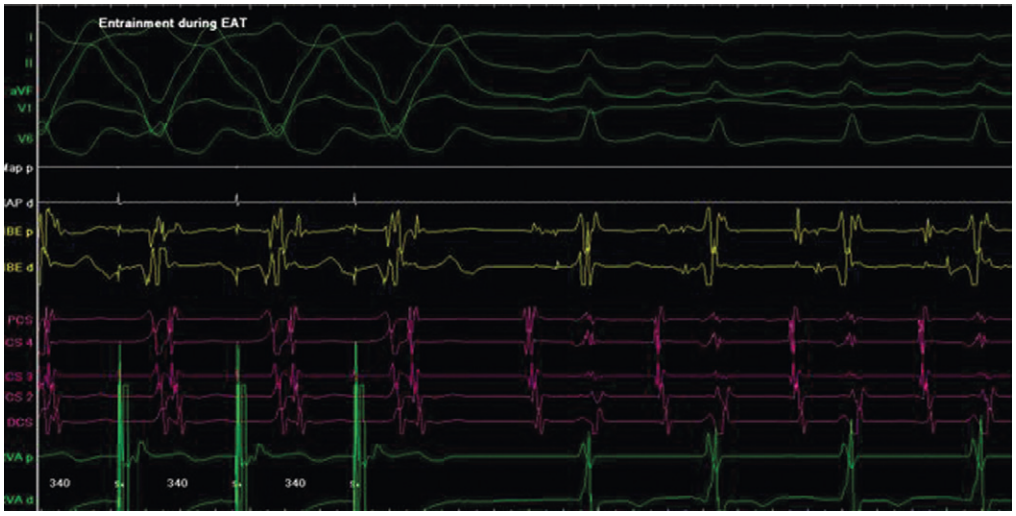


FIGURE 76-18 Ventricular pacing during ectopic atrial tachycardia shows a VA-AV response.

His. Either RF or cryo energy may be used to successfully eliminate the automatic focus.[24,25] The earliest His signal during tachycardia is targeted (Figure 76-20), and care is taken to monitor antegrade conduction and AV or P-R interval during lesion application. Postoperative JET almost never needs invasive intervention and can be managed with medications such as IV amiodarone.[19] It is self-limiting a few days after surgery once the inotropic medications are weaned and surgical stresses have abated.

Permanent Junctional Reciprocating Tachycardia

Permanent junctional reciprocating tachycardia (PJRT) is, in fact, a misnomer, as this disease is characterized by an orthodromic reciprocating tachycardia mediated by a slowly conducting concealed accessory pathway.[26] Because of the retrograde decremental pathway properties, the tachycardia may be incessant and result in tachycardia-induced cardiomyopathy. The tachycardia is characterized by narrow QRS morphology with a long R-P interval and negative P waves in leads 2 and 3 and aVF with earliest retrograde atrial activation in the posteroseptal right atrium (Figures 76-21 and 76-22). Medical management can be frustrating because of the incessant nature of the tachycardia, so catheter ablation is often the treatment of choice. Differential diagnosis includes atypical AV node re-entry tachycardia and ectopic atrial tachycardia, both of which can be associated with long R-P interval tachycardias. Diagnosis is confirmed by an EPS and maneuvers that include demonstrating atrial pre-excitation with a ventricular premature beat during His refractoriness, response to adenosine, and entrainment with ventricular pacing

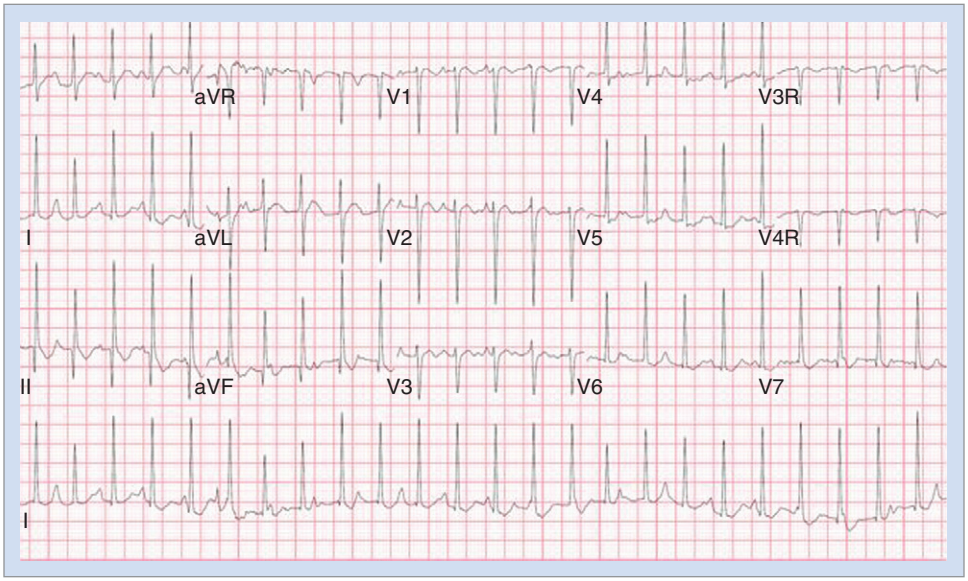


FIGURE 76-19 Fifteen-lead electrocardiogram showing congenital junctional ectopic tachycardia.

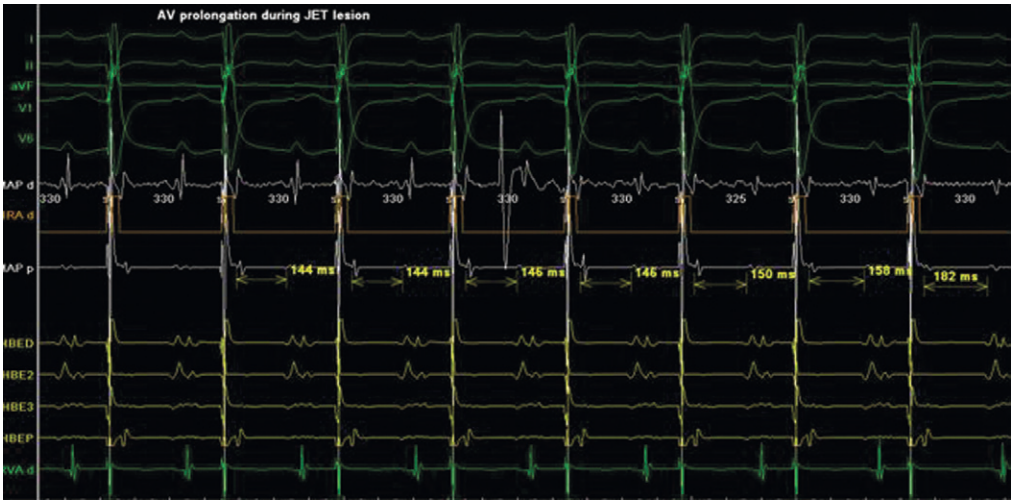


FIGURE 76-20 Shows intracardiac signals and atrioventricular prolongation during atrial pacing with radiofrequency ablation during junctional ectopic tachycardia ablation.

during tachycardia. Most of these pathways are located in the right posteroseptal region (Figure 76-23), but some have been reported in other locations such as right-lateral and left-posteroseptal AV groove.[27] Success rates of RF and cryo ablation may be as high as 95%, with a recurrence risk greater than those with other APs.[28] Complications include risk of injury to the AV node and the RCA, especially when ablating in the mouth of the coronary sinus.[6]

Ventricular Arrhythmia

Ventricular arrhythmias are uncommon in children with structurally normal hearts. However, two types of VT in this population deserve specific attention.

Outflow Tract Ventricular Tachycardia

Outflow tract ventricular tachycardias present fairly early in life, with equal distribution between the two genders.[29] Most patients are asymptomatic and are often diagnosed at routine physical examinations as having "an irregular heart beat." Other patients may experience palpitations, lightheadedness, or presyncope. Most ventricular tachycardias in the young arise from the right ventricular outflow tract (RVOT). This predisposition to a specific region of the heart (perivalvar area) raises the possibility of "fiber disruption during development" as an etiology.[30] Other etiologies such as subclinical myocarditis or pericarditis may enhance fiber disruption or cause local dysautonomic changes predisposing to triggered activity and arrhythmogenesis. These tachycardias are triggered by delayed after-depolarizations (DADs) that are

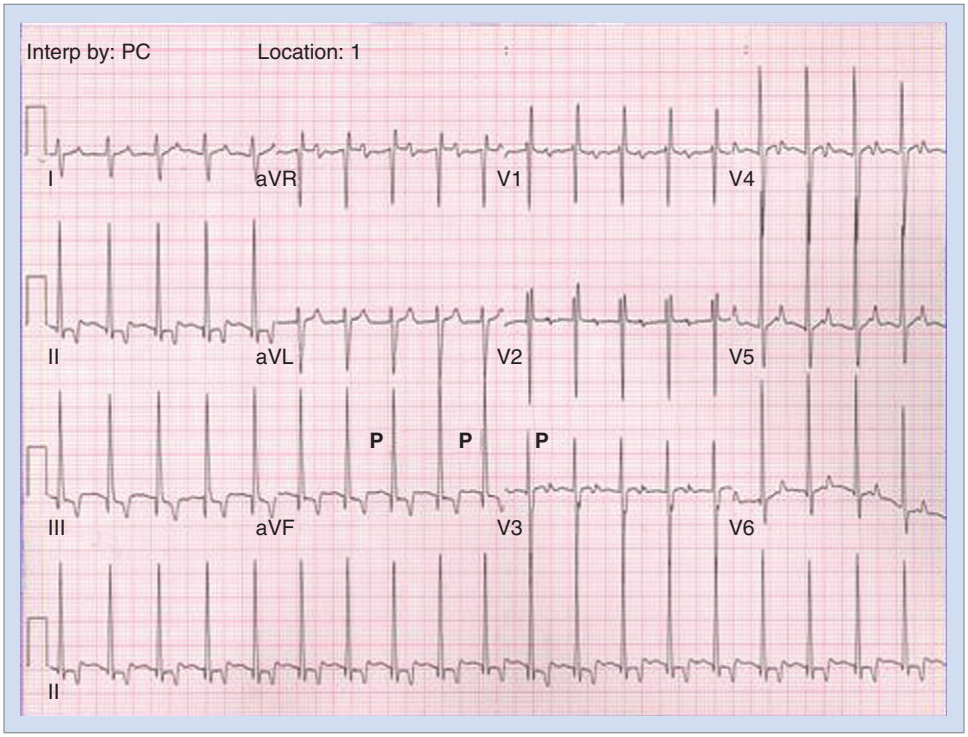


FIGURE 76-21 Fifteen-lead electrocardiogram shows persistent junctional reciprocating tachycardia. Note a long R-P interval tachycardia with negative P waves in leads 2, 3, and aVF.

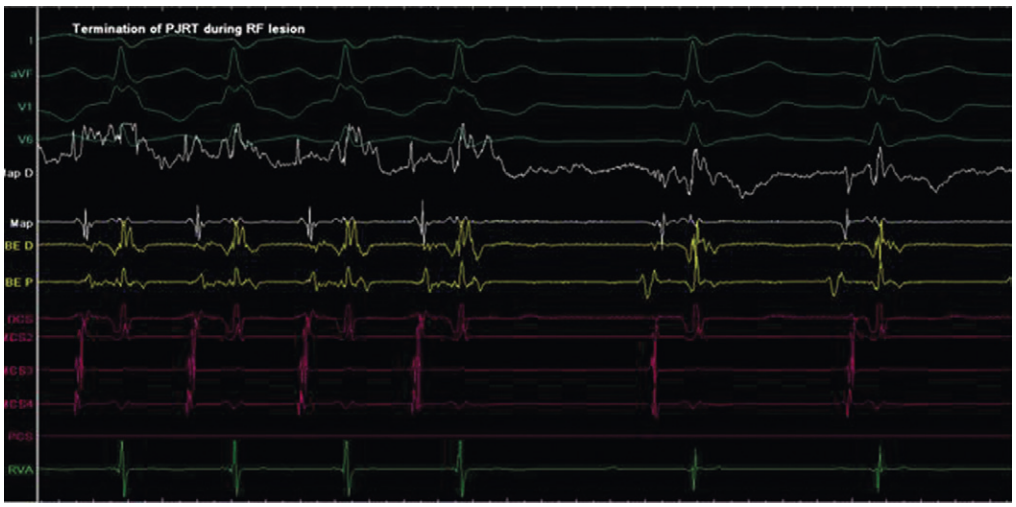


FIGURE 76-22 Intracardiac signals showing earliest retrograde atrial activation in the proximal coronary sinus. Mapping and radiofrequency ablation in this area successfully terminates supraventricular tachycardia.

dependent on calcium release, which is inhibited by adenosine, and hence they are described as "adenosine sensitive."[30] The electrocardiogram (ECG) typically shows a left bundle branch block (LBBB) with inferior axis morphology, and the tachycardia may be sustained or nonsustained (Figures 76-24 and 76-25). The tachycardia, which is usually suppressed by increasing heart rates, can be observed by 24-hour Holter monitoring or exercise stress tests. Clinical investigations, including echocardiography and magnetic resonance imaging (MRI), reveal structurally normal hearts. Since the arrhythmia is usually non–life threatening, indications for treatment include the presence of symptoms and ventricular dysfunction. Medical therapy may include β-blockers or calcium channel blockers, which have shown variable success rates.[31] Spontaneous resolution can occur in some in adolescence. Ablation success rates have been greater than 90%, but the availability of bi-plane fluoroscopy and three-dimensional mapping are essential.[31,32] The arrhythmia is often suppressed by sedation and anesthesia, necessitating isoproterenol, aminophylline, and epinephrine to enhance triggered activity and tachycardia induction. Complications to avoid include complete or right bundle

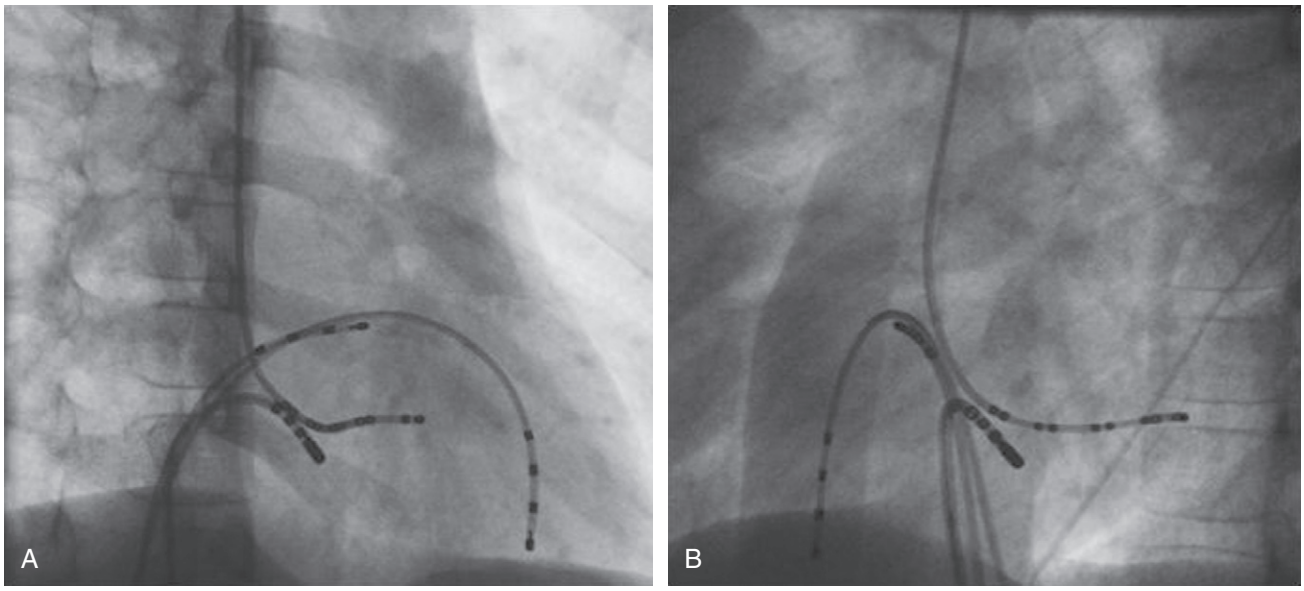


FIGURE 76-23 Fluoroscopic image showing site of successful catheter ablation in right posteroseptal region for ablation of persistent junctional reciprocating tachycardia. **A,** Right anterior oblique view. **B,** Left anterior oblique view.

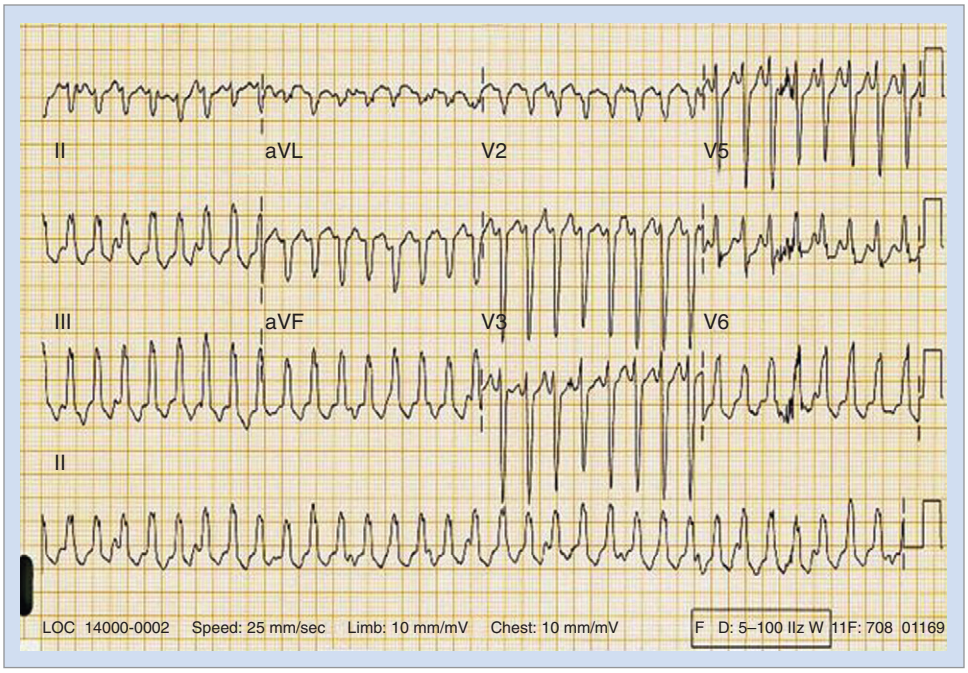


FIGURE 76-24 Twelve-lead electrocardiogram showing sustained ventricular tachycardia of left bundle branch block inferior axis morphology arising from right ventricular outflow tract.

branch block (RBBB) and damage to the coronary arteries and the aortic valve when ablation is performed in the left ventricular outflow tract (LVOT).[31]

Fascicular Ventricular Tachycardia

Fascicular ventricular tachycardia is the most common form of idiopathic left-sided VT seen in the pediatric population. It is characterized by an RBBB and left-axis deviation configuration (Figure 76-26). This VT is seen in structurally normal hearts and can be induced by atrial or ventricular stimulation, which suggests a re-entry mechanism.[33] Belhassen described verapamil sensitivity as a characteristic of this arrhythmia, so it is also called *Belhassen tachycardia*.[34] More recently three different types have been described: (1) the more common left posterior fascicular VT with a QRS morphology of RBBB and superior axis; (2) the uncommon left anterior fascicular VT with RBBB and right-axis deviation; and (3) the rare upper septal fascicular VT with a narrow QRS and normal or right-axis deviation. Different etiologies for this abnormal re-entry have been suggested, including false tendons

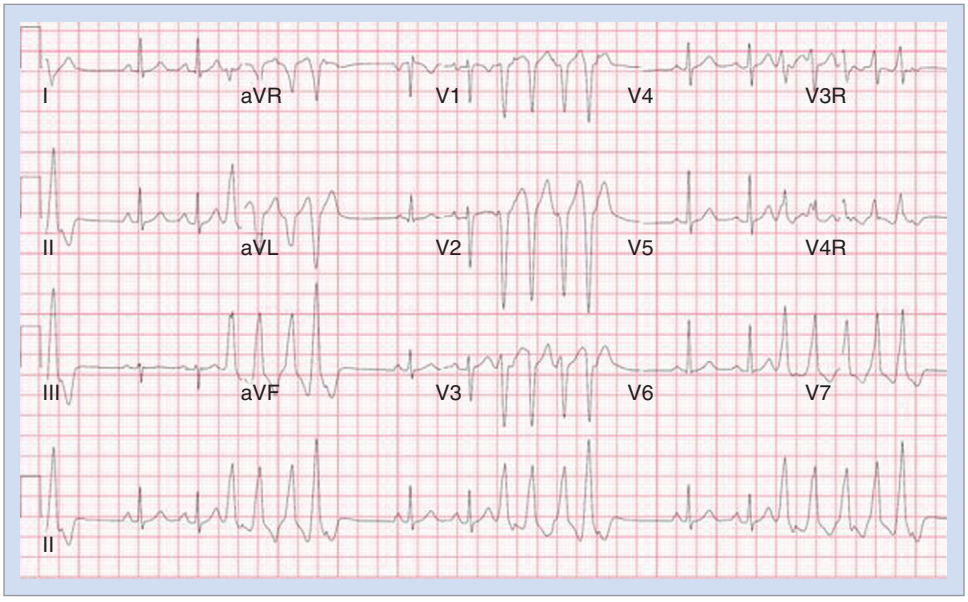


FIGURE 76-25 Fifteen-lead electrocardiogram showing nonsustained ventricular tachycardia from the right ventricular outflow tract with left bundle branch block and inferior axis morphology.

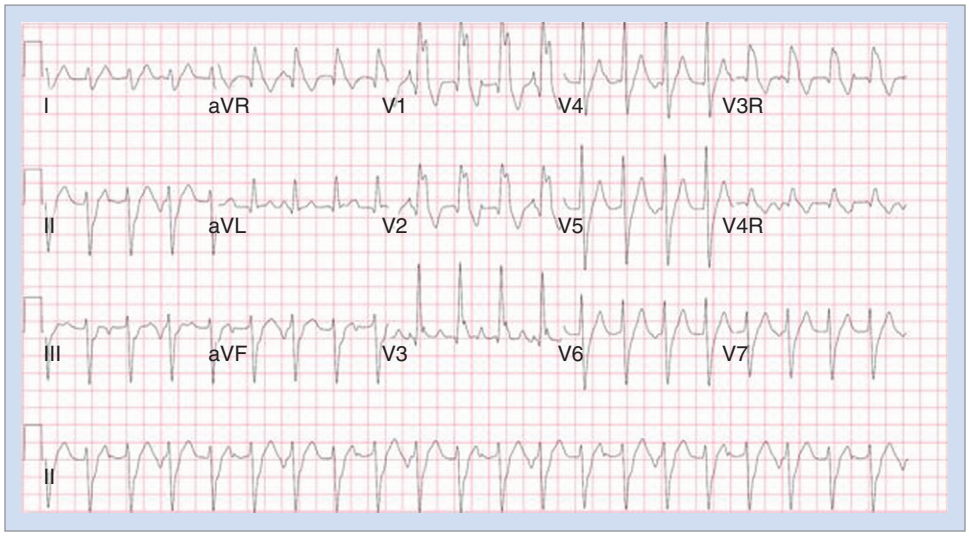


FIGURE 76-26 Fifteen-lead electrocardiogram showing wide complex tachycardia with right bundle branch block and superior axis morphology consistent with fascicular ventricular tachycardia.

extending to the basal LV septum and abnormalities in the Purkinje network that facilitate the arrhythmia.[35] Clinical presentation is often similar to that of SVT and includes paroxysmal episodes of palpitations, fatigue, and dizziness. The ECG may have typical findings of RBBB with superior axis. Twenty-four-hour Holter monitoring is helpful if the arrhythmia is nonsustained. The arrhythmia is sensitive to calcium channel blockers (such as verapamil).[34] Curative therapy using RF or cryo ablation involves mapping of the LV during tachycardia or sinus rhythm. LV access is obtained by the antegrade trans-septal approach or the retrograde aortic approach (Figure 76-27). Different strategies include targeting the diastolic potential (which represents the antegrade limb of the VT circuit) in the LV midseptum, pace mapping in the LV midseptum for a perfect QRS match, and targeting of the VT exit site at the apical septum using presystolic fused Purkinje potentials.[36] Success rates for ablation vary between 80% and 85%, with a 5% risk of recurrence.[37] Complications to avoid include damage to the femoral artery and the aortic valve and formation of a left-sided thrombus.

Use of Ablation in Patients with Congenital Heart Disease

Accessory Pathways and Dual Atrioventricular Nodal Pathways in Congenital Heart Disease

The overall incidence of CHD is approximately 1%, with almost half these patients requiring cardiac surgery.[12] The prevalence of accessory pathways in CHD varies between 1 and 3 per 1000,

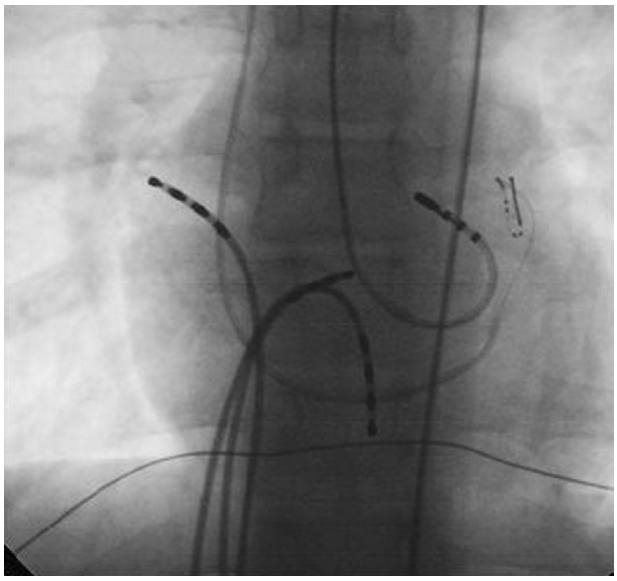


FIGURE 76-27 Right anterior oblique view of successful catheter ablation site in the left ventricle for fascicular ventricular tachycardia.

including manifest WPW and concealed APs.[38] Although these pathways have been associated with all types of anatomic CHD lesions, WPW syndrome is especially common in Ebstein anomaly and varies between 9% and 20%.[39] These pathways are often multiple and right sided. APs are seen in L-looped ventricles with associated Ebstein anomaly.[40] WPW patterns have been reported in hypertrophic cardiomyopathy.[41] AV reciprocating tachycardia has been reported with twin AV nodes and dual AV node pathways in complex congenital heart diseases such as heterotaxy syndromes with L-looped hearts.[42] These tachycardias are often poorly tolerated in the presence of residual hemodynamic issues. Although medical therapy is an option, invasive ablation therapy is preferred for a variety of reasons, including patient choice, side effects, adverse effects of medication in the presence of the congenital heart lesion, poor compliance to medical therapy, and the need for risk stratification.

Challenges in Mapping of Accessory Pathways

The different challenges in attempting an invasive EPS in CHD patients include the following:

1. Lack of peripheral venous or arterial access secondary to previous multiple catheterization or surgical procedures. This may be overcome by limiting the use of multiple diagnostic catheters, use of trans-hepatic venous cannulation, and direct transthoracic atrial access.[43,44]

2. Anatomic obstacles such as lack of antegrade access to the pulmonary venous atrium or venous access to the ventricle after the Fontan procedure and intra-atrial baffle procedures such as the Mustard and Senning procedures. In these instances, transbaffle or transconduit access to the "left atrial" side can be achieved, or a retrograde approach can be used to map APs.[45]

3. Situs abnormalities such as dextrocardia and mesocardia and heterotaxy syndromes with associated interrupted inferior vena cava (IVC) and azygous continuation. Use of biplane fluoroscopy to image complex anatomy may be helpful.

4. Abnormal displaced location of the normal conduction tissues (compact AV node and His bundle) in complex CHD, for example, displacement of normal conduction tissue posteriorly and inferiorly in AV canal defects and anterior displacement in L-transposed hearts.[46,47]

5. Specific anatomic challenges such as presence of persistent left superior vena cava (SVC) and the inferior displacement of the tricuspid valve in Ebstein anomaly. The presence of tricuspid insufficiency and the recognition that the true AV grove is at the level of the RCA and higher than the valve leaflet insertion make the mapping of APs difficult. In L-transposition, the plane of the ventricular septum is more sagittal, and the coronary sinus CS is more difficult to cannulate. Atypical and typical AVNRT may be inducible, and diagnosis may be straightforward if multiple diagnostic catheters can be positioned (Figure 76-28). However, ablation for dual AV nodes and dual AV nodal physiology may not be easy because of displacement of the AV node outside the normal triangle of Koch.[46,47] Careful mapping using biplane fluoroscopy (Figure 76-29) for appropriate signal and use of CS angiography and atrial and ventricular angiography may be helpful in avoiding damage to the normal conduction tissue.

Mapping and Ablation of Accessory Pathways in D-Transposition of the Great Arteries with Mustard or Senning Procedures

The concepts of mapping and ablation are similar to those used in structurally normal hearts. In D-transposition of the great arteries after the Mustard or Senning baffle procedure, both APs and AVNRTs have been described.[48] Three-dimensional mapping, with or without contrast angiography in the baffle, helps delineate the systemic side of the baffle. For understanding the pulmonary venous atrial anatomy, the use of pulmonary artery contrast injection with delayed acquisition of angiogram pictures in the cardiac levophase is often helpful. The His bundle electrogram may not be easily recordable from the systemic venous side and may need retrograde aortic catheter positioning. Targeting the slow pathway from the right side may be challenging, as the baffle suture lines often traverse the inferior portion of Koch's triangle. Hence, a transbaffle puncture or a retrograde aortic approach may be necessary to map the slow pathway, which is usually on the pulmonary venous atrial side.[49] Cryo ablation may need to be considered to reduce the risk of heart block, as the exact position of the compact AV node and slow pathway inputs may not be clear. Similarly, mapping of the AV grove for concealed and manifest APs can be performed with either the antegrade or the retrograde approach on the ventricular side.

Mapping and Ablation of Accessory Pathways in Hearts with a Single Ventricle

In patients with a complex single ventricle, mapping for slow pathways and APs after the Fontan procedure can be challenging. The decision to ablate is often made on the basis of symptoms and impending surgery that might block future catheter access into the atrial chambers (such as the Fontan procedure). After a Fontan procedure, transconduit or transbaffle puncture (both intracardiac and extracardiac) can be performed safely to achieve

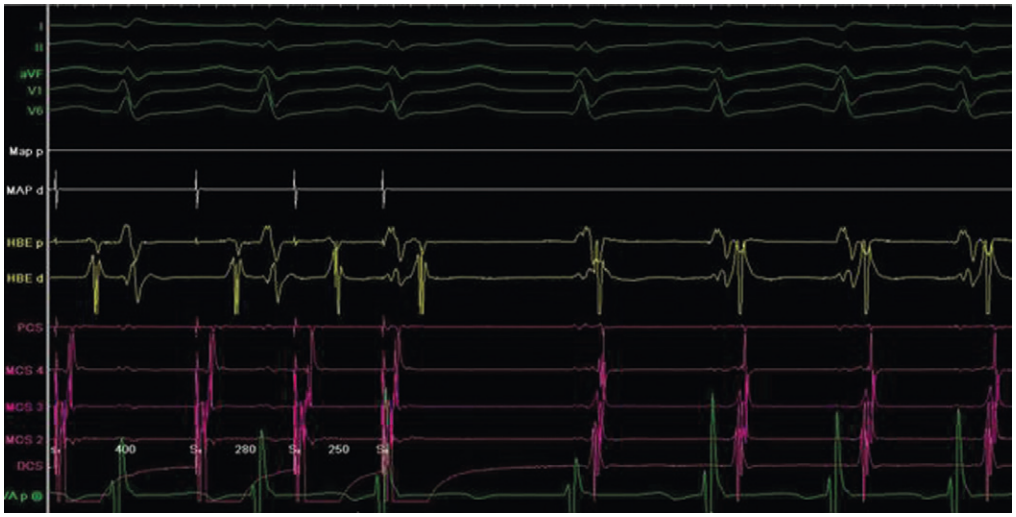


FIGURE 76-28 Intracardiac electrograms showing induction of atrioventricular nodal re-entry tachycardia in patient with L-looped transposition of great arteries. Atrial pacing is being performed from a distal coronary sinus catheter.

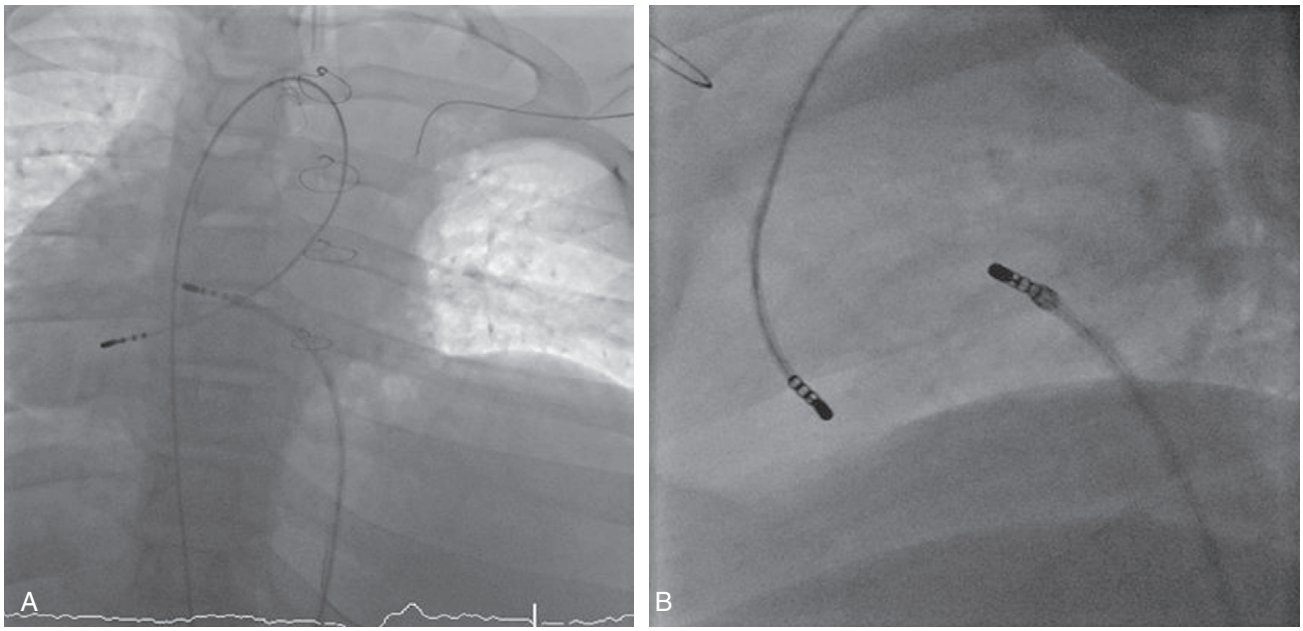


FIGURE 76-29 Fluoroscopic image showing limited catheter access and successful radiofrequency ablation site for atrioventricular nodal re-entry tachycardia in dextrocardia. **A,** Anteroposterior panel. **B,** Lateral views.

access into the pulmonary venous atrium, if needed.[50] In this patient group, careful attention needs to be paid to certain issues, including (1) arterial line placement and close monitoring of blood pressure, as tachycardia or pacing maneuvers may be poorly tolerated because of ventricular dysfunction; (2) aggressive anticoagulation protocol to avoid thrombus formation in the pulmonary venous atrium by monitoring activated clotting time (ACT) after heparin administration and maintaining it above 250 seconds. The anatomic displacement of the compact AV node and penetrating His bundle in complex CHD can result in difficulty in finding a good His bundle signal, which makes mapping of the para-Hisian and slow pathways challenging.[47,51,52] In such situations, cryo ablation may have to be considered in AVNRT and septal APs associated with complex heart disease.[53] The success rate of ablation for SVT (other than postoperative atrial flutter and atrial tachycardia) in CHD was reported to be 86.7% in the pediatric registry data.[4] The recurrence rate has been reported to be higher (15% to 20%) than in structurally normal hearts.[19]

Mapping and Ablation in Ebstein Anomaly

An increased prevalence of pre-excitation is seen in patients with the diagnosis of Ebstein anomaly. The challenges include multiple pathways, the ambiguous location of the right AV annulus, and the presence of tricuspid insufficiency. To better locate the right AV grove and the right-sided pathways, a 2F multiple-polar recording catheter is often placed from the retrograde approach in the RCA (see Figure 76-9) before mapping is started.[14] Placement of such a catheter helps identify the proximity of the right coronary artery to the AV groove and ablation site to avoid coronary artery injury. The electrograms at the successful site are often complex and fractionated.[54,55] In a series of 21 patients with 34 right-sided pathways, the acute success rate was 76% with a recurrence of 25%.[54] An analysis of the pediatric registry data showed that 16% of patients with CHD and SVT had Ebstein anomaly and that 29% of these patients had multiple pathways.[55] The acute success rate in this multiple-center trial was 83%.[55]

Atrial Arrhythmias in Congenital Heart Disease

Macro–re-entry atrial arrhythmia involving abnormal atrial muscle (resulting from scarring) is the most common arrhythmia mechanism in patients with CHD. The substrate for this abnormal atrial musculature includes suture line fibrosis and atrial septal defect (ASD) patch fibrosis, residual hemodynamic effects leading to chamber enlargement, and long-term hypoxic cellular injury after multiple cardiopulmonary bypass procedures. The different types of re-entry arrhythmias are described below.

Adult-Type Typical Atrial Flutter or Reverse Typical Atrial Flutter

These types of atrial flutter may be seen in patients with CHD in their 20s and 30s, who typically present with sawtooth P waves with a positive or negative morphology in the inferior leads. Impulse propagation in a *typical*, or *counterclockwise*, flutter involves the isthmus of atrial tissue between the IVC and the tricuspid annulus, which is called the *cavo-tricuspid isthmus* (CTI), and travels up the septal aspect along the AV groove near the His bundle and then back down the lateral wall of the atrium to re-enter the CTI.[56] The *reverse typical*, or *clockwise*, flutter has a reverse activation compared with typical flutter. These arrhythmias have been seen in all CHD lesions, including postoperative ASD, VSD, tetralogy of Fallot (TOF), D-transposition of the great arteries (D-TGA), and single-ventricle Fontan repair of hypoplastic left and right heart variants.[19,57] Attention must be paid to the anatomic barriers in the older forms of D-TGA repairs (intra-atrial baffle operations such as the Mustard and Senning procedures) and single-ventricle Fontan repairs, where the CS and part of the CTI may be on the "other side" (pulmonary venous portion) of the baffle, and catheter access to part of the CTI is by transbaffle puncture or retrograde A-A access.[58]

Mapping and Ablation of Typical Flutter

It is essential to define the anatomy using echocardiography, computed tomography (CT), MRI, angiography, or all of these *before* ablation. Noninvasive body-surface mapping of intra-atrial re-entry tachycardia (IART) has been shown to help analyze flutter wave isopotential maps and predict the activation sequence inside the atrium; this may assist in intracardiac mapping and ablation.[59] However, these techniques are more experimental and not proven to be practical for universal use.

Once the activation sequence is confirmed using intracardiac electrograms, and in some cases, advanced mapping techniques such as electroanatomic or noncontact mapping, the CTI is accessed and the flutter entrained to demonstrate the re-entry mechanism before ablation. Long sheaths may facilitate catheter stability and easy access to CTI. The use of larger-tip (8-mm and 10-mm) ablation catheters helps deliver higher power (50 to 100 W) and create larger lesions. Some operators have also used closed and open irrigated tip catheters for applying better lesions.[60] These modalities must be used with caution because of the higher risk of myocardial perforation in the pediatric population. After successful ablation, the documentation of bi-directional CTI block may be challenging because of the anatomic barriers to catheter placement (such as a baffle), but making this determination has been to shown to reduce the risk of recurrence.[61]

Atypical Flutters

Postoperative atrial flutters are classified as having macro–re-entrant or micro–re-entrant mechanisms. The more common IART is associated with surgical incisions and often referred to as *incisional flutter*. The less common arrhythmia is the nonfocal atrial tachycardia (NFAT), which is micro–re-entrant in nature.

Intra-atrial Re-entry Tachycardia

The incidence of these arrhythmias may be as high as 30% among patients who had postoperative Mustard and Senning intra-atrial repairs (surgery that is rarely performed in the current era) and 50% among patients who had the Fontan procedure within a decade following surgery.[61-63] IART can also be seen in four-chamber postoperative conditions such as TOF and ASD, along with the typical CTI-dependent flutter. Unlike some of the arrhythmias commonly seen in adults, such as AF, arrhythmia control is preferred over rate control. IART is a significant cause of morbidity and mortality in this group of patients. Even mildly elevated heart rates can cause hemodynamic alterations. Additionally, a heightened risk of atrial thrombosis is present. Even though medical therapy is often the first line of treatment, the lack of efficacy and the proarrhythmic side effects of different antiarrhythmic drugs have led to the use of ablation therapy as a common approach to the management of IART in patients with CHD.

Mapping and Ablation of Intra-atrial Re-entry Tachycardia

The P-wave morphology is often different from adult-type flutter (Figure 76-30), and the rates may be slower (because of associated scarring and fibrosis). This may lead to occasional one-on-one rapid ventricular conduction with resultant hemodynamic compromise.[64] Sustained hemodynamic stable tachycardia is essential for mapping and entrainment and is aided by advanced electroanatomic and noncontact mapping systems, which allow the creation of activation and substrate maps. To help with better understanding of the complex anatomy, MRI and CT scan images can be merged with intra-procedure geometry obtained in the EP laboratory by using advanced mapping systems. Intracardiac echocardiography has been shown to help guide atrial baffle puncture, identify anatomic structures, and monitor tissue contact during ablation.[63] Once the propagation of the

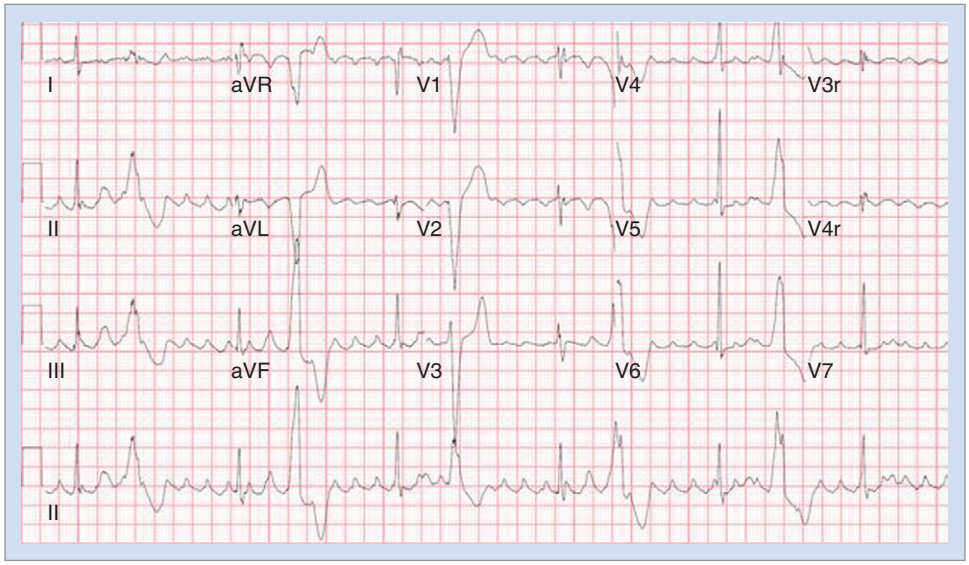


FIGURE 76-30 Fifteen-lead electrocardiogram showing atrial flutter (intra-atrial re-entry tachycardia) in a postoperative patient (Senning procedure).

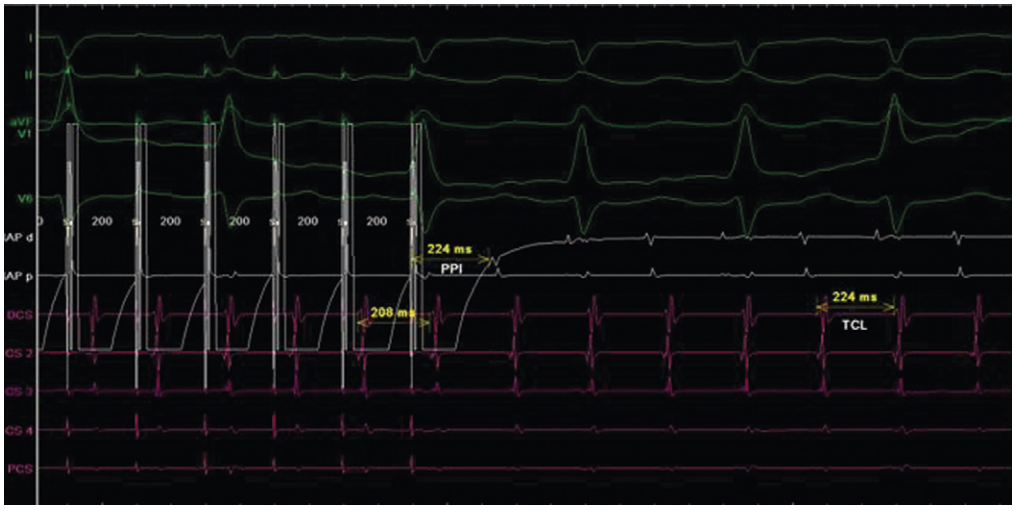


FIGURE 76-31 Intracardiac electrograms showing entrainment pacing maneuver of intra-atrial re-entry tachycardia in a patient undergoing the Senning procedure. *PPI*, Post-pacing interval; *TCL*, tachycardia cycle length, indicating proximity to tachycardia circuit.

tachycardia has been deciphered, entrainment mapping can be used to confirm the target ablation sites (Figure 76-31). The aim is to create a line of conduction block and to achieve transmural lesions; it may be necessary to resort to large-tip and irrigated-tip catheters to accomplish this.[60] The CTI is accessed with a retrograde approach, especially in patients who have had a Senning or Mustard repair (Figure 76-32). The line of block can be created by either a series of ablation applications or "drag" lesions at the proposed site. These circuits, which can be seen along the lateral wall of the right atrium at the atriotomy site and involve the crista terminalis, can combine with the CTI and cause a "figure-of-8"–type flutter configuration. The other flutter focus site could be in the lateral superior right atrial wall, which is the bypass cannulation site. The combination of advanced mapping and enhanced lesion creation has led to over 90% acute success. Unfortunately, a 40% recurrence rate has been seen in the single-ventricle population within 3 years.[65,66] This is significantly better than the 73% acute success rate observed in the multiple-institutional pediatric RF registry in 271 patients with CHD between 1989 and 1999.[4]

Nonfocal Atrial Tachycardia

NFAT emanates from a focal source and can be induced and terminated by pacing.[67] The mechanism underlying NFAT may be triggered, re-entrant, or both and is indistinguishable from other forms of atrial tachycardia on ECGs. The incidence varies from 8% to 40%.[68,69] These arrhythmias are more commonly seen in

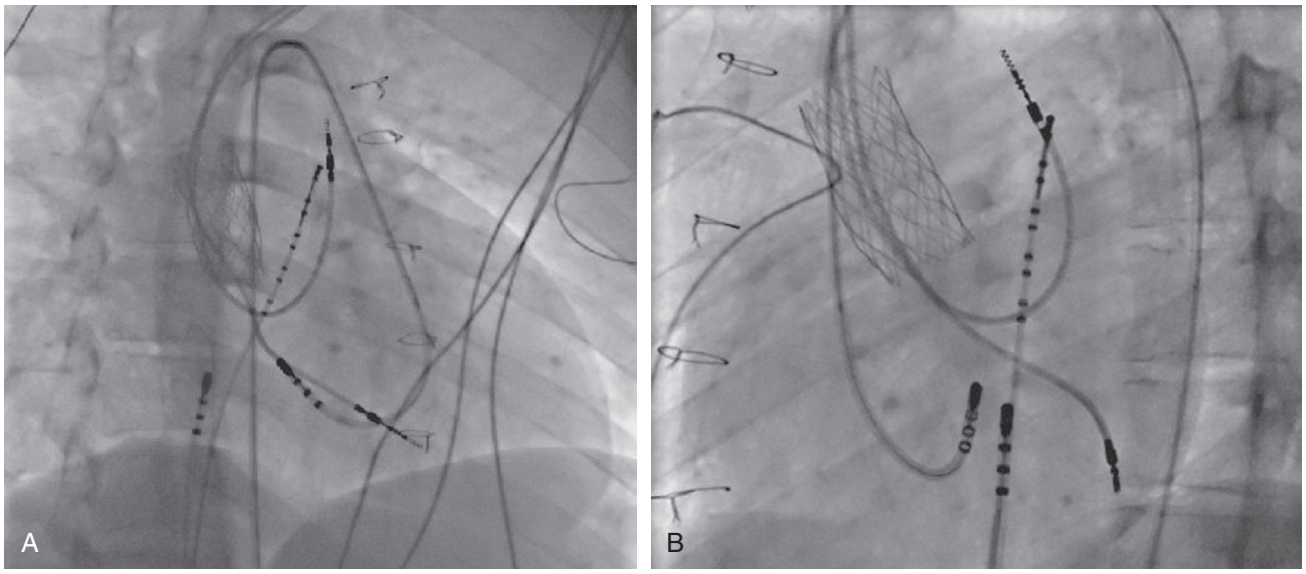


FIGURE 76-32 Fluoroscopic image of retrograde approach to cavotricuspid isthmus with an ablation catheter in a patient with Senning repair for transposition of the great arteries. **A,** Right anterior oblique view. **B,** Left anterior oblique view.

older patients who had surgery for CHD at a young age. The average age at clinical presentation was 27 years (range, 5 to 52 years) in one of the studies.[67] NFAT is distinguished from macro–re-entrant IART by careful analysis of the three-dimensional propagation map, which shows a radial spread of activation from an atrial point source. Some of the triggered NFATs may respond to adenosine because of membrane hyperpolarization and shortening of refractory periods, which may be caused by the effect on potassium channels.[70,71]

Mapping and Ablation Nonfocal Atrial Tachycardia

Focal sites have been found in both atrial chambers with ablation success rate of approximately 75%.[67-69] In a study of 62 atrial tachycardias in 43 patients following CHD surgery, the incidence of focal atrial tachycardia was approximately 15% with an acute RF ablation success of 100%.[69]

Surgical Ablation

Residual hemodynamic issues such as valvar insufficiency, severe atrial or Fontan baffle dilation, and high recurrence of IART after catheter ablation following a Fontan procedure has led to an increased use of surgical ablation as a potential treatment option with variable results. The recurrence risk of IART may be lower with surgical ablation using either RF or cryo ablation (such as surgical Fontan baffle revision with a modified right atrial Maze procedure), but the risks of such a procedure may be significantly higher than with catheter ablation.[72]

Complications

The overall risk of complications (786 with CHD of 7524 enrolled patients) was 7.8% for ablation of all SVTs in CHD.[4] Serious complications in this group were recorded as 4.2% and included third-degree AV block, brachial plexus stretch injury, cardiac arrest, Horner's syndrome, and SVC thrombus. The overall mortality risk was 0.3%. Both morbidity and mortality risks are lower in the current era.

Ventricular Arrhythmias

Ventricular Tachycardia

Ventricular tachycardia (VT) continues to be a challenge, especially in postoperative patients with TOF, and has been implicated in the etiology of sudden death in this patient population.[73,74] The incidence of VT has been reported as 11.9% in patients with TOF with a sudden death risk of 8.3% after 35 years of follow-up.[75] However, the risk of sudden death in younger patients after TOF surgery is low; the presence of inducible VT by PES (Figure 76-33) and increased QRS duration may be helpful in predicting the risk.[74] Correction of TOF involves patch closure of the VSD with relief of right ventricular outflow obstruction, which may involve infundibulectomy and trans-annular patch. Scarring and fibrosis around these sites of incision and patch repairs, as well as associated residual hemodynamic issues (such as outflow obstruction and pressure overload, pulmonary insufficiency, and volume overload, or all of these) contribute to macro–re-entrant VT.[76]

Ventricular arrhythmias and sudden death have also been described in D-TGA after a Mustard procedure (incidence of 9%) with an inverse correlation with the RV ejection fraction and a positive correlation with age and QRS duration greater than 140 ms.[77] Although atrial arrhythmias were present in 44% of their patients, the authors of this study did not predict the occurrence of VT or sudden death.[78] The risk factors for development of VT in TOF include later age at repair, moderate or severe tricuspid regurgitation, increased QRS duration, and depressed ventricular function. Clinical presentation includes isolated premature ventricular contractions, which may be monomorphic or polymorphic in 18% to 40% of the postoperative patients with TOF.[78] Other symptoms may include palpitations and syncope.

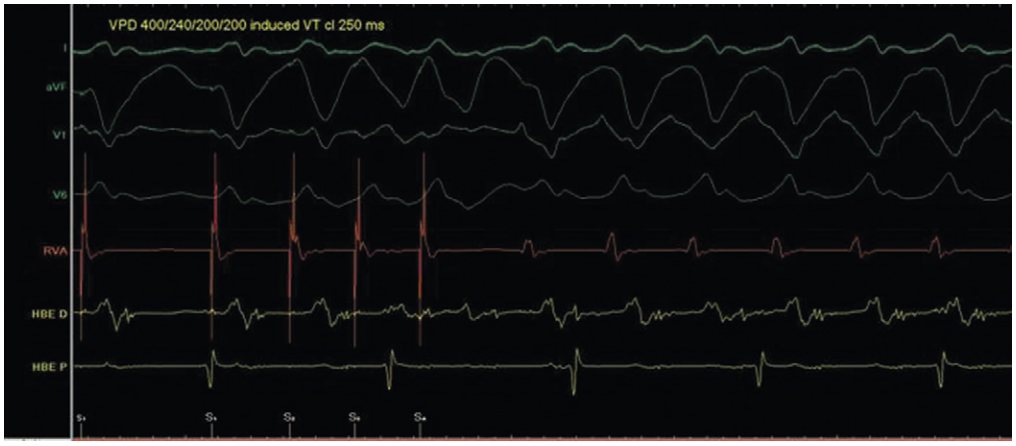


FIGURE 76-33 Intracardiac electrograms showing induction of ventricular tachycardia with programmed electrical stimulation in a patient with tetralogy of Fallot.

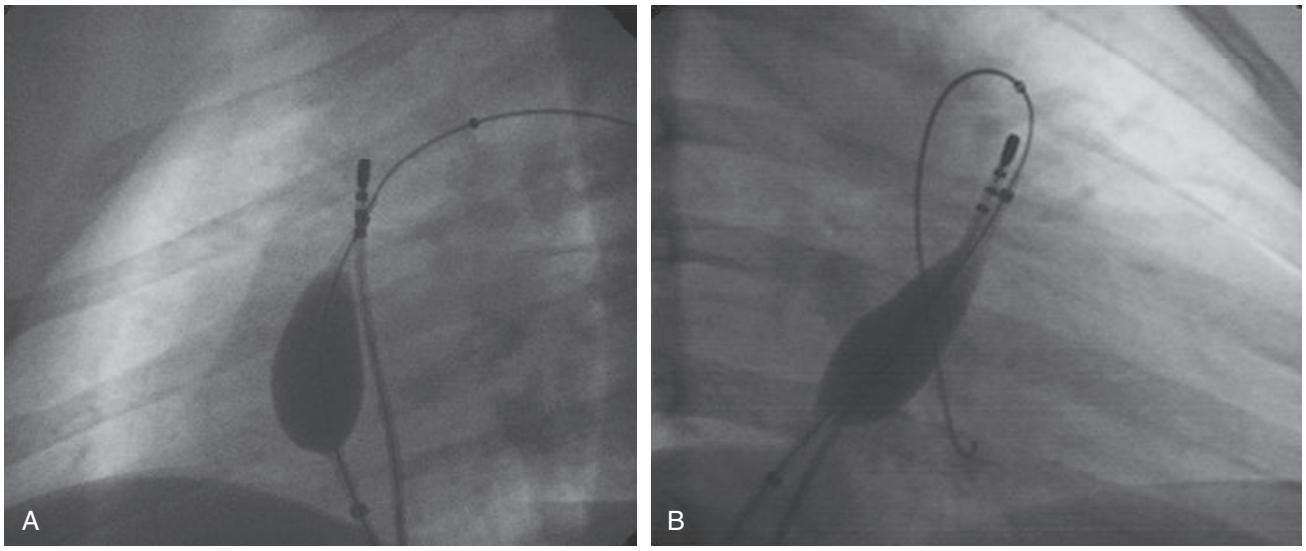


FIGURE 76-34 Fluoroscopic image showing the positioning of an EnSite balloon catheter (St. Jude Medical, Little Canada, MN) in the right ventricular outflow tract with mapping and ablation catheter. **A,** Anteroposterior view. **B,** Lateral view.

Mapping and Ablation

VT ablation in this group with CHD can be challenging because of complex anatomy, thickened hypertrophied myocardium, hemodynamic instability in the presence of ventricular dysfunction, noninducibility of clinical VTs, and broad scar-related isthmuses.[79] Different strategies have been described, including activation sequence analysis, pace mapping, entrainment maneuvers, and, more recently, substrate mapping in sinus rhythm. The last is used if the tachycardia is not inducible or poorly tolerated. It is imperative to perform three-dimensional mapping such as electroanatomic contact mapping or noncontact mapping for substrate mapping (Figures 76-34 and 76-35). The success in a series of 30 subjects described in two studies was 89% with a 20% recurrence risk.[80,81] In another series of 11 patients, where substrate mapping was used as the strategy, the acute success rate was 100% with a 9% recurrence rate after a mean follow-up of 30 months.[82] The critical isthmus in this study was within the distinct anatomic isthmuses bordered by unexcitable tissue in the RVOT at the site of trans-annular repair and around the VSD patch. Since sudden death can still occur in patients who have no inducible VT adjunct therapy after a successful RF ablation may include an implantable cardioverter-defibrillator).[83]

SUMMARY

The past 10 years have resulted in tremendous development in the field of interventional pediatric electrophysiology and a high degree of acute and chronic success with a low incidence of complications, especially in those with structurally normal hearts.

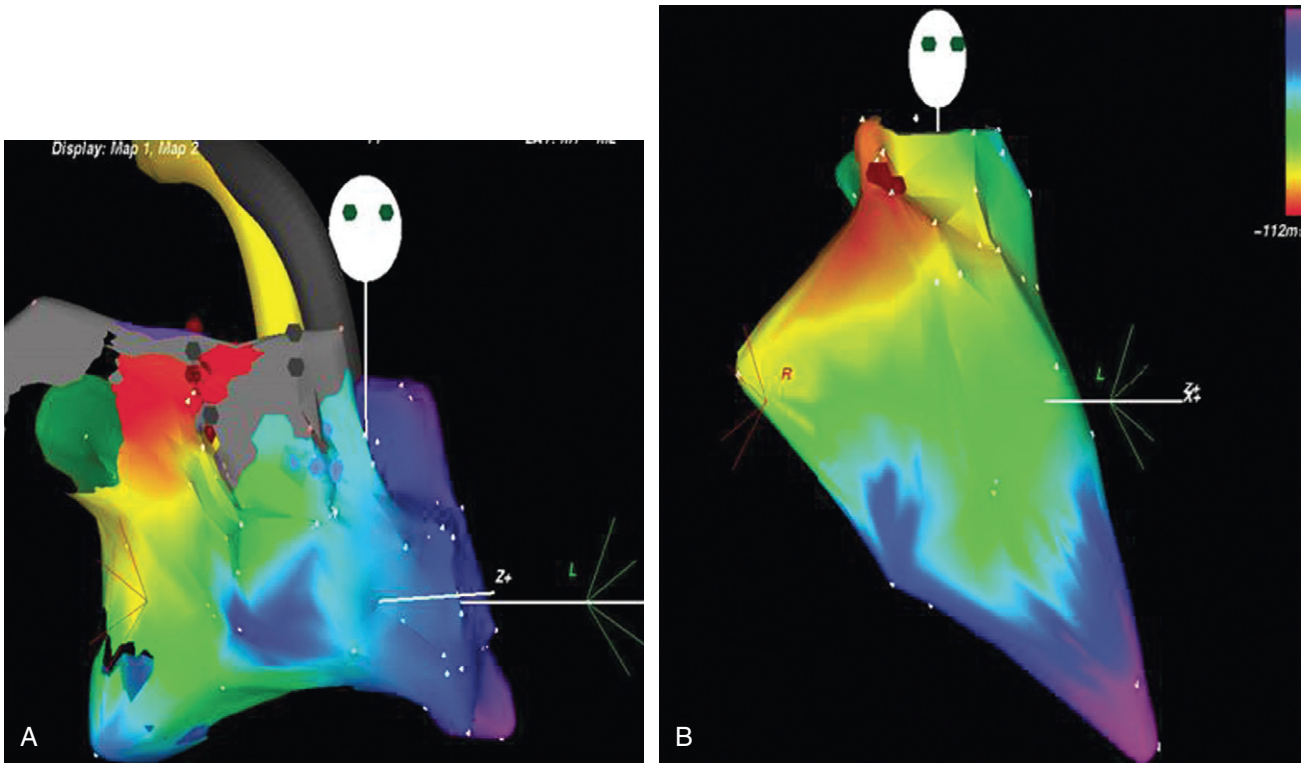


FIGURE 76-35 CARTO (Biosense Webster Inc., Diamond Bar, CA) activation map of right ventricular outflow tract ventricular tachycardia showing earliest activation site.

Invasive treatment of arrhythmias in children after surgery for CHD continues to be a challenge.

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CHAPTER 77

Pacemaker and Implantable Cardioverter-Defibrillator Therapy in Pediatric Patients with and Without Congenital Heart Disease

William J. Boney and Nandini Madan

Overview of Pacemaker and Implantable Cardioverter-Defibrillator Therapy

The task of pacing in children presents a unique set of challenges. The pediatric population requiring pacing is distinctly different from the adult population in several ways—patients are smaller; they grow significantly taller with time; they often have congenital heart disease and surgical repairs; and many will require epicardial pacing or implantable cardioverter-defibrillator (ICD) systems. Pacemakers are most commonly used in children, adolescents, and patients with congenital heart disease who have symptomatic bradycardia from sinus node dysfunction or atrioventricular (AV) nodal disease. Defibrillators are implanted in survivors of cardiac arrest and in other cases where the risk of life-threatening ventricular tachyarrhythmias is high.

No large clinical trials or prospective studies in children are available to offer guidelines for pacemaker and device implantation in children. For this reason, the adult guidelines have served as a basis for pediatric implantations. The most recent indications for device implantation are shown in Box 77-1 (pacing) and Box 77-2 (ICD or cardiac resynchronization therapy [CRT]).[1] This chapter discusses the unique circumstances and special indications in children and adolescents and in those with congenital heart disease that are not addressed by the adult studies and guidelines.

Pacemaker Therapy for Children and Patients with Congenital Heart Disease

The most common indications for permanent pacemaker implantation in children, adolescents, and individuals with congenital heart disease mirror those of adults, specifically the following:

1. Symptomatic sinus bradycardia
2. Bradycardia-tachycardia syndrome
3. Advanced second-degree or third-degree heart or AV block

Several important considerations in young patients separate them from adults. Children, especially neonates, require higher heart rates to maintain an adequate cardiac output. An increasing population of survivors of palliative procedures for various forms of congenital heart disease has suboptimal cardiovascular physiology, compromised myocardial function, or both. They are vulnerable to the effects of bradycardia, which may leave them with inadequate cardiac output and increased vulnerability to both atrial and ventricular arrhythmias. Moreover, loss of AV synchrony associated with complete heart block or junctional bradycardia may result in symptoms at heart rates that would be tolerated in individuals with normal cardiovascular physiology.[2,3] In most patients, pacemaker implantation is indicated when symptoms associated with bradycardia are present, with subsequent improvement of those symptoms with chronotropic support, restoration of AV synchrony, or both. Because of the lack of large pediatric randomized double-blind clinical trials, the level of evidence for most recommendations is based on the consensus of experts.

Specific Pacing Issues

Sinus Node Dysfunction

Isolated sinus node dysfunction is extremely rare in children with structurally normal hearts. Pediatric sinus node disease is most commonly encountered after repair of congenital heart disease, with device implantation indicated only for symptomatic patients.[4] It can be challenging to correlate bradycardia with symptoms of fatigue, dizziness, or syncope. Before implanting a pacemaker, it is important to exclude reversible causes of bradycardia such as seizure, increased intracranial pressure, hypothyroidism, hypothermia, apnea, sepsis, medications, or other systemic conditions. Since average heart rates decrease as children grow, bradycardia is a relative term, and no specific heart rate "cut-off" that defines an indication for pacing exists.

In a carefully selected subgroup of children with profound bradycardia and asystole associated with pallid breath-holding spells, pacing has been successful in alleviating symptoms.[5]

The combination of sinus bradycardia with atrial tachyarrhythmias (tachycardia-bradycardia syndrome) is becoming more common as patients survive complex repairs for congenital heart disease. The loss of sinus rhythm is considered an independent risk factor for the development of these intra-atrial re-entrant arrhythmias.[6] Although antiarrhythymic drugs may be useful, their use may be limited by pre-existing bradycardia.[7] Long-term

Box 77-1 Indications for Pacing in Children and Adolescents

CLASS I

Advanced heart block associated with symptomatic bradycardia, ventricular dysfunction, or low cardiac output

Sinus node dysfunction with correlation of symptoms with age-inappropriate bradycardia

Postoperative advanced atrioventricular (AV) block that persists for at least 7 days after cardiac surgery

Congenital third-degree AV block in an infant with a ventricular rate of <55 beats/min or with congenital heart disease and a ventricular rate <70 beats/min

CLASS IIA

Patients with congenital heart disease and sinus bradycardia for the prevention of recurrent episodes of intra-atrial re-entrant tachycardia

Congenital third-degree AV block beyond the first year of life, with an average heart rate <50 beats/min, abrupt pauses in ventricular rate that are two or three times the basic cycle length, or associated with symptoms caused by chronotropic incompetence

Sinus bradycardia with complex congenital heart disease with resting heart rate <40 beats/min or pauses in ventricular rate >3 seconds

Congenital heart disease and impaired hemodynamics caused by sinus bradycardia or loss of AV synchrony

Unexplained postoperative syncope in a patient with congenital heart disease with transient postoperative complete heart block and residual fascicular block. Other causes of syncope must be excluded.

CLASS IIB

Transient postoperative heart block, which reverts back to sinus rhythm with residual bi-fascicular block

Children and adolescents with congenital complete heart block, an acceptable ventricular rate with narrow QRS complex, and normal ventricular function

Asymptomatic sinus bradycardia following bi-ventricular repair of congenital heart disease with resting heart rate of <40 beats/min or pauses in ventricular rate of >3 seconds

Box 77-2 Indications for Implantable Cardioverter-Defibrillator Therapy in Children and Adolescents

CLASS I

Survivors of cardiac arrest after evaluation to define the cause of the arrest and exclude any reversible causes.

Patients with symptomatic sustained ventricular tachycardia associated with congenital heart disease, who have undergone hemodynamic and electrophysiological evaluation. Catheter ablation or surgical repair may offer alternatives in carefully selected patients.

CLASS IIA

Patients with congenital heart disease with recurrent syncope of undetermined origin in the presence of either ventricular dysfunction or inducible ventricular tachycardia on electrophysiological study.

CLASS IIB

Recurrent syncope in patients with complex congenital heart disease and advanced systemic ventricular dysfunction when thorough invasive and noninvasive investigations have failed to define a cause.

atrial pacing and atrial anti-tachycardia pacing (ATP) have both been used with equivocal results.[7,8]

Postoperative Atrioventricular Block

Natural history studies have established a very poor prognosis with up to 50% mortality in patients with permanent heart block after surgical repair of congenital heart disease.[9] Advanced second-degree or third-degree postoperative heart block that has persisted for at least 7 days and is not expected to resolve is considered a class I indication for pacemaker placement.[1] Patients with transient AV block after surgery have a small but definite risk of late progression to complete AV block decades after surgery and need close monitoring and follow-up.[10,11] Patients with residual bi-fascicular block and progressive P-R interval prolongation may be particularly at risk for development of late-onset AV block.[12] Because of this possibility, unexplained syncope is a class IIa indication for pacing in these patients once other cardiac and noncardiac etiologies of syncope have been ruled out.[1]

Congenital Complete Atrioventricular Block

In children with structurally normal hearts, congenital complete AV block (CCAVB) is the most common indication for permanent pacing, and accounts for 20% to 30% of the entire pediatric paced population in large single-center reports.[13,14] CCAVB is often caused by fetal exposure to maternal lupus antibodies but may be idiopathic as well. The subgroup of patients with maternal lupus associated CCAVB tend to present with the need for pacing at an earlier age and are more likely to develop dilated cardiomyopathy compared with those with idiopathic CCAVB.[15]

Class I indications for permanent pacing include a wide QRS escape rhythm, complex ventricular ectopy, or ventricular dysfunction.[1] In neonates with a narrow QRS escape rhythm, the class I indication is met when the average heart rate is below 55 beats/min or below 70 beats/min for infants with significant congenital heart disease. Beyond the first year of life, the class IIa indication states that pacing is appropriate for average heart rates below 50 beats/min, or when abrupt pauses of two to three times the basic cycle length occur, or when symptoms of chronotropic incompetence are present.[1]

Long QT Syndrome

In long QT syndrome (LQTS), pacing prevents bradycardia and pauses and may even shorten the QT interval. Pacing alone has been shown to be efficacious for certain high-risk patients with LQTS, and although most high-risk patients in the modern era are treated with ICD therapy, a simple pacemaker may be a good option for small patients in whom ICD implantation is not feasible.[16]

Lyme Carditis

Lyme disease is a common cause of acquired heart block in children and should be considered in any child presenting with heart block. In one recent large study of 207 children with Lyme disease, 33 (16%) developed carditis.[17] Nine patients had complete heart block, and three of those received temporary pacing, but no patient required permanent pacing. With very rare exceptions, heart block in the setting of Lyme disease is transient and responds to antibiotic therapy. In cases of advanced second-degree or

third-degree AV block, some have recommended corticosteroid therapy in addition to antibiotics. The opinion on using steroids is mixed, and evidence is limited to isolated case reports and series.[18]

Technical Considerations and Challenges of Implantation

General Principles

Pediatric pacemakers should be implanted by specialized teams with expertise in the unique aspects of pacing in children and familiarity with the anatomic variations associated with congenital heart disease.[19] Procedures are usually performed with the patient under general anesthesia and monitored by a pediatric cardiac anesthesiologist.

The implanter must be mindful of the fact that children often outlive the device and that leads will need to be replaced, often on multiple occasions. Since children tend to live longer than adults with pacemakers, they are more likely to experience complications, including venous occlusion and lead failure. The decisions made at the time of initial implantation facilitate successful procedures in the future and should minimize the total number of interventions and long-term risks to the patient.

The psychosocial adjustments of the patient and family must also be considered, and trained nurses, play/child-life therapists, and other psychosocial professionals should be made an essential part of the implantation team. The techniques of epicardial and transvenous pacemaker implantation are discussed in detail in other chapters of this book and elsewhere.[19]

Transvenous Versus Epicardial Systems

Transvenous systems are more reliable and have greater longevity compared with epicardial systems. In one large pediatric cohort, transvenous leads had lower thresholds and significantly more longevity compared with steroid-eluting epicardial leads.[20] Epicardial pacing is generally preferred for smaller patients and for patients with congenital heart disease who have intracardiac shunts.[21] For the infant who requires lifelong pacing, an epicardial pacing system preserves the venous anatomy and ideally defers transvenous implantation until the child has grown closer to adult size. Although transvenous pacing is technically feasible in infants, lead survival is significantly decreased, and the risk of venous occlusion may present an obstacle to placement of additional leads in the future.[22,23] As small patients grow and the distance between the generator and the heart increases, tension can develop on the lead. This problem is sometimes addressed by placing a right atrial loop to introduce more "slack" in the lead, although these loops can promote adhesions of the lead body to the vessel walls, making extraction difficult, and often may not straighten out as planned with growth.[24-26]

It is clear that infants should receive epicardial pacing systems when indicated, but the choice between the epicardial and transvenous approaches is more difficult in toddlers and young children. The transvenous approach is attractive because it avoids thoracotomy and is associated with increased lead survival time. However, venous thrombosis may be a problem when adult-sized pacing leads are placed into small vessels. One study evaluated 63 children with transvenous pacing leads with echocardiography and venography to determine the incidence of venous thrombosis and found that 18% of them had moderate or severe thrombosis at follow-up.[27] Children who had thrombosis were younger at implant (4.5 vs. 8.2 years) and had a higher ratio of lead diameter to body surface area.[27] This suggests that children in the age range of 3 to 6 years may have better long-term outcomes with epicardial pacing because venous anatomy is preserved. It also suggests that a two-lead system may have a higher thrombosis risk than a single-lead system and should be avoided unless absolutely necessary.

In the setting of congenital heart disease with intracardiac shunting, a risk of thromboembolic events exists, and epicardial pacing is preferred at any age.[21] Epicardial pacing may be used and should be strongly considered in small children, even when transvenous pacing is technically feasible in the interests of maintaining venous access for future use. Steroid-eluting epicardial leads are preferred, and the lead should be secured in a scar-free area to optimize pacing and sensing thresholds. A limited left thoracotomy approach may be successful in older children or in children with scars from prior thoracotomies.

Single-Chamber Versus Dual-Chamber Pacing

In the setting of heart block, dual-chamber DDD pacing provides AV synchrony and is obviously more physiological than single-chamber ventricular pacing. However, children with normal hearts or repaired congenital heart disease do surprisingly well with rate-responsive VVIR pacing and can be expected to lead active lives.[25] The merits of AV synchrony may be outweighed by the challenges of implanting a two-lead transvenous system, including increased surgical risk and operative time and the late risk of venous thrombosis and lead malfunction. When the child reaches adolescence or young adulthood, an upgrade to a dual-chamber system may be indicated. For infants, single-lead epicardial implantation can be accomplished with a smaller incision and with less intrathoracic dissection than in the case of a dual-chamber system. This shortens the recovery time and preserves the chest, heart, and thoracic cavity for future operations. For a school-aged child undergoing transvenous implantation, a single ventricular lead is less likely to cause venous occlusion compared with a two-lead system.

Pectoral Versus Abdominal Implantation

In general, epicardial leads are attached to abdominal pulse generators and transvenous leads are attached to pectoral devices. Although a transvenous lead can be tunneled to an abdominal device, this approach is generally avoided because it exposes the lead to trauma. Submuscular pockets are preferred for pediatric patients and are thought to minimize trauma and improve cosmetic results.[28]

Single-Lead VDD Pacing Systems

Single-lead VDD pacing combines a traditional ventricular pacing lead with atrial-sensing electrodes that make passive contact with atrial tissue and allow for atrial sensing without atrial pacing capabilities. The ACC/AHA/NASPE (American College of Cardiology/American Heart Association/National Association for Sport and Physical Education) guidelines state that VDD pacemakers are indicated for patients with AV block and normal sinus node function, and no need for atrial pacing.[29] These leads are an attractive option for pediatric patients because they provide AV sequential pacing without the need for two leads in a potentially small vascular space. The most obvious disadvantage is that atrial

pacing is not available in patients with coexisting sinus node dysfunction or bradycardia related to antiarrhythmic drug therapy. Atrial undersensing can also be a problem because a dedicated atrial lead is lacking. However, problems with atrial undersensing affect only 2% to 5% of these patients and rarely produce clinical symptoms. Data on the extractability of these leads, as compared with others, are not available.

Specific Challenges in Congenital Heart Defects

Transposition of the Great Arteries

Patients who have undergone intra-atrial baffle repair (Mustard, Senning procedures) often have sinus node dysfunction and atrial flutter as adolescents and adults related to their extensive atrial surgery. At implantation, the atrial lead must be secured to the superior aspect of the anatomic left atrium, now in the physiological right or systemic venous atrium (Figure 77-1). Care must be taken to avoid phrenic nerve stimulation when pacing in this area. Because the systemic venous ventricle is a morphologic left ventricle with smooth walls and small trabeculae, an active fixation lead is preferred.

These patients often develop obstruction of the superior vena cava (SVC), which precludes the transvenous approach to pacing; hence, venography before implantation is important to delineate venous anatomy. Placing a stent in the atrial baffle may open the obstructed area and allow passage of the transvenous leads in some cases.[30] The presence of right-to-left atrial or baffle shunts should also be identified and closed before placement of the transvenous pacing leads to prevent paradoxic emboli and strokes.

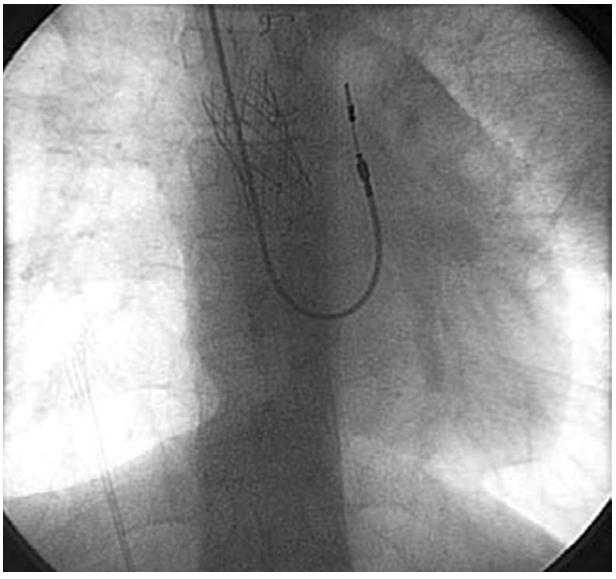


FIGURE 77-1 Stenting of the superior vena cava allows passage of a transvenous atrial pacing lead in a patient after the Mustard operation for dextro-transposition of the great arteries. *(From Emmel M, Sreeram N, Brockmeier K, Bennink G: Superior vena cava stenting and transvenous pacemaker implantation (stent and pace) after the Mustard operation. In* Clinical research in cardiology, *Berlin/Heidelberg, 2007, Springer.)*

Single Ventricle

Several anatomic substrates result in single-ventricle physiology and are ultimately palliated with the Fontan operation, the most common being hypoplastic left heart syndrome. The systemic venous return is connected directly to the pulmonary artery and hence, access for transvenous ventricular pacing is lacking. Sinus node dysfunction is very common in this group, and atrial tachyarrhythmias, especially intra-atrial re-entrant tachycardia (IART) or focal atrial tachycardia, become more common as these patients approach adulthood. In single-ventricle patients with pure sinus node dysfunction with no AV nodal disease, a single-chamber atrial pacing system can sometimes be placed via the transvenous approach, provided that no residual "fenestration" that would be a source of paradoxic emboli is present and that atrial tissue can be reached through the systemic venous connection (which may be impossible if the conduit is entirely extracardiac).[31] Because of the low-flow state in the systemic venous atrium, thrombosis is a potential concern, and epicardial pacing may be chosen even when transvenous pacing is technically possible.

In patients with previous surgery, usually large areas of atrial scarring are present, and when epicardial implants are performed, it is important to search for an area with a low stimulation threshold. A large specific-chamber electrogram and a small far-field electrogram should be performed to prevent undersensing or oversensing of the atrial or ventricle. It is important to know what type of Fontan operation was performed because an extracardiac conduit uses entirely prosthetic materials with no access to the native atrium from the transvenous side.

Many single-ventricle patients will require ventricular pacing leads as well if an AV block is present. Patients with L-looped single ventricles are at particularly high risk of heart block. Because of the high risk of thrombosis, transvenous ventricular pacing is not an option for patients with single-ventricle physiology.

Recommendations for Pacemaker Follow-up

Careful follow-up and continuity of care are required after pacemaker implantation to optimize pacemaker function and battery longevity. Programming undertaken at implantation should be re-evaluated at discharge with sufficient margin for maturation and fibrosis at the lead tip, with values of at least two to three times the threshold. Leads are generally mature and reach chronic thresholds in 6 weeks to 3 months, at which point thresholds remain stable and reprogramming is undertaken to optimize battery longevity.

The frequency and method of follow-up are dictated by multiple factors, including clinical status and patient preference. Follow-up may be remote, in-office, or a combination of both. Recent advances in remote monitoring have advanced the concept of transtelephonic monitoring (TTM), which allows estimation of capture of the paced chamber to sophisticated algorithms and remote estimation of capture and sensing thresholds, stored telemetry, and battery life. Newer devices (particularly defibrillators) allow for wireless communication with a TTM system that can be set up by the patient's bed at home. The advantage of wireless communication is that downloads do not have to be patient activated.

A complete pacemaker evaluation should be performed at least once yearly and twice yearly in many patients with

congenital heart defects. When significant interval growth has occurred, it is useful to obtain a chest radiograph to ensure that pacemaker leads remain intact and in place and that excessive traction on the leads has not occurred. Patients who are predominately paced should have a periodic echocardiographic evaluation to assess for pacing-induced ventricular dysfunction. Exercise testing is useful to optimize rate-responsive pacemakers and also to ensure that proper tracking occurs at maximal heart rates.

Atrial Arrhythmias

Atrial arrhythmias, particularly IART, are common in patients with single-ventricle physiology or complex congenital repairs such as the Mustard or Senning operation. IART is often refractory to medical therapy, and pacemakers with atrial ATP capabilities can be useful to detect and terminate atrial arrhythmias in this population (Figure 77-2).[7] ATPs have certain drawbacks. To ensure proper arrhythmia detection, bipolar leads are required. Since many patients with congenital heart disease have preexisting unipolar epicardial leads, "upgrading" to a device with ATP features may require replacement of the leads entirely. Furthermore, the risk of an atrial arrhythmia being accelerated to a faster arrhythmia does exist during an attempt to provide therapy.[7] Another drawback is that the devices generally will not deliver therapy for atrial tachycardias that have 1:1 AV conduction, which is not unusual in patients with congenital heart disease with slow atrial cycle lengths during tachycardia.[32]

Implantable Cardioverter-Defibrillators In Young Patients

As indications expand and implantation becomes technically more feasible, more children are becoming candidates for life-saving ICD therapy (Figure 77-3). Still, pediatric patients and those with congenital heart disease comprise less than 1% of the total ICD population. Implementing therapy with devices that were manufactured and designed for older patients with an entirely different disease substrate is challenging. Indications for ICD implantation in children are still poorly defined and primarily include aborted sudden cardiac arrest and symptomatic ventricular arrhythmias (secondary prevention guidelines) and other high-risk factors without documented life-threatening arrhythmias (primary prevention guidelines). The last decade has seen a surge in the total number of pediatric ICD recipients and the percentage of patients implanted for primary prevention indications. Despite significant technological advances, inappropriate shocks occur frequently, and lead-related and device-related complication rates are significant. Furthermore, unique social and emotional issues are involved, and the psychosocial impacts of ICD implantation are especially important in this

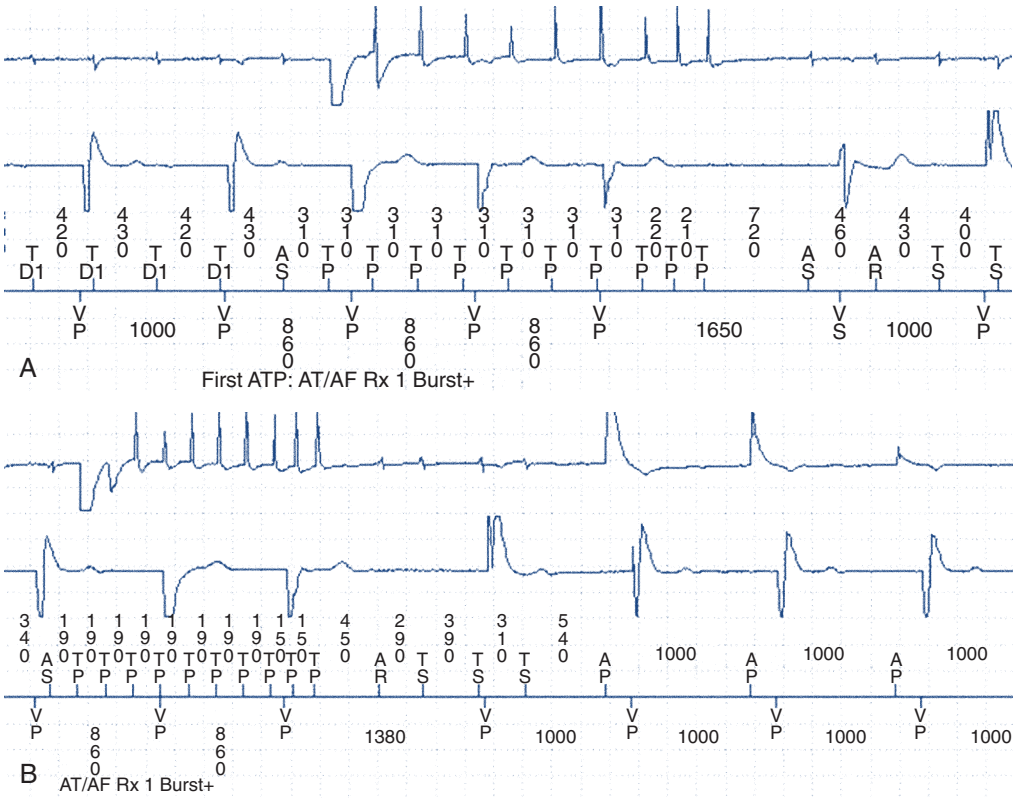


FIGURE 77-2 Intra-atrial re-entrant tachyardia in a 41-year-old patient after Fontan operation. The atrial cycle length (420 ms) is relatively slower than "typical" atrial flutter. Atrial anti-tachycardia pacing (*ATP*) is first unsuccessful (**A**) and later successful (**B**) in terminating the arrhythmia. *AT/AF*, Atrial tachycardia/atrial fibrillation.

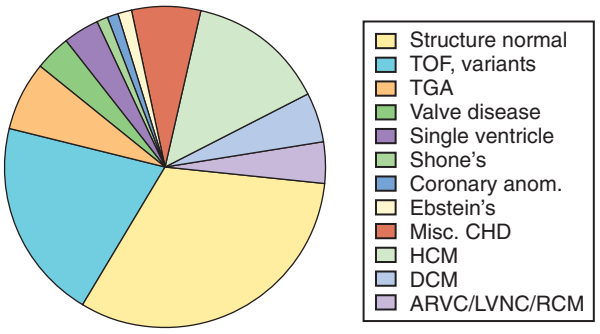


FIGURE 77-3 Anatomic diagnoses of pediatric and congenital implantable cardioverter-defibrillator recipients. Congenital heart disease accounts for 46% of total, 23% of cardiomyopathies, and structurally normal hearts with primary electrical diseases accounting for 31% of all patients. Among patients with congenital heart disease, diagnoses included tetralogy of Fallot (*TOF*), transposition of great arteries (*TGA*), atrial and/or ventricular septal defects, value abnormalities, single ventricle, Shone's complex, coronary artery congenital anomalies (*anom.*), Ebstein anomaly of tricuspid valve, and others. Cardiomyopathies included hypertrophic cardiomyopathy (*HCM*), dilated cardiomyopathy (*DCM*), arrhythmogenic right ventricular dysplasia or cardiomyopathy (*ARVC*), left ventricular noncompaction (*LVNC*), and restrictive cardiomyopathy (*RCM*).

young population and should be addressed in the case of each recipient.

Indications

The indications for ICD implantation in young patients and those with congenital heart disease have evolved and broadened in scope over the past 2 decades. These indications are primarily derived from extrapolation of data from large, randomized trials in adults. When the risks and benefits of implanting an adult-sized defibrillator in a child are weighed, it is important to remember that the risks of implantation increase as the size and age of the patient decrease. Depending on the disease substrate, the absolute risk of sudden death may be smaller in a child than in an adult with the same disease and risk factors.

Primary and secondary indications for ICD implantation have evolved rapidly. Current recommendations for ICD implantation in young patients and survivors of congenital heart disease are summarized in Box 77-2.

Data from two recent multi-center, retrospective pediatric ICD registries revealed that tetralogy of Fallot, hypertrophic cardiomyopathy, and LQTS were the most common diseases in pediatric ICD recipients.[33,34] In both studies, about half the ICDs had been placed for primary prevention.

Pediatric sudden cardiac death (SCD) constitutes a small fraction of the total SCD population. However, the cumulative lifetime risk of SCD in high-risk young patients makes the ICD an excellent option in this patient population. Moreover, long-term antiarrhythmic therapy may be unreliable because of significant toxicity and low compliance rates, which decrease its therapeutic efficacy. Prospective identification of high-risk young patients is very important, since a very low percentage of children resuscitated from out-of-hospital cardiac arrest survive to hospital discharge.[35]

The etiologies for sudden cardiac arrest (SCA) or SCD in young patients are congenital heart disease, cardiomyopathies, and inherited arrhythmia syndromes.[36] Small nonrandomized studies support the recommendation that young patients who have been resuscitated from SCA should undergo implantation of an ICD.[36-38] Other class I indications include spontaneous sustained VT or unexplained syncope in a patient with congenital heart disease with hemodynamically significant VT induced on electrophysiological study (EPS). It is important to exclude hemodynamic abnormalities that can be surgically corrected, other treatable causes for syncope such as bradycardia or Wolff-Parkinson-White (WPW) syndrome, or both before proceeding with ICD implantation.[36]

The recommendations for device therapy for primary prevention of SCD are based on limited clinical experience, general consensus of experts, and extrapolation of adult studies. The risk of SCD is not the same at all ages. For example, individuals with LQTS are more likely to have torsades de pointes and SCD in adolescence than in childhood. Certain factors used to risk-stratify adults, including markedly prolonged QTc values or severe left ventricular outflow tract (LVOT) obstructions in hypertrophic cardiomyopathy (HCM), are applicable across a range of ages.[39]

In the patient population with congenital heart disease, the heterogeneity of the substrate and the lack of prospective studies prevent the formulation of any generalized strategy for risk stratification in postoperative patients to guide decisions for ICD implantation. Although several attempts have been made to identify the risk factors in individual anatomic entities, most commonly in tetralogy of Fallot, no absolute guidelines exist. These issues are discussed in the chapters on arrhythmias in congenital heart disease. One large retrospective study reviewed patients with tetralogy of Fallot who underwent ICD implantation (68 for primary prevention and 53 for secondary prevention) and found that higher left ventricular end-diastolic pressure and nonsustained VT were independent predictors of appropriate ICD shocks.[40]

Similar studies have been undertaken in other diseases with an increased risk of SCD and arrhythmias such as D-transposition of the great vessels after intra-atrial repairs.[2,41] Presently, no good predictive factors are available to identify patients with congenital heart disease who would benefit from a primary prevention strategy.

Technical Challenges

The generators and leads used in ICD systems are substantially larger than those used in simple pacing systems, and the challenges of ICD implantation in small children are greater. Because young people lead active lives and routinely attain sinus rates close to 200 beats/min, a risk of inappropriate shocks from sinus tachycardia does exist. Small children and patients with intracardiac shunts require epicardial ICD systems, and the "size threshold" for implanting a transvenous ICD in a child is several years greater than the corresponding threshold for transvenous pacing alone as the transvenous ICD leads are considerably larger than regular pacing leads. ICD implantations are more invasive, and the consequences of lead failure are potentially more catastrophic. The relatively large sizes of the ICD generators require careful consideration of location of the device. In the adolescent patient, the standard prepectoral (subcutaneous or subpectoral) implant site may be used. In the young patient, an abdominal implant site

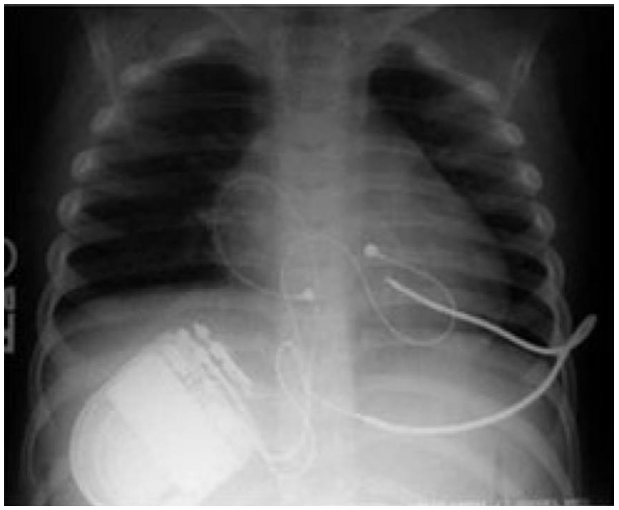


FIGURE 77-4 Dual-chamber epicardial implantable cardioverter-defibrillator system with a subcutaneous array instead of an intrathoracic shocking coil.

is often used with an epicardial lead system. Intrathoracic or intra-abdominal generator placement is a theoretical alternative but involves a significantly more invasive operation at the time of generator replacement.

Novel approaches to ICD implantation in children and patients with congenital heart disease have been developed in response to the problems seen with standard epicardial ICD systems. These newer approaches do not incorporate trans-venous shocking coils or epicardial patches and still provide acceptable defibrillation thresholds. Several groups have reported the use of subcutaneous arrays or coils alone (that were initially approved for adjunctive use to lower defibrillation thresholds) with an epicardial or transvenous lead for pacing and sensing (Figure 77-4).[42,43]

ICD systems that use entirely subcutaneous sensing and defibrillation leads are currently being developed.[44] These systems have clear advantages for pediatric patients because they can be placed without any intravascular or intracardiac hardware. However, these ICDs have several disadvantages. These "leadless" ICDs would not be able to provide pacing during bradycardia. Sensing would not be as precise without a dedicated bipolar intracardiac lead, which results in a decreased ability to identify sinus tachycardia and supraventricular arrhythmias and possibly an increased incidence of inappropriate shocks.

Implantable Cardioverter-Defibrillator Programming and Follow-up

Children should be monitored closely after ICD implantation to ensure optimal function of the system during periods of growth and as activity and lifestyle changes occur through the years. Despite careful attention to technical and programming factors at implantation, the risk of inappropriate shocks is significantly higher in younger patients, with reports of inappropriate shocks in 14% to 25% at mid-term follow-up.[34,36,40,45] Patients are typically seen every 6 months for an in-office interrogation, with transtelephonic transmissions between visits three or more additional times each year, depending on the age of the generator battery.

Arrhythmia detection can be set up with as many as three zones to provide various therapies depending on the rate and type of arrhythmia detected. Although electrophysiologists commonly set the ventricular fibrillation (VF) detection zone to treat heart rates above 188 beats/min in adults, pediatric implanters frequently set the VF zone above 200 or even as high as 220 beats/min as young, active patients may achieve sinus rates near 200 beats/min. A detailed approach to ICD programming is outlined in other chapters of this text, but topics specific to the pediatric population are discussed in this section.

Sinus Tachycardia

In general, higher heart rates should be anticipated and exercise testing may be required to evaluate the extent of the heart rate response and the appropriate sensing of the rhythm in an effort to prevent inappropriate shocks. β-Blockers are helpful in attenuating sinus tachycardia, and they may also suppress supraventricular arrhythmias often encountered in the setting of repaired congenital heart disease or for electrical conditions such as LQTS. A "monitor only" zone (180 to 200 beats/min) can be programmed to detect subthreshold ventricular arrhythmias and also to show how often the patient is experiencing significant sinus tachycardia. In our practice, we have found this to be a useful tool that identifies patients who are noncompliant with β-blocker therapy, activity restrictions, or both.

Supraventricular Arrhythmias

Supraventricular tachycardia (SVT) is common in pediatric ICD recipients and is another source of inappropriate shocks. In one study, 15% of pediatric ICD patients received an inappropriate shock for SVT.[46] By adding a second zone for VT, the programmer may activate "SVT discriminators," which are features designed to withhold therapy for sinus tachycardia and supraventricular arrhythmias even when heart rates exceed the threshold for the VT zone. In addition, the programmer can select ATP as the first-line therapy, which will defer defibrillation in that zone. ATP has been shown in large adult trials (Pravastatin or Atorvastatin Evaluation and Infection Therapy [PROVE-IT] and Pacing Fast VT Reduces Shock Therapies [PainFREE Rx]) to be a safe and effective way to terminate ventricular arrhythmias and results in a significant decrease in the number of "appropriate" shocks in primary and secondary prevention populations.[47,48] In addition, SVT episodes that are misclassified as VT may be terminated painlessly with ATP (Figure 77-5).

ATP may not be as beneficial in pediatric patients as in adults. Patients with hypertrophic cardiomyopathy, LQTS, and Brugada syndrome were specifically excluded from the adult PainFREE Rx trial because they were thought to be more likely to have polymorphic VT as their primary arrhythmia. One pediatric study of 63 ICD recipients, many with HCM or primary electrical disease, showed that ATP is rarely effective and often harmful in young ICD recipients. ATP may be more appropriate for patients with documented monomorphic VT in the pediatric setting.

T-Wave Oversensing

Patients with LQTS and HCM often have large or abnormal T waves, which can result in the ICD sensing two ventricular events for one heartbeat. It is critical to evaluate T-wave sensing

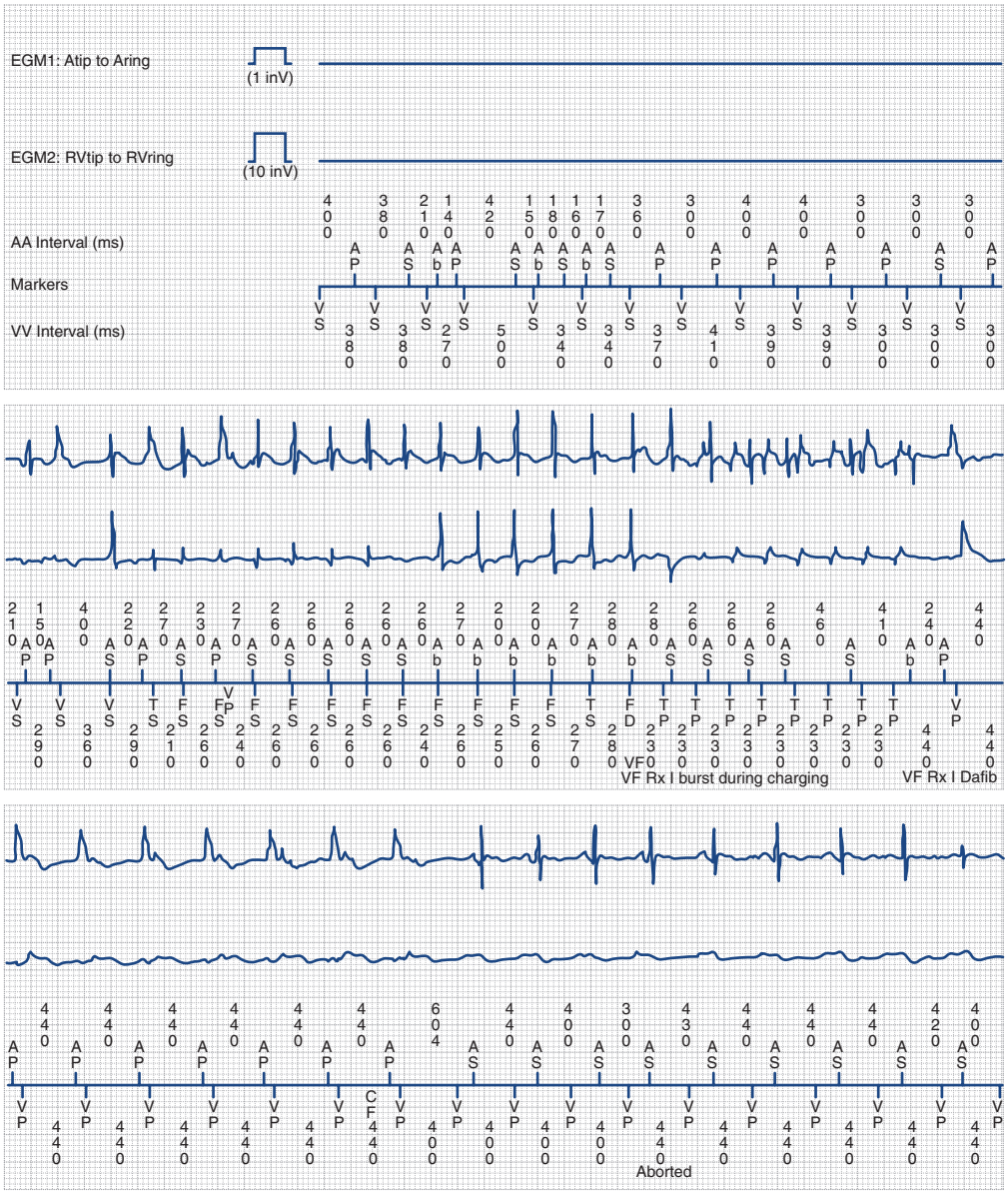


FIGURE 77-5 Supraventricular tachycardia occurs in a patient with a dual-chamber Medtronic (St Paul, MN) implantable cardioverter-defibrillator. On the basis of the heart rate, the device classifies the arrhythmia as ventricular fibrillation and begins charging. Anti-tachycardia pacing is delivered during charging, which effectively terminates the supraventricular tachycardia, and the shock is aborted.

at implantation and reposition the lead if discrimination is inadequate. Despite satisfactory results at implantation, T-wave morphologies may change with autonomic modulation and result in inappropriate shocks. Exercise stress testing with monitoring of intracardiac electrograms can be helpful in this evaluation to allow reprogramming to minimize T-wave oversensing.

Lead Fracture

Epicardial ICD and pacemaker leads have higher failure rates compared with their transvenous counterparts, and some studies have shown that pediatric patients have higher lead fracture rates than adults.[20,33] Lead fracture is a leading cause of inappropriate shocks, and it is important to closely follow lead performance with in-office and transtelephonic transmissions.

Electrical Storm

The term *electrical storm* indicates a state of cardiac electrical instability manifested by several episodes of ventricular tachyarrhythmias within a short time.[49] For patients with an ICD, electrical storm is often defined by the occurrence of two to three VT detections with therapy within a 24-hour period. This occurred in 5% of the patients in one large multi-center pediatric ICD study.[33] Electrical storm is a particular concern in pediatric patients with catecholaminergic polymorphic VT (CPVT) and LQTS because the pain of subsequent shocks leads to sympathetic

surge and continued arrhythmias. In patients with Brugada syndrome, VT storm has been successfully treated with isoproterenol infusion, oral quinidine, or both.[50]

Transtelephonic Follow-up

Advanced transtelephonic systems are available for most ICD systems and provide the physician with a detailed report of ICD performance, including pacing and high-voltage impedances, arrhythmias detected and treated, pacing and sensing thresholds, and other alerts. Newer wireless ICDs can communicate remotely with a monitor placed at the bedside, allowing for the information to be transmitted without any effort on the part of the patient. These monitoring systems usually need to be connected to a ground telephone line, which often presents a problem for some young patients who use only wireless phones.

Cardiac Resynchronization Therapy

CRT has been shown to be an effective intervention in adult patients who do not improve after optimal medical therapy.[51] The initial adult trials showed that prolonged QRS duration and decreased left ventricular ejection fraction (LVEF) predicted which patients would respond to CRT.[52,53] The value of CRT is less well established in pediatric patients and those with congenital heart disease. Many pediatric patients with heart failure have systemic right ventricles or right bundle branch block (RBBB) and right ventricular dysfunction rather than left bundle branch block (LBBB) and left ventricular dysfunction typical of adult CRT responders.[54]

Some data on CRT efficacy in pediatric patients and those with CHD are now available. Small studies have demonstrated the acute hemodynamic benefits of CRT after cardiac surgery, and three larger studies have now been published on this topic.[55,56]

A single pediatric center (Boston Children's Hospital) retrospectively reviewed 60 patients implanted over a 5-year period with a mean follow-up close to 1 year.[57] Overall, 77% had congenital heart disease, and 23% had dilated cardiomyopathy. That study reported an improvement in functional status in 87% of patients. The authors concluded that CRT is acutely beneficial in children and in patients with congenital heart disease, but implantation required unconventional approaches, often using the pericardial route.

A larger multi-center retrospective study evaluated 103 patients with short-term follow-up (mean, 4 months).[58] In that study, 71% had congenital heart disease, 16% had cardiomyopathy, and 13% had complete congenital AV block. A significant improvement was observed in the mean ejection fraction overall, and 3 of 18 patients listed for transplantation improved enough to be removed from the list.

A second European multi-center retrospective study looked at 109 patients with a longer follow-up time (mean, 7.5 months).[59] That study had 80% with congenital heart disease, 11% with congenital AV block, and 9% with dilated cardiomyopathy. Overall, 77% of the patients in that study had ventricular dyssynchrony associated with pacing. The authors reported an overall improvement in ejection fraction as well as New York Heart Association (NYHA) class.

Congestive heart failure and dilated cardiomyopathy occur in a small but significant subset of children after chronic right ventricular pacing.[60] In children with congenital heart block related to maternal lupus antibodies, it is debated whether dilated cardiomyopathy develops as a consequence of chronic right ventricular pacing or as a natural progression of that disease.[61] Heart failure associated with chronic ventricular pacing appears to be the strongest indication for CRT in pediatric and congenital heart disease patients.[59,61] In the European study, patients with systemic left ventricular dyssynchrony and pacing-associated ventricular dyssynchrony demonstrated major clinical improvement and reverse left ventricular remodeling.

The second large group of patients in these studies had CHD with systemic right ventricles, wide QRS complexes, mechanical dyssynchrony, and heart failure. Results varied, and in the Boston series, patients with systemic right ventricle and single-ventricle physiology fared much worse compared with those with systemic left ventricles.[57] The first multi-center study showed that patients with systemic right ventricles responded in a similar manner to those with systemic left ventricles.[58] This was in contrast to the European multi-center experience, which found that the presence of a systemic left ventricle was the strongest multivariable predictor of improvement.[59]

Presently, the best candidates for CRT appear to be patients with dilated cardiomyopathy, left ventricular dysfunction, and LBBB (similar to adult criteria), or congenital AV block with dyssynchrony in the setting of chronic right ventricular pacing.[59,61] Further studies are needed to determine the role of CRT in patients with systemic right ventricular failure and also in patients with single-ventricle physiology.

Long-Term Outcomes of Pacemaker and Implantable Cardioverter-Defibrillator Leads

Lead performance remains an ongoing issue of concern in young patients, especially in the era of increased need for lead extractions using multiple modalities such as radiofrequency or laser energy.[62] Several studies have examined lead performance in pediatric patients in an attempt to identify factors associated with lead failure.[20,22,63,64] The principal factor appears to be epicardial lead location. The 2-year survival rates for epicardial leads are relatively constant in multiple studies (84% to 95%) and do not vary much from that of transvenous leads (72% to 97%).[20,64] The situation dramatically changes at the 5-year follow-up with 85% survival for transvenous leads and only 58% survival for steroid-eluting epicardial leads.[20] Patient factors, which may be associated with early lead failure, include younger age at implantation and the presence of congenital heart disease.[20,22]

Lead Extraction in Pediatric Patients

With improved surgical techniques, pediatric patients and those with congenital heart disease have an increasingly positive prognosis and prolonged life expectancy. Consequently, lead failure is encountered more often and is an inevitable complication in many patients. Complete guidelines and indication for lead extraction in adults have been published and generally apply to pediatric patients as well.[65] Some of the more common indications for extraction are lead infection and venous thrombosis that precludes implantation of necessary additional leads. For pediatric patients expected to live for decades, some recommend extraction of all inactive or failed transvenous leads to reduce the lifelong risk of vascular complications and also because the

risks of extraction-related complications are higher with older leads.[62,66]

Lead extraction is not without risk. Data on adults suggest that major complications occur in 1% of procedures and include respiratory arrest, stroke, cardiac or vascular avulsion leading to hemorrhage, and death. Venous thrombosis is a concern, and the risk of thrombosis is increased in smaller patients because the transvenous lead occupies a larger proportion of the venous diameter.[27] In the case of defibrillator leads, in particular, fibrosis can form on the lead body and at the shocking coils, making extraction more difficult and predisposing to tearing of the blood vessel where the lead adheres to the SVC. Some newer ICD leads have a polytetrafluoroethylene coating, which may prevent tissue ingrowth and improve extractability.[67] Another strategy is to implant ICD leads with no SVC coil and a single shocking coil in the right ventricle.

Conclusion

Device therapy in young patients and those with CHD has increased exponentially over the past two decades. This technology has the potential to not only prevent and treat arrhythmias but also prevent and treat heart failure via CRT. Because of the broad spectrum of pediatric conditions that require pacing and device therapy, selection and implantation techniques, though broadly following guidelines, have to be tailored to each specific clinical situation. Increasing use and studies will inform these decisions in the future.

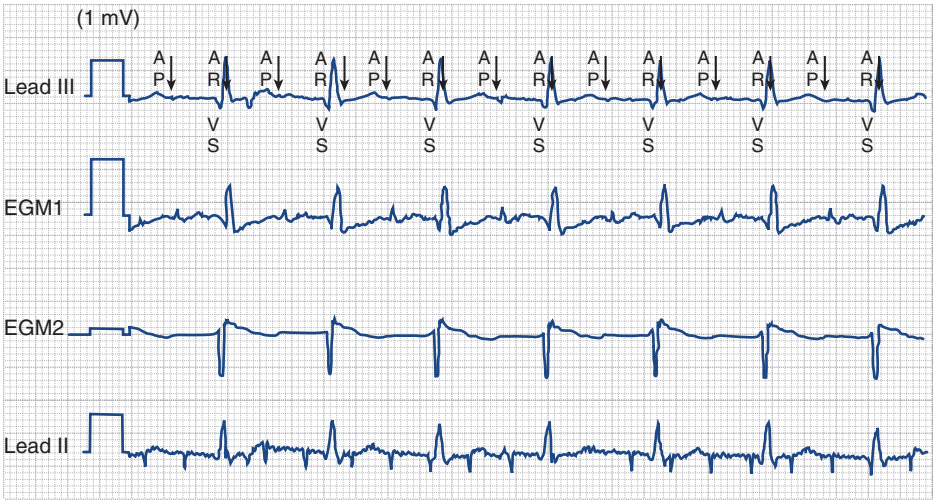
Pacemaker Troubleshooting

Case 1

An 18-year-old girl with D-TGA and mitral atresia has atrial arrhythmias after a Fontan palliation. An EnRhythm dual-chamber pacemaker (Medtronic, Inc., St Paul, MN) with ATP features is implanted. Bipolar epicardial atrial and ventricular pacing leads are used. After implantation, a large far-field ventricular signal is present on the atrial electrogram, which results in oversensing of atrial events.

1. What potential problems could result from this type of oversensing?

2. What programming changes can be made to prevent this?

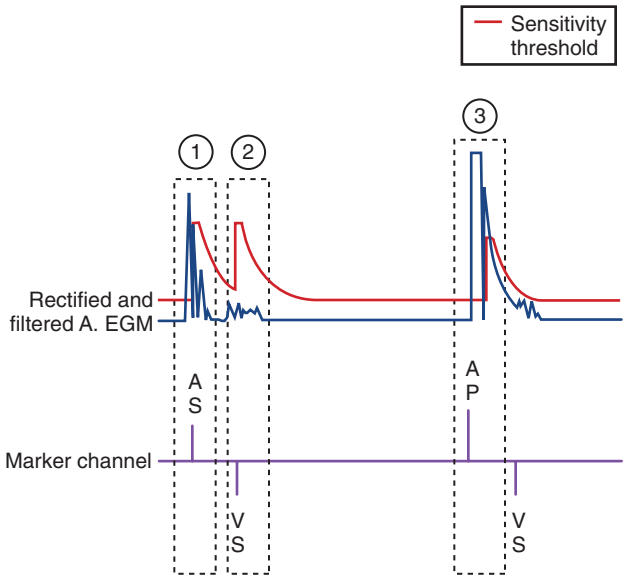


Answer

1. When "double counting" of two atrial events for each heartbeat occurs, the device may classify sinus tachycardia as atrial flutter with 2:1 AV block. This could result in inappropriate attempts at atrial ATP or mode switch to VVI if the device determines that the patient has chronic atrial arrhythmias.

Straightforward pacemakers have a postventricular blanking period programmed in automatically. ATPs and ICDs allow the physician to make one of three choices for postventricular atrial blanking: partial pulmonary vein atrial blanking (PVAB) (nominal), absolute PVAB, or partial + PVAB.

2. Changing this patient's setting to partial + PVAB will temporarily increase the atrial sensitivity threshold close to ventricular sensed events and will eliminate atrial oversensing.



1 After an atrial sensed event, the atrial sensitivity increases to 75% of the EGM peak (maximum: 8x the programmed value).
2 After a ventricular event, the atrial sensitivity threshold is adjusted to the level to which it was adjusted for the previous atrial event. If no atrial event occured during the most recent V-V interval, the atrial sensitivity is adjusted according to the minimum adjusted atrial threshold.
3 After an atrial paced event, the device adjusts the atrial sensitivity to the minimum adjusted value.

Case 2

A 30-year-old woman with D-TGA status post-Senning procedure had a Kappa dual-chamber pacemaker (Medtronic, Inc.) implanted for sinus node dysfunction and recurrent atrial tachyarrhythmias. She presents with a history of 3 days of palpitations.

1. What rhythm is revealed on interrogation of her device?

2. Why is the arrhythmia not properly sensed by the pacemaker?

3. What programming changes can be made to accurately detect atrial high rate episodes?

Pacemaker model: Medtronic Kappa KDR701 — Medtronic Kappa 700 Software 7.0
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Initial Interrogation Report — **Page 4**

Mode Switch Episodes: 746 Percent of Time: 19.1%

Date/time	Duration hh:mm:ss		Max Atrial Rate (bpm)
09/09/10 7:45 AM	:18	Last	191

Atrial High Rate Episodes: 257 Percent of Time: 6.4%

Date/time	Duration hh:mm:ss		Max Atrial Rate (bpm)
08/28/10 12:28 AM	:03	First	239
09/02/10 12:59 AM	:07	Fastest	263
09/04/10 11:46 PM	:55:25	Longest	246
09/09/10 5:46 AM	:06:36	Last	254

Ventricular High Rate Episodes: 10

Date/time	Duration hh:mm:ss		Max Vent. Rate (bpm)
09/04/10 1:42 PM	:04:25	First	256
09/04/10 2:01 PM	:04:10	Fastest	384
09/08/10 10:51 AM	:05:40	Longest	256
09/08/10 7:57 PM	:01:04	Last	240

Pacemaker model: Medtronic Kappa KDR701 — Medtronic Kappa 700 Software 7.0
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Initial Interrogation Report — **Page 6**

Modes

Mode	DDDR
Mode Switch	On
Detect Rate	180 bpm
Detect Duration	No Delay
Blanked Flutter Search	On

Rates

Lower Rate	70 ppm
Upper Tracking Rate	140 ppm
Upper Sensor Rate	140 ppm
ADL Rate	95 ppm

AV Intervals

Paced AV	250 ms
Sensed AV	240 ms
Rate Adaptive AV	Off
Search A-V	Off

Refractory/Blanking

PVARP	310 ms
PVAB	180 ms
Ventricular Refractory	230 ms
Vent. Blanking (After A. Pace)	28 ms
PMT Intervention	Off
PVC Response	On
Ventricular Safety Pacing	On

Rate Response

ADL Rate	95 ppm
Upper Sensor Rate	140 ppm
Optimization	On
ADL Response	3
Exertion Response	3
ADLR Percent	2.0%
Activity Threshold	Medium/Low
Activity Acceleration	30 sec
Activity Deceleration	Exercise
High Rate Percent	0.2%
ADL Rate Setpoint	6

Answer

1. The rhythm is atrial flutter with 2:1 block.

2. During 2:1 block, only half the atrial events are sensed by the device because the other half fall into the PVAB. Even though the patient has had constant symptoms of palpitations for 3 days, the device senses atrial high rate events only during the brief periods where 1:1 conduction occurs.

3. The PVAB can be shortened, which will allow all the atrial events to be sensed and will result in mode switch, when appropriate.

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CHAPTER 78

Arrhythmias Associated with Congenital Heart Disease

George F. Van Hare

In patients with congenital heart disease, the management of cardiac arrhythmias poses many challenges for the clinician. The occurrence of arrhythmias that are difficult to adequately control may be very disappointing and distressing to the patient, as such patients often have excellent hemodynamic surgical results but continue to require intensive medical attention because of their arrhythmias.

The mechanisms of arrhythmias in patients with congenital heart disease may be quite varied, with different arrhythmias seen in preoperative patients versus postoperative patients. The principles of management, however, share many features between the two states. This chapter will address the substrates for arrhythmia in both the preoperative and postoperative states and then discusses the various treatment modalities available.

Arrhythmia Substrates in Patients with Congenital Heart Disease

Arrhythmia Substrates in Unrepaired Patients with Congenital Heart Disease

Accessory Pathways

Congenital heart disease is relatively common in the general population (~1% of births), and accessory pathways are also somewhat common (1.6 to 3 of 1000 live births). Therefore, one would expect to observe Wolff-Parkinson-White (WPW) syndrome and supraventricular tachycardia (SVT) on the basis of these incidences alone. Indeed, in the Pediatric Radiofrequency Ablation Registry, ablations for accessory pathways have been reported in patients with most types of defects.[1] However, it is well known that certain types of congenital cardiac disease are more commonly associated with WPW syndrome. The most prominent of these defects is Ebstein's anomaly of the tricuspid valve.[2,3] In patients with these defects, the prevalence of WPW is approximately 9%. Other defects reported to demonstrate an increased association with WPW include L-transposition of the great vessels (ventricular inversion and congenitally corrected transposition) and hypertrophic cardiomyopathy.[4-8] In patients with Ebstein's anomaly, accessory pathways are often multiple and are generally right sided, although occasionally a posteroseptal pathway location is present. In L-transposition, one sees an increased incidence of Ebstein's anomaly of the left-sided (systemic) atrioventricular (AV) valve, which is morphologically always a tricuspid valve and is related to a left-sided, morphologic right ventricle. In these patients, it is thought that the increased incidence of WPW is explained by the coexistence of Ebstein's anomaly.[4-6] Finally, WPW has perhaps been overdiagnosed in patients with hypertrophic cardiomyopathy (HCM) because of the pre-existing common QRS abnormality that may resemble pre-excitation. Specifically, some patients actually have a fasciculoventricular pathway of no clinical significance.[9] However, SVT mediated by accessory pathways does occur in some patients with HCM; in these patients, SVT may be very poorly tolerated because of a coexisting hemodynamic abnormality.[7] Specifically, Danon disease, a form of glyocogen storage disease, is associated with ventricular pre-excitation.[10]

Other Substrates for Tachycardia

Other arrhythmias are occasionally seen in patients with congenital heart disease who have not had surgical repair. Atrial flutter, when seen, usually is a complication of atrial dilation on hemodynamic grounds. For example, patients with Ebstein's anomaly or other causes of severe tricuspid regurgitation may have atrial flutter, which, in turn, is most likely caused by right atrial dilation.[3] Patients with mitral valve disease, and in particular mitral stenosis, are at risk for atrial fibrillation (AF), depending on their left atrial dilation. Patients with left ventricular failure and those with pulmonary hypertension, suprasystemic right ventricular pressure, or both may also have increased atrial pressures, with consequent atrial arrhythmias, and may also have ventricular ectopy, ventricular tachycardia (VT), or ventricular fibrillation (VF).

Atrioventricular Block

Certain groups of patients are predisposed to the development of complete AV block, independent of attempted surgical repair. First, patients who have L-transposition, also known as *ventricular inversion* or *congenitally corrected transposition of the great vessels*, are at risk for the development of complete AV block spontaneously throughout their lives. The yearly incidence has been estimated at approximately 2% per year.[11] This is attributed to the abnormalities of the conduction system, in which malalignment exists between the atrial and the ventricular septa, and the normal compact AV node cannot make contact during embryologic development with the distal conducting system. A more anterior AV node forms instead and is thought to be more fragile.

Second, a syndrome of familial AV block associated with various septal defects has recently been described. Heterozygous

mutations in NKX2.5, a homeobox transcription factor, lead to the spontaneous development of complete AV block, as well as associated cardiac defects, of which atrial septal defects (ASDs) are the most common.[12] Ventricular septal defects (VSDs) may also be seen, particularly those associated with tetralogy of Fallot.

Arrhythmia Substrates Following Surgery for Congenital Heart Disease

When a child is born with congenital heart disease and requires surgical repair of the heart defect, most of the focus of the surgeon, cardiologist, and parents is on obtaining as good a hemodynamic result as possible. For many defects, such as ASDs, VSDs, AV canal defects, and tetralogy of Fallot, surgical results are excellent, and one can expect to have a perfect or nearly perfect hemodynamic result. Also, with more complex defects, such as truncus arteriosus and transposition of the great arteries, surgery can be expected to produce a normal or nearly normal hemodynamic situation, with an excellent long-term prognosis for the child. In even the most complex defects, including single-ventricle lesions, good results can be obtained as well, prolonging the person's life well into adulthood. It is in this setting that one must consider the impact of late postoperative arrhythmias, both on the child who has undergone cardiac repair, as well as on the parents of that child. These arrhythmias can be annoying, debilitating, or even life threatening.

Because late postoperative arrhythmias contribute significantly to morbidity and mortality, it is logical that every effort is made to treat patients with such arrhythmias and prevent any recurrences. Such treatments have included therapy with antiarrhythmic agents, implantation of cardiac rhythm control devices, catheter ablation, and surgical ablation. Unfortunately, serious limitations to the effectiveness, applicability, and safety—both of antiarrhythmic drug therapy and of device therapy—exist. Not surprisingly, ablative techniques, which potentially offer a curative treatment, are popular, but such techniques are challenging this patient population.

Principal Patient Groups

Based on the type of defect, the type of tachycardia, and current success rates of radiofrequency (RF) ablation attempts, postoperative tachyarrhythmias tend to fall into four main groups. The first group, referred to as *simple atriotomy-based atrial flutter*, includes patients who have had simple cardiac repairs, such as ASDs, VSDs, tetralogy of Fallot, AV canal defects, and related defects. The second group, termed *intra-atrial re-entry following atrial repair of transposition,* includes patients who have had either the Mustard or the Senning procedure. The third group, termed *intra-atrial re-entry following the Fontan procedure*, includes patients who have undergone the various forms of the Fontan procedure. Finally, a fourth group, termed *ventricular tachycardia following tetralogy repair*, includes patients with tetralogy of Fallot, as well as those with related lesions, such as certain types of double-outlet right ventricle. For each group, the anatomic details that support the tachyarrhythmia and that are important in ablation will be discussed.

Anatomic and Developmental Considerations

As atrial flutter and nearly all types of postoperative atrial tachycardia (AT) seem to involve only the anatomic right atrium, the exact anatomy of the right atrium becomes important in understanding these arrhythmias. Therefore, a detailed knowledge of right atrial anatomy is essential for the effective mapping and ablation of intra-atrial re-entrant tachycardia (IART) and atrial flutter.

During cardiac embryologic development, the right atrium is derived from three sources[13]: (1) The primitive right atrium forms adjacent to the tricuspid annulus and gives rise to the heavily trabeculated right atrial free wall and right atrial appendage. (2) The sinus venosus is incorporated into the right atrium and provides the origin for the smooth-walled portion of the right atrium (sinus venarum) that exists between the cavae posterior to the primitive right atrial structures. (3) Finally, septation of the primitive common atrium is accomplished by the formation of the atrial septum from the septum primum and the septum secundum. The ostium secundum is a foramen that forms in the septum primum, which is subsequently closed by the septum secundum, which forms a flap over this ostium to create the foramen ovale. In the fetus, the foramen ovale provides a route for right atrial blood to cross to the left atrium. All along the junction between the primitive right atrium and the sinus venosus portion of the right atrium is the crista terminalis ("terminal crest"), which appears as a ridge along the inner surface of the right atrium. The crista terminalis runs superior to inferior along the lateral wall of the right atrium. At its superior edge, near the junction between the superior vena cava (SVC) and the right atrium, is the sinus node pacemaker complex. As it arches inferiorly toward the inferior vena cava (IVC), it gives rise to the eustachian valve ridge (EVR), which appears as more of a flap than a ridge. The EVR is a remnant of the primitive right sinoatrial valve, guarding the ostium between the sinus venosus and the primitive right atrium. The EVR runs anterior to the IVC orifice and posterior to the posterior portion of the tricuspid valve annulus. As such, in the fetal circulation, the EVR acts to direct the IVC flow away from the tricuspid annulus and toward the foramen ovale. As the EVR arches toward the inferior atrial septum, it passes just superior to the ostium of the coronary sinus. It joins with the valve of the coronary sinus to form the tendon of Todaro, which inserts on the atrial septum near the bundle of His. With the coronary sinus ostium and the tricuspid annulus, the tendon of Todaro forms the triangle of Koch, and at the apex of this triangle, the compact AV node is found.

Adult-Type Atrial Flutter

Classic atrial flutter is characterized by atrial rates of up to 300 beats/min, with typical and very characteristic saw-tooth flutter waves visible on the surface electrocardiogram (ECG). This suggests the presence of nearly continuous atrial electrical activity because of the relative lack of a long atrial isoelectric interval in most patients. In typical atrial flutter, the flutter waves are prominent and are negative in leads II, III, and AVF, suggesting inferior to superior atrial activation. Although initially thought to represent re-entry around the caval veins or around the tricuspid valve annulus, the work of multiple investigators has clearly established the actual circuit. Impulses emerge from an isthmus of atrial tissue between the IVC and the tricuspid annulus to spread up the atrial septum, activating the atrium at the site where the bundle of His is recorded, and then down the right atrial free wall to enter the isthmus again.[14] This counterclockwise activation has been categorized as *typical* atrial flutter, whereas atrial flutter that uses the same circuit but in the clockwise order of activation has been categorized as *reverse typical* atrial flutter.[15]

In addition, further details have been provided using techniques of entrainment pacing, which depend on the demonstration of equivalence of the postpacing interval (PPI) during entrainment and the tachycardia cycle length (TCL) to establish that any given site is in the circuit (PPI = TCL). These studies have demonstrated the importance of the crista terminalis and the EVR as sites of conduction block during atrial flutter.[16-18] Conduction block is suggested by the demonstration that sites along the ridge where double potentials can be recorded are present.[17-20] The importance of such areas of conduction block is strengthened by entrainment pacing, demonstrating that the atrial myocardium on one or another side of the line of conduction block is part of the circuit. The critical nature of these lines of block is proved by RF ablation lesions that are designed to bridge from one line of block to another, with resultant abolition of the atrial flutter.[21-23] These criteria have been satisfied with both typical and reverse typical atrial flutter, and the features of this arrhythmia circuit now seem well characterized.

As previously described, the wave of activation leaves the region of the tricuspid valve–IVC isthmus to climb the interatrial septum and enter the heavily trabeculated right atrial free wall in the region of the SVC. It then spreads down the right atrial free wall, with the crista terminalis behind and the tricuspid annulus in front, turning counterclockwise around the tricuspid annulus when viewed from below (left anterior oblique view fluoroscopically). As the wave of activation turns posterior, it enters a "funnel," as described by Nakagawa and colleagues, created because the distance between the crista and the tricuspid annulus becomes progressively shorter.[18] The wave is funneled to the isthmus between the IVC and the tricuspid valve annulus, now with the annulus anterior and inferior and the EVR (the extension of the crista terminalis) posterior and superior. It is important to note that at this site, the EVR bisects the isthmus between the IVC and the tricuspid valve and that it is the EVR, not the IVC, that provides the critical site of conduction block. As it enters the interatrial septum, the wave again spreads in a superior fashion along the septum for the next circuit. Atrial flutter can be effectively dealt with using RF ablation either at the septal site of EVR insertion, by lesions that bridge from the tricuspid valve to the EVR, or posterior, from the tricuspid annulus down to the IVC.[18,21]

Simple Atriotomy-Based Atrial Flutter

When performing surgery to repair a simple secundum ASD, the surgeon typically places a long incision in the right atrial free wall, which is oblique and runs from the right atrial appendage laterally down *toward*, but not *to*, the tricuspid annulus or the IVC. Care is taken to avoid the sinus node, and this concern results in the crista terminalis typically not being incised by the surgeon. This incision gives adequate exposure for the repair of ASDs and is also used for the atrial approach to repair VSDs, either alone or as part of tetralogy of Fallot and related defects. The ASD itself is commonly closed by using sutures, but for large defects a patch may be employed. Occasionally, a patent foramen is left open. The occurrence of atrial flutter in patients with repaired tetralogy of Fallot deserves special mention; in some series, it is at least as common as VT, and the presence of right bundle branch block (RBBB) may lead to its being confused with VT.[24]

This surgical approach clearly creates a long line of permanent conduction block that is entirely in the trabeculated right atrium, anterior to the crista terminalis. This anatomy potentially creates a tunnel of atrial tissue between the crista and the atriotomy and another between the atriotomy and the tricuspid annulus. Such tunnels can easily be imagined as the required protected zones of conduction, mediating IART. Numerous cases of patients who exhibit "incisional" IART in which the atriotomy seems to act as the critical barrier have been reported.[25] In such patients, RF application from the atriotomy to the IVC, the tricuspid annulus, or the SVC has been successful in terminating tachycardia and preventing re-induction.

Because the atrial structures that support typical atrial flutter are also present and because these patients often have other risk factors for the development of flutter (atrial dilation, fibrosis, etc.), they may also have typical atrial flutter postoperatively. Furthermore, as has become apparent in patients with otherwise structurally normal hearts, such IART and flutter circuits can run in either direction (counterclockwise or clockwise). Indeed, several series reported a more common occurrence of typical or reverse typical atrial flutter than true incisional flutter in these patients.[26,27] In patients who have undergone patch closure of a secundum ASD, the patch itself has been reported to be a possible site of conduction block, mediating tachycardia, although this is less common.[21] The potential variability in circuits and rotation creates the possibility for several distinct P-wave morphologies and AT cycle lengths.

Any given patient may, of course, have several re-entrant circuits. A typical atrial flutter and, after successful ablation, a second IART with a longer or shorter TCL and noninvolvement of the flutter isthmus or of any structure posterior to the crista terminalis are commonly observed. One can speculate that the slower cycle length of such ATs is caused by conduction that is confined to the heavily trabeculated atrial free wall (in which atrial conduction may be slower) or longer circuits arising from dilation, or it may reflect slow conduction caused by fibrosis.

Intra-atrial Re-entry Following Atrial Repair of Transposition

The Senning and Mustard procedures, which are similar operations to address the hemodynamic abnormality in transposition, direct systemic return to the left ventricle and pulmonary artery and the pulmonary venous return to the right ventricle and aorta.[28,29] Although very successful, these operations are rarely performed in the current era, in part because of the success of the arterial switch procedure and in part because of the high incidence of sinus node dysfunction, atrial arrhythmias, and increased risk of sudden cardiac death (SCD). However, interest has recently increased in the so-called *double switch* procedure as a strategy for managing patients with L-transposition (congenitally corrected transposition). A Senning atrial baffle is constructed in this procedure.[30] Thus, this surgical substrate may not, in fact, disappear. In the Mustard procedure, after a long atriotomy anterior to the crista terminalis and the resection of the atrial septum, a baffle is constructed and sewn into place around each caval vein, through the isthmus between the IVC and the tricuspid annulus, and to the posterior wall of the left atrium so that caval flow is direct to the mitral annulus.[29] Pulmonary venous flow travels around the baffle and finds the tricuspid annulus. It is important to note that the baffle, where it is sewn into place along the tricuspid annulus, has the same function as the EVR in fetal life, which is to prevent IVC flow from reaching the tricuspid valve. Furthermore, surgical technique is directed at avoiding injury to the sinus node, so the crista terminalis is not disturbed. Finally, various approaches are used to avoid AV block, and often these lead to the coronary sinus

being incorporated into the pulmonary venous atrium rather than the systemic venous atrium.[31] These details leave the entire right atriotomy as well as the isthmus of atrial tissue between the EVR and tricuspid annulus in the new pulmonary venous atrium.[32,33] The one exception is the situation where the coronary sinus drainage is the systemic venous atrium, in which a catheter can reach the flutter isthmus from the IVC.[32]

In most respects, the Senning procedure is similar electrophysiologically to the Mustard procedure. The Senning procedure was designed to use mostly atrial tissue versus artificial material to construct the baffle.[28] In order to accomplish this, two atrial incisions are made. The first is in the right atrium, longitudinal, parallel, and anterior to the crista terminalis. The second, in the left atrium, is parallel to the first and between the right pulmonary veins and the interatrial septum. A U-shaped incision is made in the atrial septum, just above the coronary sinus, leaving the flutter isthmus intact. This flap of atrial septum is sewn to the back of the left atrium, to the left of the left pulmonary veins. The flap of right atrial free wall is sewn into place near or at the site of the EVR, preventing IVC flow from crossing the tricuspid valve. The left atrial incision is closed by sewing to the other edge of the right atrial incision. As in the Mustard procedure, both the flutter isthmus and the right atriotomy are part of the new pulmonary venous atrium.

Typically, and predictably based on the foregoing, one commonly finds two types of IART in these patients. First, typical or reverse typical atrial flutter is usually present, using the usual anatomic structures as barriers to support re-entry. Second, true "incisional" IART may also be found and is confined to the anatomic trabeculated right atrium, with the wave of activation passing between the lower limit of the atriotomy and the tricuspid annulus.

Intra-atrial Re-entry Following the Fontan Procedure

The Fontan procedure has changed many times since its development as a palliative procedure for patients without two functional ventricles, as a way of relieving ventricular volume overload and of normalizing arterial saturations.[34] Initially, it was thought that the right atrium could be used as an effective pumping chamber, provided that pulmonary artery pressures were low (atriopulmonary connection). Largely as a result of an extremely high incidence of atrial arrhythmias after such procedures, as well as concerns about hydraulic energy loss in the system and pulmonary venous obstruction, this approach has been abandoned in favor of approaches that bypass the heart entirely (total cavopulmonary connection via the lateral tunnel or via an extracardiac conduit).[35-37] Within each of the two categories, many modifications exist. Despite the approach of total cavopulmonary connection, atrial arrhythmias continue to be observed, although some large series now report a lower incidence of arrhythmias with the external conduit Fontan when compared with the lateral tunnel.[38] In any case, surgical details are critical in planning mapping and ablation procedures in these patients. In particular, difficulties in access are common and may limit the number of catheters that can be placed in the heart. Novel approaches such as the direct transthoracic approach are reported (Figure 78-1), and one may also consider perforating the baffle or approaching the atrial mass via the SVC and the left pulmonary artery.[39-41]

A long atriotomy is placed with the various forms of atriopulmonary connection. In patients who had a conduit from the right atrium to the pulmonary artery and in those in whom the right atrial appendage was connected directly to the pulmonary artery or to the right ventricular outflow tract (RVOT; the Bjork modification), this atriotomy was anterior to the crista terminalis. Often in these patients, patch augmentation of the right atrium was performed, using a piece of pericardium or other material incorporated into the closure. Invariably, closure of a large ASD was also necessary. As in the simpler situation of ASD repair (see earlier), both typical atrial flutter and incisional re-entry around the anterior atriotomy are possible and have been observed. Triedman and colleagues demonstrated slow conduction up the lateral wall in their excellent multiple-site mapping studies using basket catheters[42]; and this configuration fits the concept of conduction in a long isthmus bounded by the atriotomy and the crista terminalis. Re-entry around the ASD patch is also possible. Finally, patch closure of the tricuspid annulus has been occasionally performed in patients with a single ventricle without tricuspid atresia, potentially creating areas of slow atrial conduction on the other side of the suture line. Entrainment pacing is useful in identifying areas that are in the circuit and might be potential targets for ablation (Figures 78-2 and 78-3).[43] Alternatively, the use of dense voltage maps has been reported to be of value in identifying areas of scar and corridors of low-voltage myocardium, which can be targeted for ablation lesions, with some success.[44]

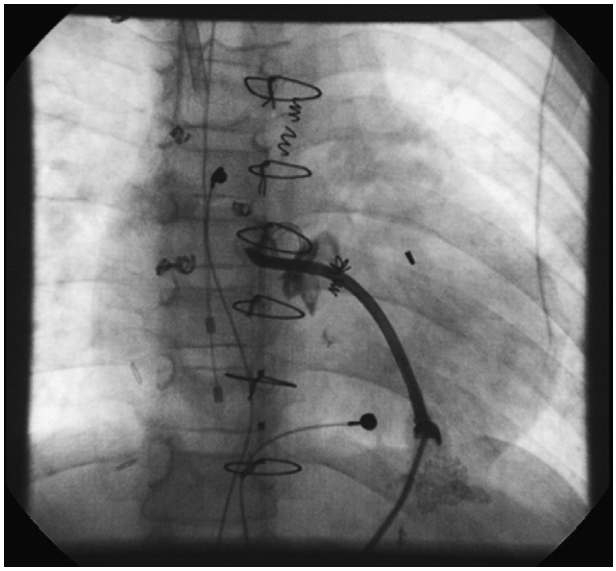

FIGURE 78-1 Posteroanterior fluoroscopy image showing transthoracic access to the heart in an 11-year-old with an external conduit Fontan. Note the staining of the atrial wall with radiographic contrast as well as the use of a bipolar esophageal lead.

Ventricular Tachycardia Following Repair of Tetralogy of Fallot

VT continues to be a difficult problem in the management of patients who have undergone surgical repair of tetralogy of Fallot and other related congenital heart defects. The actual etiology of SCD in patients following tetralogy repair is still somewhat uncertain. However, because of the frequent occurrence of premature ventricular contractions (PVCs), nonsustained and sustained VT in patients who have undergone complete repair of tetralogy of Fallot and related defects such as double-outlet right ventricle,

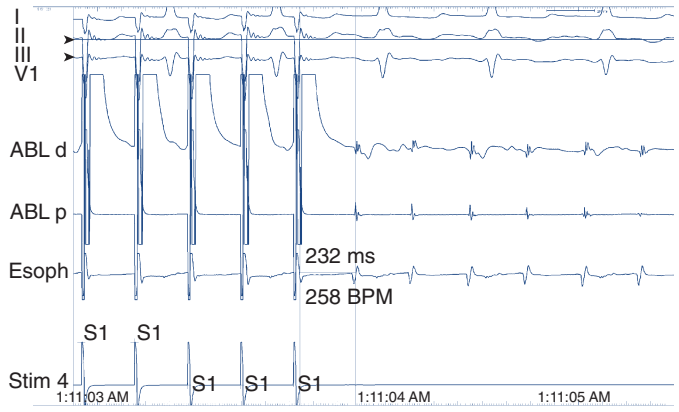

FIGURE 78-2 Surface and intracardiac electrogram tracings during the electrophysiology study in the patient shown in Figure 78-1. Atrial tachycardia is entrained via pacing through the ablation catheter at a candidate site, and the postpacing interval is equivalent to the tachycardia cycle length, demonstrating that this site is in the atrial tachycardia circuit.

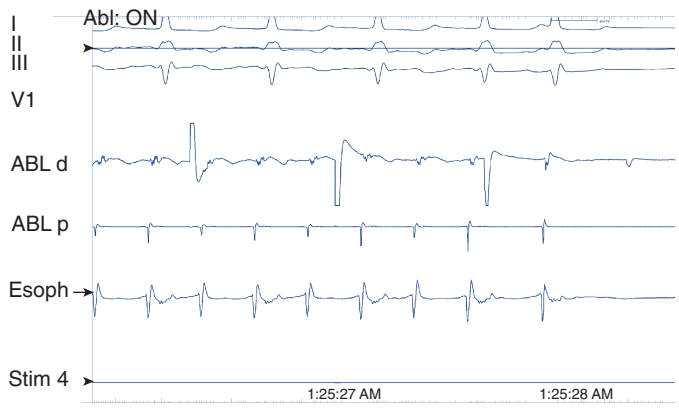

FIGURE 78-3 Tracings in the patient shown in Figures 78-1 and 78-2 showing the application of radiofrequency energy, with slowing and termination of the tachycardia about 5 seconds into the lesion.

VT has been implicated in the etiology of SCD in this patient group.[45-51] It is known that postoperative tetralogy of Fallot is the single most common condition that causes SCD among children between the ages of 1 and 16 years.[52]

Most of the available information concerning patients with VT and congenital heart disease pertains to tetralogy of Fallot compared with other forms of congenital heart disease. Ventricular arrhythmias do occur but are much rarer in patients with other lesions.[53] For the purposes of management, tetralogy of Fallot can be viewed as an archetype for other lesions when patients with other lesions present with ventricular arrhythmias in the setting of ventriculotomy, right ventricular dysfunction, or both.

Controversy still exists regarding the relative importance of various risk factors for the occurrence of ventricular arrhythmias and SCD, the exact relationship between ventricular arrhythmias and SCD, the role of electrophysiology study (EPS) and other procedures for risk stratification, and, ultimately, the appropriate management of postoperative patients with VT.

Patients with tetralogy of Fallot prior to repair have a large VSD with (usually severe) RVOT obstruction, which leads to cyanosis. The placement of a systemic-to-pulmonary artery shunt as a palliative procedure adds the element of potential left ventricular volume overload. Correction of the defect involves patch closure of the VSD with relief of the right ventricular obstruction. In nearly all patients, this requires resection of a significant amount of right ventricular muscle. Early in the experience, this was not done via an atriotomy with retraction of the tricuspid valve but, instead, required a ventriculotomy. Finally, in tetralogy of Fallot, the pulmonary annulus is typically smaller than normal. This has been approached by the placement of a transannular patch, which leads to chronic pulmonic insufficiency. Pulmonic insufficiency may be very severe if it is associated with downstream obstruction related to significant pulmonary arterial stenosis. It has been hypothesized that ventricular arrhythmias are caused by the effects of years of chronic cyanosis, followed by the placement of a ventriculotomy, with elevation of right ventricular pressures arising from inadequate relief of obstruction, and severe pulmonic regurgitation with right ventricular dysfunction and enlargement.[45,54-56] Factors such as wall stress and chronic cyanosis, coupled with the passage of time, may lead to myocardial fibrosis and result in the substrate for re-entrant ventricular arrhythmias. This hypothesis is supported by histologic examination of the hearts of patients with tetralogy of Fallot who died suddenly. These studies have shown extensive fibrosis.[57] The hypothesis is also supported by the observation of fractionated electrograms and late potentials recorded from the right ventricle at EPS, suggesting the presence of slow conduction.[58,59] Despite the presence of a 5% incidence of coronary artery abnormalities in tetralogy of Fallot that put the left anterior descending coronary artery or other large branches at risk at the time of complete repair, such potential damage has not been implicated in the etiology of ventricular arrhythmias or of SCD in most patients.

Careful studies in patients with VT following surgery for tetralogy, as reported by Zeppenfeld et al, have supported the concept that the mechanism of VT is macro–re-entry, which involves a limited number of critical isthmuses in the right ventricle, either at the site of anterior right ventriculotomy or related to the site of a VSD patch.[60] Transient entrainment has been documented, with constant fusion at the paced cycle length and progressive fusion at decreasing cycle lengths.[61,62] Successful ablation of these isthmuses is effective in preventing the recurrence of VT.

Early reports noted the frequent occurrence of PVCs in patients who had previously undergone repair of tetralogy of Fallot. Gillette and coworkers identified PVCs on routine ECGs in 18% of patients.[45] With exercise testing, the incidence may increase—to around 20%, as shown in one study.[50] With Holter monitoring, the incidence of ventricular ectopy is reported to be as high as 48%.[63] In about half of these patients, ventricular ectopy is complex, defined as multiform beats, couplets, or VT. In the great majority of patients, this ventricular ectopy is entirely asymptomatic.

Many investigators have tried to correlate the incidence of ventricular ectopy with various factors, including age at presentation, age at time of repair, and various hemodynamic features. Four factors seem to be the most important: (1) age at initial repair; (2) time since repair; (3) presence of residual right ventricular obstruction; and (4) presence of significant pulmonic insufficiency. In Chandar and colleagues' multicenter study, older age at time of repair, especially beyond 10 years of age, was associated with nearly a 100% incidence of ventricular arrhythmias, regardless of the follow-up interval.[63] In the same study, time since repair also predicted the occurrence of ventricular ectopy, which occurred in all 4 patients followed up for more than 16 years, despite repair in infancy. Walsh and colleagues, however, showed that in a group of patients who underwent repair at less than 18 months of age, ventricular ectopy was rare on ECG (1%) but more common on Holter monitoring (31%) after an average of 5 years of follow-up.[64]

Garson and associates, in a study of 488 patients with repaired tetralogy of Fallot, showed that the incidence of ventricular arrhythmias was closely related to right ventricular hemodynamics.[65] The incidence of ventricular arrhythmias was significantly higher in those with a right ventricular systolic pressure greater than 60 mm Hg, and in those with a right ventricular end-diastolic pressure greater than 8 mm Hg, suggesting that residual RVOT obstruction and pulmonic insufficiency negatively influence outcome. They also found a relationship to age at surgery, but this was not as important as the follow-up interval. Zahka and coworkers, in a prospective study of 59 patients with tetralogy of Fallot repaired prior to 11 years of age, found that the degree of pulmonary regurgitation was, by far, the most important predictor of the frequency and severity of spontaneously occurring ventricular arrhythmias.[54] Although the degree of residual RVOT obstruction was not a predictor in this study, significant residual obstruction was rare in their study group.

Spontaneously occurring sustained VT is, in fact, fairly uncommon among patients with repaired tetralogy, despite the high incidence of ventricular ectopy. The best data in this regard come from the study by Harrison and associates that included patients with repaired tetralogy of Fallot attending an adult congenital heart disease clinic.[66] Eighteen of 210 patients (8.6%) had either documented sustained VT, syncope, or near-syncope, with palpitations and inducible sustained monomorphic VT at EPS. VT was closely related to right ventricular hemodynamics, particularly RVOT aneurysms and pulmonic insufficiency. This finding is consistent with the earlier report by Zahka and coworkers, which emphasized the importance of pulmonic insufficiency as a risk factor for ventricular ectopy.[54]

The occasional but persistent observation of unexpected SCD in this group of patients with repaired congenital heart disease, along with the high incidence of spontaneously occurring ventricular arrhythmias, both simple and complex, has led to the hypothesis that SCD in such patients is caused by VT. During the 1970s and 1980s, it was standard practice to perform EPSs in a large proportion of patients who had undergone repair of tetralogy of Fallot or of related congenital defects. Antiarrhythmic drug therapy was often prescribed on the basis of the results of such studies. This approach has, for the most part, been abandoned because of the lack of strong evidence supporting the proposition that SCD can be prevented with this approach as well as worries about the proarrhythmic effect of the antiarrhythmic medications chosen for treatment. In a large multicenter retrospective review that used a variety of electrophysiological protocols, Chandar and colleagues reported the experience with 359 postoperative patients with tetralogy of Fallot who underwent invasive EPS.[63] VT could be induced in 17% of patients but not in any patient who was asymptomatic and had a normal 24-hour ECG. Although late SCD occurred in five patients, none of these patients had inducible VT at EPS.

It is also interesting that the risk of VT can be assessed from QRS duration on the surface ECG. Gatzoulis and associates found that in a group of 48 well-studied postoperative patients with tetralogy of Fallot, those with a QRS duration greater than 180 ms had a greatly increased risk of spontaneous VT, SCD, or both.[55] Similarly, Balaji and coworkers showed that a QRS duration greater than 180 ms predicts the finding of inducible sustained monomorphic VT at EPS.[67] The cause of this relationship is almost certainly related to the tendency of chronic pulmonic insufficiency to cause right ventricular dilation with more severe right ventricular conduction delay, for which lengthening of the QRS is a marker.

Clear evidence that the risk of SCD may increase at late follow-up exists. In a careful study of 490 survivors of tetralogy of Fallot repair at a single center, Nollert and colleagues constructed actuarial survival curves out to 36 years following surgery.[68] In this study, the yearly actuarial mortality rate during the first 25 years was 0.24% per year, but mortality increased dramatically after 25 years to 0.94% per year. Most deaths were from SCD. The mortality risk was also related to date of repair (highest before 1970), the degree of preoperative polycythemia (highest with hematocrit >48), and the use of an RVOT patch (highest with a patch). The last factor is most likely related to the presence of pulmonic insufficiency, as suggested earlier.

The close linkage of pulmonic insufficiency, right ventricular dilation, and VT/SCD suggests that the management of pulmonic insufficiency in patients with tetralogy of Fallot should be more aggressive. However, pulmonary valve placement is problematic in young children with small hearts because of issues related to growth, and valves predictably fail, necessitating reoperation. The earlier the first valve is placed, the more surgeries the patient must undergo over his or her lifetime. However, it is ideal to intervene with pulmonary valve replacement before the development of significant right ventricular dysfunction. While QRS duration is an easily obtained indicator of right ventricular dilation, attention has lately focused on the evaluation of right

ventricular volume by cardiac magnetic resonance imaging (MRI). Therrien et al have observed that in adults with tetralogy of Fallot, a right ventricular end-diastolic volume of greater than 170 mL/m^2 predicted a failure of the right ventricle to return to normal size following PVR, while all patients with volumes less than 170 mL/m^2 had complete normalization.[69] Geva has proposed a right ventricular end-diastolic volume of 160 mL/m^2 or more as a criterion for PVR, among other criteria and has also recommended an earlier operation for patients with defects originally repaired at age 3 years or later.[70] It remains to be seen whether the widespread adoption of these protocols will have an effect on the incidence rates of SCD.[71]

Surgically Induced Atrioventricular Block

The risk of complete AV block as a result of surgery depends on the type of repair that is attempted. At highest risk are patients who undergo closure of AV septal (canal or endocardial cushion) defects and those having closure of VSDs involving the perimembranous region of the ventricular septum.[53,72,73] In such defects, the distal conducting system is in a location that is difficult to avoid during surgical closure of the defect. The repair of subaortic stenosis is often complicated by AV block because of the need, in many cases, to resect muscle from the left side of the ventricular septum. Muscular VSDs and supracristal (doubly committed subarterial) VSDs are distant from the conducting system and, therefore, are not highly associated with AV block. Likewise, the repair of ASDs is only rarely complicated by postoperative AV block, and its occurrence should raise the possibility of an NKX-2.5 mutation.[53,74]

Postoperative Sinus Node Dysfunction

Any operation that involves surgery on the right atrium may lead to postoperative sinus node dysfunction; this problem is often not evident early after surgery but may take years to manifest. The mechanism of sinus node damage is not well known, but most likely, the damage results from direct injury to the sinus node pacemaker complex, interference with the blood supply to this structure, or both. The repair of simple ASDs is only rarely followed by sinus node dysfunction, whereas the risk is higher with the repair of sinus venosus ASDs. Sinus node dysfunction is most common following the Senning or the Mustard procedure for transposition, the hemi-Fontan procedure, and the Fontan procedure.[53]

Treatment of Arrhythmias in Patients with Congenital Heart Disease

Antiarrhythmic Drug Therapy

Decisions Regarding Treatment

Sustained tachycardia may be more poorly tolerated in this patient population because of poor systemic ventricular function. In addition, the use of antiarrhythmic agents is problematic in this patient population because of the increased prevalence of sinus node dysfunction after atrial surgery, such as the Mustard, Senning, or Fontan procedures, as well as the potential for proarrhythmia, which is exacerbated by systemic ventricular dysfunction.[75] These issues all need to be evaluated in the choice of antiarrhythmic agents in this population.

The treatment decision in patients with ventricular ectopy, VT, or both following correction of congenital heart disease may be directed at one or both of two goals: (1) the prevention of SCD and (2) the suppression or termination of symptomatic episodes of VT. Treatment may involve antiarrhythmic medication, RF catheter ablation, surgical cryoablation, or implantation of a tiered-therapy device providing anti-tachycardia pacing and cardioversion or defibrillation.

It is difficult to know which patients require EPS, treatment, or both. When one considers that no prospective studies have demonstrated that SCD can be prevented in any group of postoperative patients by treatment of any type, it does not seem that one should recommend routine EPS and treatment of asymptomatic patients with ventricular ectopy or other arrhythmias. It seems likely in certain subgroups carefully chosen antiarrhythmic therapy may exert a beneficial effect in lowering mortality; it is also quite possible that in some subgroups, the proarrhythmic potential of antiarrhythmic medications more than makes up for any beneficial effect, a result similar to that seen in the Cardiac Arrhythmia Suppression (CAST) trial.[76,77] Until such prospective, controlled trials are performed, therapy with drugs such as flecainide, propafenone, and quinidine cannot be recommended for most asymptomatic patients. An argument can be made for selecting certain patients for prophylactic treatment with β-blockers, as Garson and associates have suggested.[78] Examples of such patients might include those with significant pulmonic regurgitation, residual right ventricular obstruction and complex ventricular ectopy, or both. One can also argue that these patients should be considered for cardiac surgery to correct hemodynamic abnormalities such as residual obstruction, especially branch pulmonary artery stenosis, and should also be considered for placement of a homograft valve to eliminate pulmonic insufficiency.

If the goal of therapy is to prevent the recurrence of clinically documented VT, then proceeding in a fashion similar to that with other forms of VT might be considered. EPS for the induction of VT with subsequent drug testing is reasonable; but it should be kept in mind that some proarrhythmic risk to the use of certain medications, especially quinidine, procainamide, flecainide, and propafenone, may very well be present. Exercise testing may also be used as a means of inducing VT in certain patients. The choice of a pharmacologic agent for long-term treatment is then based both on the suppression of the arrhythmia by the drug and on its proarrhythmic potential. In the former consideration, investigators have reported some success with most class I agents, especially quinidine, procainamide, propafenone, and flecainide, as well as with β-blockers. The latter consideration, proarrhythmia, is difficult to judge. A high incidence of documented proarrhythmia with flecainide and encainide in patients with structural cardiac disease has been reported by Fish and associates in a pediatric series.[79] Furthermore, cardiac arrest and deaths occurred predominantly among patients with underlying heart disease. Sotalol is also known to be proarrhythmic, particularly in patients with significant ventricular dysfunction.[80] D-sotalol has been found to increase mortality in post-infarction patients with ventricular dysfunction (the SWORD trial).[81] These findings suggest that sotalol and class IC agents should be used with extreme caution in patients with repaired tetralogy of Fallot and ventricular dysfunction. This, of course, leaves amiodarone, which has the advantage of little-reported proarrhythmia, even in patients with significant ventricular dysfunction. Concerns have been raised over long-term side effects such as pulmonary fibrosis, ocular abnormalities, thyroid dysfunction, transaminase elevations, and

significant bradycardia in children and young adults[82-84]; the use of this agent in a young person means that the medication is likely to be needed for several decades at least. These concerns naturally have led to the consideration of nonpharmacologic therapy.

Digoxin

Digoxin has a long history of use in children, in particular in patients with atrial flutter and intra-atrial re-entry. Although the drug exerts a direct effect on the cardiac cell membrane, most of its antiarrhythmic properties are a result of its indirect actions mediated through the autonomic nervous system.[85] The direct and indirect effects of digoxin on the AV node prolong the refractory period and slow conduction. In general, digoxin is not an effective drug for the acute conversion of atrial flutter. In the collaborative study by Garson and coworkers, digoxin used alone was successful in preventing recurrences of atrial flutter in only 44% of patients.[86] Of the conventional agents, the most effective treatment for preventing recurrences (53%) was the combination of digoxin with a type IA agent such as quinidine or procainamide. However, the use of digoxin may be beneficial in the control of ventricular rate during atrial flutter.

Class I Antiarrhythmic Medications

When using the sodium channel blocking agents to manage arrhythmias in patients with congenital heart disease, the likelihood of success must be carefully balanced against the possibility of proarrhythmia. Class IA agents (quinidine, procainamide, and disopyramide) as well as class IC agents (flecainide and propafenone) are useful in treating atrial flutter and ventricular arrhythmias as well as in controlling SVT mediated by concealed or manifest accessory pathways. Because of their vagolytic properties, class IA medications, particularly disopyramide, need to be given in combination with digoxin preparations or other AV node–blocking agents to lessen the likelihood of 1:1 AV conduction should atrial flutter occur. Class IB agents (lidocaine, tocainide, mexiletine, phenytoin, and moricizine), however, are not considered particularly useful in atrial arrhythmias, although moricizine has been used effectively in some studies. These agents are primarily used in treating ventricular arrhythmias. They are all effective in suppressing PVCs, and for many years, phenytoin has been a favorite antiarrhythmic medication for suppressing PVCs in patients following tetralogy of Fallot repair.[65] Whether suppression of PVCs is an important goal in the population is open to speculation. No clear evidence exists to show that VT and SCD can be prevented by the use of these agents. Furthermore, classes 1A and 1C agents share a propensity to proarrhythmia, particularly in patients with ventricular dysfunction, and so should be used with caution.[79]

Class II Antiarrhythmic Medications

β-Adrenergic blocking agents such as propranolol and atenolol may be useful for rate control in patients with chronic atrial flutter and have the advantage of not being proarrhythmic. For other forms of SVT, the β-blockers are often effective in preventing recurrences. Patients with concomitant sinus node dysfunction may require permanent pacing if β-adrenergic blocking agents are used. Some evidence exists to show that the use of propranolol is safe and effective in the management of ventricular arrhythmias following repair of tetralogy of Fallot.[78]

Class III Antiarrhythmic Medications

Class III agents are thought to exert their actions primarily by prolonging action potential duration and refractoriness without significantly affecting conduction. The agents in this category are amiodarone and sotalol. Garson and colleagues had an opportunity to use amiodarone in a group of 39 patients with congenital heart disease, critical tachyarrhythmias, and arrhythmias not responsive to conventional agents.[87] Sixteen of the 39 patients had recurrent atrial flutter, and 15 of the 16 had complete elimination of the flutter. Sotalol has been used more recently with good results.[88-89] It combines class III action with β-adrenergic blocking activity and so may not be tolerated by patients with poor ventricular dysfunction. Both these agents also may exacerbate sinus node dysfunction.

Class IV Antiarrhythmic Medications

Class IV drugs (e.g., verapamil), given intravenously, have been used almost exclusively as an acute intervention. Conversion of atrial flutter to normal sinus rhythm occurs rarely after the intravenous administration of verapamil. However, what does occur is a lowering of the ventricular rate secondary to delayed conduction through the AV node or conversion from atrial flutter to AF with a reduction in conducted impulses. Verapamil may be an effective agent for a rapidly deteriorating patient with atrial flutter and 1:1 AV conduction. However, extreme caution must be exercised when using this medication in younger children, and verapamil should *never* be given to those younger than 6 months.[90] Another option for the rapid control of the ventricular rate is the continuous infusion of diltiazem, another class IV agent.

Results of Antiarrhythmic Drug Therapy

Unfortunately, medical therapy has been disappointing in the management of patients with postoperative arrhythmias. In general, a fairly low success rate has been observed with a variety of antiarrhythmic agents for the prevention of recurrent atrial flutter or IART. Garson and associates showed that even if an antiarrhythmic agent was found to be successful in suppressing episodes of atrial flutter, a significant incidence of SCD was present, which suggests that life-threatening proarrhythmia may be a serious potential problem in postoperative patients.[86] Finally, although Garson and colleagues presented retrospective evidence that the suppression of ventricular ectopy was associated with a lower incidence of SCD among patients with tetralogy of Fallot, no prospective trials have been performed to support this concept.[65]

Ablation of Accessory Pathways in Patients with Unrepaired Congenital Heart Disease

In considering the technical factors that lead to success in the ablation of accessory pathways in patients with associated congenital heart disease, those relating to venous and arterial access, those relating to visceral situs, those relating to the location of the atrioventricular conducting tissue, and those relating to the specific cardiac defect may be considered. In general, however, no two patients are identical, neither in the cardiac anatomy confronting the electrophysiologist nor in the approach that will be necessary to successfully ablate the pathway. The electrophysiologist needs to combine a detailed knowledge of the patient's exact

intracardiac anatomy with the ability to be creative and persistent in the ablation attempt.

Venous and Arterial Access

Patients who have had multiple procedures or who have had long stays in the intensive care unit with indwelling lines may have limited venous access because of iliofemoral thrombosis. When such thrombosis is bilateral, this problem may prevent a normal approach to the right atrium. In patients who have undergone the bi-directional Glenn procedure, direct access to the right atrium from the SVC is not available because of the direct connection of the SVC to the pulmonary artery. In both situations, approaching the right atrium from the other cava may be considered, for example, from the SVC, when bilateral iliofemoral thrombosis is present. Reports of the use of a transhepatic approach for diagnostic and interventional catheterization suggest that this route might also be efficacious for catheter ablation.[91,92] Left-sided accessory pathways may, of course, be ablated by a retrograde approach in larger patients, but this approach is not recommended in children weighing less than 15 to 20 kg or in those with aortic valve disease.[93]

Situs

The existence of situs abnormalities can render a catheter ablation procedure potentially confusing because of the nonstandard location of veins, arteries, and the heart itself, but these problems are not insurmountable if one possesses knowledge of congenital cardiac pathology. Such abnormalities are, unfortunately, not limited to simple mirror-image arrangements. Standard fluoroscopy planes for normal anatomy may make little sense in the setting of situs abnormalities. When needed, transthoracic or transesophageal echocardiography may be used to confirm catheter tip locations.[94-96] Finally, patients with heterotaxy syndromes may have interruption of the IVC with azygous continuation. In these patients, a catheter passed from the femoral vein will traverse the azygous system to join the SVC and enter the atrium from above. In these patients, an ablation catheter may be introduced from the internal jugular or subclavian vein to allow more straightforward catheter manipulation. In this area of difficulty, the use of advanced catheter navigation technologies such as Stereotaxis, which has been reported to aid in the maneuvering of catheters remotely in patients with complex congenital heart disease, can be considered.[97]

Atrioventricular Conduction Structures

The ability to successfully ablate septal accessory pathways without the complication of AV block in patients with normal intracardiac anatomy depends, in large part, on the electrophysiologist's detailed knowledge of the location of the compact AV node and the bundle of His in relation to other structures in the heart. In several forms of congenital heart disease, the AV conducting tissue is located differently, and this anatomy must be kept in mind.[98] For example, patients with a complete AV canal as well as those with ostium primum ASD have AV conducting tissue displaced posteriorly toward the coronary sinus.[99] Ablation of posteroseptal accessory pathways would, therefore, likely carry a higher risk of complete AV block. In tetralogy of Fallot, the conducting system is at risk as well, being at the margin of the VSD.[100] Patients with L-transposition have AV conducting tissue located more anteriorly, and it is thought to be more fragile and prone to accidental damage during catheterization.[101] The anatomy for other rarer forms of congenital heart disease has also been defined.[98] The current availability of transcatheter cryoablation now allows a safer alternative for ablation of septal pathways in patients with abnormal AV conduction systems.[102]

Defect-Specific Factors

Factors that are characteristic of particular defects are clearly quite numerous and cannot be fully listed here. However, in some situations, the specific congenital heart defect may make the approach to ablation more straightforward. For example, in the presence of an ostium primum or secundum ASD, the left atrium is quite easily entered and mapped. Similarly, the presence of a left superior vena cava (LSVC)–coronary sinus connection renders the coronary sinus very large and easy to enter, although catheter contact may not be as good as in the normal-sized coronary sinus, and the anterolateral left AV groove may be difficult to map because of the tendency of the catheter to enter the LSVC from the coronary sinus. Conversely, abnormalities of particular structures may dictate a different catheter course than is usual for a particular operator. For example, a patient with aortic stenosis or regurgitation should have ablation of a left-sided accessory pathway by an antegrade (trans-septal) route, to avoid crossing the abnormal valve.

The situation with Ebstein's anomaly can be quite challenging. The presence of significant tricuspid regurgitation may make stable catheter position difficult on the right AV groove. Similarly, the downward displacement of the tricuspid valve leaflets (principally the septal and posterior leaflets) makes stable positioning on the AV groove difficult. However, the single most difficult factor in such patients is the difficulty in achieving an adequate temperature at the catheter tip despite maximal voltage, most likely because of the capacious right atrium and the atrialized right ventricle. This, combined with the propensity of patients with Ebstein's anomaly to have multiple accessory pathways and a tendency to AF, often makes such procedures long, grueling, and ultimately unsuccessful. A variety of catheter approaches, both from the IVC as well as from the internal jugular vein or the right subclavian vein should be tried, and the use of long venous sheaths to allow for better catheter stability might be considered.[103] For the fluoroscopic identification of the right AV groove and for precise mapping of signals at the AV groove, some investigators have used a 2 Fr custom mapping wire introduced directly into the right coronary artery and advanced around the AV groove.[104-106] The use of temperature monitoring, temperature control, or a combination of both is mandatory in patients with Ebstein's anomaly to allow differentiation between two scenarios: (1) lack of success because of incorrect catheter position and (2) inadequate temperature.[107]

In patients with L-transposition, the malalignment of the atrial and ventricular septa creates a complex anatomy when dealing with septal accessory pathways. Typically, the ventricular septum is in the sagittal plane, whereas the atrial septum is more normally positioned, but close to the AV groove. The coronary sinus may be difficult to enter. The propensity to AV block in such patients (mentioned earlier) must be kept in mind. The presence of significant left-sided AV valve regurgitation with left-sided Ebstein's anomaly may dictate an antegrade approach to the ablation of left-sided accessory pathways because positioning under the left-sided tricuspid leaflets might not allow close enough contact with

the true AV groove. This approach may be chosen also out of a desire to avoid creating further regurgitation with catheter ablation attempts. Trans-septal puncture can certainly be accomplished, but the angle of attack may not be standard because of the abnormal septal orientation. When in doubt, pulmonary angiography to define the left atrium on levophase, intraoperative echocardiography, or a combination of both may be used.[95,96]

Saul and associates have documented in patients with more complex anatomy the presence of dual AV conducting systems, which may mediate AV reciprocating tachycardia. These have been patients with AV discordance with or without atrial situs inversus.[108] The second, or accessory, AV node and distal conducting system resemble Mahaim-type atriofascicular accessory pathways seen in patients with otherwise normal cardiac anatomy and can be mapped and ablated with similar techniques.

Radiofrequency Ablation of Atrial Arrhythmias in Postoperative Patients with Congenital Heart Disease

With the advent of catheter procedures using RF energy and, more recently, cryothermal energy, to eliminate the substrate for conditions such as WPW syndrome and AV node re-entry, ablation of atrial flutter and IART became possible.[109-112] Using the surgical experience as a guide, as well as techniques for demonstrating concealed entrainment, Feld and coworkers were able to demonstrate initial success with type 1 ("typical") atrial flutter by placing RF lesions at the isthmus between the IVC and the tricuspid valve annulus.[22] RF lesions placed in these regions were often successful in terminating atrial flutter, and long-term success has been accomplished. Subsequently, other centers have also demonstrated that high success rates are possible in adults with type 1 flutter, with an acceptable incidence of recurrence.[18,113]

These concepts have further been extended to patients with atypical atrial flutter following extensive atrial surgery.[25,106,114-116] In these patients, the substrate for atrial flutter consists of natural anatomic obstacles to impulse propagation such as the IVC, coronary sinus, tricuspid annulus, and so on as well as surgically created obstacles such as atriotomy sites, intra-atrial baffles, and conduits. Transient entrainment may be used to demonstrate the re-entrant mechanism, and sites of slow conduction are sought where concealed entrainment (entrainment without visible fusion on the surface ECG) can be demonstrated. Lesions at these sites are placed in an attempt to bridge the zone of slow conduction and terminate tachycardia. Encouraging results have been reported, but the incidence of recurrence after an initially successful procedure is significant, particularly in more complex heart defects.

Despite having had an atriotomy, many of these patients are found, by careful mapping, to have atrial flutter, which involves the typical isthmus between the tricuspid annulus and the IVC. This is, in fact, quite common in patients who have had simple atrial surgery, as described earlier. In these patients, when typical or reverse typical atrial flutter is documented and clearly involves this isthmus, the ablation procedure may proceed by standard methods for the ablation of typical atrial flutter, and documentation of bi-directional block in the isthmus is a goal of ablation. When such an approach is taken, the results of ablation are very good.[26]

In patients who have had the Mustard or the Senning procedure for transposition who also have atrial flutter, most of the critical structures that support atrial re-entry are in the new pulmonary venous atrium. The presence of a suture line at the site of the EVR in such patients might cause fibrosis and conduction delay, perhaps dramatically increasing the likelihood that atrial re-entry will occur. In any case, typical and reverse typical atrial flutters are also quite common in this patient population. The approach for ablation is not straightforward when the target is in the pulmonary venous atrium and, often, the arrhythmia must be approached either via a leak or a separation in the baffle or by a retrograde transaortic approach.[32] In addition, studies have shown that after successful RF ablation at the flutter isthmus, patients have exhibited a sudden shift from one tachycardia involving the flutter isthmus to a second tachycardia not involving this isthmus but instead involving the atriotomy. Such a phenomenon may be an indication of true "figure of eight" re-entry, with the ablation of one, but not both, limbs of the figure of eight.

Catheter ablation in the atriopulmonary connection type of Fontan has been quite disappointing in contrast to the experience in patients who have had ASD repair and the Mustard and Senning procedures.[25,32,114,117,118] Multiple tachycardia circuits and a high incidence of recurrence after initial success have been observed. It may be that with high atrial pressures, the resulting thickening of the atrial wall from atrial hypertrophy prevents the development of full transmural lesions. Alternatively, sluggish blood flow may not allow adequate tip cooling, limiting energy delivery and resulting in ineffective lesions, but this problem is obviated by the use of irrigated tip RF ablation.[119]

More recent innovations involving total cavopulmonary connection by the lateral tunnel technique are clearly associated with better hemodynamics and lower atrial pressures. Unfortunately, IART is still frequently observed in these patients. In order to exclude the atrium, the SVC is connected directly to the pulmonary artery, and a tunnel is created to direct IVC flow to the underside of the pulmonary artery. The baffle that accomplishes this is similar to that used in the Mustard or the Senning procedure, with a line of sutures going through the region of the EVR and with the baffle directing IVC flow away from the tricuspid annulus. The long atriotomy used to construct the lateral tunnel is closed, and this suture line is in the new pulmonary venous atrium. This anatomy creates the potential for re-entry in the usual flutter circuit, as well as incisional IART involving the right atriotomy, which has been elegantly demonstrated in an animal model by Rodefeld and colleagues.[120] Experience with RF ablation in this particular anatomic substrate is not sufficient to comment on its effectiveness, but similar results to those reported for the Senning and Mustard procedures could be expected.

It is encouraging that some authors have reported a lower incidence of atrial arrhythmias in patients who have undergone the Fontan procedure by means of an external conduit.[121] In this approach, the SVC is connected to the pulmonary artery directly, and the IVC is connected to the pulmonary artery through the use of aortic allograft material or polytetrafluoroethylene; ideally, this involves no atriotomy, except for cannulation. However, intracardiac repair is often needed, typically via an atriotomy; so generally, no access to the atrium via the IVC or the SVC is available. In this situation, access may be gained by creating a fenestration in the external conduit or by direct transthoracic entry into the atrium.[122,123]

Radiofrequency Ablation of Ventricular Arrhythmias in Postoperative Patients with Congenital Heart Disease

If VT is easily inducible and well tolerated hemodynamically, RF ablation may be considered. Because most evidence supports

the concept of macro–re-entry as the mechanism of such well-tolerated VT, the use of entrainment pacing and mapping techniques is indicated. Investigators have reported successful procedures using RF energy.[124-129] Successful sites have included the area between the pulmonic annulus and the outflow tract patch, the isthmus of ventricular tissue between an outflow tract patch and the tricuspid annulus, and the region of the VSD patch.[124,126,129]

Although well-tolerated VT can be mapped in the electrophysiology laboratory, many patients have ventricular dysfunction, rapid VT rates, or both and will not tolerate this. Several investigators have reported intraoperative mapping and ablation.[124,130-133] In particular, Downer and colleagues have used intraoperative mapping of the RVOT in the beating heart, employing an endocardial electrode balloon and a simultaneous epicardial electrode shock array.[132] Ablation was carried out with good success in three patients by applying cryotherapy lesions during normothermic cardiopulmonary bypass with the heart beating or during anoxic arrest.

One exciting development is the advent of substrate mapping of the important isthmuses in congenital heart disease and VT by using an electroanatomic map obtained during sinus rhythm, as reported by Zeppenfeld et al.[60] A high-density voltage map of the right ventricle is obtained, and areas of likely scar and patch are confirmed by lack of capture using high-output unipolar pacing. This group reported that the substrate-supported VT in patients with tetralogy of Fallot is limited to four isthmuses: (1) the tricuspid annulus and scar or patch in the anterior RVOT, (2) the pulmonary annulus and right ventricular free wall scar or patch, (3) the pulmonary annulus and septal scar or patch, and (4) the septal scar or patch and the tricuspid annulus (Figure 78-4). These observations reveal the possibility of effective ablation of VT by attacking these isthmuses with RF energy, at the time of surgical revision, or both.

Device Therapy

Pacemaker Therapy

Patients with the sick sinus syndrome who require an antiarrhythmic agent other than digoxin to prevent recurrences of arrhythmia are at risk for very slow heart rates. The Joint American College of Cardiology/American Heart Association/Heart Rhythm Society Task Force recommended that these patients have pacemakers implanted.[134] Furthermore, many of these patients will have symptoms caused by slow heart rates, such as exercise intolerance or syncope, and should also receive pacemakers. The loss of AV synchrony may not be well tolerated in patients with borderline ventricular function, and pacing is sometimes recommended for patients with few symptoms as a means of optimizing hemodynamic function.

All patients who have persistent AV block as a result of cardiac surgery should receive permanent pacemakers. However, spontaneous resolution of AV block in the immediate postoperative period is often observed; therefore, a reasonable period of postoperative observation is recommended before the decision concerning permanent pacing is made; this observation period should be at least 5 to 6 days.

One type of implantable pacemaker is the anti-tachycardia device, which can be used to achieve paced conversion of atrial flutter to sinus rhythm or an atrial paced rhythm. The techniques for conversion are programmable and may include underdrive pacing to overdrive pacing, and programmed extrastimuli to scanning methods.[135] Anti-tachycardia pacing is generally chosen if an arrhythmia is refractory to medication, the patient is intolerant of medication, or the attacks are frequent and of long duration. An additional advantage is that many patients have tachycardia-bradycardia syndrome, and after overdrive pacing of atrial flutter, the pacemaker is on standby to begin pacing if the patient's spontaneous rate is not adequate. Gillette and coworkers

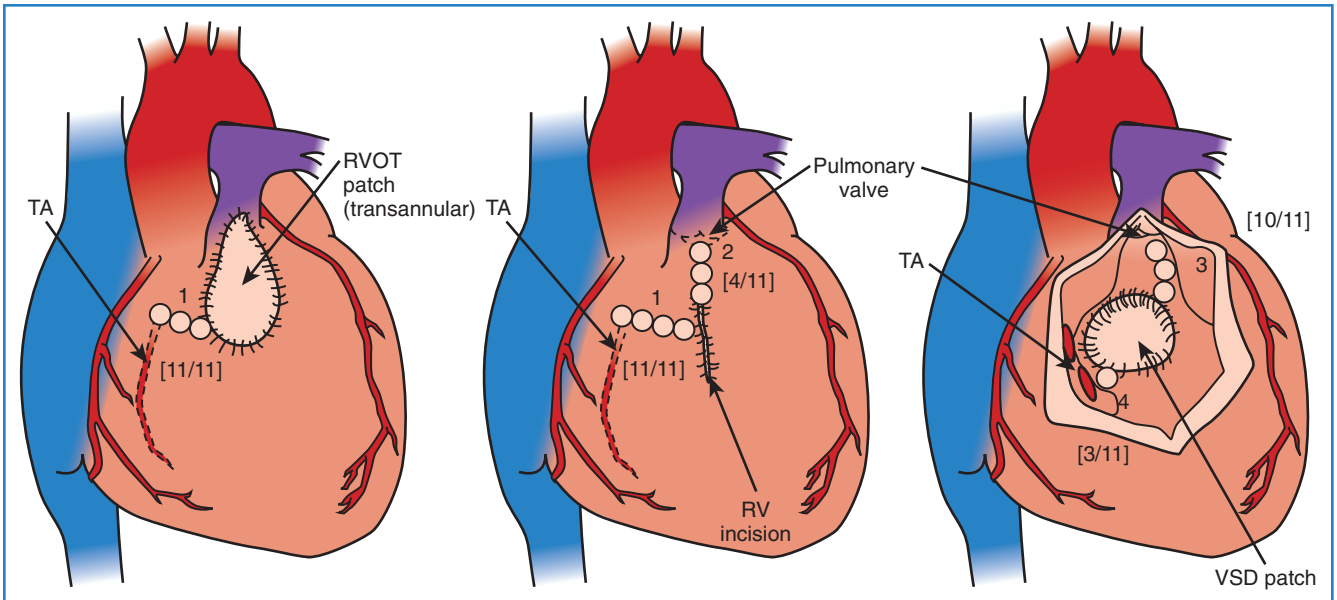

FIGURE 78-4 Schematic of the localization of anatomic boundaries for ventricular tachycardia after repair of congenital heart disease and the resulting anatomic isthmuses. Frequency of the distinct isthmuses in 11 patients are shown in brackets. *TA,* Tricuspid annulus; *RVOT,* right ventricular outflow tract; *RV,* right ventricle; *VSD,* ventricular septal defect. *(From Zeppenfeld K, Schalij MJ, Bartelings MM, et al: Catheter ablation of ventricular tachycardia after repair of congenital heart disease: electroanatomic identification of the critical right ventricular isthmus,* Circulation *116:2241, 2007.)*

reported their extensive experience with anti-tachycardia pacing in patients with congenital heart disease and atrial flutter, using the Intertach II device (Inter Medics, Mumbai, India).[135,136] Although many patients with this type of pacemaker still required visits to the hospital for cardioversion, these visits were clearly much less frequent. Of some concern is the observation by Rhodes and associates of a patient whose anti-tachycardia pacemaker converted an episode of atrial flutter to AF with a rapid ventricular response, which resulted in SCD.[137] Such pacemakers must be used with concomitant administration of effective AV node blocking agents such as propranolol, diltiazem, or verapamil. Another approach is to program the device to be manually activated so that the patient can be under medical observation when attempts at pace conversion occur.

Although the Intertach II device is no longer on the market, a new generation of devices is now available, and these devices provide dual-chamber pacing and anti-tachycardia pacing (AT500, Medtronic, Minneapolis, MN). Some experience is available in patients with congenital heart disease.[138] In addition, the latest generation of implantable cardioverter-defibrillators (ICDs) has the capability to perform atrial anti-tachycardia pacing as well as tiered therapy in the ventricle. Finally, ICDs that provide cardioversion shocks to the atrium are in development and may eventually be useful in the population of patients with repaired congenital heart disease.

Implantable Cardioverter-Defibrillators in Tetralogy of Fallot

With the rapid changes recently in lead and generator technology, ICDs have become a more viable option for the treatment of patients with VT following repair of congenital heart disease. Patients with repaired congenital heart disease made up 18% of patients with ICDs in the multiple-center review by Silka and colleagues of 125 pediatric patients.[139] Most reports to date have dealt mainly with devices attached to epicardial patches, but recent reports have included patients with transvenous systems.[140] SCD continues to be a serious concern in postoperative patients, particularly in patients who have had repair of tetralogy of Fallot who are at least 25 years beyond surgical repair, and in patients who have had the Mustard and the Senning procedures.[68,86] The role of ICDs in the management of patients with congenital heart disease is undergoing rapid evolution, as implantable units become smaller and more multifunctional. Now that transvenous lead technology is well developed, implantation of ICDs in patients with prior sternotomies has become less problematic.[141] However, congenital heart disease poses many challenges to the placement of such leads. Clearly, patients with persistent intracardiac shunting are not candidates for transvenous defibrillator leads because of the risk of thromboembolism. The use of active-fixation leads may well be necessary because of distortions of ventricular anatomy or the need to place such leads in a smooth-walled, morphologic left ventricle. In the past, the frequent occurrence of atrial arrhythmias in this patient population limited the usefulness of ICDs because of the tendency for atrial tachyarrhythmias with brisk AV conduction to be detected within the rate criteria for ICD therapy, which leads to inappropriate shocks. The availability of dual-chamber ICDs.[142,143] with atrial sensing via an atrial lead makes implantation in patients with congenital heart disease more feasible.[142,143] The indications for such implants should be similar to those for the population with adult noncongenital disease, namely, aborted SCD. Large multiple-center studies may eventually identify subpopulations of postoperative patients with congenital heart disease who are at high enough risk of SCD to justify prophylactic ICD implantation. Most data will be available in adults with congenital heart disease, and recent studies have shown ICDs to be effective, but with a high incidence of complications.[144]

Conclusion

It is clear that the field of both catheter-based cardiac ablation and surgically based cardiac ablation is evolving rapidly. In most cases, definitive treatment by either type of ablation should be preferable to long-term antiarrhythmic therapy, especially considering the numerous potential side effects of antiarrhythmic medication in this patient population. The results of catheter ablation, unfortunately, are not as good as those for ablation of more routine arrhythmias in the population of patients with otherwise normal hearts. Although this may partly be because of a lack of understanding of the exact macro–re-entrant circuits that exist in each patient, it is more likely that the ability to make long linear and transmural lesions is limited. Future progress in catheter and lesion formation technologies, as well as further experience with surgical ablation, may allow more of these patients to benefit from the advantages of definitive cure.

The field of catheter ablation in patients with arrhythmias following repair of congenital heart disease urgently requires innovation. Success in this endeavor will call for the development of energy sources that (1) allow the formation of deep, transmural lesions as well as lesions that are linear and (2) can be designed to bridge the gap between anatomic and surgically created obstacles to cardiac conduction. Success will also require an extensive understanding of both the pre-existing cardiac anatomy, the details of the surgical procedures that have been performed, and the mapping systems that allow for detailed reconstruction of the conduction patterns that exist in these patients. Fortunately, ongoing developments of exciting new technologies, both in new mapping systems and new energy sources, promise to accelerate progress in this field in the next several years.

All references cited in this chapter are available online at expertconsult.com.

CHAPTER 79

Arrhythmias and Adult Congenital Heart Disease

Melissa Robinson and Edward P. Gerstenfeld

Congenital heart defects complicate approximately 0.5% to 1% of all live births. More than 1 million adults in the United States are estimated to have repaired or unrepaired congenital heart disease.[1] Approximately 50% of this group has a congenital heart defect categorized as moderate or severe by the American Heart Association/American College of Cardiology (AHA/ACC) task force on adult congenital heart disease (ACHD); this group of patients is at the greatest risk for cardiac arrhythmias.[2] This number can only be expected to increase in the future.[3] Advances in surgical technique now allow many patients with previously fatal congenital defects to survive into adulthood. However, the electrophysiological and physiological/hemodynamic consequences of these lesions often manifest as arrhythmias in young adults. In many patients, arrhythmias are a leading cause of functional decline as well as sudden cardiac arrest.[4,5] A recent survey showed that hospital admissions for ACHD doubled between 1998 and 2005; the most common reason for hospital admission was a cardiac arrhythmia.[6] Knowledge of the anatomy and physiology of congenital heart defects is critical to managing cardiac arrhythmias in this unique ACHD patient population.

The increasing prevalence of cardiac arrhythmias in the ACHD population has led to many of the modifications in surgical repairs for congenital heart disease. The cavopulmonary Fontan procedures connect the venous circulation to pulmonary arteries by a variety of techniques, including the lateral tunnel and extracardiac modifications. These Fontan modifications decrease the degree of atrial arrhythmias that were common with the classic atriopulmonary Fontan repair. Many patients with the atriopulmonary Fontan, Mustard, and Senning repairs are now reaching adulthood. Knowledge of the cardiac anatomy and physiology of these patients is critical to managing their arrhythmias. Comprehensive arrhythmia care for these patients involves cooperation between the cardiologist, the electrophysiologist, and the surgeon specializing in congenital heart disease.

Despite differences among the underlying cardiac defects, many patients with single ventricle physiology undergo a similar repair (e.g., Fontan procedure for tricuspid atresia, double-inlet left ventricle, or hypoplastic left heart syndrome). Knowledge of the sequelae of the most common surgical repairs is essential for managing patients with different congenital lesions. The anatomic obstacles created by the creation of incisional scars, suture lines, and insertion of patch material, along with the ensuing slow conduction caused by progressive myocardial fibrosis and associated residual hemodynamic abnormalities, create the ideal substrate for re-entrant atrial and ventricular arrhythmias.

Because few randomized studies have been conducted in the ACHD population, the management of both atrial and ventricular tachyarrhythmias remains largely empiric. The choice of antiarrhythmic therapy often is limited by sinus node dysfunction, atrioventricular (AV) conduction disease, ventricular dysfunction, and the risk of proarrhythmia. Extrapolation of data from acquired cardiovascular disease such as ischemic cardiomyopathy may not always be appropriate in determining antiarrhythmic or device therapy.

Percutaneous catheter mapping and ablation of atrial and ventricular arrhythmias in the ACHD population have undergone significant advances in the past decade. In particular, the advent of electroanatomic three-dimensional mapping and its integration with cardiac imaging such as computed tomography (CT) or magnetic resonance imaging (MRI) have helped the electrophysiologist define the precise electroanatomic substrate for the arrhythmias that develop in this complex population.[7] Percutaneous access to the cardiac chambers often presents unique challenges in this patient population, requiring detailed knowledge of the lesion and anatomic repair as well as familiarity with procedures such as trans-septal and trans-baffle puncture. In addition, ACHD patients present significant hemodynamic challenges because they have lower cardiac reserve and greater physiological instability in response to anesthesia or with the occurrence of rapid heart rates.

General Principles

When a patient with ACHD presents with a cardiac arrhythmia, whether the arrhythmia is the consequence of an underlying hemodynamic stress caused by a structural or functional abnormality should first be determined. Baffle obstruction or leak, worsening of valvular or conduit stenosis or regurgitation, and worsening of right or left ventricular function may all initially manifest as a cardiac arrhythmia. Comprehensive imaging with echocardiography, CT angiography (CTA) or magnetic resonance angiography (MRA) should be performed to define the cardiac anatomy and physiology when possible and to exclude the progression of disease or any abnormalities that require surgical repair. If a surgical repair is deemed necessary, linear ablation to prevent or treat arrhythmias can often be incorporated into the surgical procedure. A preoperative electrophysiological study (EPS) may still be useful in this situation to define the mechanism of the arrhythmia and to guide the placement of surgical ablation

lesions if they cannot be achieved preoperatively. Once a surgical baffle or valve replacement has been performed, access to the cardiac chamber for the treatment of these arrhythmias may become much more challenging.

It cannot be overemphasized that a thorough understanding of the individual anatomy and physiology of the patient with congenital heart disease is essential before planning and performing any invasive electrophysiological procedure. Prior operative and catheterization reports should be reviewed in detail. Noninvasive imaging such as echocardiography, MRA, or CTA should be reviewed with a physician experienced in interpreting studies of patients with ACHD.[8] Patients must be viewed within the historical context of the type of cardiac repair they have received; different variations of surgical repairs for the same congenital heart defect may yield vastly different electrophysiological outcomes. Venous access may be altered by the surgical procedure or by prior catheterizations, and standard approaches to the chamber of interest may not be possible.[9]

Antiarrhythmic Drug Therapy

Despite the large burden of arrhythmias in this patient population, these are no randomized studies evaluating the efficacy and safety of antiarrhythmic drugs in the ACHD patient. For benign atrial or ventricular ectopy, β-blockers are often the initial agent of choice. Rapid ventricular rates caused by sustained atrial arrhythmias are often poorly tolerated in the ACHD population because these patients often are hemodynamically dependent on adequate ventricular filling or preload. β-Blockers are frequently used together with other antiarrhythmic agents to control the ventricular rate in patients with atrial fibrillation (AF) or flutter. If the β-blocker dose is limited by hypotension or fatigue, digoxin may be added. Digoxin is commonly used in the ACHD population because of its once-daily dosing, lack of vasodepressor effect, and renal metabolism. Calcium channel blockers can also be used in the patient with ACHD but should be avoided in patients with ventricular dysfunction.

When an antiarrhythmic agent is required, sotalol, a U.S. Food and Drug Administration (FDA) class III antiarrhythmic, is often the initial agent of choice. Sotalol is a racemic mixture of d-sotalol, which is a potent potassium channel blocker and works primarily by lengthening atrial refractoriness, and l-sotalol, which has β-blocking properties. Because sotalol has no long-term organ toxicity, it can be safely used for extended periods in the patient with ACHD. However, care must be exercised in patients with underlying conduction disease, renal dysfunction, or asthma. Sotalol should be initiated in the inpatient hospital setting, where telemetric monitoring of the Q-T interval and rhythm can be performed. Prolongation of the QTc can be associated with *torsades de pointes*, a potentially life threatening arrhythmia. We aim to keep the QTc at less than 500 ms in patients with a narrow QRS or the QTc at less than 400 ms in patients with bundle branch block, a common finding in patients with ACHD. We usually initiate sotalol at a dose of 80 mg twice daily and increase administration up to 160 mg twice daily, if needed, to achieve the minimal dose necessary for arrhythmia control that does not cause excessive QTc prolongation. If diuretics are used with sotalol, care should be taken to avoid hypokalemia.

FDA class 1C agents (flecainide, propafenone) have been shown to be proarrhythmic in adults with ischemic heart disease. Nevertheless, they are often efficacious in the treatment for supraventricular and ventricular arrhythmias and are sometimes used in the pediatric patient with congenital heart disease because these agents are well tolerated and pose no risk of organ toxicity.[10] These agents should be used with caution in the patient with ACHD; they may have a role in the presence of a backup implantable cardioverter-defibrillator (ICD).

A more recent addition to the antiarrhythmic armamentarium is dofetilide. Although studies have demonstrated safety in the adult population with prior myocardial infarction (MI), studies on its efficacy or toxicity in the ACHD patient population have not been done.[11] Dofetilide is a potent potassium channel blocker and must be initiated in the inpatient setting, where monitoring of the QTc interval can occur. Unlike sotalol, dofetilide has no β-blocking properties and therefore is less likely to cause significant bradycardia or AV conduction block. However, concomitant β-blocking agents typically are required to slow the ventricular rate in response to atrial arrhythmias. Verapamil is contraindicated in patients taking dofetilide because of its interaction with hepatic metabolism; diltiazem, diuretics, and digoxin may also increase the risk of proarrhythmia and should be used with caution.

In patients with significant systemic ventricular dysfunction, amiodarone is the agent of choice. Amiodarone therapy often slows conduction velocity in an already diseased atrial substrate and may therefore facilitate 1:1 A:V conduction during atrial flutter or intra-atrial re-entrant tachycardia (IART) leading to hemodynamic compromise or silent ventricular dysfunction. This is uncommon because of the associated effect of slowing AV nodal conduction. The known risk of hepatic dysfunction with amiodarone may be worsened in the ACHD population because chronic hepatic venous congestion is common. In addition, patients should be monitored for pulmonary, thyroid, and ocular toxicities. Because of its long-term toxicities, amiodarone is typically reserved for patients with recurrent, poorly tolerated arrhythmias not amenable to catheter ablative therapy or for those with significant coexistent ventricular dysfunction. Typically, the lowest dose of amiodarone effective in suppressing arrhythmias—often 100 mg daily—is sufficient. Amiodarone can be safely initiated in the outpatient setting, typically at 400 mg daily and then titrated downward; however, in patients at risk for significant bradycardia, inpatient monitoring is advised. Dronedarone—a new antiarrhythmic agent with similar structure to amiodarone, but without amiodarone's iodine moiety or long-term organ toxicity—has recently been approved for use in atrial arrhythmias and may provide another option for the patient with ACHD.[12]

Invasive Electrophysiology Study

Recent advances in imaging, mapping, and ablation technologies have made catheter ablation an important option for treating arrhythmias in the ACHD population. As with all procedures in the patient with ACHD, careful consideration of the patient's anatomy, routes of vascular access, and hemodynamic status are critical to a successful and safe procedure. Vascular anomalies such as an interrupted inferior vena cava (IVC) or a persistent left superior vena cava (SVC) may make even simple procedures challenging. The location of the bundle of His should be noted because the AV conduction system may be displaced or not easily accessible. Given the potential for hemodynamic compromise in patients with poor ventricular function, the presence of an

anesthesiologist experienced in treating patients with ACHD is recommended when use of sedation or general anesthesia is anticipated. In addition, we recommend the use of intravenous line air filters for any patient with right-to-left shunting to avoid air embolism in the systemic circulation.

The advent of three-dimensional electroanatomic mapping techniques allows realistic depiction of the patient's anatomy combined with three-dimensional visualization of the tachycardia circuit. Electroanatomic mapping systems use magnetic fields or impedance measurements to locate a catheter in space. By moving the catheter around the chamber of interest, a shell of the chamber can be created. At each point on the shell, both the local recorded bipolar voltage and the activation time during a tachycardia can be annotated and color coded. The voltage map, in combination with pace mapping, can be quite useful for denoting areas of scar (low voltage) or prosthetic baffle material (no voltage) when developing an ablation strategy.[13] Activation mapping denotes the local activation time relative to another fixed reference catheter. In the general adult patient with atrial arrhythmias, the coronary sinus (CS) catheter is used as the reference. In the ACHD population, the CS may not be accessible and any stable catheter position such as the atrial appendage can be used. The use of active fixation leads for this purpose in complex cases has been described.[14] The combined voltage and activation maps, coupled with standard entrainment mapping, can be used to tailor an ablation strategy. These advanced technologies have improved the outcomes of catheter ablation but do not substitute a thorough understanding of the anatomy and electrophysiology associated with the arrhythmia occurring in these patients. Integration with CTA or MRA angiographic imaging can be performed to obtain a more realistic depiction of the complex anatomy of the patient with ACHD (Figure 79-1). In our experience, the main usefulness of CTA image integration is to confirm that the entirety of a particular cardiac chamber has been mapped.

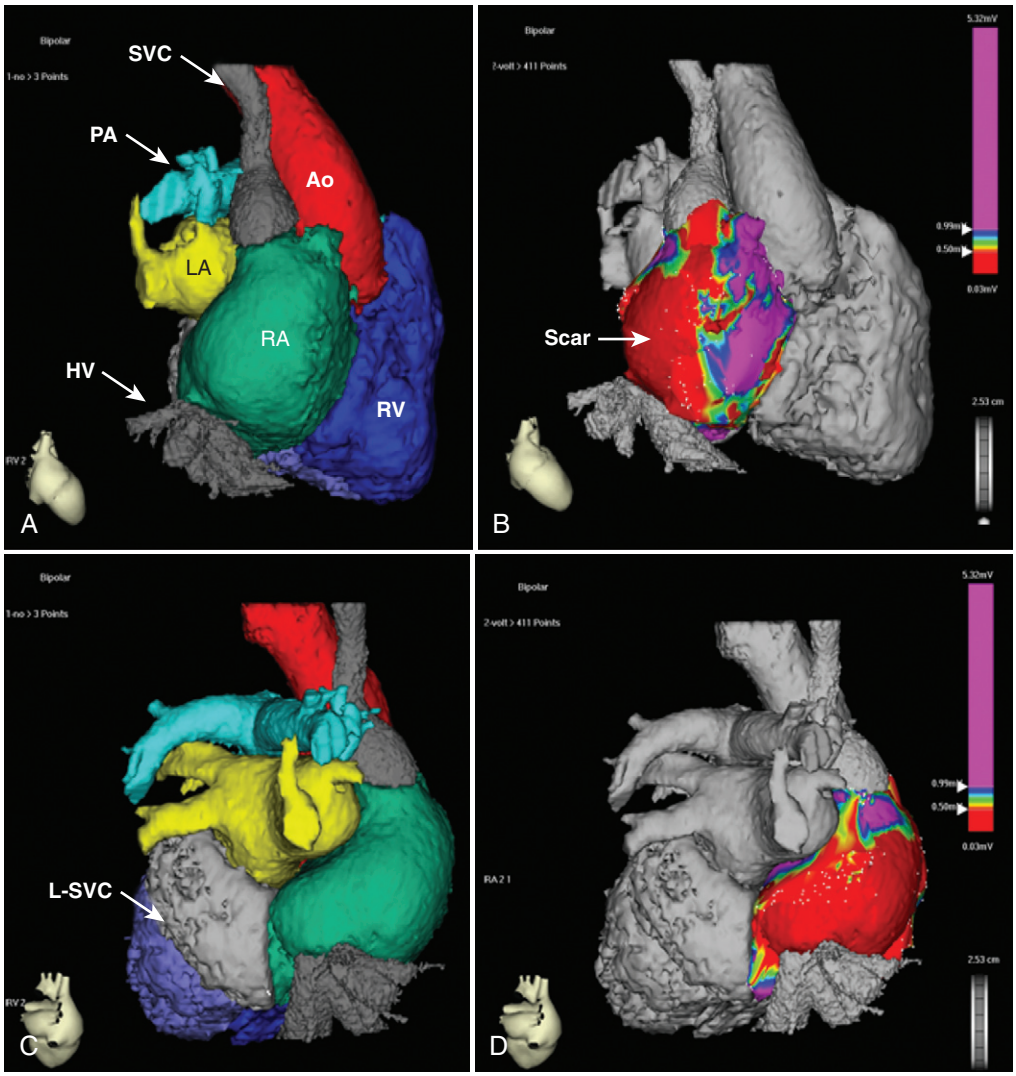

FIGURE 79-1 Electroanatomic map registered with a computed tomographic (CT) image in a patient who had incessant atrial tachycardia and double-outlet right ventricle (*RV*) repair, persistent left superior vena cava (*L-SVC*) interruption, and prior inferior vena cava interruption. **A,** Right lateral projection of the CT scan. Note the diminutive right-sided SVC and network of hepatic veins (*HV*) draining into the posterior right atrium (*RA*). **B,** Right lateral projection of bipolar voltage map projected onto the CT anatomy. An extensive area of posterolateral low voltage is depicted in *red*. **C,** Posteroanterior view of the CT anatomy showing the presence of a large persistent left L-SVC emptying into the CS. **D,** Posteroanterior view of the bi-polar voltage map. *PA*, Pulmonary artery; *Ao*, aorta; *LA*, left atrium.

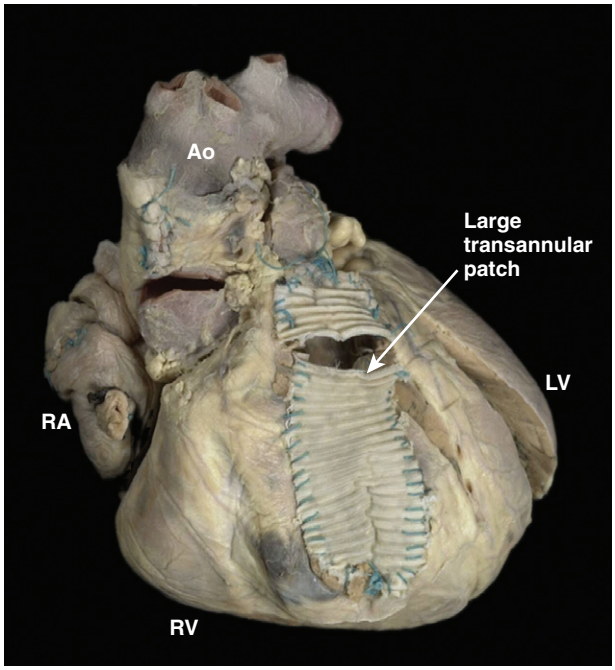

FIGURE 79-2 Autopsy specimen from a patient with tetralogy of Fallot who underwent a large trans-annular patch of the right ventricle (*RV*) after resection of the outflow tract obstruction. The ventricular septal defect (VSD) patch is not seen. Ventricular arrhythmias in these patients are caused by re-entry around these fixed barriers or slow conduction caused by extensive fibrosis surrounding the right ventricular outflow repair. Ventricular tachycardia can also involve the atriotomy used to access the VSD repair or the region around the VSD itself. *Ao*, Aorta; *RA*, right atrium; *LV*, left ventricle. *(Courtesy Paul Weinberg, MD, Children's Hospital of Philadelphia.)*

As described above, re-entry around anatomic obstacles such as surgical incisions or patch material is the dominant mechanism of both atrial and ventricular arrhythmias in patients with ACHD. A typical example is seen in repaired tetralogy of Fallot (TOF), in which patch material is often used to close the ventricular septal defect (VSD) and may be needed to expand the right ventricular outflow tract (Figure 79-2). During ablation, linear lesions can be created between low-voltage regions or anatomic barriers to transect a critical isthmus of the tachycardia circuit and interrupt the tachycardia. Creation of long linear lesions in scarred atrial tissue often is difficult; irrigated catheters have improved the outcome and should be considered when performing an ablation in this patient population. Whenever possible, proof of block across a linear lesion should be obtained with pacing maneuvers to minimize the likelihood of slow conduction across the line leading to a recurrent tachycardia. Less frequently, atrial stretch can lead to "focal" atrial tachycardia. This tachycardia can be focally ablated at the site of earliest activation, often identified by low-amplitude fractionated electrograms.

The remainder of this chapter is dedicated to a discussion of the most common groups of ACHD lesions seen in patients with arrhythmias: atrial septal defects (ASDs), Fontan procedures, transposition of the great arteries after an intra-atrial repair, and TOF. These repairs represent the majority of patients seen in the ACHD arrhythmia clinic. Although less common, Ebstein's anomaly also is discussed given its unique electrophysiological consequences. The common strategies applied to the arrhythmias encountered with these lesions can often be extrapolated to other patient groups not discussed here, including those with scar-related arrhythmias after VSD repair or AV canal repair. The reader is directed to the recently published guidelines for the management of ACHD as well as for device therapy.[2,15]

Atrial Septal Defects

ASDs are among the most common congenital heart lesions and often are associated with atrial arrhythmias, both preoperatively and after repair.[16] The majority of ASDs are of the secundum type (75%). Secundum ASDs occur within the oval fossa, although they may extend outside the fossa when an associated deficiency of the atrial septum exists. The electrocardiogram (ECG) in patients with secundum ASDs typically shows evidence of a vertically oriented P wave, right-axis deviation of the QRS complex, and incomplete right bundle branch block (RBBB). Primum ASDs, which are a type of endocardial cushion defect, occur less commonly (15% to 20%) than secundum ASDs and often are associated with mitral or tricuspid valve regurgitation. The ECG in a patient with a primum ASD typically has left-axis deviation of the QRS complex. Primum ASDs can be associated with AV conduction disturbances and, occasionally, with complete heart block. Sinus venosus ASDs (5% to 10%) occur in either the superior or inferior paraseptal region, at the mouth of the IVC or the SVC. Superior sinus venosus ASDs may be associated with sinus node disease and typically have left-axis deviation of the P wave on the ECG. Least common is the coronary sinus septal defect, a defect between the wall of the coronary sinus and the left atrium. All the above ASDs lead to left atrial enlargement, fibrosis, and changes in atrial refractoriness.[17] These changes in response to the chronic volume overload often lead to the development of both AF and atrial flutter.

Of the patients referred for the surgical closure of an ASD, 10% to 20% would have had at least one episode of AF or atrial flutter.[15] Risk factors for atrial arrhythmia after surgical ASD closure include older age at the time of repair (>40 years), elevated pulmonary arterial pressure, preoperative atrial arrhythmia, and postoperative junctional rhythm. Given the continued risk of arrhythmia, combining the Maze procedure with septal defect repair should be considered in those patients with a history of AF or atrial flutter. Whether prophylactic Maze surgery has a role in the treatment of those patients at highest risk of AF undergoing ASD repair remains controversial. Incisional atrial flutters after ASD repair typically occur around the posterior right atriotomy incision rather than around the ASD patch itself. Catheter ablation can be extremely effective. The long-term occurrence of atrial arrhythmias after transvenous ASD closure is unknown, but one promise of this technology is a potential reduction in incisional re-entrant tachycardias.

Ebstein's Anomaly of the Tricuspid Valve

A wide range of severity in hemodynamic abnormalities and arrhythmia occurrence exists in patients with Ebstein's anomaly of the tricuspid valve. The structural abnormality involves the apical displacement of the septal leaflet of the tricuspid valve, often with displacement of the mural (posterior) leaflet and atrialization of the basal portion of the right ventricle. The valve itself is malformed and regurgitant, and an ASD or patent foramen

ovale, often with right-to-left shunting, is present in one third of patients.[19] This combination leads to severe right atrial dilation and a susceptibility to atrial arrhythmias. Ebstein's anomaly can also be seen in congenitally corrected transposition of the great arteries (L-TGA).

Ebstein's anomaly is commonly associated with Wolff-Parkinson-White (WPW) syndrome, with a reported prevalence of 10% to 40%.[20-22] Accessory pathways in patients with Ebstein's anomaly are typically right sided, and multiple accessory pathways are often present (30% to 50%). In addition to classic AV pathways, variants such as slowly conducting atriofascicular fibers are also more common in patients with Ebstein's anomaly.[23] In this population, the clinician should take care not to overlook subtle pre-excitation, which may manifest as absence of the expected RBBB.[24] Because Ebstein's anomaly may be clinically silent into adulthood, echocardiography should be performed in any adult with right-sided accessory pathways and evidence of right atrial enlargement on the ECG to exclude this abnormality.

As with many other congenital lesions associated with right atrial enlargement, atrial flutter and AF are commonly seen in adults with Ebstein's anomaly.[25] The atrial arrhythmia burden remains high even after surgical repair, with at least one third of patients having AF observed in long-term follow-up.[26]

Ablation of supraventricular tachycardia (SVT) related to accessory pathways has become standard therapy for these patients. If surgical repair is planned, an electrophysiology study (EPS) should be performed before the operation in any patient with known or suspected pre-excitation. The absence of a RBBB pattern in lead V1 has been shown to be predictive of an occult accessory pathway in this group.[27] Catheter ablation should be attempted before surgery, with intraoperative mapping performed if catheter ablation cannot be performed or has been unsuccessful.

Catheter ablation of the accessory pathways can be highly successful, although it remains a challenging procedure. Overall acute success rates for catheter ablation of accessory pathways are lower (80%), and recurrence rates are higher than in patients who do not have Ebstein's anomaly. This is most likely caused by the presence of multiple pathways and catheter instability along the tricuspid annulus (which is displaced from the valve leaflets themselves) and because of the presence of tricuspid regurgitation.[28] Use of long sheaths and a multipolar halo catheter along the tricuspid annulus may be helpful to guide the ablation and improve catheter stability. In addition, the use of a microcatheter placed within the right coronary artery may help with pathway localization when traditional endocardial catheters such as the multipolar halo catheter are unhelpful.[29] As with patients who do not have Ebstein's anomaly, coronary artery occlusion remains a risk of ablation in this region.[30]

Typical isthmus-dependent right atrial flutter is also common in patients who do not have Ebstein's anomaly. Mapping and ablation often is more difficult in these patients compared with the standard adult patient because of the presence of significant tricuspid regurgitation. Importantly, atrial arrhythmias may be the first symptoms experienced by a patient with Ebstein's anomaly, and in the setting of severe tricuspid regurgitation, the need for surgical repair of the tricuspid valve should be considered. If operative repair is planned, cryoablation between the IVC and the tricuspid annulus can be highly effective for treating cavotricuspid isthmus–dependent atrial flutter. If AF is present, a concomitant right atrial Maze procedure should be considered.

Because the right ventricle is the primary site of abnormality in Ebstein's anomaly, it is not surprising that ventricular tachycardia (VT) has been described in Ebstein's anomaly.[31,32] VT can arise from within the functional right ventricle itself or from within the atrialized portion of the right ventricle, which retains ventricular electrophysiological properties. As with atrial arrhythmias, the occurrence of VT in a patient with unrepaired Ebstein's anomaly who has significant tricuspid regurgitation should initiate consideration of surgical repair. Because repair of the tricuspid valve may not always be feasible, we recommend an EPS and attempted ablation of VT before surgery. VT is typically focal and located in the basal atrialized portion of the right ventricle (Figure 79-3). Catheter ablation can be helpful in these patients and, if unsuccessful, can guide surgical cryoablation at the time of valve repair or replacement. This is particularly important if mechanical tricuspid valve replacement is required because future percutaneous access to the right ventricle will be eliminated.

Fontan Operation

Originally performed for the palliation of tricuspid atresia, the Fontan operation is applied to numerous congenital heart lesions when single-ventricle physiology exists. The classic Fontan operation involved the creation of a direct connection from the right atrium to the pulmonary artery, completely bypassing the right ventricle, leading to passive filling of the pulmonary arterial tree and elevated right atrial filling pressures. The occurrence of atrial arrhythmias over time is the major complication of the subsequent right atrial volume overload. In addition to AF and typical atrial flutter, incisional or IART may be seen.[18]

The Fontan operation has undergone numerous modifications in an effort to reduce perioperative mortality rates and to improve hemodynamic and electrophysiological outcomes. The most recent modification is the extracardiac cavopulmonary Fontan operation, which creates a conduit between the IVC and the SVC, which is then anastomosed to the pulmonary artery, completely bypassing the right atrium and the right ventricle. The lateral tunnel Fontan operation and the extracardiac Fontan operation have largely replaced the atriopulmonary connection in patients with a single ventricle and have resulted in improvements in hemodynamic and arrhythmia outcomes.[33]

The onset of atrial arrhythmias in patients with atriopulmonary Fontan repairs often prompts evaluation for conversion to a cavopulmonary Fontan repair. The risks of a repeat operation need to be balanced against the benefit of Fontan conversion and individualized for each patient. In experienced centers, conversion to a total cavopulmonary Fontan repair in patients with preserved left ventricular function has been associated with reduced long-term morbidity and mortality rates. Concomitant arrhythmia surgery is recommended with a modified right-sided Maze procedure in patients with IART or atrial flutter.[34] Some have recommended the Maze as a prophylactic procedure in those undergoing Fontan conversion regardless of prior arrhythmias. A standard lesion set involves cryoablation lesions applied at the time of Fontan conversion connecting the superior atrial septum to the right atrial appendage, connecting the posterior atrial septum to the incised posterolateral atrial wall transecting the crista terminalis, and a cavotricuspid isthmus ablation.[35,36] Lesion sets may need to be modified depending on the underlying anatomic substrate. Despite these remarkable technical advancements, atrial arrhythmias remain a common problem in this population.

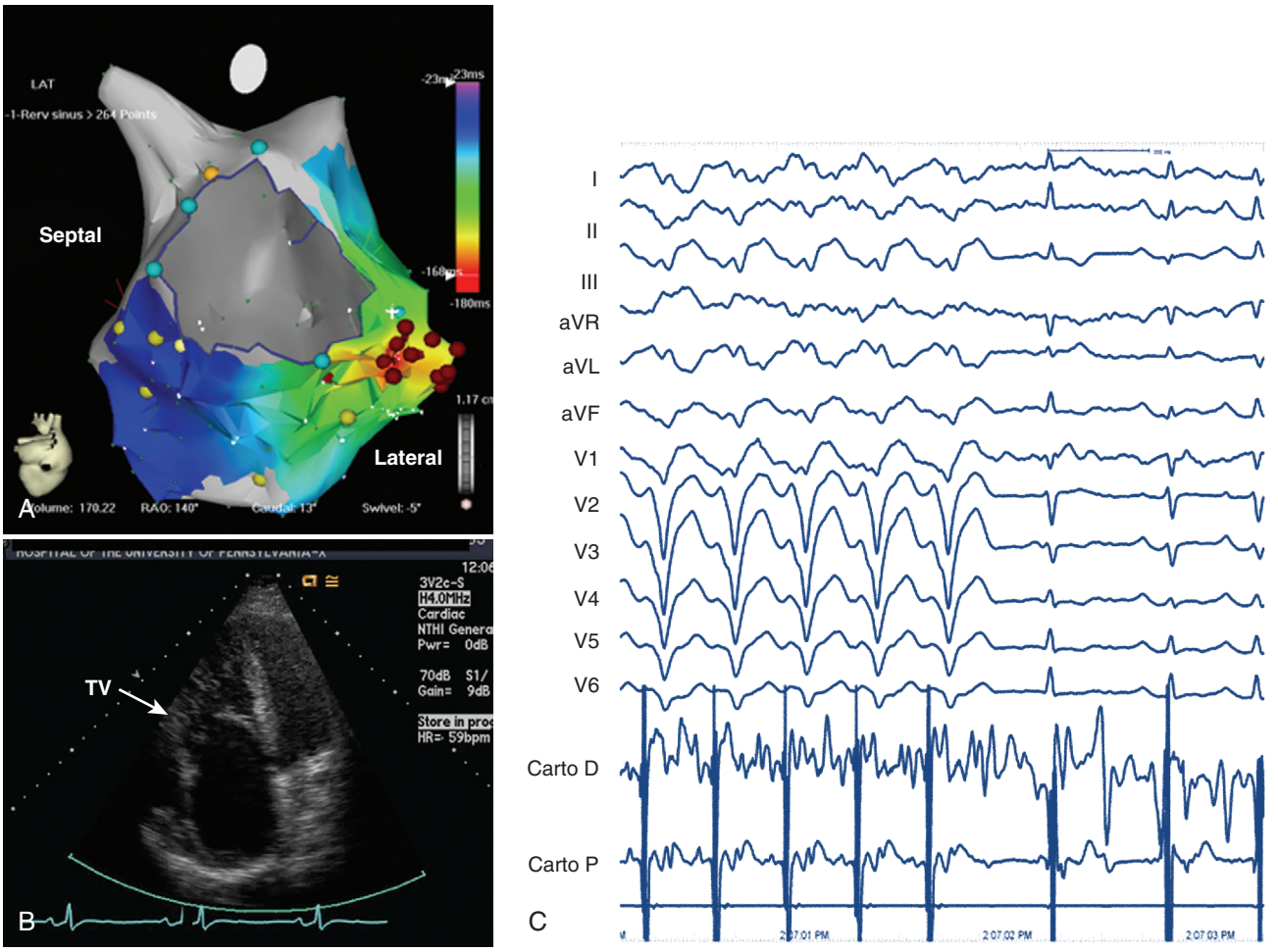

FIGURE 79-3 Ventricular tachycardia in a patient with Ebstein's anomaly. **A,** Electroanatomic activation map, posteroanterior view, showing earliest site of activation (*light red*) at the basal free wall of the right ventricle. *Dark red circles* denote ablation sites. **B,** Apical four-chamber view on transthoracic echocardiography of the apically displaced tricuspid valve (*TV*). **C,** Left bundle, left superior axis ventricular tachycardia terminating during ablation at site of earliest activation (*arrow*).

Nearly half the adult patients with congenital heart disease who have undergone a Fontan operation will be seen to have atrial arrhythmias in follow-up.[37] These arrhythmias include AF, atrial flutter, IART, and SVT. The presence of AV valvular regurgitation is associated with atrial tachyarrhythmias and the development of Fontan obstruction; therefore a hemodynamic evaluation often is warranted in any patient with a new atrial arrhythmia after a Fontan repair. Given the lack of active transport within the right atrium and the presence of prosthetic material in these patients, atrial arrhythmias should be anticoagulated with warfarin.[5] Once diagnosed, atrial arrhythmias tend to recur in these patients. Concomitant sinus node dysfunction as well as AV conduction disease can complicate medical therapy for tachyarrhythmias, making a percutaneous ablative approach very appealing in patients who have not undergone surgery.

Intra-atrial Re-entrant Tachycardia

Although typical isthmus-dependent right atrial flutter revolving around the tricuspid valve is commonly seen in patients who have had the Fontan operation, multiple re-entrant and non–re-entrant circuits are often present.[38] IART seen in patients who have had the Fontan operation is often caused by a combination of the atrial barriers created at the time of surgery and progressive atrial scarring. Risk factors for IART include older age at the time of surgery, sinus node dysfunction, and abnormal right atrial and ventricular hemodynamics.[37] The combination of atrial enlargement, atrial scarring with resultant slow conduction, and the use of antiarrhythmic drug therapy can often lead to slow IARTs with the potential for 1 : 1 AV conduction or increased heart rates that can cause significant hemodynamic deterioration, especially in poorly functioning single or systemic right ventricles.

Antiarrhythmic therapy for IART has been disappointing, even when potent antiarrhythmic agents such as amiodarone are used. Many centers now consider catheter ablation for IART as an early therapy depending on the underlying substrate. In patients who have had the Fontan operation, if percutaneous access to the right atrium can be obtained, catheter ablation for IART can be reasonably successful, with acute efficacy ranging from 60% to 80% but long-term recurrence rates of approximately 40%.[39] Patients who have had the Fontan operation with a lateral tunnel may require a surgical approach; however, trans-baffle puncture into the native

right atrium is an option for experienced surgeons. Catheter-based treatment of IART requires careful definition of the anatomic circuit. Locating scar material within the atrium usually allows the identification of a critical isthmus between the anatomic barriers and the creation of a linear ablation lesion between these barriers to interrupt the tachycardia circuit.[40] The use of three-dimensional electroanatomic mapping along with entrainment is critical for defining the circuit and the anatomic barriers more completely.[41–42]

Mustard and Senning Repairs for D-Transposition of the Great Arteries

The arrhythmias associated with complete transposition of the great arteries (D-TGA) depend on the type of surgical repair. The majority of patients with D-TGA with arrhythmias would have undergone an atrial-level repair, that is, the Senning or the Mustard procedure. The Mustard procedure incorporates the resection of the interatrial septum and the creation of a pantaloon-shaped baffle, redirecting the systemic venous return from both the SVC and the IVC to the mitral annulus. Pulmonary veins then drain around this baffle to the tricuspid valve orifice. The Senning procedure leads to similar anatomy; however, the baffles are created via a series of incisions and suture lines using the patient's native atrial tissue. Importantly for the electrophysiologist, the coronary sinus may be on either the systemic side or the pulmonary venous side with an atrial-level repair, depending on the particular surgical approach. Patients born in the 1980s to 1990s who have D-TGA will undergo a primary arterial switch procedure; however, electrophysiologists will continue to see adult patients who underwent either the Mustard or the Senning repair before that time.

Only 40% to 50% of patients will remain in sinus rhythm 15 to 20 years after a Mustard repair.[43,44] Both bradycardias and tachycardias develop over time in this group. Sinus node dysfunction is thought to be related to progressive scarring near the suture lines in the high right atrium–SVC junction or to damage to the sinus node artery during surgery. Patients with postoperative sinus node dysfunction after intra-atrial repairs present most commonly with exercise intolerance, fatigue, presyncope, or syncope. In addition, the long-short cycles created by ectopy in the setting of sinus node dysfunction can precipitate re-entrant atrial arrhythmias such as typical atrial flutter or IART.[45,46] AV node conduction abnormalities are relatively rare in this population, which allows the use of single-chamber atrial lead pacemakers if AV nodal function is determined to be normal.

IART is the most common arrhythmia seen after atrial-level repair of D-TGA. Despite the multiple, complex incisions required for the Mustard or the Senning repair, atrial flutter rotating around the tricuspid valve, similar to cavotricuspid isthmus–dependent right atrial flutter, remains the most common form if IART seen.[47] IART along the lateral right atrium can also be seen and can be distinguished from peri–tricuspid valve flutter by using entrainment mapping. Given the complicated anatomy and the risks of invasive catheter-based therapy, treatment with antiarrhythmic drugs is often first-line therapy in patients with D-TGA who have atrial arrhythmias after the Mustard or the Senning repair, but this can be limited by concomitant sinus node dysfunction. However, for recurrent or refractory atrial flutters, electrophysiological mapping and ablation can be effective. In cavotricuspid isthmus–dependent atrial flutter, the circuit revolves around the tricuspid valve annulus, which lies anterior to the right atrial baffle suture line and typically is not accessible from the caval venous system. The tricuspid annulus usually requires a retrograde approach via the aortic valve (Figures 79-4 and 79-5). However, a trans-baffle approach can be used via preexisting baffle leaks or a lateral puncture of the baffle.[48] As noted above, access to the coronary sinus during EPSs may be either via the systemic or the pulmonary venous atria and may not be easily entered. IARTs frequently occur in patients with D-TGA and usually involve an activation wavefront passing between the

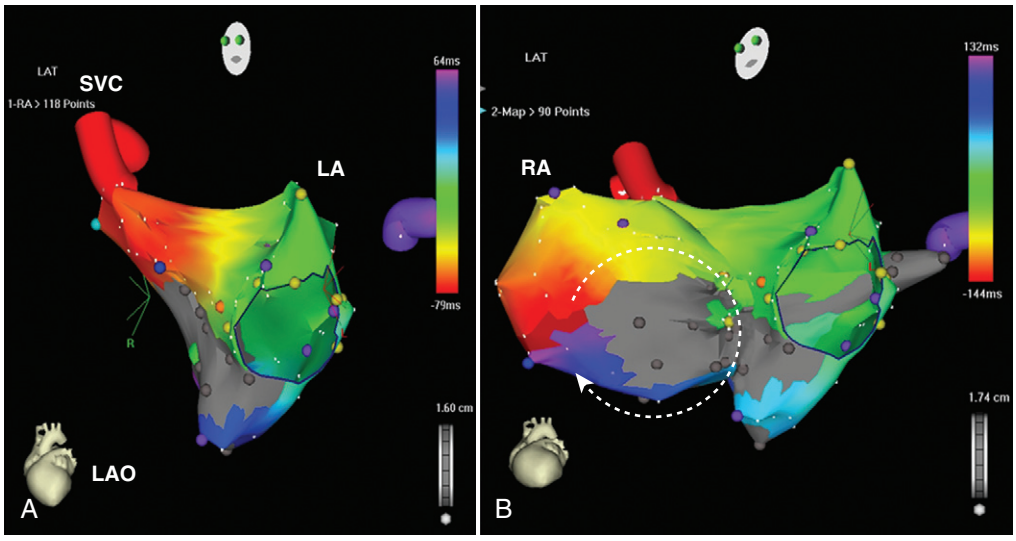

FIGURE 79-4 Cavotricuspid isthmus–dependent atrial flutter in a patient after the Mustard repair of transposition of the great arteries. **A,** Electroanatomic map of the systemic atrium via the superior vena caval (*SVC*) baffle. Earliest activation (*red*) of the tachycardia appears to occur focally from the atrium adjacent to the baffle. **B,** Activation map after inclusion of the pulmonary venous atrium, mapped in a retrograde fashion via the systemic right ventricle. Activation of the tachycardia can now be appreciated to occur in a clockwise fashion around the tricuspid valve annulus (*dashed arrow*). *LA*, Left atrium; *LAO*, left anterior oblique [view].

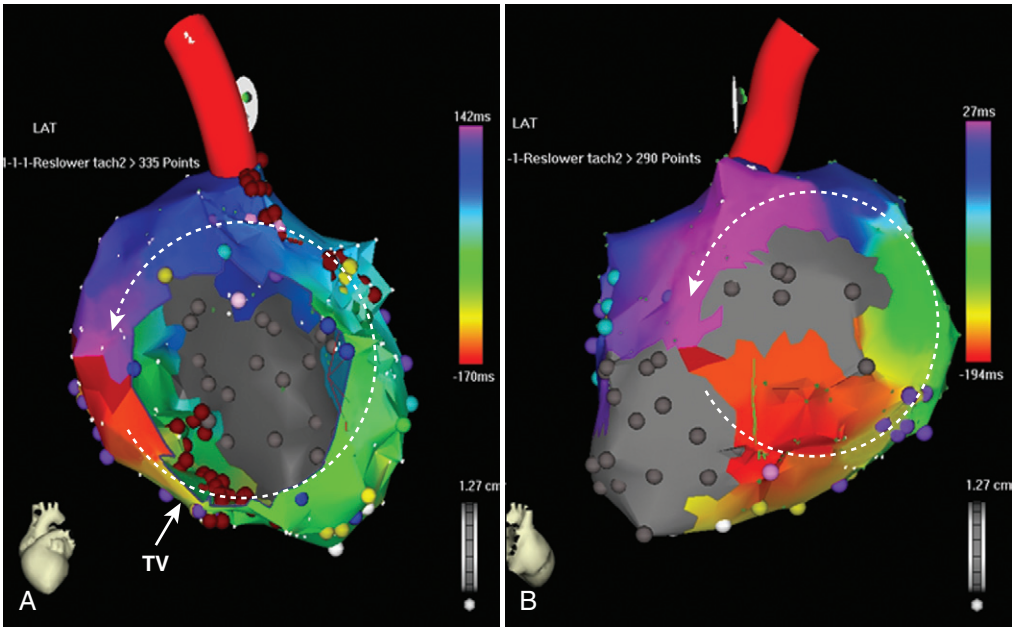

FIGURE 79-5 Atrial flutter and intra-atrial re-entrant tachycardia in a patient after the Mustard repair for transposition of the great arteries. The pulmonary venous atrium mapped in a retrograde fashion via the aorta and systemic right ventricle. **A,** Left anterior oblique view through the tricuspid valve (*TV*), with baffle material seen posteriorly (*gray*), showing counterclockwise cavotricuspid isthmus–dependent atrial flutter (*dashed arrow*). Ablation lesions were delivered along the isthmus posteriorly to the baffle material, terminating the tachycardia. Bi-directional block was confirmed across the ablation line. **B,** Right lateral view of a second tachycardia induced after termination of the cavotricuspid isthmus–dependent flutter. Two areas of low voltage (*gray*) are depicted, with re-entry occurring around the superior low-voltage region (*dashed arrow*). Focal ablation in the critical isthmus between the two areas of low voltage (*yellow line*) terminated this tachycardia.

lateral right atrial incision and the tricuspid annulus. AV nodal re-entry tachycardia (AVNRT) has also been described in this population.[49,50]

Patients with atrial-level repair of transposition remain at risk for sudden cardiac death (SCD) from ventricular arrhythmias as well as from supraventricular arrhythmias with rapid AV conduction. Awareness of the risk for sustained VT in long-term follow-up—previously believed to be a rare occurrence—has increased, with a prevalence reported to be 10%. Risk factors for SCD or VT include systemic ventricular dysfunction or the presence of additional lesions such as VSD or ventricular outflow obstruction.[51,52] The presence of atrial arrhythmias or a QRS duration greater than 140 ms has been found to be predictive of sudden death in some studies but not others.[51,52] Defibrillator implantation in this population is left to the discretion of the treating physician. Programmed electrical stimulation in these patients has not gained favor. Most devices are being implanted in the highest risk patients as secondary prophylaxis against SCD or a high burden of nonsustained VT (see below).[53]

Tetralogy of Fallot

TOF is the most common cyanotic congenital heart condition, comprising approximately 10% of the ACHD patient group.[54] Adult patients with a history of surgical repair of TOF now have excellent overall long-term survival; however, they remain at risk for atrial and ventricular arrhythmias and SCD (1% to 2.5% per decade).[55–56] Fortunately, they are among the most studied group of patients with congenital heart disease. Arrhythmias in patients with TOF primarily appear to arise from the right ventricular substrate as a result of surgical incisions, suture lines, patch insertion, and resection of muscular obstruction at the time of operative repair, often in association with both right and left ventricular dysfunction and residual hemodynamic abnormalities.

The morphologic abnormalities in unrepaired TOF are the presence of some degree of right ventricular infundibular stenosis, a VSD, an overriding aorta, and concomitant right ventricular hypertrophy. Many patients have small pulmonary valves and infundibular stenosis, and some may have peripheral pulmonary artery stenosis.[57] The original surgical approach to repair of TOF involved a right ventriculotomy to access the VSD and infundibular stenosis. A trans-annular patch (see Figure 79-2) often is needed to augment the outflow tract, which results in pulmonic regurgitation. This approach has resulted in a significant risk of clinical arrhythmias and SCD. Risk factors have included right ventricular volume and pressure overload. In the current era, surgery at an earlier age with a combined trans-atrial/trans–pulmonary artery approach has led to a reduction, although not elimination, of late ventricular arrhythmias.[58]

Atrial Arrhythmias

Atrial arrhythmias occur in approximately one third of patients in long-term follow-up after repaired TOF and may be a cause of significant morbidity and even SCD when rapid AV conduction is present.[59] Moderately elevated heart rates are poorly tolerated in the presence of residual hemodynamic abnormalities or poor ventricular function. Prolonged QRS duration longer than 160 ms is a risk factor for supraventricular arrhythmias after late

reoperation for TOF.[60] The QRS width is considered a surrogate marker for right ventricular pressure and volume overload as well as increased right atrial pressure and stretch. Additional risk factors for atrial arrhythmias include older age at repair and moderate or severe tricuspid regurgitation.[61]

Similar to other congenital lesions with a surgical approach that involves a right atriotomy, the most common atrial arrhythmias include cavotricuspid isthmus–dependent atrial flutter or IART around the lateral right atrial atriotomy scar, occasionally occurring in a figure-of-8 pattern (see Figures 79-4 and 79-5). In contrast to other more complex ACHD lesions, mapping and ablation of these flutters often is more straightforward and can now be considered primary therapy. Ablation of the tricuspid annular circuit and the atriotomy circuit should be performed to minimize recurrences and the need for long-term antiarrhythmic therapy. The tricuspid annular circuit is ablated in the standard fashion, with a linear lesion placed between the IVC and the tricuspid annulus. The posterior atriotomy can be identified by wide split potentials along the posterolateral right atrium. In the case of re-entry around the atriotomy scar, an ablation line can be empirically drawn from the posterior atriotomy scar to the level of the IVC or the tricuspid annulus. Although typically extending the atriotomy incision inferiorly will result in tachycardia termination, the use of noninducibility as the sole endpoint in the early years of IART ablation led to suboptimal long-term efficacy.[62] Achieving conduction block across lines of ablation has led to improved arrhythmia control in the long term.[63] High output pacing should also be performed along the intended ablation path in the lateral atrium to exclude phrenic nerve capture because the phrenic nerve often is found in this region and can be damaged with ablation.

Ventricular Tachycardia

Surgical repair of TOF relieves RVOT; however, as patients age, progressive pulmonary regurgitation inevitably occurs. The ensuing right ventricular dilation, together with the surgical incisions, scarring, and fibrosis, can lead to the substrate for VT. Approximately 10% to 15% of patients with repaired TOF will have VT during long-term follow-up.[61] Sustained VT in a patient with repaired TOF should always prompt a full hemodynamic assessment. Surgical intervention has classically been considered in the case of progressive pulmonic insufficiency or marked right ventricular dilation.[5] However, in a retrospective study of patients with TOF undergoing pulmonary valve (PV) replacement, no reduction in VT or SCD was seen compared with a matched group of patients who did not undergo valve replacement.[64] However, the group of patients undergoing PV replacement in this retrospective study had larger right ventricle dimensions (RV end diastolic volume index 196 ± 76 vs. 132 ± 38 mL/m^2; $P < .001$) compared with the conservatively managed control group with a similar mortality outcome. Therefore an argument could be made that PV replacement may have been beneficial. We believe that the decision to pursue PV replacement should be based on hemodynmic and right ventricle volume measurements. If surgical valve replacement is to be performed, electroanatomic mapping and ablation of VT before surgery still have a role because the tachycardia circuit and critical isthmuses supporting VT can often be more easily mapped in the electrophysiology laboratory. In the case of unsuccessful catheter ablation, cryoablation can be performed in the operating room on the basis of the mapped tachycardia circuit. The advent of percutaneous PV repair may reduce or eliminate the need for open operative PV replacement. Catheter ablation of VT before percutaneous valve insertion should also be considered because the presence of valve conduit material may limit the efficacy of ablation near the PV.

The VT circuits in repaired TOF typically involve isthmuses between the right ventriculotomy incision or patch, the VSD patch and the tricuspid and PV annuli (see Figure 79-2). The ECG morphology of VT in these patients is variable but typically has either a left bundle morphology with an inferior axis and late precordial transition if activation occurs in a clockwise direction around the right ventricular free wall or a right bundle branch superior axis pattern in the case of counterclockwise activation of the right ventricular free wall.[65] VT can also occur between the VSD patch and the tricuspid annulus and typically results in a left bundle inferior axis morphology with an early precordial transition. Entrainment often indicates a broad wavefront of activation, incorporating much of the free wall of the right ventricle. Ablation typically requires delivery of linear pattern of lesions between the RVOT patch and the tricuspid annulus or the VSD patch. Ablation through areas of late potentials can also be important in slowing and terminating the tachycardia circuit. Because of the heavy fibrosis and scarring associated with the outflow tract repair, ablation with conventional 4-mm or 8-mm tip catheters can be challenging. Irrigated tip catheters should be used when available.[66] In the case of a poorly tolerated VT, areas of scar or electrically unexcitable tissue can be identified and the barriers connected with ablation to interrupt the tachycardia circuit. With this approach, successful ablation can be performed even in sinus rhythm (Figure 79-6). Documentation of conduction block across the linear pattern of lesions can be difficult to achieve but is important for reducing recurrences after ablation.[67,68] Ablation of VT in repaired TOF has a high acute success rate and will likely be applied on a wider scale to this population in the future.[69]

In patients with repaired TOF without VT, programmed ventricular stimulation can be used to aid risk stratification of SCD. The largest study to date combined data from 252 patients with repaired TOF and noninvasive risk factors for SCD.[70] One third of patients were inducible for monomorphic VT at EPS, and 4.4% were inducible for polymorphic VT. Inducibility for either monomorphic or polymorphic VT had 78% sensitivity and 80% specificity for the combined endpoint of sustained VT or SCD over a 6.5-year follow-up, with a 92% negative predictive value. The presence of inducible polymorphic VT had added value to inducible monomorphic VT, improving sensitivity with only a small decrease in specificity. Whether programmed stimulation should be performed routinely in the otherwise asymptomatic patient with TOF with a wide QRS remains controversial. We reserve invasive electrophysiological evaluation for those patients with evidence of nonsustained VT (NSVT) on a yearly screening Holter monitor, left ventricular dysfunction, presyncope, or syncope. Other noninvasive risk markers of SCD in patients with TOF are discussed in detail in the section on defibrillator therapy.

Device Therapy

When pacemaker or defibrillator implantation is considered in a patient with ACHD, pre-procedural planning is critical. Venous access is often not straightforward, especially with heterotaxy syndromes, and in patients in whom Fontan repairs have been performed. Nonstandard routes of access, such as a trans-hepatic approach or, more commonly, an epicardial surgical approach,

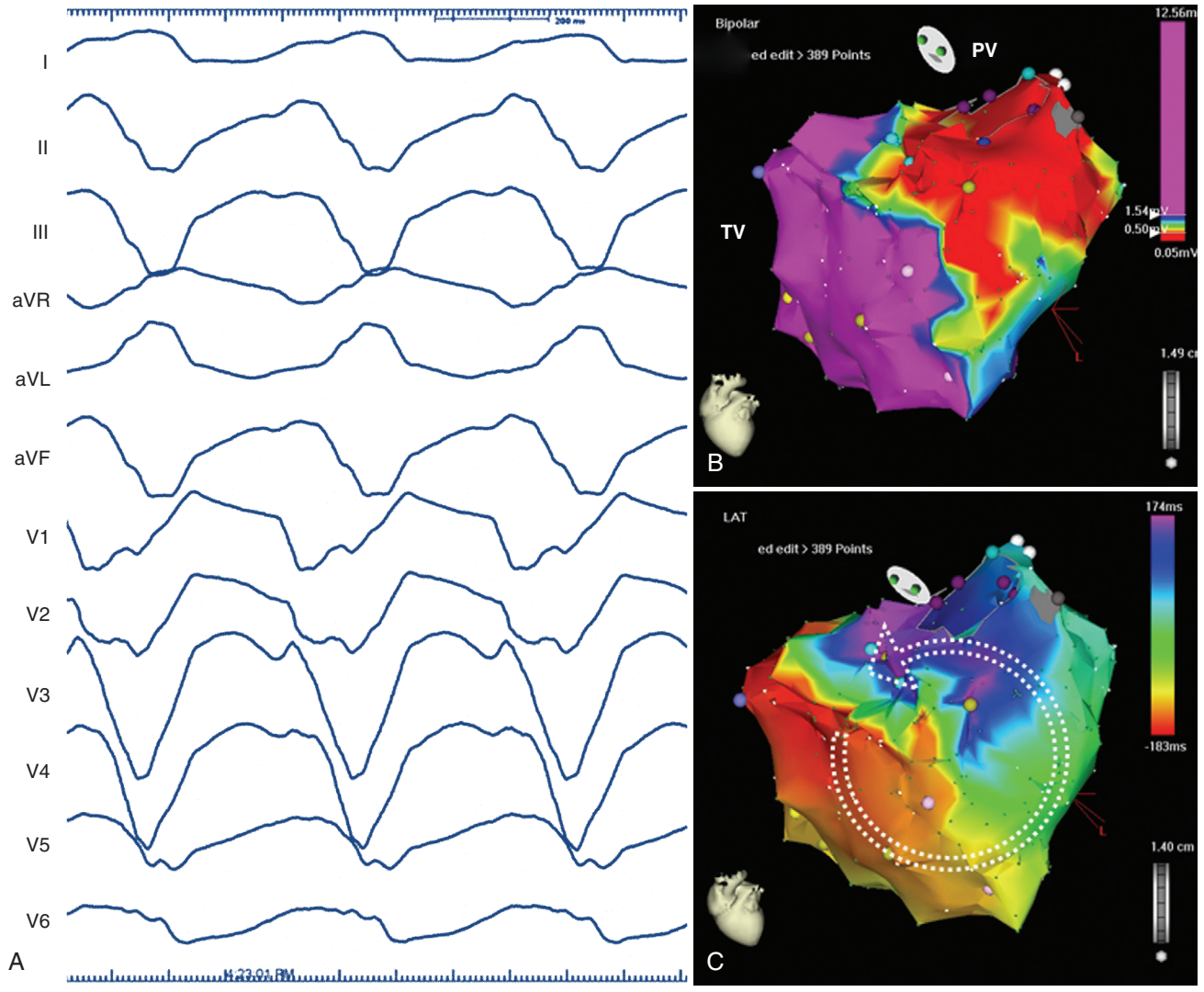

FIGURE 79-6 Ventricular tachycardia (VT) in a patient with repaired tetralogy of Fallot. **A,** Twelve-lead electrocardiogram showing left bundle, left superior axis VT. **B,** Electroantomic bipolar voltage map of the right ventricle (left anterior oblique view) depicting a large area of low voltage (*red*) in the area of prior ventriculotomy. **C,** Activation map during tachycardia showing re-entry occurring in a counterclockwise direction (*dashed arrow*) in the region of low voltage. Ablation through this low-voltage area from the tricuspid annulus to the pulmonic valve led to termination and noninducibility of the VT. *PV*, Pulmonary vein; *TV*, tricuspid valve.

may be needed in many patients.[71] Intracardiac shunts may necessitate closure before device placement, anticoagulation, or a surgical approach to device placement. Venous or intra-atrial baffle obstruction may require dilation and stent placement before the placement of leads. Concomitant minor vascular anomalies that impact on device placement, such as the presence of a left-sided SVC, may also be present. Left-arm peripheral venography, echocardiography, catheterization, CTA, MRA, or a combination of these may be required before device implantation.

Pacing

Sinus node dysfunction often is seen in patients with ACHD who have had repairs that require surgery near the sinus node such as D-TGA with intra-atrial repairs or in predisposed patients, such as those with heterotaxy syndromes and sinus venosus ASDs. In patients who have undergone a Fontan repair, sinus node dysfunction or AV conduction disturbances, often worsened by the effects of drug therapy, may necessitate pacing. Access to the ventricle is always prohibited, but depending on the type of Fontan repair, limited transvenous access to the atrium may exist as well. Therefore epicardial pacing wires often are placed at the time of surgery if the need for atrial pacing is anticipated. Even in patients with older-generation repairs, transvenous atrial lead placement is not desirable in the presence of any right-to-left atrial shunting because of the risk of systemic embolism.[72] In addition, the low-flow state in the Fontan atrium can result in thrombus formation even when no lead is present.

Defibrillator Therapy

Patients with ACHD and sustained VT or abrupt syncope should be considered for implantation of an ICD if they have a reasonable life expectancy (>1 year). This secondary prophylaxis group has

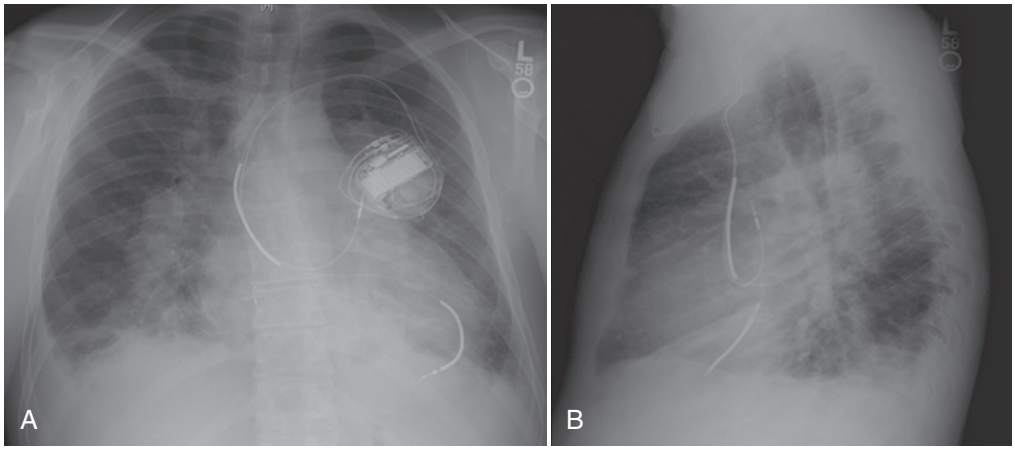

FIGURE 79-7 Dual-chamber defibrillator implantation in a patient with the Mustard repair for transposition of the great vessels. **A,** Anteroposterior view showing leads traversing the superior baffle to the left atrium and left ventricle. **B,** Lateral view showing the posterior position of the left atrial lead.

been found to have a high rate of appropriate ICD shocks in follow-up.[73] Prophylactic defibrillator insertion in the setting of depressed ventricular function is a more controversial issue and has little prospective supportive data in the literature.[74,75]

The role of programmed electrical stimulation (PES) for risk stratification in the general ACHD population remains unclear. As previously mentioned, patients with repaired TOF comprise the most studied group.[70] In one study, a large group of both asymptomatic patients with ACHD and NSVT and symptomatic patients with varied lesions underwent PES, with somewhat conflicting results. Although inducibility was shown to be significantly associated with an increased risk of death in follow-up (hazard ratio, 6.1), a significant false-negative rate was seen in patients with documented VT. In addition, the studies were frequently complicated by both bradyarrhythmias and atrial arrhythmias.[76]

Given these uncertainties, we typically do not perform PES in the general patient with ACHD and recommend defibrillator implantation in patients with severely reduced systemic ventricular function and NSVT or syncope. The risk and route of device placement also need to be considered. In patients without endocardial access to the ventricle, such as after Fontan repair, the risk of a repeat sternotomy makes the threshold for device placement quite high and often reserved for those with sustained VT or for survivors of SCD.

Endocardial device placement can be surprisingly straightforward in the patient with D-TGA after the Mustard or the Senning repair; however, careful pre-procedure planning is required. An evaluation with CTA, MRA, or cardiac catheterization should be performed to assess potential baffle stenosis, obstruction, or leaks. SVC baffle obstruction often is asymptomatic and may require stenting before device insertion. Baffle leaks can be either left to right or right to left, especially if subsequent baffle obstruction develops. Leaks should always be repaired before device insertion to prevent systemic thromboembolism from debris on device leads; this can typically be performed with percutaneous closure devices. Warfarin can also been used in patients requiring device therapy who have unrepairable baffle leaks, although this remains controversial.[72] It should always be noted that the presence of a left-sided SVC may require modification of the implantation approach. During atrial lead insertion, care should be taken to avoid placement of the device into the left atrial appendage, which usually is the region most easily approached from the SVC baffle. Far-field oversensing of ventricular signals and phrenic nerve capture can be problematic in this area. Ventricular leads are placed via the baffle and the mitral valve into the systemic venous, left ventricle (Figure 79-7). When implanting defibrillator leads, a single coil lead is recommended to avoid additional risk of SVC baffle obstruction, which is not uncommon in these patients.

Patients with repaired or nonrepaired TOF are at risk for SCD. Numerous studies have examined the risk factors for future SCD with somewhat mixed results. Generally agreed-on risk factors include a QRS width greater than 180 ms, older age at the time of repair, presence of a trans-annular RVOT patch that permits free pulmonic regurgitation, frequent ventricular ectopy on Holter monitoring, increased right ventricular systolic pressure and volume, and complete heart block.[61,77] The presence of left ventricular systolic dysfunction has also recently been shown to be an independent predictor of SCD in patients with repaired TOF.[78] Although the majority of ventricular arrhythmias are still thought to arise in the right ventricle, it is possible that they are more poorly tolerated in the setting of bi-ventricular failure.

Despite these studies, no discrete algorithm exists for primary defibrillator implantation in the patient with repaired TOF. The authors of this chapter typically perform yearly Holter monitoring to screen for ventricular arrhythmias. As stated above, invasive electrophysiological evaluation is done in those patients with NSVT, left ventricular dysfunction, presyncope, or syncope. Asymptomatic patients should have defibrillators implanted if they have inducible VT or are deemed to be at particularly high risk, on the basis of the above criteria.[79] Among patients with ACHD, patients with TOF who have defibrillators represent the largest group, with approximately half the devices implanted for primary indications and half for secondary indications.[80] Patients with TOF have a reported rate of appropriate ICD therapy it (approximately 10% per year in one study), which would seem to justify it, but these patients have also been reported to have inappropriate shocks and device-related complications.[81,82]

Cardiac Resynchronization Therapy

Cardiac resynchronization therapy (CRT) has been described in adults with bundle branch block, left ventricular dysfunction, and congestive heart failure. The electrical dyssynchrony of bundle branch block can worsen ventricular function in patients with congestive heart failure. Placement of pacing leads in the right and left ventricles (via the coronary sinus) can improve symptoms of heart failure by "resynchronizing" the ventricles by atrial synchronous biventricular pacing. Biventricular pacemakers have been proven to reduce symptoms, improve left ventricular function, and perhaps even reduce mortality in adults with heart failure and bundle branch block.[83-87]

CRT has been described in patients with ACHD who have heart failure and bundle branch block, but its role in the population as a whole is unclear. The contribution of conduction system disease to ventricular dyssynchrony in patients with congenital heart disease is complex, especially in those with single-ventricle physiology, and the presence of bundle branch block may be seen in the absence of electrical or mechanical dyssynchrony. The benefit of bi-ventricular pacing in patients with ACHD who have congestive heart failure and bundle branch block is based on several small case series.[88] Of particular interest is the patient with a systemic right ventricle. In a patient with transposition who has undergone the Mustard or the Senning repair and has RBBB with systemic right ventricular dysfunction, the coronary sinus travels its usual course along the left AV groove. Therefore a systemic right ventricular lead must be placed either epicardially during a repeat operative procedure or endocardially through the atrial baffle, which we do not favor because of the risk of systemic emboli. The risk of a repeat operation is not small and should be weighed against the potential benefit of resynchronization therapy. Such a procedure may be useful in selected patients. CRT is also being investigated for the prevention of systemic right ventricular failure.[89] Although dramatic improvement in cardiac function has been reported, the role of this therapy as primary prevention remains unproven.

One special population worthy of comment is the patient with poor ventricular function who has undergone Fontan repair. The modified Fontan procedure remains a palliative procedure in patients with single-ventricle physiology. Patients who have had Fontan repair remain at risk for progressive ventricular dysfunction, congestive heart failure, and SCD. Multiple-site ventricular pacing via epicardial leads placed surgically on the system ventricle has been shown to improve the immediate postoperative course after the Fontan procedure.[90] Some evidence in small series has shown some benefit of the Fontan repair for patients with severe ventricular dysfunction or those awaiting cardiac transplantation.[91] However, the potential benefit should be weighed against the risk of repeat sternotomy for epicardial lead placement because the subxyphoid approach rarely gives adequate visualization to allow multiple-site lead placement.

Summary

Despite advances in surgical technique and improvements in overall survival, adults with congenital heart disease remain at risk for atrial and ventricular arrhythmias and sudden cardiac arrest. Patients with ACHD who present with cardiac arrhythmias should first undergo evaluation to exclude an underlying hemodynamic cause. Symptomatic bradyarrhythmias, in general, require pacing, which poses the inherent challenge of endovascular access after complex surgical repairs or in the setting of intracardiac shunts. Tachyarrhythmias, both atrial and ventricular, can cause significant morbidity and mortality. Even though these patients are traditionally managed with antiarrhythmic drug therapy, alterations in surgical technique together with advancements in mapping and ablation technologies have provided new treatment options for these patients. The ICD can provide lifesaving therapy for those patients at high risk of SCD, although vascular access issues remain and data supporting proper risk stratification are lacking. Appropriate management of arrhythmias in adults with congenital heart disease requires a collaborative approach among cardiologists, electrophysiologists, cardiothoracic surgeons, and anesthesiologists who are familiar with the specific anatomic, hemodynamic, and psychosocial challenges of this unique patient group.

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CHAPTER 80

Antiarrhythmic Drugs

Dobromir Dobrev and Bramah N. Singh

There has been a considerable change in recent years in the role of antiarrhythmic drugs, and a number of factors have played critical roles in the ongoing reorientation of therapy for disorders of cardiac rhythm. In the case of supraventricular tachyarrhythmias, a precise understanding of the mechanisms of these arrhythmias has led to electrode catheter ablation, which has resulted in cure in most patients except those with atrial fibrillation (AF). On the one hand, less emphasis is placed now on long-term suppression except for symptom relief. On the other hand, available drugs given intravenously may induce conversion in nearly all patients with re-entrant supraventricular tachyarrhythmias but not to the same extent in atrial flutter (AFL) and AF, which may often require electrical conversion.

In the case of life-threatening ventricular arrhythmias, the focus is more on the use of implantable devices to prevent sudden cardiac death (SCD), and drugs are used as adjunctive therapy to prevent symptoms from shocks. Unlike the case of supraventricular tachyarrhythmias, conversion of ventricular tachycardia (VT) and ventricular fibrillation (VF) is largely achieved by electrical energy because of the left-threatening nature of the arrrhythmias, and pharmacologic conversion by intravenous drugs is used largely in asymptomatic patients with stable hemodynamics. Prophylactic therapy is used increasingly in the case of patients at high risk for sudden arrhythmic deaths, a setting in which pharmacologic therapy may still be pre-eminent.

Reorientation of drug therapy has also been necessary in the wake of the knowledge that certain antiarrhythmic agents, while suppressing supraventricular and ventricular arrhythmias, may increase mortality by their associated proarrhythmic effects. This was demonstrated in the Cardiac Arrhythmia Suppression Trial.[1] The findings have important clinical implications with respect to the choice of antiarrhythmic agents in the short-term, long-term, and prophylactic control of arrhythmias. The issue is critical in the choice of intravenous therapy of ventricular arrhythmias not only in hospitalized patients but also in those developing out-of-hospital VT or VF, especially in the choice of agents as an integral part of the current Advanced Cardiovascular Life Support (ACLS) guidelines.[2]

Classification of Antiarrhythmic Drugs Revisited

Interest in the mechanisms of action of pharmacologic agents has provided the basis for their classification since the 1970s.[3-9] The original intent was to classify the *mechanisms of action of antiarrhythmic drugs and not the drugs themselves.* Such an approach permitted grouping of drugs by their dominant action with the inevitable realization that many antiarrhythmic drugs in the clinic exerted single actions (e.g., β-blockers) or a varying spectrum of actions (sotalol and amiodarone) with their defined overall clinical effects both beneficial as well as deleterious.

The attempts at classification of the manner in which antiarrhythmic agents might work beneficially in the control of disorders of rhythm; this follows closely in the wake of a series of experimental studies of a number of structurally disparate compounds having certain discrete electrophysiological actions.[3-5,8,9] These compounds were local anesthetics or sodium channel blockers, β-adrenoceptor blockers, drugs that were also found to have anti-fibrillatory actions in the context of their property to selectively prolong cardiac repolarization, and those that were found to selectively block calcium channels at the membrane level. The premise of the initial classification was that each of the mechanisms described exerted, although in differing ways, an anti-fibrillatory effect in a standardized experimental model of VF.[5] The evolution of the steps in the classification of antiarrhythmic mechanisms of drugs that are now widely used stems from the original framework, which has subsequently been modified slightly, the most recent being by Nattel and Singh.[3-5,8,10] The final step completed in 1979 is shown in Figure 80-1.[11] The need for the classification of antiarrhythmic drug mechanisms was conceived almost simultaneously and independently on both sides of the Atlantic. It will be noted that the Hoffman and Bigger attempt at classifying antiarrhythmic drugs placed compounds such as quinidine and procainamide, which had been known to slow conduction as well as to prolong repolarization in one category (type 1), and lidocaine and diphenylhydantoin (DPH), which also inhibited conduction but *shortened repolarization* into another category (type 2).[12] Because propranolol in high doses exhibited potent conduction blocking properties, it was included among type 1 antiarrhythmic compounds.

On the basis of the findings in the experimental laboratory, it was suggested that type 1 compounds terminated or prevented arrhythmias by converting uni-directional block into a bi-directional one in an arrhythmia circuit, whereas the type 2 agents acted by eliminating uni-directional block by *increasing* conduction velocity. Subsequently, as an integral part of a series of studies on which the conventional antiarrhythmic classification has been based, it was found that this observation might have occurred as a consequence of the use of potassium ion (K^+) concentration of 2.7 mEq/L in the perfusion media.[9] The retesting of the effects of lidocaine and DPH in media containing physiological levels of

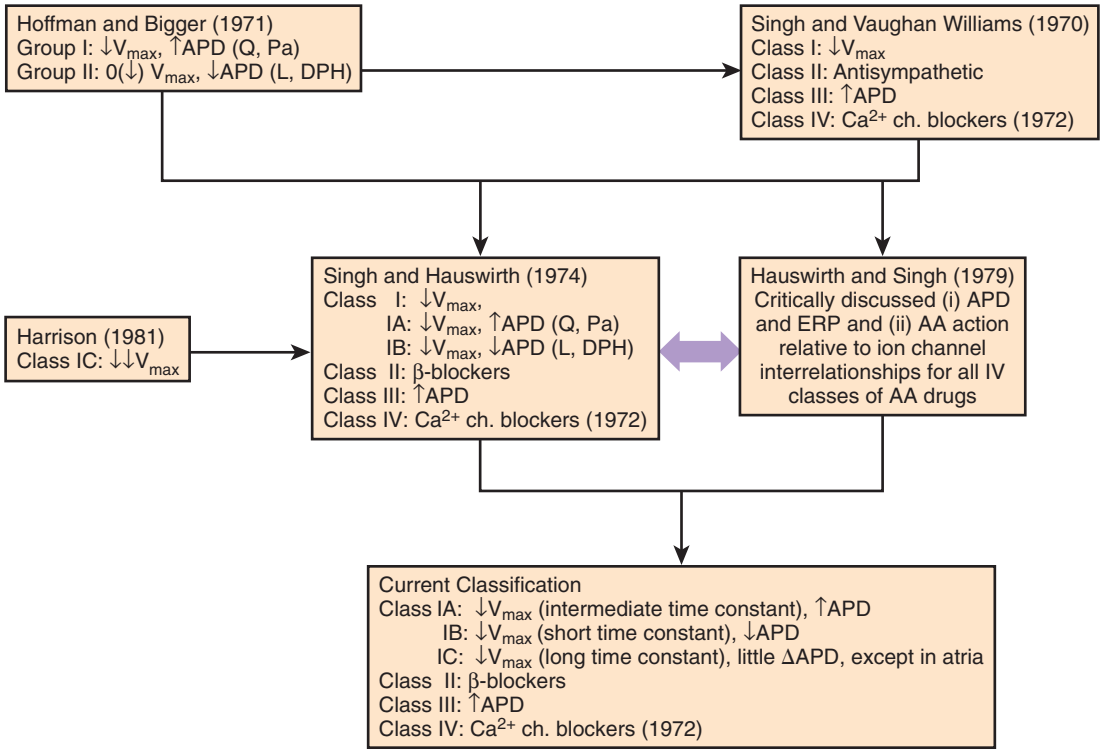

FIGURE 80-1 Evolution of the current classification of antiarrhythmic drugs. V_{max}, Maximal rate of change in the velocity of depolarization; *APD*, action potential duration; *Q*, quinidine; *P*, procainamide; *L*, lidocaine; *DPH*, diphenylhydantoin; *ERP*, effective refractory period; *AA*, antiarrhythmic; ↑, increase; ↓, decrease. *(Modified from Nattel S, Singh BN: Evolution, mechanisms, and classification of antiarrhythmic drugs: Focus on class III actions,* Am J Cardiol *84:11–19, 1999.)*

potassium ions clearly established that both the compounds had their predominant actions as inhibitors of sodium (Na) channel–mediated conduction. It also became evident that in clinically significant concentrations, propranolol exerted no local anesthetic actions.[8]

In contrast, in the comprehensive classification scheme suggested by Singh, and Singh and Vaughan Williams, all drugs that exerted local anesthetic actions in the nerve as well as in the myocardial membrane (including lidocaine, quinidine, procainamide, disopyramide, and DPH among numerous others) were thought to act via class I actions; and propranolol and other β-adrenoceptor–blocking compounds that exhibited sympatholytic actions were characterized as acting via class II antiarrhythmic actions.[3,5,7]

When it was found that compounds such as sotalol (a β-blocker) and amiodarone, which prolonged repolarization, exerted unequivocal anti-fibrillatory actions not accounted for by class I or class II actions, the possibility of a class III action was suggested.[3] Subsequently, on the basis of the electropharmacologic effects of the drug verapamil, a fourth class of antiarrhythmic actions was added by Singh and Vaughan Williams in 1972.[7] Hauswirth and Singh subdivided class I compounds into those that suppressed sodium channels in all cardiac fast-channel tissues, as typified by quinidine and procainamide (class IA agents), and those that inhibited sodium channels only in diseased or depolarized tissues (class IB: lidocaine and DPH).[11] Another difference between these two subclasses was that in the case of the 1A agents, repolarization was also prolonged, whereas in the case of 1B agents, repolarization was abbreviated. Harrison completed the subclassification by assigning the potent class I agents flecainide and encainide into a group designated as class IC.[13] Experimental studies by Campbell validated the separation of subclasses of sodium channel blockers on the biophysical basis; he found that class IA agents had sodium channel–blocking kinetics between those of class IB agents (very fast) and IC compounds (very slow).[14]

This classification of antiarrhythmic drugs is still widely used in clinical practice. It has been the basis for the development of newer antiarrhythmic compounds. It was recognized early that a direct extrapolation of the experimental data to the clinical setting in this regard might not be readily possible. However, it was considered that for advances in understanding drug action, it was desirable to explore the effects of various classes of antiarrhythmic drugs in myocardial cells and membranes in terms of ion channels and related parameters, on the one hand, and relate them to their clinical effects, on the other hand.[8,11] This approach was first suggested in detail by Hauswirth and Singh in 1979, and it re-emerged subsequently in the form of the Sicilian Gambit in 1991, incorporating an increasing understanding of membrane currents with the introduction of the patch clamp technique.[11,15]

The conventional classification has been of fundamental importance for the synthesis and initial characterization of new antiarrhythmic compounds (as has been the case of pure class III agents) as well as in terms of choosing an agent for the management of a particular arrhythmia.

The classification does appear to have direct relevance in terms of impact on mortality in patients with significant cardiac disease. For example, in patients with cardiac disease, class I agents may increase mortality via the development of proarrhythmic reactions, especially in patients with coronary artery disease (CAD). As a consequence, the role of sodium channel blockers is declining—being restricted to alleviating arrhythmia symptoms in patients without heart disease. In contrast, class II agents (β-blockers) uniformly prolong survival in numerous subsets of patients because of their multiplicity of actions that include antifibrillatory effects in patients with a varying spectrum of severity of heart disease.

Amiodarone and sotalol—two unique compounds—the dominant electrophysiological property of which is the prolongation of repolarization, formed the basis for the class III action.[3,4,7,16-18] Amiodarone and sotalol have provided the background for the synthesis and characterization of simpler compounds (such as dofetilide and azimilide) as well as the impetus to develop other agents with similar properties but safer electropharmacologic profiles. The main properties of the major agents are discussed in this chapter relative to their roles in the control of supraventricular and ventricular tachyarrhythmias. Recently approved compounds for AF treatment, such as dronedarone and vernakalant, are also discussed. Certain electrophysiological properties of antiarrhythmic compounds are of much importance in the clinical area. They will be emphasized at the outset.

Heart Rate Dependency of the Action of Antiarrhythmic Agents

The electrophysiological property that also appears to be of major clinical interest is the rate-dependent effect of the compounds on the action potential duration (APD) and refractoriness.[19] *Rate dependency* refers to a different effect at varying heart rates, with reverse-rate dependence (less effect at higher rates) being of great clinical importance. The differences in this parameter among the various agents may be of therapeutic relevance. This issue is of particular relevance in the case of their role in the control of AF. The drugs that exert the classic reverse-rate dependency (dofetilide, quinidine, and d,l-sotalol) appear to exhibit a similar ceiling of efficacy for maintaining the stability of sinus rhythm and a similar propensity for inducing torsades de pointes (TdP). Their effect on prolonging the APD and the effective refractory period (ERP) in the atrial muscle decline as the stimulation frequency increases. All such compounds are powerful blockers of the delayed rectifier current (I_{Kr}), and they are likely to be more effective in terminating AFL than AF when acutely administered. They are moderately effective in preventing recurrences of AF and AFL in the paroxysmal and persistent forms of these arrhythmias.

In contrast, compounds such as azimilide and possibly ambasilide, which may also inhibit the slow component of the delayed rectifier current (I_{Ks}), exhibit a different pattern of rate dependency of action with respect to the APD and associated refractoriness. Under the action of the drugs, a parallel increase occurs in the APD and the ERP, as shown in Figure 80-2. Whether this is clinically significant may require a direct comparison of these compounds with those of other so-called class III compounds such as dofetilide. In the case of azimilide, the available data suggest a low incidence of TdP, a neutral effect on mortality in high-risk patients with previous myocardial infarction (MI) and at least moderate efficacy in maintaining the stability of sinus rhythm in patients with AF.[20,21] Large pivotal placebo-controlled trials with respect to azimilide are in progress.

Of particular interest, the action of amiodarone and that of dronedarone, with respect to rate-dependent effects, are similar, as they are associated with a parallel shift (i.e., ERP increases in a parallel fashion over a wide range of frequencies), as noted in the case of azimilide and ambasilide.[10,22] In the case of amiodarone evidence for the effectiveness of the drug for maintaining the stability of sinus rhythm is growing. Its potency (see later) appears the highest among all class III antiarrhythmic compounds, and it is associated with the lowest incidence of TdP in the context of the longest Q-T interval that amiodarone may produce during the course of long-term treatment. The precise reason for this combination of drug effects remains unclear, but the observations are clearly of theoretical importance for the purposes of developing compounds in the future. Perhaps of great importance also is the observation that in the case of flecainide (presumably also propafenone) is the nature of their effects on the ERP and the APD as a function in atrial tissue. Wang and coworkers found that in a variety of mammalian atria, flecainide (and presumably propafenone acts in a similar manner) had the property of prolonging the APD and the ERP as a function of rate.[23] For example, greater effects were seen as the stimulation rates were increased (Figure 80-3) (see the discussion on atrial-selective drugs below). The available data suggest that the rate-related effects of antiarrhythmic drugs may vary in differing cardiac tissues, which is possibly a reflection of the differential action of drugs on the ion channels that they may inhibit to varying extents.

Class I Antiarrhythmic Compounds

As a class, this group of agents share one common and dominant property: They slow conduction in those myocardial tissues in which conduction velocity is controlled by the fast sodium channels with variable, often inconsistent, effects on the refractory period in ventricular tissues. The proarrhythmic effects may also vary in relation to the additional electrophysiological properties certain class I agents might have—as is the case with prolongation of repolarization in quinidine, procainamide, or disopyramide (class IA drugs), which may contribute to the prolongation of the refractory period, but with the propensity to induce TdP.

Conversely, lidocaine and its oral congeners, mexiletine and tocainide, and DPH (class IB agents), in fact, *shorten* repolarization and hence refractoriness, in addition to slowing conduction. The actions of class I agents are usually more intense in diseased tissues that are partially depolarized, such as in myocardial ischemia. Here, their proarrhythmic effects in settings of ischemia or left ventricular dysfunction are often much greater and may prove fatal—as in the case of flecainide, encainide, and propafenone (class IC compounds), which are contraindicated in patients with significant ventricular dysfunction. As a class of antiarrhythmic drugs, the use of sodium channel blockers is declining because none of the agents has the potential to increase survival by controlling cardiac arrhythmias. If they are administered to patients with potentially serious cardiac disease, the risk of mortality may increase.[24] Their main usefulness is in the conversion of AF to sinus rhythm and in maintaining the stability of sinus rhythm in patients in whom the arrhythmia occurs with normal or near-normal ventricular function. Relevant aspects of individual agents are presented below.

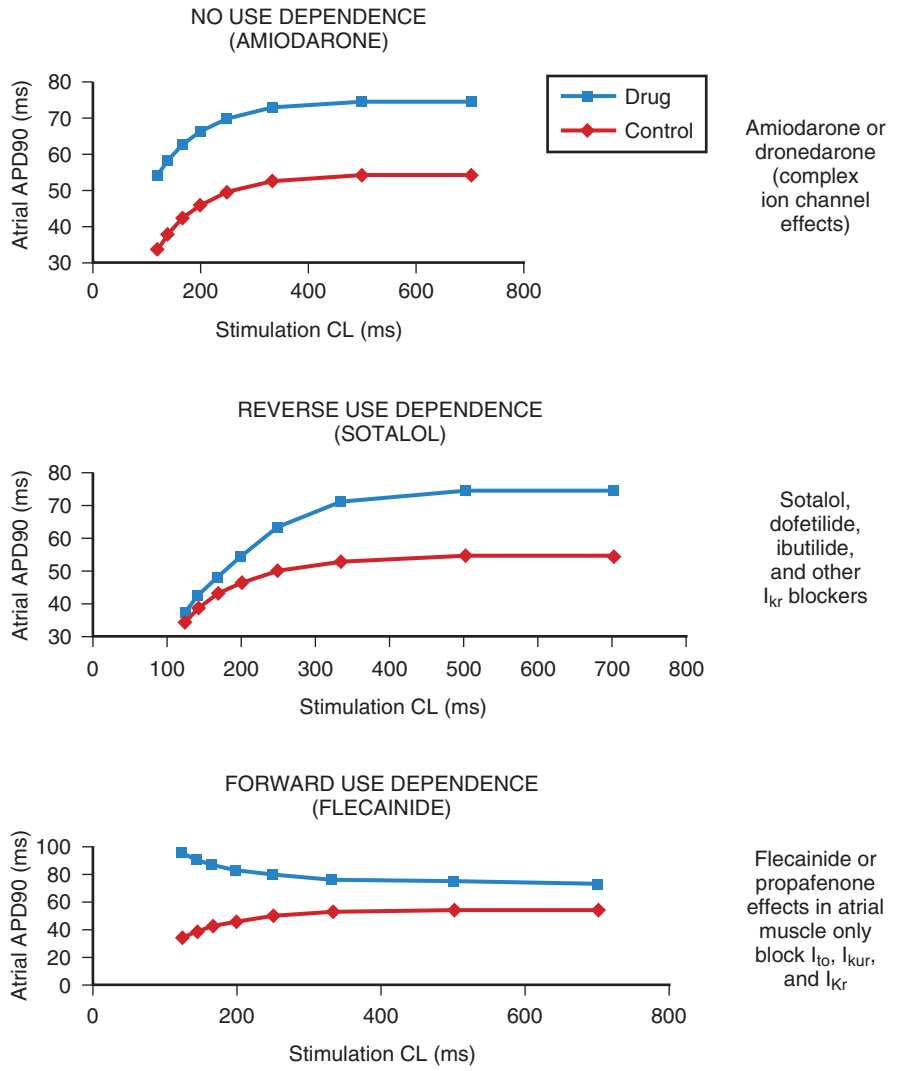

FIGURE 80-2 Influence of changes in stimulation frequency in time course of myocardial atrial repolarization induced by various antiarrhythmic drugs. Three patterns are illustrated: no use dependence, reverse rate, and forward use dependence. In the first, as illustrated by amiodarone, no effect occurs on the action potential duration (*APD*) or effective refractory period (ERP) as the cardiac frequency increases; in the cases of sotalol and other I_{kR} blockers, the APD and ERP shorten as the cardiac frequency increases, and forward use dependence occurs, as has been demonstrated in the case of flecainide in the atria. These differences may be of much significance clinically as well as for the development of atrial-specific anti-fibrillatory agents. *(From Sarma JSM, Singh BN, 2001, unpublished data.)*

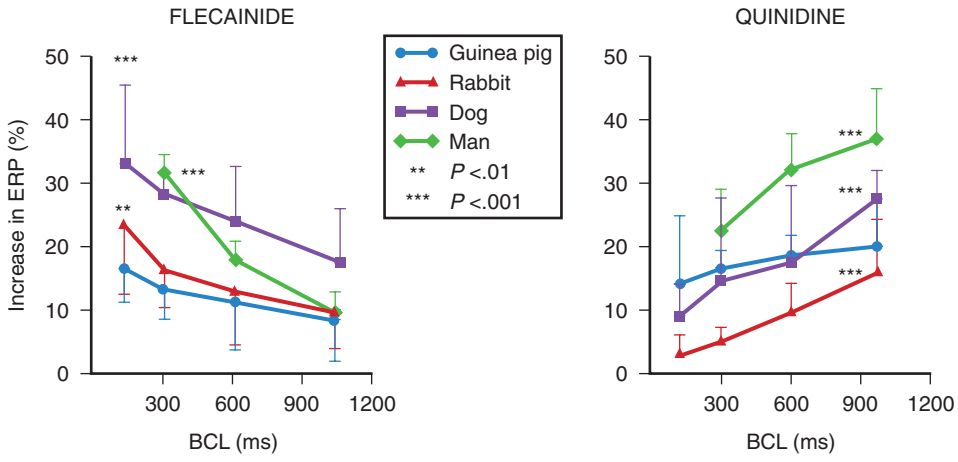

FIGURE 80-3 Rate-dependent effects of flecainide and quinidine on effective refractory period (*ERP*) in mammalian atria. The data contrast the forward use dependence of flecainide with the reverse use dependence of quinidine (see Figure 80-2). *(From Wang Z, Pelletier LC, Talajic M, Nattel S: Effects of flecainide and quinidine on human atrial potentials: Role of rate dependence and comparison with guinea pig, rabbit and dog tissues,* Circulation *82:274–283, 1990.)*

Table 80-1 Effects of I_{Kr} Inhibition on Effectiveness in Maintaining Sinus Rhythm in AF Relative to the Development of TdP and Total Mortality with and Without Blocking Other Ionic Currents

ANTIARRHYTHMIC AGENT	IONIC CURRENTS OR RECEPTOR BLOCKED	EFFECTIVENESS IN AF (1 yr)	TdP	MORTALITY
Amiodarone	I_{Kr}, I_{Ks}, I_{to}, I_{Na}, β-receptor	60%-70%	<0.5%	Neutral or lower
d,l-Sotalol	I_{Kr}, β-receptor	<50%	>2%-3%	Neutral
d-Sotalol	I_{Kr}	20%-30%	>2%-3%	Increased
Dofetilide	I_{Kr}	50%-60%	>2%-3%	Neutral
Azimilide	I_{Kr}, I_{Ks}, I_{ca}	50%	1%-2%	Neutral (ALIVE)
Quinidine	I_{Kr}, I_{Kl}, I_{kur}, I_{to}	50%	3%-5% or higher	1%-3% (meta-analysis)

i_{Kr}, *Delayed rectifier current;* AF, *atrial fibrillation;* TdP, *torsades de pointes;* ALIVE, *Azimilide Post-Infarct Survival Evaluation trial.*

Quinidine

Quinidine has the dual electrophysiological properties of prolonging repolarization and slowing conduction by blocking inward sodium current, thereby slowing conduction and by blocking a variety of outward potassium currents; the effects of the drug on myocardial ion channels are compared with those of other antiarrhythmic drugs in Table 80-1. The drug is available in injectable and oral forms, but the injectable formulation is now rarely used. Quinidine may increase heart rate and facilitate AV nodal conduction by its vagolytic actions and increase ventricular response in AF. The major electrophysiological effect of clinical utility relative to the drug's antiarrhythmic actions is the prolongation of the APD and the ERP (a class III action); the effects on both are attenuated as the heart rate increases. The drug has been used in patients with impaired ventricular function, but it may depress myocardial contractility. The elimination half life of quinidine is 8 to 9 hours, its metabolism being largely by hepatic hydroxylation. The usual oral dose of the drug is 1.2 to 1.6 g/day in 8 to 12 hourly divided doses relative to the preparation in use.

The most common adverse effects of quinidine include diarrhea, nausea, and vomiting, which occur in one third of all patients. Quinidine can also cause cinchonism (headache, dizziness, and tinnitus), and quinidine can cause syncope, a syndrome characterized by lightheadedness and fainting. The major shortcomings of quinidine are severe diarrhea, frequently caused by the drug, and TdP, which develops in 2% to 5% in association with a prolonged Q-T interval. Rarely, TdP may be fatal. In a detailed meta-analysis of the trials in AF involving quinidine, an increase in mortality has been reported.[25] For these reasons, when considered in conjunction with the limited ceiling of effectiveness of the drug in ventricular arrhythmias as well as in supraventricular arrhythmias, the clinical utility of quinidine is limited. Its continued use can be justified only marginally.

Procainamide

This drug acts largely by prolonging the APD and refractoriness in atrial and ventricular tissues, with little or no effect on nodal tissues; it does affect conduction with a modest anticholinergic effect. It has no antiadrenergic actions. Its major metabolite is *N*-acetyl-procainamide (NAPA), which contributes to the overall electrophysiological component of the parent compound. The elimination (renal) half life of procainamide is less than 4 hours, although slow-release formulations (q6h) have been in use. The electrophysiological properties of the drug resemble those of quinidine.

Available as an oral form (1 g loading dose and 500 mg q3h or equivalent of slow-release formulation q6h) and injectable (100-mg bolus up to 25 mg/min to 1 g in the first hour, then 2 to 6 mg/min), procainamide has been used in the past to treat supraventricular and ventricular arrhythmias. Although procainamide produces a lower incidence of TdP compared with quinidine, its clinical utility has declined substantively in recent years. Its role in the acute conversion of AFL and AF has been superseded by that of intravenous class III agents, especially ibutilide in most, if not all, clinical settings. The intravenous drug, however, is still useful in the conversion of monomorphic VT in a patient who is not severely hypotensive and in the conversion of AF, complicating Wolff-Parkinson-White (WPW) syndrome. The oral formulation of the drug exhibits a significant hypotensive effect by virtue of its vasodilator and negative inotropic actions; however, it cannot be used for prolonged periods because hematologic adverse reactions and, in particular, lupuslike syndromes can complicate its prolonged use. Thus, the oral form of the drug is now obsolete.

Disopyramide

As in the case of quinidine and procainamide, disopyramide as a class IA antiarrhythmic agent has limited clinical use. Its electropharmacologic profile is similar to that of quinidine, but it has a more potent anticholinergic action and it produces a lesser degree of gastrointestinal disturbance. The elimination half life of the drug is about 8 hours, but slow-release formulations have been introduced. The effects of the drug in arrhythmia control have not been extensively studied except for the suppression of premature ventricular contractions (PVCs). Disopyramide has been used largely in the oral form at a dose of 100 to 200 mg q6h, but it is now rarely used for the control of ventricular tachyarrhythmias. Like quinidine, it does prolong the Q-T interval and may produce a variable incidence of TdP; of particular importance, in patients with impaired ventricular function and in those with heart failure, it is likely to severely aggravate cardiac decompensation by its potent negative inotropic actions. However, such a property may be of therapeutic value in the syndrome of idiopathic

hypertrophic cardiomyopathy (HCM), a setting in which the drug produces a greater negative inotropic effect than do β-blockers with which disopyramide can be combined. Although not approved in the United States, disopyramide may have a significant anti-fibrillatory effect in AF in two settings where its role in controlling this arrhythmia may be unique—in patients with HCM who develop AF and in patients whose AF is entirely caused by excessive vagal tone.[26] In the latter setting, the drug's anticholinergic actions may be a specific therapy, which might be strikingly effective. It should be emphasized, however, that the drug's anticholinergic actions may lead to serious adverse reactions in the form of urinary retention, worsening of glaucoma or myasthenia gravis, and severe constipation.

Lidocaine, Mexiletine, and Tocainide

The properties and the roles of intravenous lidocaine and its two orally active congeners, mexiletine and tocainide, as class IB compounds, will be discussed only briefly because their roles have declined considerably in recent years and they are likely to be only of historic interest. Despite the suppression of ventricular arrhythmias that class IB agents produce, data on their adverse effects on mortality continue to accrue.[27,29] Lidocaine, a class I antiarrhythmic, is available as an injection. Lidocaine action is characterized by a fast, on-off block of sodium ion channels in both the activated and inactivated states, with a preference for inactivated state sodium channels. It also shortens the duration of the APD (hence the Q-T interval), and refractoriness, and has been shown in the experimental setting to *elevate* the ventricular defibrillation threshold. Thus, the drug and its oral congeners (also available as intravenous formulations) may act largely by slowing conduction rather than prolonging refractoriness. However, their actions in terminating and preventing arrhythmias may also stem from the conversion of unidirectional block to a bidirectional block in the arrhythmia re-entrant circuit although the proof for this in the clinical setting is lacking. Lidocaine is metabolized rapidly in the liver, and it is administered generally as an initial bolus of 100 to 200 mg, followed by 2 to 4 mg/min for varying durations of time (usually 24 to 36 hours) aiming at serum levels of 1.4 to 5 μg/mL.

Lidocaine gained prominence as a prophylactic agent in the early days of the inception of coronary care units and subsequently as the first-line agent in the control of VT/VF in all acute care units, including the emergency department, and in the resuscitation of those developing out-of-hospital cardiac arrest. The use of lidocaine and, indeed, other antiarrhythmic drugs in these settings was not based on data from controlled clinical trials. It is of interest to note that in a direct blinded comparison, intravenous lidocaine converted 18% of VT to sinus rhythm compared with 69% conversion with intravenous sotalol.[30] The Cardiac Arrhythmias Suppression Trial on the drugs encainide, flecainide, and moricizine indicated a dichotomy between arrhythmia suppression and mortality.[1] Abundant data now suggest that intravenous lidocaine and mexiletine are similarly ineffective in the setting of postmyocardial infarction and raise the issue that they might also be similar in the control of destabilizing VT or VF as well as in the survivors of out-of-hospital cardiac arrest.[27-29] It is not surprising that in line with the data, the most recent AHA/ACC/ACLS (American Heart Association/American College of Cardiology/Advanced Cardiac Life Support) Guidelines have relegated the use of lidocaine as being "indeterminate."[2] This issue will be discussed in depth later in this chapter when the effects of intravenous lidocaine and intravenous amiodarone will be discussed relative to the broader implications of the choice antiarrhythmic agents in the control of life-threatening ventricular arrhythmias in various clinical settings.

Class 1c Agents

This class of antiarrhythmic agents developed on the basis of the belief that the suppression of ambient arrhythmias—whether PVCs, sustained VT, or nonsustained VT—by antiarrhythmic drugs should result in prevention of arrhythmic death and in the prolongation of survival. The fact that such a hypothesis was not vindicated has had a number of therapeutic consequences: (1) near-complete or complete suppression of PVCs in the patient with previous MI is associated with an increased mortality rate in those with cardiac disease and indicates that this class of drugs cannot be used with impunity even for the control of symptoms caused by arrhythmias; (2) increased observed mortality induced by class IC agents may be a property of class I agents in general and is also found in the case of lidocaine; and (3) data do not exclude the possibility for using such agents for controlling arrhythmia symptoms or for restoring and maintaining sinus rhythm in AF or AFL *in patients without structural heart disease*. This is especially so in the case of flecainide and propafenone. Moricizine is often included in the category of class IC agents, but its properties are difficult to classify, and it may not have any advantages over flecainide or propafenone. These agents slow conduction velocity profoundly but have little, if any, effect on refractoriness in ventricular tissues; and theoretically, they eliminate re-entry by slowing conduction to a point where the impulse is extinguished and cannot propagate further. This may be the basis of their effectiveness in markedly reducing ventricular ectopy. Their actions in atrial tissues differ markedly compared with those in the ventricle. *They increase the ERP in the atria as a function of increases in heart rate,* an effect that is likely to be the basis of their effectiveness in restoring and maintaining sinus rhythm.[23] This is their major clinical utility as antiarrhythmic drugs.

Flecainide

Flecainide is a powerful blocker of sodium channels in virtually all cardiac tissues, but it does not significantly inhibit the pacemaker current or the calcium channels. It has effects on K^+ channels but without a major effect on repolarization, except in the atria, where repolarization is prolonged and the effective period is lengthened. The drug has a significant negative inotropic effect especially at higher doses. The plasma half-life of the drug is 13 to 19 hours; two thirds of it is metabolized in the liver. The usual dose of flecainide is 100 to 300 mg, given twice daily. The intravenous formulation is available but is not used routinely. One clinical utility of flecainide is in the control of intractable symptoms caused by PVCs in patients with no significant cardiac disease. Perhaps its greatest value is in the restoration and prevention of recurrences of AF but only in patients without structural heart disease because of its serious proarrhythmic reactions in patients with cardiac disease.[31] In the prophylactic control of AF or AFL, the drug should be combined with an AV nodal blocking drug (β-blockers or calcium channel blockers) to avoid the development of facilitated conduction across the AV node as the atrial rate slows under the action of the drug. In recent years, single oral doses (200 to 300 mg) of the drug have been successfully used for

the acute termination of paroxysms of AF ("pill in the pocket" approach).

Propafenone

Propafenone is also a powerful class IC agent with an electrophysiological activity profile similar to that of flecainide; it also has a mild degree of β-blocking action, which does not appear to be clinically relevant.[32] Its actions in the atria may also be similar to those of flecainide, and the drug does not prolong repolarization in ventricular tissues. The drug is rapidly absorbed with the bioavailability of 50%, its elimination half-life being 2 to 10 hours in normal subjects and 12 to 32 hours in poor metabolizers. Orally, propafenone is administered as 150 to 300 mg three times daily, and a longer acting formulation has been introduced. The drug can also be administered intravenously and as single oral doses (300 or 600 mg) for the acute conversion of paroxysms of atrial AF. As in the case of flecainide, propafenone should not be used in patients with significant cardiac disease, and its two main indications are for the suppression of resistant symptomatic PVCs and for the restoration and maintenance of sinus rhythm in the case of AF in patients with structurally normal hearts. Its efficacy rivals that of flecainide, although direct comparisons have not been made. As in the case of flecainide, propafenone should be combined with an AV nodal blocking drug to reduce the possibility of accelerated conduction with the slowing of atrial rate induced by the drug.

β-Adrenergic Blockers as Antiarrhythmic and Anti-fibrillatory Compounds

β-Blockers as a class of drugs exert distinctive antiarrhythmic and anti-fibrillatory effects because of their properties of consistently alleviating symptoms and prolonging survival in a wide subset of patients. The electrophysiological and anti-fibrillatory effects are most striking in the clinical context of most intense sympathetic stimulation. They prevent the development of VF in a variety of experimental animal models. The beneficial effects in this setting could not be accounted for by any known electrophysiological mechanisms. However, in the clinic, the antiarrhythmic potential of β-blockade was greatly overshadowed by its anti-ischemic actions for which this class of drugs was synthesized. Thus, the recognition of the fact that blunting the effects of catecholamines on the heart might be a potent anti-fibrillatory mechanism was slow in coming. It has been known for many years that increased activity of the sympathetic nervous system might induce cardiovascular morbidity and mortality through a variety of mechanisms. For example, given the appropriate pathologic substrate, increased sympathetic activity may be associated with sudden arrhythmic death.[33-35] This is now known to be particularly striking in the case of patients developing MI with or without heart failure.

The intrinsic effects of β-blockers may be modified to varying extents by the associated pharmacologic properties that individual agents may have. For example, in the case of propranolol at high concentrations the sodium channel is significantly inhibited. Some agents (e.g., acebutolol, atenolol, bisoprolol, carvedilol, and metoprolol) are relatively cardioselective for blocking β_1-adrenoceptors, and others are nonselective (propranolol, nadolol, timolol, and sotalol) with respect to β_1- and β_2-adrenoceptors. However, evidence that these varying degrees of selectivity of action significantly alter the antiarrhythmic and anti-fibrillatory actions of β-blockers in patients is scarce. However, little doubt exists that the presence of marked agonist actions (e.g., in pindolol) is associated with often significant *increases* rather than decreases in heart rate that largely offset the antiarrhythmic and anti-fibrillatory actions of a given agent.[36]

Electropharmacologic Properties and Anti-fibrillatory Actions

The precise effects of β-antagonists on ionic currents in differing myocardial cells in terms of depolarization and repolarization are difficult to characterize.[37] It should be recognized that for a given agent within the broad class of these compounds, the effects may stem from their intrinsic properties of blocking β-receptors as well as from their associated pharmacologic actions. The dominant effect, however, is from β-receptor blockade, which has minimal effects on calcium channels ($I_{Ca\text{-}L}$) or various potassium channels (I_K). It is known that sympathomimetic amines exert a stimulant effect on the pacemaker current (I_f), which is markedly inhibited by β-blockers. Indeed, the blocking effect of the pacemaker current by β-blockers is the most readily defined pharmacodynamic property of this class of drugs and one that correlates well with the beneficial effects on mortality in patients with cardiac disease. The effects of β-blockade on the nodal tissues are, therefore, significant with the slowing of the heart rate by effects in the sinoatrial (SA) node and by prolonging refractoriness in the AV node, which may be of clinical utility in terminating SVTs and slowing the ventricular response in the setting of AFL and AF.

The electrophysiological effects in other tissues are variable in terms of changes in conduction and refractoriness. The effects are minimal or modest in atrial and ventricular muscle; thus, when acutely administered, they do not consistently convert AFL and AF or VT to sinus rhythm, although the last has not been widely studied. Similarly, they have little effect on Purkinje fibers or the accessory bypass tracts. The acute effects of β-blockade on repolarization in isolated tissues and in the intact heart are variable, and minor increases or decreases in the Q-T interval after long-term continuous drug administration have been reported.

Antiarrhythmic Actions of β-Blockers

It is inherently likely that the major basis for the beneficial effects of β-blockers in cardiac arrhythmias stems from their property of counteracting the arrhythmogenic effects of catecholamines. However, their exact mechanism may differ in various disorders of rhythm in differing clinical settings. As a class, β-blockers exert a modest effect in suppressing ventricular and supraventricular arrhythmias (PVCs, PACs, and nonsustained VT) documented on Holter recordings. However, they increase VF threshold and reduce dispersion of repolarization, especially in the ischemic myocardium. On the one hand, they have very little effect in preventing the inducibility of VT or VF in patients with sustained symptomatic VT or VF. On the other hand, they are the most potent antiarrhythmic and anti-fibrillatory agents with consistent effects on SCD and all-cause mortality without the propensity for the development of discernible proarrhythmic reactions.

Perhaps, the antiarrhythmic and anti-fibrillatory actions of β-blockers are best characterized in terms of their property of attenuating the deleterious effects of excess catecholamines. The electrophysiological consequences of sympathetic hyperactivity have been extensively documented in numerous experimental

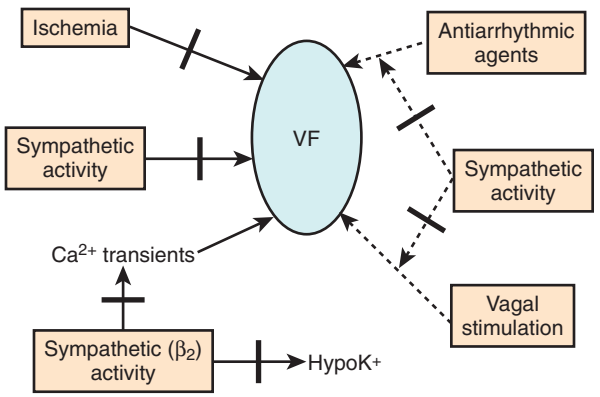

FIGURE 80-4 Model of possible anti-fibrillatory effects of β-blockade. Myocardial ischemia and increased adrenergic tone favor the development of ventricular fibrillation (*VF*) shown by *solid arrows*. Such effects are attenuated by the anti-ischemic and adrenergic antagonism of β-blockers indicated by *crossed lines*. β_2-Agonists also favor the development of VF by promoting calcium transients or hypokalemia. These effects are blocked by nonselective β-blockers. Vagal stimulation and some antiarrhythmic agents act to prevent the development of VF (*dashed lines*), but these actions are reversed by sympathomimetic stimulation. β-Blockade is likely to prevent this reversal and would again be anti-fibrillatory. *(From Reiter MJ: Antiarrhythmic impact of anti-ischemic, antifailure and other cardiovascular strategies,* Cardiac Electrophysiol Rev *4:194–205, 2000.)*

Table 80-2 Principal Uses of β-Blockers to Reduce Life-Threatening Ventricular Arrhythmias and Control Postoperative Atrial Fibrillation After Cardiac Surgery

INDICATIONS	COMMENTS
Cardiac arrest survivors	No controlled clinical trials but uncontrolled data compelling Adjunctive therapy to ICDs Controlled data still to be obtained, but support for VT/VF strong from large uncontrolled database
Congenital long QT syndrome	Compelling but uncontrolled data used a single drug modality, now being replaced with ICDs, with which they often need to be combined
MI survivors	Most consistent antiarrhythmic agents increase survival in this setting, reduce total mortality, sudden death, and re-infarction rates Overwhelmingly positive data from controlled clinical trials
Congestive cardiac failure	Reduce total mortality and sudden death in CHF of ischemic and nonischemic origins: role well established
Prevention of AF	Prophylactic administration reduces the incidence of AF in postoperative cardiac patient undergoing cardiac surgery

AF, Atrial fibrillation; ICDs, *implantable cardioverter-defibrillators;* MI, *myocardial infarction;* VT/VF, *ventricular tachycardia/ventricular fibrillation.*

and clinical studies.[33-35] In the experimental setting, they have included (1) shortening of the ventricular APD, and hence the ERP; (2) augmenting ventricular conduction; (3) increasing ventricular automaticity; (4) reducing vagal tone; (5) decreasing VF threshold; and (6) the reversal or attenuation of the effects of antiarrhythmic drugs being administered in the expectation of preventing arrhythmic deaths. Conversely, it is known that the depletion of the adrenergic transmitters to the heart increases VF threshold; and in experimental models in which VF could be induced reproducibly, the arrhythmia is preventable by sympathetic blockade.[33] Aspects of the anti-fibrillatory effects of β-adrenergic blocking drugs are shown in Figure 80-4.[36] In fact, the appreciation of such an anti-fibrillatory effect was the basis for classifying it as a class II antiarrhythmic action.[3-8]

β-Blockade

Impact on Sudden Cardiac Death and Total Mortality in Survivors of Myocardial Infarction and in Patients with Heart Failure

β-Adrenergic blocking drugs are effective in reducing mortality in many subsets of patients with manifest arrhythmias and in those at high risk of dying from arrhythmic deaths.[37-42] For example, they reduce death rates in patients with congenital long Q-T syndrome (LQTS), in survivors of cardiac arrest, and in selected cases of VT, although the data supporting these conclusions have not always been from controlled clinical trials.[39-43] However, they are in line with the compelling data from randomized, placebo-controlled β-blocking trials, in which consistent and significant decreases in mortality have occurred, especially in survivors of acute MI (AMI) and in those with congestive heart failure.[44-51] These trials have usually been of adequate sample size and of acceptable protocol design with features that include double-blind comparison in placebo-controlled studies. They have shown that these agents, as a class, not only bring about a beneficial change in total mortality but also on sudden, presumably arrhythmic death (Table 80-2). The overall clinical utility and versatility of this class of antiadrenergic compounds are well documented as indicated in Table 80-3.[36]

β-Blockers, as a class, consistently reduce the incidence of SCD and total mortality in the survivors of AMI and in patients with cardiac failure of ischemic and nonischemic origins. In the case of patients with MI, beneficial effects on SCD and total mortality have been documented at the time of diagnosis out of the hospital, during hospital stay, and following discharge from the hospital. In the latter case, SCD and total mortality were reduced from 18% to 39% during the first year. It is presumed that the benefit in survival is from the prevention of VF. It is noteworthy that with β-blockers, mortality is reduced over the first 10 days when the drugs are given in an initial intravenous dose followed by oral therapy as well as when they are given in conjunction with thrombolytic therapy during the early stages of AMI. Two other features of the response to β-blockers in this setting should be emphasized. First, unlike trials such as CAST, β-blocker trials have not been arrhythmia suppression trials, but the degree of benefit on survival correlated linearly with the degree of heart rate reduction, in the case of MI as well as with cardiac failure.[1] Second, evidence from two post-MI trials showed that total mortality reduction was greater when amiodarone was administered in combination with β-blockers versus when it was used alone in the drug treatment limb.[52-54]

As summarized recently, β-blockers, given in controlled and graduated dose regimens, have been shown to variably but significantly reduce mortality in subsets of patients with advanced congestive cardiac failure.[5,55-61] The outcomes of three recent trials with three different β-blockers should be emphasized (Table 80-4).[56,57,60]

In the trial involving the use of metoprolol in 3991 patients with largely New York Heart Association class II to IV heart failure (LVEF <40%), randomized to long-acting metoprolol (n = 1990) in graduated doses of up to 200 mg/day or placebo (n = 2001), the primary endpoint was all-cause mortality, analyzed by intention to treat. The mean follow-up was 1 year. During the period of follow-up, 147 deaths (7.2%) occurred on metoprolol versus 217 deaths (11.0%) on placebo ($P < .00009$). A statistically significant reduction in SCD on metoprolol was seen compared with placebo.[56]

Similar data have been reported from a double-blind, multicenter study on the drug bisoprolol in 2647 patients randomized to a β-blocker (n = 1327) or placebo (n = 1320). The patients were all in classes III and IV with left ventricular ejection fraction (LVEF) of 35% or lower and all were taking diuretics and angiotensin-converting enzyme (ACE) inhibitors as in the case of Metoprolol Controlled-Release Randomised Intervention Trial in Heart Failure (MERIT-HF). All-cause mortality was 11.8% (156 deaths) versus 17.3% (17.3%). This difference was significant ($P < .0001$). The drug was effective in reducing SCD significantly. Cardiovascular deaths on bisoprolol were significantly fewer, fewer patients were admitted to the hospital, and the difference for the combined endpoints was also significant. The numbers of permanent treatment withdrawals were similar for bisoprolol and placebo. In the case of carvedilol, a number of relatively smaller individual trials have been conducted, but the cumulative data have been sufficiently compelling for making it the first β-blocker to be approved for use in congestive heart failure in the United States.[60] The composite data from all the trials of β-blockers performed to date support the routine use of this mode of prophylactic therapy in all patients in whom β-blockers are not contraindicated.

Table 80-3 Actions of Intravenous Amiodarone Compared with Long-Term Amiodarone

ACTIONS	INTRAVENOUS AMIODARONE	LONG-TERM AMIODARONE
Repolarization (Q-T interval) prolongation (atria and ventricles)	+	++++
Conduction velocity (atria and ventricles reduced)	++	++ (as a function of rate)
Sinus rate reduced	+	+++
AV nodal conduction slowed	+	++
AV nodal refractoriness increased	++	+++
Atrial refractoriness increased	+	+++
Ventricular refractoriness increased	+	+++
Noncompetitive α- and β-blocking activities	+	++

AV, Atrioventricular.

Drugs Acting by Prolonging Repolarization

Of the currently available antiarrhythmic compounds, β-blockers, sotalol, amiodarone, ibutilide, and dofetilide are likely to remain the prototypes of the drugs of the future. Amiodarone and sotalol are of the greatest interest.[62-67] They prolong repolarization and refractoriness in atria and ventricles while blocking sympathetic stimulation, although by differing mechanisms. Their propensities to decrease heart rate and to modulate the AV node function, and thereby slow ventricular response in AF and AFL, have additional value for the control of many arrhythmias. Thus, they have the greatest clinical utility for controlling ventricular as well as supraventricular arrhythmias. Their respective roles are further bolstered by controlled trials showing superiority over class I agents in patients with VT or VF.[68,69] The perception that in spite being powerful sympathetic antagonists, sotalol and amiodarone acted

Table 80-4 Results of Some Endpoint Trials of β-Blockers

TRIAL/DRUG	NO. PATIENTS	β-BLOCKER (N)	TOTAL MORTALITY REDUCTION	SUDDEN DEATH REDUCTION
Cumulative (Post-MI)	>50,000	Various (45)	23% ($P < .01$)	23% ($P < .001$)
BHAT-CHF	710	Propranolol (55)	27% ($P < .05$)	28% ($P < .05$)
MC Carvedilol Trials	1094	Carvedilol (59)	65% ($P < .001$)	55% ($P \leq .001$)
CIBIS-II	2647	Bisoprolol (57)	34% ($P < .001$)	44% ($P = .0011$)
MERIT-HF	3991	Metoprolol (56)	34% ($P = .0002$)	34% ($P = .0002$)
COPERNICUS	2289	Carvedilol (58)	35% ($P = .0014$)	41% ($P = .0001$)
BEST	2708	Bucindolol (60)	8% (NS)	10% (NS)

MI, Myocardial infarction; BHAT, *Beta-Blocker Heart Attack Trial;* CHF, *congestive heart failure;* CIBIS-II, *Cardiac Insufficiency Bisoprolol Study;* MERIT-HF, *Metoprolol Controlled-Release Randomised Intervention Trial in Heart Failure; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival Study;* BEST, *Beta-Blocker Evaluation Trial;* NS, *not significant.*

dominantly by prolonging the APD led to the search for pure compounds devoid of other associated properties having simpler adverse effect profiles.[70-73] Intravenous amiodarone has recently been studied extensively in clinical trials in destabilizing VT or VF in the hospital and in shock-resistant VF following out-of-hospital cardiac arrest.[2,74-78]

Current data suggest that compounds that induce an isolated or "pure" prolongation of the APD accompanied by a proportional lengthening of myocardial refractoriness may be anti-fibrillatory.[37] Under certain circumstances, they have advantages over complex compounds such as sotalol or amiodarone. This has been the case with dofetilide, ibutilide, and azimilide.[79] The properties of tedisamil, which is also under development, are somewhat more complex.[37] Such compounds may be the result of the block of a single repolarizing ionic current (e.g., dofetilide) or multiple currents (ibutilide, tedisamil, or azimilide). Thus, for the present, it would appear that two subclasses of such agents might be appropriate to develop—those that are either safer and more effective chemical derivatives of sotalol and amiodarone or those that are relatively pure prolongers of repolarization and refractoriness. All such agents may need to produce a homogeneous lengthening of repolarization by selectively inhibiting multiple or single ionic channels in the myocardium with a minimal proclivity to cause TdP.

Amiodarone as a Versatile and Complex Class III Agent

Amiodarone was synthesized as an antianginal drug in 1962, but attention was not drawn to the compound for its unique properties until 1970 when Singh and Vaughan Williams showed the properties of the drug to prolong cardiac repolarization, with anti-fibrillatory properties and the potential for slowing heart rate because of its nonspecific antiadrenergic actions.[4] Since these early studies, it has become increasingly evident that amiodarone is an exceedingly complex antiarrhythmic compound (Figure 80-5).

The electrophysiological effects of amiodarone administered acutely and after a period of long-term drug therapy differ markedly (see Table 80-3), both associated with distinct and potent antiarrhythmic actions.[36] The electropharmacologic effects of the compound are multi-faceted.[80] The most striking long-term property is the ability of the drug to increase the APD in atrial and ventricular tissues following long-term drug administration. Little or no effects occur in Purkinje fibers and M cells, a phenomenon that leads to the reduction in QT dispersion.[81-83] The drug is also unique in that its effect on repolarization is not influenced by heart rate.[84,85] In isolated myocardial fibers, it eliminates the tendency for the development of early afterdepolarization (EAD) produced in Purkinje fibers and in M cells. The ionic channels that amiodarone blocks after long-term drug administration are not fully defined, but it has been shown to block I_{to} and I_K as well as I_{Na} and I_{ca}.[64] It abolishes EADs induced in isolated cardiac tissue.[84] In humans, despite producing marked slowing of the heart rate and considerable increases in the Q-T or QTc interval, the drug has a very low propensity for producing TdP.[84] Amiodarone rarely exhibits proarrhythmic actions typical of class I agents, although it is a fairly potent sodium channel blocker, especially at high heart rates. The salient pharmacodynamic features of amiodarone are summarized in Figure 80-5.

The clinical pharmacologic effects are complex with an elimination half life of 30 to 60 days (longer for the main metabolite, desethylamiodarone), bioavailablity of about 40%, and a large volume of distribution, over 98% protein bound. Very little of the drug is excreted by the kidney, and elimination is largely by hepatic metabolism, with the biotransformation occurring by desethylation via human cytochrome (CYP) 34A. Neither the levels of the parent compound nor those of the metabolite levels accurately predict the therapeutic effects of the drug. Numerous drug–drug interactions involving amiodarone do occur, perhaps the most clinically significant being with warfarin, digoxin, and verapamil. The drug is best not combined with other compounds that also prolong cardiac repolarization. In clinical practice, a variable loading regimen is desirable; in the past, a dose as high as 2 g/day had been used, but such regimens are now rarely used. In practice, the aim is to use the lowest dose that produces the defined therapeutic effect.

Amiodarone has a broad-spectrum antiarrhythmic effect with a varied adverse effect profile, which is generally dose and duration dependent. Included in Table 80-5 are the main potential clinical indications that have been accepted. Intravenous amiodarone is effective in the control of hemodynamically significant and refractory VT or VF (to lidocaine and procainamide), with a

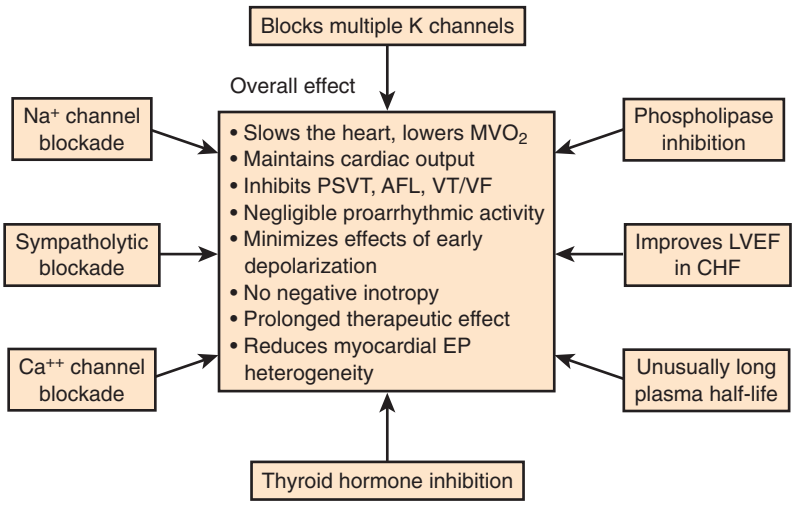

FIGURE 80-5 Multiplicity and complexity of amiodarone action. Note that the drug exhibits all four actions cited in the conventional classification of antiarrhythmic actions but not the deleterious effects of the same actions occurring independently in other compounds. The drug does not have the proarrhythmic actions of class I agents, or minimal or negligible rate of torsades de pointes despite lengthening the Q-T interval markedly and slowing the heart significantly; it improves ventricular function and is effective in almost the entire spectrum of atrioventricular and ventricular arrhythmias. *PSVT*, Paroxysmal supraventricular tachycardia; *AFL*, atrial flutter; *VT/VF*, ventricular tachycardia/ventricular fibrillation; *EP*, electrophysiological; *LVEF*, left ventricular ejection fraction; *CHF*, congestive heart failure.

Table 80-5 Major Uses of Amiodarone in the Control of Ventricular and Supraventricular Arrhythmias

INDICATIONS	COMMENTS
Cardiac arrest survivors	Superior to class I agents (guided therapy); tolerated in VT/VF and in all levels of LVEF and CHF; low incidence of torsades de pointes Increasingly perceived as the most potent antiarrhythmic agent, especially in the setting of low LVEF but being increasingly replaced with ICDs for primary therapy in many subsets of patients with VT/VF May increase VT defibrillation threshold; clinical significance unclear
Adjunctive therapy to ICDs	Controlled data still to be obtained but support for VT/VF is strong from large uncontrolled database; preferred agent in patients with significantly impaired LVEF and CHF
Conversion of VT to SR by IV regimen	Precise efficacy not known
Intravenous amiodarone in destabilizing refractory VT/VF	Superior to lidocaine and procainamide; efficacy equal to that of bretylium but with less hypotension; increases survival to hospitalization in patients with out-of-hospital cardiac arrest (ARREST and ALIVE trials) First-line antiarrhythmic agent in cardiac arrest resuscitation
Post-MI survivors	Numerous uncontrolled positive mortality studies; two recent placebo-controlled studies—EMIAT and CAMIAT—significant reduction in arrhythmic deaths, trend toward total mortality reduction in one of the studies, augmented effect, if combined with β-blockers Meta-analysis of all data consistent with reduction in total mortality and in sudden death while on drug
Congestive cardiac	Two controlled trials, one blinded placebo-controlled (CHF STAT) and one blinded (GESICA) indicate a spectrum of failure effects from reduction in total mortality (GESICA) and neutral (CHF STAT) with a trend in selective favorable effects in nonischemic cardiomyopathy Amiodarone increased LVEF
ATRIAL FIBRILLATION	
Acute conversion	Variable efficacy but systematic placebo-controlled study against a comparator agent not available
Maintenance of SR	Up to 60% or greater at 12 months after restoration of SR; maintains ventricular on relapse to atrial fibrillation on oral drug (controlled trials in progress)
Effect on AF prevention in postoperative cardiac surgery	Preoperative administration of oral drug reduces incidence of postoperative AF; IV drug given postoperatively may shorten hospital stay by reducing AF.

AF, *Atrial fibrillation;* CHF, *congestive heart failure;* ICD, *implantable cardioverter-defibrillator;* IV, *intravenous;* LVEF, *left ventricular ejection fraction;* MI, *myocardial infarction;* SR, *sinus rhythm;* VT/VF, *ventricular tachycardia and ventricular fibrillation;* ARREST, *Amiodarone in Out-of-Hospital Resuscitation of Refractory Sustained Ventricular Tachyarrhythmias trial;* ALIVE, *Azimilide Post-Infarct Survival Evaluation trial;* EMIAT, *European Myocardial Infarct Amiodarone Trial;* CAMIAT, *Canadian Amiodarone Myocardial Infarction Arrhythmia Trial;* CHF STAT, *Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy;* GESICA, *Grupo de Estudio de la Sobrevida en la Insuficienca Cardiaca en Argentina.*

potency at least as high or higher than that of intravenous bretylium.[74,75] The drug exerts a powerful suppressant effect on PVCs and nonsustained ventricular tachycardia (NSVT) and provides control in 60% to 80% of recurrent VT or VF when conventional drugs have failed during continuous oral therapy.[86] In only a small number of patients does the drug prevent inducibility of VT or VF, there being little or no systematic relationship between the prevention of inducibility of VT or VF and the long-term clinical outcome.[87]

The properties of amiodarone during long-term administration permit predictable control of recurrent paroxysmal SVTs, slowing of the ventricular response in AF and AFL, and maintaining the stability of sinus rhythm after chemical or electrical conversion.[88] Amiodarone is the most potent drug for maintaining the stability of sinus rhythm in patients converted from AF. The drug is currently being compared with placebo and sotalol in a number of major multi-center studies.

Amiodarone is effective in converting AF to sinus rhythm both in valve disease as well as in patients with nonrheumatic AF.[88,89] With respect to AF occurring after cardiac surgery, the drug has been studied in three different trials.[90-92] Hohnloser and colleagues studied amiodarone in a randomized, double-blind, placebo-controlled study in 77 patients after coronary artery bypass surgery.[90] They gave a 300-mg bolus of intravenous amiodarone followed by 1200 mg daily every 24 hours for 2 days and 900 mg daily for the next 2 days. At the end of the study period, the overall incidence of AF in the placebo group (n = 38) was 21%; in the amiodarone group (n = 39) it was 5% ($P < .05$).

More recently, Guarnieri and his associates have provided further supportive data from a larger double-blind study, in which they randomized 300 patients to placebo (n = 142) and to intravenous amiodarone (n = 158); 2 g of amiodarone were given over 2 days (1 g/day) through a central venous line started shortly after the completion of open heart surgery.[91] In the placebo group, 67 (47%) of 142 patients developed AF compared with 56 (35%) of 158 in the amiodarone limb ($P < .039$). The time to the onset of AF in the amiodarone limb was significantly longer than in the placebo (2.9 vs. 2.2 days; $P < .006$).

Daoud and colleagues recently reported the first of the two studies on the effects of orally administered amiodarone in preventing postoperative AF in patients undergoing heart surgery.[92] Their study was performed in 124 patients randomized to placebo (n = 60) and to amiodarone (n = 64) for a minimum of 7 days preoperatively (600 mg/day), followed by 200 mg/day until discharge from the hospital. Postoperative AF developed in 32 (53%) of the 60 patients in the placebo group and in 16 (25%) of the 64

patients in the group given amiodarone. Patients in the amiodarone group were hospitalized for significantly fewer days compared with those on placebo.

The unique pharmacodynamic profile of amiodarone holds much interest as the prototype of complex compounds that might be necessary to develop for anti-fibrillatory actions in atria and ventricles, provided the drug's adverse effect profile can be improved.[93-95] Clearly, along with sotalol, amiodarone has now emerged as one of the two leading antiarrhythmic drugs currently in use for the control of life-threatening ventricular tachyarrhythmias. However, their therapeutic roles in this setting need to be placed in perspective relative to the expanding indications in the use of implantable cardioverter-defibrillators (ICDs) to prevent arrhythmic deaths in patients with significant structural heart disease.[95]

Intravenous Amiodarone

Intravenous amiodarone has now emerged as the most powerful antiarrhythmic drug in the treatment of destabilizing VT or VF in hospitalized patients and as an antiarrhythmic agent for the resuscitation of patients developing cardiac arrest out of the hospital.[74-77] It has also been shown to convert recent-onset AF to sinus rhythm, although it is not used widely for this indication because of slow onset of action. However, the intravenous drug is used prophylactically for the prevention of AF and AFL in patients who have undergone cardiac surgery.[90,91] The major utility of intravenous amiodarone now is in the acute control of destabilizing VT or VF in hospitalized patients and in the resuscitation and continued control of pulseless VT or VF in patients surviving out-of-hospital cardiac arrest.[74-77]

A number of studies were performed in the early 1990s in destabilizing VT or VF, including those from electrical storm in patients resistant to lidocaine or procainamide. In particular, two amiodarone dose-response studies (125, 500, and 1000 or 2000 mg per 24 hours) with the drug, and one comparative trial with bretylium (2500 mg/24 hours), provided the initial data that intravenous amiodarone may exert a superior effect in controlling VT or VF (including electrical storm) in patients who were refractory to lidocaine or procainamide. In a direct comparison with intravenous bretylium in 305 patients in the randomized double-blind study, amiodarone showed a strong trend for a greater efficacy in reducing VT or VF events, but the difference did not reach statistical significance. However, the data provided the rationale for the exploration of the role of intravenous amiodarone in this setting. Two blinded randomized studies conducted in patients with persistent or recurrent pulseless VT or VF in patients developing out-of-hospital cardiac arrest have now been reported.[76,77] In the Amiodarone in Out-of-Hospital Resuscitation of Refractory Sustained Ventricular Tachyarrhythmias (ARREST) trial, 504 patients experiencing out-of-hospital cardiac arrest with recurrent or persistent pulseless VT or VF were enrolled in a prospective randomized double-blind study in which the effects of intravenous amiodarone (300 mg) were compared with those of placebo against the background of an ACLS regimen, which included lidocaine in both limbs of the trial. The data revealed that amiodarone-treated patients were more likely to survive to reach the hospital compared with those in the placebo group (44% vs. 34%, $P = .03$). The difference was larger among the 221 patients in whom the arrest was witnessed ($P = .008$), possibly because of the shorter interval from the occurrence of the arrest and the administration of drug therapy.

ARREST did not directly compare the efficacy of amiodarone to that of lidocaine because the latter was an integral part of *both* treatment limbs. However, superiority of amiodarone demonstrated in ARREST was considered compelling enough to be acknowledged in the "Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care."[2] The evidence ("fair to good evidence") was considered to be in favor of amiodarone as a class IIB indication; the drug was considered "acceptable, safe and useful," and the evidence with respect to lidocaine was deemed "indeterminate" because the "research quantity and quality fell short of supporting a final class decision."

The Azimilide Post-Infarct Survival Evaluation (ALIVE) trial was undertaken by Dorian and associates to compare the effects of lidocaine and amiodarone in shock-resistant patients with VF with out-of-hospital cardiac arrest.[77] In ALIVE, 347 patients were enrolled if they were resistant to three shocks, intravenous epinephrine, and further shock or if they had recurrent VF after initial successful defibrillation. The randomization was in a double-blinded manner so that the drugs were given either as intravenous amiodarone plus lidocaine placebo or as lidocaine plus amiodarone placebo. The primary endpoint was the percentage of patients who survived to reach the hospital. On amiodarone, 22.8% of 188 patients reached the hospital compared with 12% of 167 patients on lidocaine. The difference was highly statistically significant ($P = .009$; odds ratio, 2.17; 95% confidence interval, 1.21 to 3.83). The comparative data from the ALIVE trial are summarized in Figure 80-6.

The cumulative clinical investigative data on intravenous lidocaine and intravenous amiodarone in the setting of cardiac resuscitation and in the control of ventricular tachyarrhythmias in the hospital and out of the hospital, when interpreted in light of the

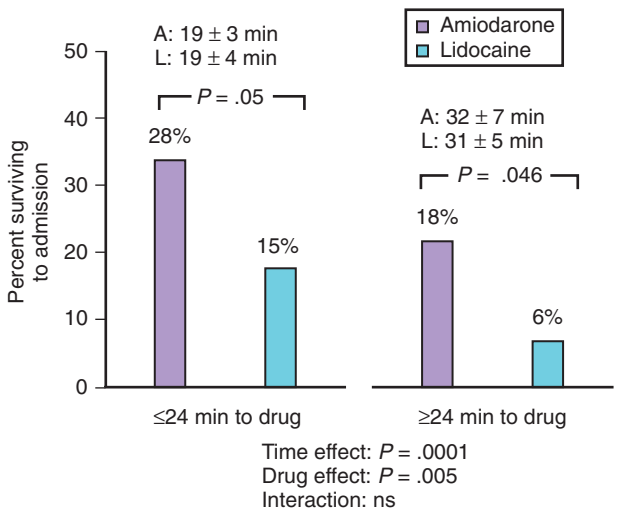

FIGURE 80-6 Comparative actions of intravenous lidocaine (*L*) and intravenous amiodarone (*A*) on the numbers of patients with shock-resistant persistent or recurrent ventricular tachycardia or ventricular fibrillation after out-of-hospital cardiac arrest on reaching the hospital. Note that at both lower and upper median times (24 minutes) from dispatch to study drug administration, the numbers of patients reaching the hospital are significantly greater in the case of intravenous amiodarone compared with intravenous lidocaine. *ns,* Not significant. *(From Dorian P, Cass D, Schwartz, et al: Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation,* N Engl J Med *346:884–890, 2002.)*

outcomes of the ARREST and ALIVE trials, permit a number of conclusions. The most compelling is the issue that intravenous lidocaine is inferior to intravenous amiodarone in increasing the numbers of cardiac arrest survivors reaching hospital admission. Lidocaine does not appear to have a role in the control of life-threatening ventricular tachyarrhythmias, so its continued use in this setting is no longer justifiable.[30] Current data support the premise that intravenous amiodarone should now supersede intravenous lidocaine as the first-line antiarrhythmic drug in the resuscitation of patients with shock-resistant VT or VF.[30,77]

Sotalol as an Antiarrhythmic Drug

The overall action of sotalol is dominated by its dual propensity for competitively blocking β-adrenoceptors without selectivity for β_1- or β_2-adrenoceptors and by the property for prolonging the myocardial APD. Sotalol is a racemate of D- and L-isomers, both of which have equal class III activity, only the L-isomer having significant β-adrenoceptor-blocking activity.[96,97]

Electrophysiological Actions

Sotalol is a nonselective β-adrenoceptor-blocking drug with little or no sodium channel–blocking actions without intrinsic sympathomimetic activity. In 1970, Singh and Vaughan Williams found that sotalol markedly prolonged the APD in isolated atrial and ventricular multi-cellular preparations.[3] This was classified as a class III antiarrhythmic mechanism. Sotalol slows the sinus node frequency by depressing phase 4 depolarization. Sotalol increases the APD primarily by blocking the time-dependent outward delayed rectifier potassium current (I_k). The effect of increased frequency of stimulation leading to decreases in the APD has been termed reverse-rate dependency.[19] The drug prolongs the Q-T and QTc intervals without significant effects on QRS or P-R intervals, with no effect on the His-Purkinje (H-V interval), or ventricular (Q-R interval) conduction velocity.[98]

Pharmacokinetics of Sotalol and Optimal Dosing

Because the drug is fully bioavailable, not metabolized, and not bound to plasma proteins, fluctuations in serum concentration are small, the plasma half life is long (10 to 15 hours), and plasma levels are linearly related to dose. The usual starting dose is 80 mg bid (rarely 40 mg bid), with stepwise increases (120 mg bid, 160 mg bid, rarely higher) for optimal effect. Because sotalol is largely excreted by the kidneys in an unchanged form, the plasma concentrations of the drug vary linearly with creatinine clearance. Dose adjustment is necessary in proportion to the degree of renal dysfunction present. For a creatinine clearance greater than 60 mL/min, 12-hour dosing intervals are appropriate. The interval may be increased to 12 to 24 hours when the creatinine clearance is 30 to 69 mL/min and 36 to 48 hours for patients with the clearance of 10 to 30 mL/min. However, it may be clinically prudent not to use the drug when creatinine clearance is less than 60 mL/min. Emerging data suggest that a close monitoring of the Q-T interval relative to the dose may be effective in preventing the development of TdP. Numerous pharmacodynamic interactions with numerous cardioactive compounds are likely. This is especially likely in the case of other antiadrenergic drugs (verapamil, diltiazem, and amiodarone) and other QT-prolonging agents (class III agents, including amiodarone, tricyclic antidepressants, and phenothiazines). Coadministration with erythromycin and other QT-prolonging drugs should also be avoided. Intravenously (not approved by the U.S. Food and Drug Administration), it is given in a dosage of 0.2 to 1.5 mg/kg of dl-sotalol over 2 to 3 minutes under electrocardiographic and hemodynamic control. Although doses of up to 960 mg/day had been used in the past, especially in investigative protocols, it is now clear that higher doses are rarely necessary and may be associated with a greater incidence of TdP, heart failure (NYHA classes III and IV), or severe bradycardia.[66,67] Although in rare patients, 80 mg/day may be effective, the range of total daily doses of 240, 360, and 480 mg administered in two equally divided doses allows flexibility of optimal dosing in most patients. In a recent study in AF, 240 mg (as 120 mg bid) was found to be the optimal daily dosage in terms of efficacy and safety.

Control of Cardiac Arrhythmias with Sotalol

The main clinical indications for the use of sotalol in supraventricular and ventricular arrhythmias are shown in Table 80-6. The spectrum of sotalol effects in arrhythmias is wider than that of

Table 80-6 Major Uses of Sotalol in the Control of Ventricular and Supraventricular Arrhythmias

INDICATIONS	COMMENTS
Cardiac arrest survivors	Superior to class I agents (guided therapy); VT/VF may be comparable with amiodarone (no significant direct comparison but incidence of TdP higher Now being increasingly replaced with ICDs for primary therapy in many subsets of patients
Adjunctive therapy to ICDs	Controlled data still to be obtained but support for VT/VF is strong from large uncontrolled database
Conversion of VT to SR by IV regimen	Superior to lidocaine; use not approved in the United States
MI survivors	Positive in one study with an 18% reduction in total mortality but not statistically significant
Congestive cardiac failure	No controlled studies performed
ATRIAL FIBRILLATION	
Acute conversion	Variable efficacy but systematic placebo-controlled study or against a comparator agent not available
Maintenance of SR	Up to 50% at 12 months after restoration of SR; maintains ventricular rate on relapse to atrial fibrillation Results of placebo-controlled trials imminent
Prevention of postoperative sequelae	Up to 50% reduction when drug given orally before period of cardiac surgery and after cardiac surgery

The role of sotalol in supraventricular arrhythmias, other than atrial fibrillation, is not discussed in this review.
ICD, *Implantable cardioverter-defibrillator;* IV, *intravenous;* MI, *myocardial infarction;* SR, *sinus rhythm;* TdP, *torsades de pointes;* VT/VF, *ventricular tachycardia and ventricular fibrillation.*

conventional β-blockers on the one hand and wider than that for the pure class III agents on the other hand.[67] Sotalol has a modest suppressant effect on PVCs; it is generally not used for this indication. It exerts a variable effect in suppressing inducible VT or VF, but this approach is no longer used in the control of VT or VF. The two main uses of the drug are in the control of cardiac arrhythmias: (1) as an adjunctive therapy with the ICD for reducing the number of shocks and (2) for the maintenance of sinus rhythm in patients with AF restored to sinus rhythm either chemically or by DC cardioversion. Both indications have been substantiated in controlled clinical trials.[99-101]

Experience has indicated that concomitant anti-arrhythmic therapy with an ICD is an integral part of therapy of recurrent VT or VF.[101] Sotalol may slow the VT rate and aid termination by anti-tachycardia pacing; it may decrease the defibrillation threshold and facilitate termination at lower energy levels and reduce the number of shocks by suppressing episodes of supraventricular (including AF) and ventricular tachyarrhythmias. The overall effects of sotalol (as is the case with any other pharmacologic agent now being introduced) in supraventricular arrhythmias should be viewed in relation to the changes that have occurred in the electrode catheter ablation of paroxysmal supraventricular tachycardias (PSVTs) with or without accessory tracts in the heart and many cases of AFL.[98] Because these newer approaches carry an extremely high frequency of success with prospects for cure, prophylactic drug therapy of PSVTs is likely to be used much less often than previously in areas of the world where ablative techniques are readily available.

The predictive accuracy of the acute response for the long-term effects of the drug remains unclear, however. The antifibrillatory effects of sotalol as a result of its class III action are likely to make it more effective in maintaining sinus rhythm in patients with AF and AFL after cardioversion.[65-67] A well-defined electrophysiological rationale exists for the potential usefulness of sotalol for the acute conversion of AFL and AF to sinus rhythm and for maintaining the stability of sinus rhythm during long-term drug prophylaxis.[66,67] Conversion rates have been variable, but a slowing of the ventricular rates has been consistent, as might be expected for a β-blocker. The conversion rate may be up to 40% to 50% of selected patients, which compares favorably with intravenous procainamide and possibly with intravenously administered newer class III agents (ibutilide or dofetilide) or class IC agents (e.g., flecainide). The maintenance of sinus rhythm after conversion is potentially of greater practical importance. Sotalol is as effective as propafenone or quinidine in maintaining sinus rhythm in patients with AF but appears to be less effective than amiodarone in direct comparisons.[93,94,102-104]

Of particular interest are two placebo-controlled trials that dealt with stability of sinus rhythm under the action of dl-sotalol. Benditt and colleagues conducted a double-blinded placebo-controlled trial in which they compared the efficacy, safety, and dose-response relationship of three doses of d,l-sotalol (80, 120, and 160 mg twice daily) for the maintenance of sinus rhythm in 253 patients converted to sinus rhythm.[99] Compared with the placebo (27 days), the time to recurrence was significantly prolonged by two doses of the drug—226 days on 120-mg dose ($P = .001$) and 175 days on 160-mg dose ($P = .012$). No deaths or cases of TdP sustained VT or VF occurred. A number of controlled studies have indicated the efficacy of sotalol in preventing the occurrence of AF and AFL developing in patients undergoing cardiac surgery.[105,106] Although no cases of TdP occurred, it is known from studies in patients receiving the drug for other arrhythmias that the incidence of TdP varies with dose and can be higher than 5% at the highest doses of the drug sometimes used.[107]

Bretylium Tosylate

Developed as an antihypertensive agent, bretylium gained prominence for many decades as an intravenous anti-fibrillatory agent for the control of destabilizing VT or VF, especially in the resuscitation of patients experiencing out-of-hospital cardiac arrest. Its introduction into therapeutics was based largely on studies in animal models and comparative studies with lidocaine in the acute control of VT or VF.[108,109] No superiority over lidocaine has been demonstrated. Bretylium was recently compared with intravenous amiodarone in a multi-center study of patients with VT or VF who were refractory to or intolerant of lidocaine and procainamide. Bretylium showed equivalent efficacy, measured as time to recurrence and survival but caused more adverse effects (e.g., hypotension) compared with amiodarone.[75] Bretylium drug is no longer included in the list of antiarrhythmic drugs in the latest ACLS Guidelines in the control of destabilizing VT or VF developing in or out of the hospital and is no longer available.[2] Thus, as an antiarrhythmic drug, along with lidocaine, it is likely to become only of historic interest.[30]

"Pure" Class III Antiarrhythmic Drugs

Compounds such as dofetilide, ibutilide, and azimilide among others are examples of pure class III agents.[71-73] Isolated or pure prolongation of the APD accompanied by a proportional lengthening of myocardial refractoriness is now accepted as antifibrillatory therapy.[16-18] Under certain circumstances, drugs with such effects may have advantages over complex compounds such as sotalol or amiodarone.

Ibutilide, a Prototype of Intravenous Class III Agents

Ibutilide was the first of the "pure" class III agents approved by the FDA for the acute termination of AFL and AF.[110-117] It does this by prolonging the atrial action potential and refractoriness.[72,110]

Electropharmacology and Pharmacokinetics

The class III action of the drug stems from its property of blocking the rapid component of the delayed rectifier current (I_{Kr}); at much lower concentrations the drug also activates a slow inward sodium current, which is not blocked by I_{Kr} blockers.[72,110] In isolated atrial and ventricular muscle preparations, ibutilide increases the APD and the ERP, effects on both of which are attenuated at increasing rates. In humans, the drug produces concentration-related increases in the Q-T and the QTc intervals.[111,112] Ibutilide, like most other class III compounds, is likely to produce antifibrillatory as well as profibrillatory actions.[72]

Ibutilide exerts little or no effect on sinus rates or AV nodal conduction in healthy volunteers and patients with a minimal influence on the P-R or the QRS intervals.[114] Also, it does not lower blood pressure or worsen heart failure because it does not exert a negative inotropic effect in the atria or the ventricles.[72] It exhibits no significant interaction with the autonomic nervous system. The property that is critical for its therapeutic utility is the acute prolongation of the atrial ERP leading to rapid

termination of AF and AFL and the lowering of the energy for atrial defibrillation when these arrhythmias are not amenable solely to electrical conversion.[72,112]

Ibutilide is only available as an intravenous formulation, as the drug is rapidly metabolized because of a strong first-pass effect in the liver. For this reason, the oral formulation is unlikely to be effective. The elimination half life is variable (2 to 12 hours; mean, 6 hours). The drug is extensively metabolized and excreted largely by the kidney but intravenous dosing does not require dose adjustment relative to changes in renal and hepatic functions. Coadministration of ibutilide with digoxin, calcium channel blockers, or β-blockers exerts effects in the pharmacokinetics, safety, or the efficacy of the drug for the conversion of AF or AFL. Similarly, patient age and gender or the nature of the arrhythmia may have an effect on the drug's pharmacokinetics.[72]

Ibutilide in Conversion of Atrial Fibrillation and Atrial Flutter

The effectiveness of ibutilide in converting AF and AFL to sinus rhythm when given intravenously has been established in two pivotal controlled studies.[111,112] For example, intravenous ibutilide was studied in 200 patients who were hemodynamically stable, free of heart failure and angina but who had AF and AFL with a duration of between 3 hours and 90 days. They were randomized in equal numbers to placebo and four doses of the drug (0.005, 0.010, 0.015, and 0.025 mg/kg given over 10 minutes). The conversion rate on placebo was 3%. In those for the four ascending doses of ibutilide, the corresponding rates of conversions were 12%, 33%, 45%, and 46%, respectively.[110] The overall rate of conversion in the case of AF was 29% and 38% for AFL. The mean time to conversion was 19 minutes, with conversion being accompanied by the prolongation of the Q-T and QTc intervals on the electrocardiogram (ECG); six patients in the study developed polymorphic VT (3.6%).

The second study involved 266 patients who had AF or AFL, with a duration of 3 hours to 45 days.[112] They were randomized to be given up to two 10-minute infusions of ibutilide (1 and 0.5 mg, or 1 and 1 mg) or placebo. Most patients had a history of cardiac disease with an enlarged left atrium. The conversion rate was 2% on placebo and 47% on ibutilide (63% in AFL and 31% in AF). The mean time to conversion was 27 minutes, with an incidence of TdP of 8.3% (12.5% in AFL, 6.2% in AF), with1.7% being sustained requiring DC cardioversion. These experiences with ibutilide have been confirmed in subsequent clinical experience.

The major issues regarding the use of pure class III agents in the acute conversion of AF and AFL have been discussed critically by Singh and Roden.[116,117] The conversion rates exceed 30% in the case of AF and approximately 50% in the case of AFL of recent onset. The associated rate of TdP developing during the conversion has been as low as 2% to 3% in the case of AF and as high as 8% to 12% in AFL. These data provide the basis for the use of intravenous ibutilide in the acute conversion of AF and AFL.[118] To date, this is the only intravenous compound that has been formally approved in recent years by the FDA for the standardized chemical conversion of AF and AFL; meaningful comparisons with other drug regimens, oral or intravenous, have not been established. It is of much interest that the conversion of AF and AFL by intravenous ibutilide in patients treated long term with amiodarone has recently been reported. In 70 such patients, the conversion of AF by ibutilide was 54% in AFL and 39% in AF, with one instance of nonsustained TdP (1.4%) in the entire study. Data suggest that despite the combination of amiodarone and ibutilide producing a further increase in the Q-T interval, amiodarone appeared to decrease the incidence of TdP usually associated with intravenous ibutilide.

Facilitation of Trans-thoracic Cardioversion with Ibutilide Pretreatment

Pure class III agents predictably lower the threshold for defibrillation in atria and ventricles. Recently, Oral and colleagues reported that patients with AF who have not been electrically cardioverted may be successfully cardioverted if they are pretreated with intravenous ibutilide.[114] They randomized 100 such patients who had AF for a mean duration of 117 days to undergo trans-thoracic cardioversion, with or without pretreatment with 1 mg of ibutilide. The protocol for conversion was a step-up process involving sequential shocks of 50, 100, 200, 300, and 360 J. If the trans-thoracic shock failed to cardiovert in the absence of ibutilide, the drug was given, and the shock protocol was repeated. Cardioversion to sinus rhythm in the group who had not been given ibutilide was 36 (76%) of 50 patients, but all 50 patients pretreated with ibutilide could be cardioverted (100%; $P < .001$). It was of interest that all 14 patients who did not cardiovert with the initial direct-current cardioversion could be cardioverted following ibutilide pretreatment. The results reported by Oral and coworkers are striking and need to be confirmed, as the approach will undoubtedly have major implications for clinical practice, especially in conjunction with biphasic cardioversion shocks.[114]

Adverse Effects

The safety profile of intravenous ibutilide on the basis of experience with the drug in 586 patients involved in phase II and III clinical trials has been reported.[120] Noncardiac adverse effects were indistinguishable from those of placebo, as were hypotension, conduction block, or bradycardia. The most significant adverse reaction was the overall incidence of 4.3% in the case of TdP, with 1.7% requiring cardioversion. In almost all patients, the onset of the arrhythmia was within 40 minutes of the commencement of the drug infusion.

Drug Dosage and Administration

Considerable experience with intravenous ibutilide for the conversion of recent onset AF has now been accumulated. A number of precautions increase the safety margin of the drug's use in this setting. Clearly, patients at high risk for the development of proarrhythmia include those with prolonged baseline QTc (>440 ms), severe bradycardia, low levels of serum K and Mg (unless correctable), and the background use of other QT-prolonging drugs (amiodarone may be an exception) or patients with a previous history of TdP induced by other antiarrhythmic drugs. The recommended dose of the drug is 1 mg administered over a 10-minute period in patients weighing more than 60 kg. Generally, the same dose is repeated if the arrhythmia termination does not occur at the end of the first infusion. Patients are generally monitored for a period of 4 hours following drug administration; QT-prolonging drugs should not be commenced until after this period.

Use of Dofetilide in Maintaining the Stability of Sinus Rhythm in Atrial Fibrillation

Dofetilide (Tikosyn) is the prototype of pure or simple class III antiarrhythmic agent. Its oral formulation was approved by the FDA for the maintenance of sinus rhythm in patients with

paroxysmal and persistent AF and AFL. Like ibutilide, the drug is effective in terminating recent-onset AF and AFL, although this indication has not yet been approved for routine clinical use.[121]

Pharmacodynamics and Pharmacokinetics

The drug is a highly selective agent that delays repolarization in the atria, ventricles, and Purkinje fibers by I_{Kr} blockade. Such an I_{kr} block is the sole identifiable action of the drug in cardiac muscle, although it is likely that M-cell APD may be prolonged by the reduction of I_{Ks}. The compound exerts no effects on sodium and calcium channels and, as such, has minimal effects on conduction velocity. It has no significant effect on the antagonizing autonomic transmitters.[70,122] Thus, it does not alter the P-R interval or the QRS duration of the surface ECG.[30] Its sole measurable electrophysiological action is the lengthening of cardiac repolarization as reflected in the Q-T or QTc interval, an effect that correlates directly with the lengthening of the ERP. The drug has no effect on myocardial contractility or on systemic hemodynamics. It does not depress systemic blood pressure. Therefore, the drug can be used in the control of AF in patients with heart failure. The drug is excreted largely via the kidneys, so dose adjustment is necessary in patients with impaired renal function.

The impact of the drug on mortality in the patient with previous MI has been found to be neutral in patients with left ventricular dysfunction with or without cardiac failure.[71] However, these studies have shown that the safety of the compound is critically dependent on the use of appropriate doses of the drug relative to renal function, therapy initiation in the hospital, and subsequent monitoring of the patient by following the changes in the Q-T and QTc intervals with adjustment of drug dose.

Effectiveness of Dofetilide in Atrial Fibrillation and Atrial Flutter

Two blinded placebo-controlled pivotal studies have provided the pivotal data on the effectiveness of the compound. The first trial, European and Australian Multicenter Evaluative Research on Atrial Fibrillation of Dofetilide (EMERALD), the effects of three doses of dofetilide (25, 250, and 500 μg bid) were compared with placebo over a 12-month period in 534 patients with AF or AFL durations of between 1 week and 2 years since onset.[123] The conversion rate to sinus rhythm at the highest dose was 29% compared with 1% in placebo ($P = .001$). Those not converting on the drug were restored to sinus rhythm by electrical conversion; in all, 427 patients who did convert by either means were followed up for arrhythmia recurrence. At the highest dose, 66% remained in sinus rhythm compared with 26% on placebo ($P = .001$) at the end of the first year. The median time to relapse of AF or AFL at the two higher doses of the drug was greater than 365 days compared with 34 days for placebo.

In the second study (Symptomatic Atrial Fibrillation and Randomized Evaluation of Dofetilide [SAFIRE-D]) involving 325 patients, three doses of the drug (as in EMERALD) were compared with placebo for the conversion and maintenance of sinus rhythm in patients with chronic AF or AFL of durations between 2 weeks to 6 months. Thirty percent of patients converted on the 500-μg bid dose, 70% of such conversions occurring during the first 24 hours. At 48 hours, patients not converting on drug alone were cardioverted. Those not converting were excluded from the trial. The 250 patients who achieved sinus rhythm were followed up for stability of sinus rhythm. The response showed a dose dependence, but only at the highest dose (500 μg bid) was the overall effect significantly different from that of placebo. The probability of the patients on 500 μg bid remaining in sinus rhythm at the end of 12 months was 58% in the case of dofetilide compared with 25% on placebo ($P = .001$). The median time for the patients to relapse into AF or AFL was over 365 days on the active drug compared with 27 days on placebo.

The data from the EMERALD and SAFIRE-D studies indicate, therefore, that dofetilide in a defined group of patients with AF or AFL is a useful anti-fibrillatory agent for restoring and maintaining sinus rhythm.[123,124] Supportive data have also been reported from the Danish Trial in Acute Myocardial Infarction on Dofetilide (DIAMOND).[71] The major aspect of this study focused on mortality rate in two groups of patients after MI—those with ventricular dysfunction and those with overt congestive heart failure. The study included 1518 patients, who were randomized to dofetilide or placebo. After a median follow-up of 18 months, no impact on mortality was observed. In the patients (n = 506) who had AF or developed AF during the course of the study, dofetilide was effective in converting AF to sinus rhythm (12% vs. 2% on placebo); once the sinus rhythm was restored in these groups, either chemically or electrically, the 1-year maintenance of sinus rhythm was 79% in the group taking dofetilide versus 42% in that on placebo. These data are consistent with the effects of the drug given intravenously to patients with AF or AFL; in 91 patients (75 with AF and 16 with AFL), Falk and colleagues found a conversion rate of 31% in AF patients given 8 μg/kg of dofetilide intravenously in a double-blinded study; the conversion rate was 12.5% on 4 μg/kg, there being no conversions on placebo.[121] In AFL, the conversion rate was 54%. However, the major significance of dofetilide in clinical therapeutics is likely to be the maintenance of sinus rhythm in patients with paroxysmal or persistent AF as indicated by the outcomes of placebo-controlled clinical trials discussed above. Indication for its use in the prophylactic therapy of AF is likely to be the major niche for dofetilide in patients with or without heart failure.[125]

Adverse Reactions and Contraindications

The pattern of adverse reactions noted in the placebo-controlled studies has been 5% to 10%, including headache, chest pain, dizziness, respiratory infection, dyspnea, and nausea. Quantitatively, these were indistinguishable from those in the placebo limb of the clinical trials. The most significant adverse effect attributable to dofetilide has been the occurrence of TdP. In the two pivotal trials (EMERALD and SAFIRE-D) on AF or AFL, 9 of the 11 cases of TdP were symptomatic, and 8 required intervention, but no deaths were attributable to the arrhythmia. In the DIAMOND trials involving 518 patients, in the drug limb involving 762 patients with previous MI and ventricular dysfunction or heart failure, 29 of the 32 patients with TdP were symptomatic, 23 requiring intervention for termination. In this group two deaths occurred, but no deaths were attributable to TdP in the DIAMOND-AF subgroup.

The concomitant use of certain drugs during dofetilide therapy is contraindicated, especially those that may substantially increase the plasma concentrations of dofetilide. The prominent among these are verapamil, ketoconazole, cimetidine, trimethoprim or sulfamethoxazole, prochloperazine, and magesterol. Dofetilide is also contraindicated in patients with severe renal impairment and

in those with acquired or congenital LQTS. A previous history of TdP in those either on dofetilide or any other QT-prolonging compounds is also a contraindication to the use of the drug for the treatment of AF or AFL.

Dosing Recommendations and Safety Enhancement

Because a reasonably linear relationship exists among plasma concentrations, drug dose, and the Q-T and QTc intervals and because all of them are determinants for the development of TdP, it is critical to determine the appropriate initiating and steady-state dosing regimens for the safe use of dofetilide. As mentioned earlier, the drug dose is adjusted relative to the patient's renal function. For patients with creatinine clearance greater than 60 mL/min, the recommended starting dose is 500 μg bid; for clearances between 40 and 60 mL/min, the starting dose is reduced to 250 μg bid; and it is further reduced to 125 μg bid for clearance between 20 and 40 mL/min. A baseline Q-T or QTc (determined when sinus rhythm is present) interval exceeding 440 ms (or >500 ms in cases of intra-ventricular conduction defect) or a creatinine clearance of less than 20 mL/min are contraindications for the use of dofetilide. The bulk of the cases of TdP have been noted in patients during the initiation of therapy which, of necessity, should be in a monitored setting in the hospital for a period of 3 days or for five doses of the drug. A reduction in the dose of the drug is also recommended if the Q-T and QTc intervals increase by more than 15% or extend beyond 500 ms. These precautions have been shown to markedly reduce the incidence of TdP during the use of dofetilide in patients with AF or AFL treated for maintaining the stability of sinus rhythm.

Calcium Channel Blockers, Adenosine, and Digoxin

The electropharmacologic properties and the clinical utility of structurally disparate compounds will be considered together because the bulk of their actions relative to their antiarrhythmic effects involves the inhibition of the AV node to varying extents. Transient complete block of anterograde conduction at the AV node by these agents has been used for the termination of re-entrant supraventricular tachycardias either for therapeutic purposes or for differentiating narrow-QRS tachycardia on the surface electrocardiogram.[38] The blocking actions of verapamil, diltiazem, and adenosine induce a prompt and predictable conversion of PSVT in 80% to 100% of cases of the arrhythmia. The conversion rate is achieved by intravenous therapy with 3 to 5 mg (in children) to 10 to 15 mg (in adults) with verapamil, 17 to 25 mg of diltiazem, and 6 to 12 mg of adenosine. Adenosine is now the most frequently used compound in this setting because of near complete efficacy and ultrashort elimination half life accounting for the nature of the drug's transient adverse effects. However, in some clinical settings, the use of the drug may not be appropriate. Adenosine is preferred in patients with depressed ventricular function and who have recently received β-blockers and in neonates. Alternatively, for termination of PSVT, verapamil may be preferable in patients on drugs known to interfere with the actions of adenosine or its metabolism or in patients with bronchospasm. In patients in whom the diagnosis of PSVT is suspected but not certain, it might be preferable to use verapamil or diltiazem because either drug will not produce sustained hypotension.

Two calcium channel blockers (diltiazem and verapamil) act by blocking the L-type calcium channel and, to a lesser degree, by nonspecific antiadrenergic actions. The latter action is significant because it offsets the reflex increase in heart rate because of the peripheral vasodilator actions of these agents. In the case of adenosine, the AV block is achieved by the inhibiting purinergic receptors; in the case of digoxin, the effect stems largely from the augmentation of vagal actions by the cardiac glycoside. The modulation of AV nodal refractoriness by calcium channel blockers and digoxin, given intravenously or orally, results in slowing of the ventricular response in AF and AFL. The reduction of the ventricular response is the basis of termination of recent-onset AF, an effect that does not stem from the intrinsic anti-fibrillatory actions of these agents in atrial muscle.

Calcium Channel Blockers as Antiarrhythmic Drugs

Verapamil and diltiazem have no significant electrophysiological effects on atrial, ventricular, or His-Purkinje fiber refractoriness or conduction. However, they may shorten the APD in atria and uncommonly induce AF.[38] They slow the phase 4 depolarization in the SA and AV nodes, with slowing of conduction mediated by the block of L-type calcium channels. Their major effect is in the AV node, where they reduce conduction and prolong the effective and functional refractory periods in the anterograde as well as retrograde directions. The major depressant effects of verapamil and diltiazem on the AV node are also used in three other specific settings: (1) In the prevention of the recurrences of episodes of PSVT, they can be combined with digoxin or β-blockers, but this use of the drugs is declining with the increasing preference for cure with radiofrequency (RF) ablation of the arrhythmia; (2) they are used for rapid acute control of ventricular response in the case of AFL and fibrillation; and (3) they bring about chronic modulation of the ventricular rate in these arrhythmias when rate control is deemed to be the preferred approach in treatment. In this context, calcium channel blockers can be combined with varying doses of digoxin, β-blockers, or both.[126] Limited data are available to support the possible value of verapamil in the acute control of multi-focal atrial tachycardia, but its efficacy in the long-term prophylaxis of the arrhythmia remains uncertain.[38] Recent data suggest the interesting possibility that the use of calcium-lowering drugs, such as verapamil given during AF, may reduce the recurrence of AF after electrical cardioversion.[127,128]

Because the electrophysiological effects of calcium channel blockers are minimal in the ventricular muscle, they are unlikely to be potent antiarrhythmic agents in most types of ventricular tachyarrhythmias.[128,129] For the same reasons, these compounds do not appear to induce proarrhythmic reactions and have not been shown to adversely affect mortality, although this may possibly occur by virtue of the negative inotropic actions in patients with advanced levels of heart failure. The role of calcium channel blockers in the treatment of ventricular arrhythmias is limited—as might be expected from the nature of their actions in ventricular muscle. They are poor suppressants of premature ventricular premature beats and nonsustained or sustained VT. It is possible that in some subsets of patients with ischemic heart disease, calcium channel blockers may prevent VT or VF by the anti-ischemic actions, but such a possibility has not been tested in relevant clinical models.

In addition to their use in supraventricular tachyarrhythmias, including for rate control in AFL and AF, at least two relatively uncommon forms of VT respond to calcium channel blockers.[126,128,129] Such arrhythmias occur in the context of what appears to be a structurally normal heart. The first is the syndrome of the left ventricular septal VT. Such a VT occurs largely in males, and electrocardiographically, it has a right bundle branch block (RBBB) pattern, with left axis deviation; it can be induced by rapid atrial pacing or by programmed electrical stimulation. It can be terminated by intravenous verapamil but not by adenosine. The arrhythmia can be controlled by oral calcium channel blockers, especially verapamil, but the primary mode of treatment is by RF ablation. The other idiopathic VT that may respond to calcium channel blockers (also to β-blockers) is the right ventricular outflow tract (RVOT) tachycardia. It has the left bundle branch block (LBBB) pattern on the ECG, with a vertical axis, and occurs more frequently in females. The arrhythmia is not readily induced by programmed electrical stimulation but can be induced by exercise or by isoproterenol infusion. The arrhythmia is terminated predictably and promptly to intravenous verapamil or adenosine. Again, the primary mode of therapy is catheter ablation, but it is also controlled by β-blockade or calcium channel blockers and may respond to β-blockers.

Verapamil

The electrophysiological properties of this compound formed the basis for the so-called class IV antiarrhythmic actions.[7] When verapamil is administered intravenously (5 to 20 mg over 2 minutes), the peak effects on the AV node occur in 10 to 15 minutes, the effects lasting for 6 hours. After oral administration, the drug acts in hours, with a peak effect occurring at 3 hours, with an elimination half life of 3 to 7 hours, but the effects last much longer as a function of duration of drug administration. For sustained oral therapy for modulating the ventricular response, the usual dose range is 80 to 120 mg three times daily or four times daily. Alternatively, single oral doses of the long-acting preparations (240 to 480 mg/day) may be used. The major cardiovascular adverse effect of the drug relates to excessive depressant action on the AV node. Drug-drug interactions are with digoxin and amiodarone.

Diltiazem

The electrophysiological properties of diltiazem are similar to those of verapamil, with possibly a similar degree of negative inotropic actions. Its antiarrhythmic actions have not been as widely explored, having been limited to supraventricular arrhythmias and with its use focused largely on the short- and long-term control of the ventricular response in patients with AFL and AF. After oral administration, the drug is more than 90% absorbed, but with a bioavailability of 45%; onset of action is 15 to 30 minutes; the peak action is 1 to 2 hours; and elimination half-life is 4 to 7 hours. Only 35% of the drug is eliminated by the kidneys, the remainder being eliminated by the gastrointestinal tract. For the rapid control of the ventricular response, a bolus dose of 20 mg is given intravenously for 2 minutes, with a repeat bolus for 15 minutes, if required; this is followed by a 5- to 15-mg/hour infusion for prolonged effect. Oral therapy now is usually a sustained-release diltiazem once daily (90, 120, 180, 240, or 300 mg). The major therapeutic usefulness of diltiazem, either as a single agent or in combination with digoxin or a β-blocker, in the control of arrhythmias is the long-term control of ventricular response. The adverse effect profile of diltiazem is similar to that of verapamil, but diltiazem does not have major drug interactions with digoxin, quinidine, or amiodarone.

Adenosine

The electrophysiological actions of adenosine are mediated via a receptor-effector mechanism that includes the A_1 receptor and a guanine nucleotide–binding G protein. The primary direct actions of adenosine are the activation of an outward potassium current (known as $I_{K,ACh}$ or I_{Kado}) present in atria and the SA and AV nodes but absent in ventricles. In the AV node, the drug depresses the nodal action potential; and in the sinus node, the sinus rate slows with shifts of the pacemaker and hyperpolarization. As mentioned earlier, the major therapeutic effect of adenosine is the consistent and predictable termination of all forms of PSVT in which the antegrade limb of the arrhythmia is in the AV node. It should be emphasized that adenosine does shorten the APD in atria, making them susceptible to the initiation of AF, which in the case of patients with the WPW syndrome, may be potentially dangerous. Adenosine does not have a major role in the control of arrhythmia generated in ventricles. The role of the drug in the acute termination and the diagnosis of supraventricular tachyarrhythmias is now well established.[130,131]

Digoxin

Classifying digoxin as an antiarrhythmic agent has always been controversial. The major effects of the cardiac glycoside are mediated by the drug's central and peripheral actions to increase vagal activity.[132] Such an action has two electrophysiological effects: in atria, the atrial refractory period (conducive to the development of AF) is shortened, and on the AV node, the vagal effect leads to delay in conduction and an increase in the ERP, which slows the ventricular response in AF and AFL, a slowing that may lead to conversion of these arrhythmias to sinus rhythm. Such a conversion does not appear to be caused by the direct anti-fibrillatory actions of the drug. This may also be the mechanism of conversion of recent-onset AF and AFL by β-blockers as well by calcium channel blockers. The effects of digoxin on the myocardium stems from the drug's propensity to inhibit sodium-potassium adenosine triphosphatase (ATPase), with an increase in the intracellular concentration of calcium by the modulation of the calcium channels and the inhibition of sodium-calcium exchange. This may be the basis for the drug's known, although weak, positive inotropic effects in the ventricular myocardium. The effect of digoxin on the ventricular myocardium is in therapeutic concentrations (0.8 to 2.0 ng/mL). However, at higher doses, it may produce electrocardiographic changes; in toxic doses, it may induce premature atrial and ventricular arrhythmias such as AT with block, premature atrial and ventricular contractions, and bi-directional VT. However, in a large clinical trial that included patients with heart failure, it had a significant adverse effect on total mortality.

The elimination half life of digoxin is 1.5 days, and its excretion is largely renal. Antiarrhythmic drugs such as amiodarone, quinidine, propafenone, and verapamil affect its pharmacokinetics. Except in the treatment of heart failure, digoxin is used largely for the control of ventricular response in patients with AF, especially in combination with β-blockers and calcium channel blockers; the effects of such combinations are additive and may possibly be synergistic.

Table 80-7 Inhibitory Effects of Dronedarone on Individual Cardiac Ion Channels and Receptors

TARGET	EFFECT	SPECIES/CELL TYPE	REFERENCE
I_{Na}	97% block at 3 μmol/L	Human atrial myocytes	139
$I_{Ca,L}$	IC_{50}: ~0.18 μmol/L	Guinea pig ventricular myocytes	135
I_{to}	No effect at 10 μmol/L	Canine ventricular myocytes	138
I_{Ks}	IC_{50}: ~10 μmol/L	Guinea pig ventricular myocytes	135
I_{Kr}	IC_{50}: ~3 μmol/L	Guinea pig ventricular myocytes	135
I_{K1}	IC_{50} >30 μmol/L	Guinea pig ventricular myocytes	135
$I_{K,ACh}$	IC_{50}: ~10 nmol/L	Guinea pig atrial myocytes	137
β-adrenoceptors	IC_{50}: ~1.8 μmol/L	Rat heart	136

See text for expansion of ion channels.

Recently Approved Antiarrhythmic Drugs

Currently, much interest has been shown in the possibility that the so-called class III agents, which might exert their actions on the myocardial membrane by simultaneously blocking multiple ion channels, could have a more favorable electrophysiological profile in terms of their proarrhythmic potential. Molecular modification of the highly effective multi-channel blocker amiodarone to improve safety and tolerability has led to the development of dronedarone. Another strategy for new drug development is atrial selectivity because it promises to avoid deleterious proarrhythmia effects in the ventricle. Atrial selectivity could be achieved through different approaches. One approach is targeting of ion channels exclusively or predominantly expressed in atria, such as I_{Kur} and $I_{K,ACh}$. Another approach is to produce atrial-selective sodium channel blockade, either by exploiting channel state-selective blocking properties that cause stronger block of atrial versus ventricular action potential dynamics or by exploiting very fast sodium channel unblocking to achieve effects that are highly selective for rapid rhythms such as AF (see below). Vernakalant is the first atrial-selective anti-AF drug to reach the clinical setting.

Dronedarone

In 2009, dronedarone was approved by the FDA for sinus rhythm maintenance in patients with a history of AF or AFL with ejection fractions greater than 35%, on the basis of the results of several randomized clinical trials. This compound is the noniodinated derivative of amiodarone, a compound that was created to reduce the adverse effect profile of amiodarone without the loss of its complex electrophysiological and pharmacologic profile.[22,133–134] Besides the deletion of the iodine in the benzene ring, a methane sulfonamide group has been included in the benzofuran ring, and the ethyl groups in the side chain have been replaced by butyls in dronedarone. Such structural changes have led to the shortening of the elimination half life to 20 to 30 hours, no effect on thyroid hormone metabolism, and the propensity to block M_2 receptors so that, despite a significant noncompetitive antiadrenergic action, a somewhat lower heart rate-reducing effect compared with amiodarone is achieved.

Dronedarone is a multi-channel blocker that also inhibits atrial-selective currents (I_{Kur} and $I_{K,ACh}$) and possesses antiadrenergic properties (Table 80-7).[135-139] In other respects, experimental and preliminary clinical studies have shown that the electropharmacologic effects of dronedarone and amiodarone are similar. For example, in acute electrophysiological studies, in vitro dronedarone shortened the APD in cardiac muscle but, like amiodarone, induced significant prolongation of the APD and the ERP in the atrial as well as ventricular myocardium and in the AV node, with the depression of the phase 4 depolarization in the SA node following 1 week of drug administration. The effects of dronedarone on Purkinje fibers as well as in M cells have been reported to be similar to those in the case of amiodarone, suggesting that the drug is likely to exhibit a negligible incidence of TdP, although the clinical experience with the drug has not been extensive. Thus, dronedarone prolongs atrial and ventricular APD and reduces heart rate, with low risk of ventricular TdP arrhythmias.[140] Amiodarone suppresses APD abbreviation during experimental AF, and it has, therefore, been assumed that prevention of ion channel remodeling (suppression of $I_{Ca,L}$ reduction) may contribute to amiodarone's superior efficacy in AF.[141] Inhibition of two-pore-domain TASK-1 leak channels, which are preferentially expressed in atria, may also contribute to amiodarone's anti-AF efficacy.[142] It is not known whether suppression of $I_{Ca,L}$ remodelling and inhibition of TASK-1 channels contribute to the antiarrhythmic effects of dronedarone.

As in the case of amiodarone and other so-called class III compounds, two properties of dronedarone—Q-T and QTc intervals and heart rate—are of much importance in the role of the drug as an anti-fibrillatory agent for the treatment of AF and AFL on the one hand and VT and VF on the other. Beat-by-beat analysis over 24-hour Holter recordings has established that dronedarone increases heart rate Q-T and QTc intervals as a function of dose (1200 to 3200 mg/day), the magnitude of changes being somewhat lower than those on steady state amiodarone administration and the effects being discernible at higher drug doses. The clinical effects of the drug are under study in several large studies in AF and on mortality in high-risk patients with cardiac disease.

Table 80-8 summarizes the prospective randomized clinical trials with dronedarone.[143-148] In the European Trial in Atrial Fibrillation Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm (EURIDIS) and Atrial Fibrillation or Flutter

Table 80-8 Effects of Vernakalant on Individual Cardiac Ion Channels

TARGET	EFFECT	SPECIES/CELL TYPE/CONDITIONS	REF.
I_{Na}/Nav1.5	IC_{50}: ~9 μmol/L	Heterologous expression in HEK cells, recording at RT	154
I_{to}	IC_{50}: ~15 μmol/L	Rat ventricular myocytes, recording at RT	154
HERG	IC_{50}: ~21 μmol/L	Heterologous expression in HEK cells, recording at RT	154
Kv1.5	IC_{50}: ~13 μmol/L	Heterologous expression in HEK cells, recording at RT	154
I_{K1}	IC_{50} >1 mmol/L	Guinea pig ventricular myocytes, recording at RT	154
$I_{Ca,L}$	IC_{50}: ~220 μmol/L	Guinea pig ventricular myocytes, recording at RT	154
$I_{K,ACh}$	IC_{50}: 10 μmol/L	Rat atrial myocytes	155

Patients for the Maintenance of Sinus Rhythm (ADONIS) trials, the median times to recurrence of paroxysmal and persistent AF (primary endpoint) were significantly longer, and ventricular rates during AF recurrence were lower for dronedarone compared with placebo.[144] Post hoc analyses of both trials demonstrated that dronedarone significantly reduced the combined endpoint of hospitalization or death. The Antiarrhythmic Trial with Dronedarone in Moderate-to-Severe CHF Evaluating Morbidity Decrease (ANDROMEDA) trial investigated patients with systolic left ventricular deterioration but was prematurely discontinued because of increased mortality from heart failure worsening in the dronedarone droup.[146] Therefore dronedarone is contraindicated in class III and IV heart-failure.

In the 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 (ATHENA) trial, dronedarone significantly reduced the primary study endpoint (all-cause mortality and cardiovascular hospitalization) of AF patients by 24% and the total hospitalization burden by 28%.[147] A post hoc analysis on non-prespecified secondary endpoints also showed that dronedarone reduced the risk of stroke (ischemic or hemorrhagic) in patients with AF or AFL adequately treated by standard therapy, including anti-thrombotics in 34%.[147] Dronedarone prolonged the median time to first AF or AFL recurrence (dronedarone, 737 days vs. placebo, 498 days) and reduced the likelihood of permanent AF or AFL.[149] The overall efficacy for AF suppression was approximately 50%.[147] Heart rate during AF or AFL was lower with dronedarone than with placebo.[149] Thus, dronedarone exerts both rhythm and rate control effects in patients with AF or AFL and may reduce the risk of hospitalization for and death from cardiovascular diseases. because of these issues the recently published European guidelines for AF management have suggested dronedarone as first-line drug option for patients with nonpersistent AF.[150] Although the mechanism of stroke reduction still needs to be determined, it is possible, but not proven, that dronedarone itself may reduce the stroke risk in AF, an effect that has not previously been observed with antiarrhythmic drugs. However, because stroke was not a prespecified endpoint resulting from post hoc subanalyses of ATHENA only, this assumption can be regarded as hypothesis-generating at best. It is possible that prevention of thromboembolism is attributable to reduction in AF burden, reductions in blood pressure, and the potential anti-ischemic properties of dronedarone. Further prospective studies are required to definitively prove the efficacy of dronedarone to reduce stroke incidence in AF patients. Although the mechanism of stroke reduction is unknown, the ATHENA results suggest the possibility that dronedarone itself reduces stroke risk in AF, an effect that has not previously been observed with antiarrhythmic drugs.

However, in the head-to-head Randomized, Double-Blind Trial to Evaluate the Efficacy and Safety of Dronedarone (400 mg bid) Versus Amiodarone (600 mg qd for 28 Days, then 200 mg qd Thereafter) for at least 6 months for the Maintenance of Sinus Rhythm in Patients with AF (DIONYSOS) trial, amiodarone was shown to be superior to dronedarone for the maintenance of sinus rhythm in patients with persistent AF.[148] These preliminary results show that AF recurrence during 7-month follow-up after electrical cardioversion was greater with dronedarone (63.5%) than with amiodarone (42.0%), whereas drug discontinuation was more frequent with amiodarone (13.3%) than with dronedarone (10.4%). These data point to a higher tolerability but less efficacy for dronedarone compared with amiodarone. Of note, amiodarone was associated with a trend toward greater all-cause mortality and more adverse effects leading to more frequent drug discontinuation. These results, together with those from ANDROMEDA, underscore the need for head-to-head mortality trials and stroke-prevention studies to more precisely define the therapeutic value of dronedarone in the treatment of AF.

The reason for the inferior efficacy of dronedarone compared with amiodarone is unclear and likely involves multiple factors. Greater cardiac accumulation of amiodarone than of dronedarone and the greater efficacy of N-desethylamiodarone (the major amiodarone metabolite) compared with that of N-debutyldronedarone are potential but unproven candidate mechanisms.[151] It is possible that amiodarone interactions with thyroid hormones, dependent on the iodide moieties that are absent in dronedarone, are important for its antiarrhythmic efficacy. Regardless of the reasons, dronedarone has much lower anti-fibrillatory efficacy, and, as can be estimated from an indirect treatment-effect comparison, the fact that switching patients from amiodarone to dronedarone increases the risk of AF recurrence fivefold to eightfold should be kept in mind.

Clinical trials with dronedarone have provided no evidence of thyroid dysfunction or pulmonary toxicity. The most frequently reported adverse events for dronedarone versus placebo in ATHENA were gastrointestinal disorders (26% vs. 22%), skin disorders (10% vs. 8%), and increased blood creatinine (4.7% vs. 1%) because of the inhibition of its renal tubular secretion, which is not considered of clinical relevance. Of note, in EURIDIS,

ADONIS and ATHENA, patients with class III heart failure, class IV heart failure, or both were excluded.[144,147,149] The increased incidence of hospitalization for worsening congestive heart failure or death in the dronedarone group of the discontinued ANDROMEDA trial raises safety concerns for patients with CHF and moderate to severe left ventricular dysfunction.[146] In DIONYSOS, the dronedarone group experienced more diarrhea, vomiting, and nausea but less cardiac adverse effects (bradycardia or Q-T interval prolongation), than amiodarone. Despite its improved safety profile, recent cases of significant liver toxicity related to dronedarone have been reported (www.fda.gov/Drugs/DrugSafety/ucm240011.htm); considering the structural similarities between dronedarone and amiodarone, this is not unexpected and requires routine liver function tests. The overall incidence and significance of dronedarone-related hepatic toxicity are currently unknown, and prospectively collected data in larger patient cohorts are needed to further evaluate the safety profile of dronedarone in different patient subpopulations. A recent study showed adverse outcomes in patient with permanent atrial fibrillation (Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy [PALLAS], personal communication, 2011).

Vernakalant

In 2010, vernakalant was approved by the European Commission for the rapid conversion of recent-onset AF to sinus rhythm. The atrial-selective effects of vernakalant were initially explored in a vagotonic canine model of AF.[152] The clinical relevance of its atrial selectivity has been confirmed in human electrophysiology studies demonstrating significantly greater atrial than ventricular ERP prolongation.[153] Vernakalant affects a variety of cardiac ion channels (Figure 80-7 and Table 80-9), but its atrial-selective action most likely results from inhibition of ion currents exclusively present in atria (I_{Kur} and $I_{K,ACh}$) and from a selective inhibition of atrial sodium channels.[154,155] The sodium channel–blocking potency of vernakalant, particularly during AF, is likely underestimated because of the experimental conditions needed to record sodium currents and because the vernakalant-induced sodium channel block is substantially enhanced at the very rapid rates of the fibrillating atrium (see below).[154-155]

The biophysical properties of atrial sodium channels differ from those of ventricles. For instance, the sodium current has larger amplitude in atria and inactivates at a more negative half-inactivation potential, causing less available current at any given membrane potential.[156] In addition, the resting membrane potential is more depolarized in atrial cardiomyocytes than in ventricular cardiomyocytes, leaving a larger fraction of sodium channels in their inactivated state.[156] Therefore, application of activated-state sodium channel blockers such as vernakalant suppress sodium channel–dependent parameters (e.g., action potential upstroke velocity, conduction velocity, and diastolic threshold of activation) predominantly in the atria. In addition, the very rapid atrial activation during AF reduces the duration of the diastolic interval in atria, which decreases the dissociation rate of the blocker from the resting sodium channel in atria, whereas the long diastolic interval in ventricles allows enough time for drug dissociation from the channel. As a consequence, the combination of a predominant open-channel block and an inhibitory effect on late sodium current produces rate-dependent depression of sodium channel parameters and atrial excitability.[156] Thus, vernakalant's atrial anti-fibrillatory activity, but the absence of pro-fibrillatory effects at ventricles, is most likely caused by a combination of rapidly unbinding sodium channel blocking action with atrial-selective inhibition of I_{Kur} and $I_{K,ACh}$.[154-157]

At faster rates, amiodarone and dronedarone, both of which are inactivated-state sodium channel blockers with rapid dissociation kinetics, have a greater potential to depress I_{Na} properties in atria than in ventricles.[158] Recently, the combination of the two mechanistically different sodium channel blockers—*ranolazine*, an activated-state sodium channel blocker like vernakalant, and *dronedarone*, an inactivated-state sodium channel blocker—was highly effective for AF termination and prevention, with the

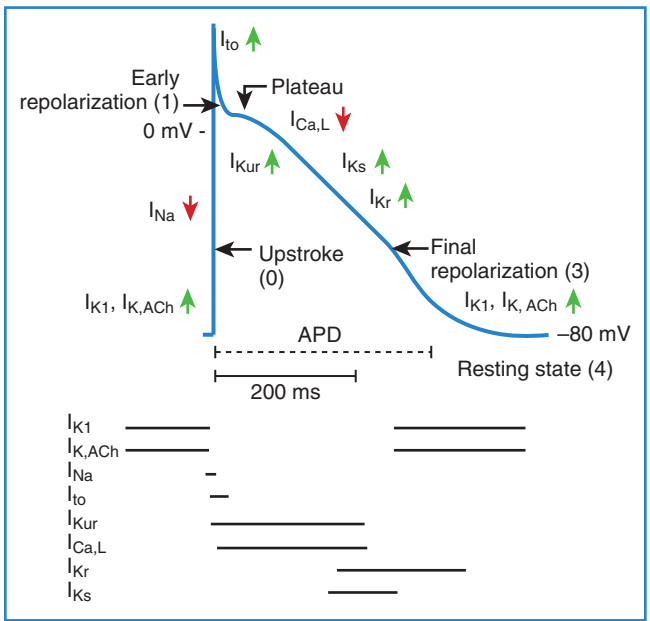

FIGURE 80-7 Cardiac ion channels. *APD*, Action potential duration.

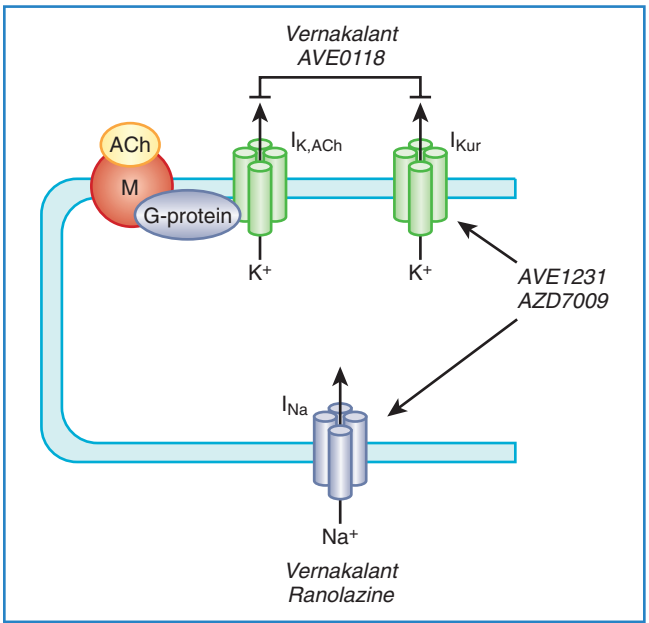

FIGURE 80-8 Atrial-selective targets for antiarrhythmic drugs.

Table 80-9 Efficacy of Dronedarone in Randomized Clinical Trials in Patients with Atrial Fibrillation or Heart Failure

STUDY	DAFNE[143]	EURIDIS/ADONIS[144]	ERATO[145]	ANDROMEDA[146]	ATHENA[147]	DIONYSOS[148]
Inclusion criteria	Persistent AF	Paroxysmal AF	Permanent AF	NYHA class III-IV CHF with LVEF <35%	Paroxysmal/persistent AF or atrial flutter + age ≥70 (later age ≥75) + ≥1 risk factor: high BP, DM, Stroke/TIA, LA ≥50 mm or LVEF <40%	Persistent AF >3 days; anticoagulation
Exclusion criteria	Permanent AF or atrial flutter; NYHA class III-IV CHF; LVEF <35%	Permanent AF; NYHA class III-IV CHF; renal failure	NYHA class III-IV CHF	Recent MI; acute pulmonary edema	Permanent AF; hemodynamic instability; NYHA class IV CHF	NYHA class III-IV CHF; unstable angina pectoris or recent MI
Treatment	Placebo vs. dronedarone (800-1600 mg/day)	Placebo vs. dronedarone (400 mg twice daily)	Placebo vs. dronedarone (400 mg twice daily)	Placebo vs. dronedarone (400 mg twice daily)	Placebo vs. dronedarone (400 mg twice daily)	Dronedarone (400 mg twice daily) vs. amiodarone (600 mg/day followed by 200 mg/day)
Follow-up	6 months	12 months	6 months	2 months	21 months	7 months
Patients	270	615/629	174	627	4628	504
Primary endpoints	Time to AF recurrence: P, 5.3 vs. D, 60 days SR at 6 months: P, 10% vs. D, 35%	Time to AF recurrence: P, 53 days vs. D, 116 days Rate of AF recurrence: P, 75.2% vs. D, 64.1%, HR = 0.75 (0.65-0.87)	Mean ventricular rate on day 14: P, reduced by 0.4 beats/min (2.2-2.9) vs. D, reduced by 12.3 beats/min (10.0-14.6)	All-cause death or hospitalization from worsening CHF: P, 12.6% vs. D, 17.1%, HR = 1.38 (0.92-2.09)	First hospitalization for cardiovascular events or death from any cause: P, 39.8% vs. D, 31.9%, HR = 0.76 (0.69-0.84)	AF recurrence or premature drug discontinuation for intolerance or lack of efficacy: D, 75.1% vs. A, 58.8%, HR = 1.59 (1.28-1.98)
Secondary endpoints	Spontaneous conversion to SR: P, 3.1% vs. D, 5.8%	Ventricular rate at AF recurrence: P, 117.1 ± 30.4 vs. D, 103.4 ± 25.9 beats/min Hospitalization or death: P, 30.9% vs. D, 22.8%, HR = 0.73 (0.57-0.93)	Ventricular rate during exercise: P, reduced by 2.2 beats/min vs D, reduced by 25.6 beats/min ($P < .0001$)	All-cause death: P, 3.8% vs. D, 8.1%, HR = 2.13 (1.07-4.25) Hospitalization: P, 15.7% vs. D, 22.9%	Death from any cause: P, 6.0% vs. D, 5.0%, HR = 0.84 (0.66-1.08) Cardiovascular deaths: P, 3.9% vs. D, 2.7%, HR = 0.71 (0.51-0.98) Hospitalization for cardiovascular events: P, 36.9% vs. D, 29.3, HR = 0.74 (0.67-0.82)	AF recurrence: D, 63.5% vs. A, 42.0% Premature drug discontinuation: D, 10.4% vs. A, 13.3%

AF, *Atrial fibrillation;* NHYA, *New York Heart Association;* P, *placebo;* D, *dronedarone;* CHF, *congestive heart failure;* LVEF, *left ventricular ejection fraction;* BP, *blood pressure;* DM, *diabetes mellitus;* TIA, *transient ischemic attack;* LA, *left atrium.* HR, *hazard ratio.*
Numbers in parentheses indicate confidence intervals.
From Dobrev D, Nattel S: New antiarrhythmic drugs for treatment of atrial fibrillation, Lancet *375(9721):1212–1223, 2010.*

Table 80-10 Efficacy of Vernakalant in Randomized Clinical Trials in Patients with Atrial Fibrillation

STUDY	CRAFT[160]	ACT I[161]	ACT II[162]	ACT III[163]
Inclusion criteria	Sustained AF for 3 h to 3 days	Sustained AF for 3 h to 45 days	Postoperative AF or atrial flutter for 3 h to 3 days	Sustained AF for 3 h to 45 days
Exclusion criteria	Reversible cause of AF, CHF	Atrial flutter, class NYHA IV CHF	CHF	CHF
Treatment	2-3 mg/kg IV	2-3 mg/kg IV	2-3 mg/kg IV	2-3 mg/kg IV
Follow-up	24 h	24 h	24 h	24 hours
Patients	56	336	161	276
Primary endpoints	Termination of AF: P, 5% vs. V, 61% ($P < .0005$)	Conversion of short-duration AF (3 h to 7 days) to SR: P, 4.9% vs. V, 62.2% for AF lasting 3 to 48 h (difference of success, 57.2% [CI, 46.4-68.0]) AF lasting 3 to 7 days: P, 0% vs. V, 23.8% (difference of success, 23.8% [CI, 10.9-36.7])	Conversion of AF/atrial flutter to SR: P, 15% vs. V, 45% ($P = .0002$) Conversion of AF to SR: P, 14% vs. V, 47% ($P = .0001$)	Conversion of AF (3 h to 7 days) to SR: P, 3.6% vs. V, 51.2% ($P = .001$) Conversion of AF (8 to 45 days) to SR: P, 2.7% vs. V, 9.4% (P = NS)
Secondary endpoints	Patients in SR at 1 h: P, 5% vs. V, 53% ($P = .0014$) Patients in SR at 24 h: P, 45% vs. V, 79% ($P = .005$) Median time to SR conversion: P, 162 vs. V, 14 min ($P = .016$)	Conversion of long-duration AF (8 to 45 days) to SR: P, 0% vs. V, 7.9% for AF lasting 8 to 45 days, $P = .09$); no significant conversion of atrial flutter to SR	No significant conversion of atrial flutter to SR	No significant conversion of atrial flutter to SR

AF, *Atrial fibrillation;* NHYA, *New York Heart Association;* SR, *sinus rhythm;* P, *placebo;* V, *vernakalant;* CHF, *congestive heart failure;* CI, *95% confidence interval;* NS, *not significant.*
From Dobrev D, Nattel S: New antiarrhythmic drugs for treatment of atrial fibrillation, Lancet *375(9721):1212–1223, 2010.*

combination being much more effective than expected from the mathematical sum of the two separate efficacy values.[159] Although similar beneficial efficacy effects could also result from the combination of vernakalant and dronedarone, this hypothesis requires direct experimental proof.

Vernakalant's main use is as an intravenous drug for rapid AF termination. Several studies have shown substantial efficacy, approximately 50% (compared with nearly 0% for placebo), with very few adverse effects (Table 80-10).[160-163] Efficacy is high for recent-onset AF (<48 hours), whereas longstanding AF is resistant to vernakalant. Vernakalant is useless in patients with AFL, perhaps because of insufficient I_{Kr} inhibition. The higher efficacy of class I antiarrhythmic drugs such as vernakalant to cardiovert recent-onset AF versus persistent AF might result from the lower degree of atrial remodeling in recent-onset AF.[164] Because of the more complex pathophysiology in longstanding persistent AF with progressive structural changes in both atria (structural remodeling), AF stabilization in such patients depend more on structural, rather than ion channel, remodeling. Complex interaction patterns between cardiomyocytes and fibroblasts may lead to re-entrant circuits that depend to a lesser extent on functional re-entry determinants such as the properties of sodium currents.

The efficacy of vernakalant for acute AF termination appears comparable with other available compounds, although head-to-head comparative studies have not been performed yet.[165] The Phase III Superiority Study of Vernakalant vs. Amiodarone in Subjects with Recent Onset Atrial Fibrillation (AVRO) trial compared intravenous vernakalant versus amiodarone in recent-onset AF, but because of slow (up to 24 hours) onset of action, amiodarone is less suitable for acute AF cardioversion and thus is not the right comparator when assessing the short-term (90 minutes) success rate of pharmacologic cardioversion.[166,167] Head-to-head trials with intravenous flecainide are needed to validate the superiority of vernakalant for acute AF cardioversion in different patient populations. In addition, the AF conversion rate with vernakalant is substantially lower in congestive heart failure (26.9%) than in hemodynamically stable patients (54.1%), clearly suggesting its reduced efficacy in patients with structural heart disease.[161,162,166] Intravenous ibutilide and dofetilide are approved for acute AF cardioversion, but they have lower efficacy and higher risk for proarrhythmia because of their inhibitory effects on I_{kr}, which are not shared by vernakalant.[154,168]

The most common adverse effects of vernakalant are sneezing and dysgeusia related to sodium channel blockade of the central nervous system. Adverse hemodynamic effects such as hypotonia may occur, particularly in the setting of pre-existing ventricular dysfunction, but are rarely observed. Because of its short plasma half life, oral administration of vernakalant as pure salt is clinically not practical, but a slow-release preparation is currently in development.[169] The value and safety of the oral agent for sinus rhythm maintenance remain to be established.

Newer Antiarrhythmic Drugs Under Development

Currently, interest continues to grow in the development of agents that exert their actions blocking multiple ion channels because such agents are effective without substantial proarrhythmic potential. The most advanced agent is azimilide.

Azimilide

The structure of this compound does not include the methane sulfonamide group present in sotalol, dofetilide, or ibutilide. Azimilide, although not a benzofuran, in some respects, resembles amiodarone, which, like azimilide, maintains a class III effect at high stimulation frequencies.[170-173] Azimilide is likely to exhibit a lower incidence of TdP compared with the other pure class III agents (d-sotalol, dofetilide, and ibutilide). The terminal half life of azimilide is 4 to 5 days, and it can be administered once daily. It is eliminated by hepatic metabolism.[174] It takes approximately 2 weeks for the drug to achieve steady state if no loading regimen is administered. No clinically significant pharmacokinetic interactions have been observed between azimilide and warfarin or digoxin.

The compound prolongs the myocardial APD by predominantly blocking the slow component of the delayed rectifier current (I_{Ks}) with presumably a somewhat smaller effect on the rapid component (I_{Kr}). Such a property may not be associated with reverse use and rate dependency of action on repolarization. Thus, azimilide is likely to be less "torsadogenic" compared with other specific I_{Kr} blockers. The effect of the drug on the M cells in the mid-myocardial region of ventricular tissue is not fully defined, but in other tissues, the drug prolongs the cardiac APD and ERP. Like other pure class III agents, the drug does not slow conduction across the AV node. In isolated human atrial and ventricular myocytes, azimilide produces a concentration-dependent inhibition of both I_{Ks} and I_{kr}. In intact animal models, azimilide has been shown to suppress both atrial and ventricular arrhythmias and has the potential to prevent SCD following coronary artery occlusion.[37] Of particular interest, the drug has been found to be unusually and consistently effective in terminating AF and AFL in various canine models.

The available clinical data on the hemodynamic and electrophysiological effects of azimilide are predictable on the basis of its known electropharmacologic properties. In healthy volunteers, oral azimilide in doses of up to 200 mg/day was well tolerated and produced a maximal increase in the Q-T interval between 24% and 28%, although individual values ranged from 4% to 42%. The Q-T interval increases were dose dependent, without significant increases in the P-R or QRS intervals or in heart rate or blood pressure, suggesting that the drug does not have sodium channel– or calcium channel–blocking actions or any significant influence on the sympathetic or parasympathetic nervous systems.

In three regimens (50, 100, and 125 mg) in patients, as in healthy volunteers, azimilide has been shown to produce consistent prolongation of Q-T and QTc intervals in a dose-dependent manner in the absence of clinically significant effects on heart rate, P-R interval, and QRS interval.

As indicated previously, in the currently changing therapeutic landscape of arrhythmia control, azimilide may have particular value in the acute conversion of AFL and AF with a potential for maintaining sinus rhythm after pharmacologic or electrical conversion of these arrhythmias.[63] The overall efficacy of the drug is likely to rival that of dofetilide (see Table 80-2), and as in the case of other pure class III agents, it is likely to be of value in the reduction of the number of shocks in patients with ICDs for VT or VF. On theoretical grounds, the drug is of much interest as the first example of a class III agent that blocks both I_{ks} and I_{Kr}. Thus, its effects in patients with recent MI to improve survival by reducing the risk for sudden arrhythmic deaths, as shown in a controlled study, will be of much interest and significance.

It should be emphasized that as in the case of other pure class III agents, the greatest usefulness of the drug is likely to be in the prophylactic therapy of AF. A number of studies have determined the effect of 35 to 125 mg/day of azimilide on the time to first recurrence of a symptomatic atrial arrhythmia. Analyses of combined data for 100 mg doses and data for the 125 mg dose have shown statistically significant differences from placebo. A dose-dependent response has been observed, with placebo patients having an 83% greater recurrence rate versus patients treated with 125 mg of azimilide. To date, the most effective dose of azimilide in preventing recurrences of AF is 125 mg/day. For example, Pritchett and colleagues found that in symptomatic patients, the mean recurrence time for AF was 17 days for placebo, 22 days for 50 mg dose, 41days for 100 mg dose (all nonsignificant), but 130 days when the dose was 125 mg/day ($P = .002$).[175]

The risk of mortality was similar between azimilide (0.9% [9 of 1004 patients]) and placebo (0.7% [4 of 569 patients]) in completed supraventricular arrhythmia (SVA) placebo-controlled studies. On the basis of the adverse events (AE) reported in completed SVA studies, once-daily doses of 100 or 125 mg of azimilide are safe and generally well tolerated in patients with AF, AFL, and PSVT. The most frequently reported AEs included headache and asthenia; both occurred at rates similar to those of placebo. Other significant AEs included TdP, neutropenia, and mild increases in liver enzymes. The incidence of TdP and other ventricular arrhythmic events in patients treated with azimilide were low and consistent with those with class III antiarrhythmic agents. TdP was reported in less than 1% of patients receiving azimilide. Risk factors for TdP included female gender, use of diuretics, and bradycardia.

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CHAPTER 81

Clinical Application of New Antiarrhythmic Drugs for Atrial Fibrillation

Gerald V. Naccarelli

Atrial fibrillation (AF) is the most common sustained arrhythmia requiring medical care. Oral antiarrhythmic drugs are effective in controlling AF in 50% to 65% of cases but have limitations, including subjective adverse effects, ventricular proarrhythmia, and end-organ toxicity.[1] In addition, therapeutic options available to the majority of patients with AF associated with significant structural heart disease are limited. Therefore, more effective and safer antiarrhythmic drugs for the termination and prevention of AF are needed (Figure 81-1).[2] Although many new antiarrhythmic drugs are at various degrees of development, this chapter will limit discussion to a recently released antiarrhythmic, dronedarone, a commercially released anti-anginal medication with antiarrhythmic properties; vernakalant; several drugs furthest along in development, such as celivarone, budiodarone, and ranolazine.

Dronedarone (Multaq)

Dronedarone is a non-iodinated benzofurane derivative, structurally related to amiodarone, developed by Sanofi-Aventis. The addition of a methyl-sulfonamide grouping made the drug less lipophilic with a shorter half-life than that of amiodarone (Figure 81-2).

Electrophysiology

In vitro, dronedarone blocks I_{Kr}, I_{Ks}, I_{to}, I_{Na}, and $I_{Ca\text{-}L}$.[3] Dronedarone prolongs the action potential duration in the atria and ventricles with no significant reverse-use dependence. In vivo, dronedarone has been shown to actively block the following channels: $I_{Na,}$ I_{Kr}, $I_{Ks,}$ I_{KACh}, and $I_{Ca\text{-}L}$ and inhibit α-adrenoceptors and β-adrenoceptors. Although its effect is similar to that of amiodarone, the magnitude of the effect is different. For example, dronedarone is 10 times more effective in blocking $I_{Na,}$ and 100 times more effective in blocking I_{KACh}, compared with amiodarone. In addition, blockade of isoprenaline β_2-adrenoceptor–mediated decrease in blood pressure is more pronounced with dronedarone than with amiodarone. Other amiodarone-like electrophysiological effects include alpha, beta, and muscarinic blocking effects.[3] Dronedarone slows sinus rate, prolongs atrioventricular (AV) nodal refractory periods, and slows AV nodal conduction. Dronedarone increases the Q-T interval but has a low propensity to cause torsades de pointes, since dronedarone reduces the transmural dispersion of ventricular refractoriness and protects from class III antiarrhythmic-induced early after depolarizations.[3]

Dronedarone exhibits significant antiarrhythmic properties in the ventricle and is effective against arrhythmias arising as a result of myocardial ischemia; in murine studies, it has also been shown to be effective against arrhythmias arising as a result of sudden reperfusion of the ischemic myocardium. In ischemic porcine hearts, dronedarone appears to be more potent than amiodarone in suppressing ventricular arrhythmias.[3]

Pharmacokinetics and Metabolism

Similar to amiodarone, over a two-fold increase is seen in the serum concentration of dronedarone when taken with food. With twice-daily dosing, the drug reaches steady-state levels in 4 to 7 days. The elimination half-life of dronedarone ranges from 13 to 30 hours.[3] Dronedarone is a substrate for and an inhibitor of CYP3A4. Therefore, dronedarone should not be used concomitantly with potent CYP3A4 inhibitors such as ketokonazole or macrolide antibiotics. Dronedarone has similar amiodarone-like drug interactions with simvastatin and digoxin, but, importantly, no significant dronedarone interaction with warfarin occurs. Dronedarone increases the tubular secretion of creatinine by about 10%, with no effect on the glomerular filtration rate.

Clinical Efficacy

On the basis of dronedarone's electrophysiological effects, one would expect the drug to have antiarrhythmic efficacy in suppressing premature ventricular complexes and ventricular tachycardia (VT) or ventricular fibrillation (VF). However, data from human studies on the drug's ventricular antiarrhythmic potential are not available at this time.

Several clinical trials have assessed the efficacy of dronedarone in suppressing AF in humans. The Dronedarone Atrial Fibrillation study after Electrical Cardioversion (DAFNE) was the first prospective randomized trial evaluating the efficacy and safety of dronedarone.[4] In this dose-ranging study, placebo or dronedarone 400 mg, 600 mg, or 800 mg twice daily was randomly given to 199 patients with AF longer than 3 days but less than 365 days. Patients were then followed up for 6 months to measure the primary endpoint of time to AF recurrence. In comparison with placebo, dronedarone 400 mg twice daily significantly prolonged the time to recurrence of AF (median time 60 days in the dronedarone group versus 5.3 days in the placebo group, $P < .001$; relative risk reduction, 55%; confidence interval [CI], 28% to 72%). At doses higher than 400 mg twice daily, no efficacy in preventing the recurrence of AF was noted; an adverse effect—a dose-response curve of gastrointestinal side effects (diarrhea, nausea) requiring drug discontinuation—was, however, noted. The DAFNE demonstrated that dronedarone, at a dose of 400 mg

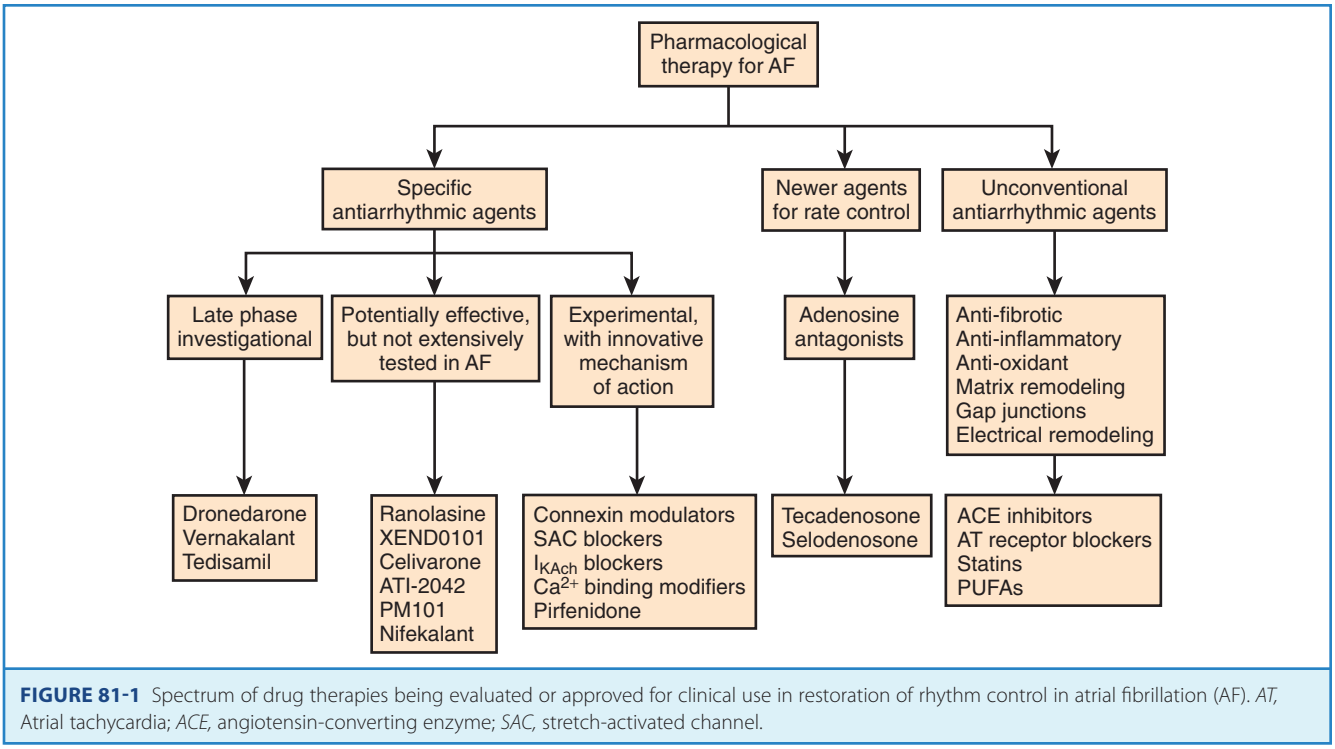

FIGURE 81-1 Spectrum of drug therapies being evaluated or approved for clinical use in restoration of rhythm control in atrial fibrillation (AF). *AT,* Atrial tachycardia; *ACE,* angiotensin-converting enzyme; *SAC,* stretch-activated channel.

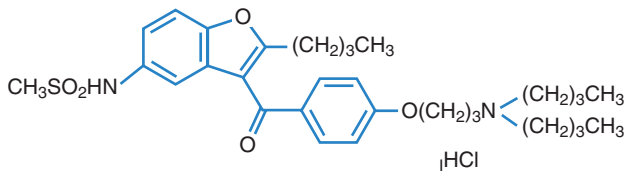

FIGURE 81-2 Chemical structure of dronedarone. Dronedarone HCl is a benzofuran derivative with the empirical formula $C_{31}H_{44}N_2O_5$ S, HCl and a relative molecular mass of 593.

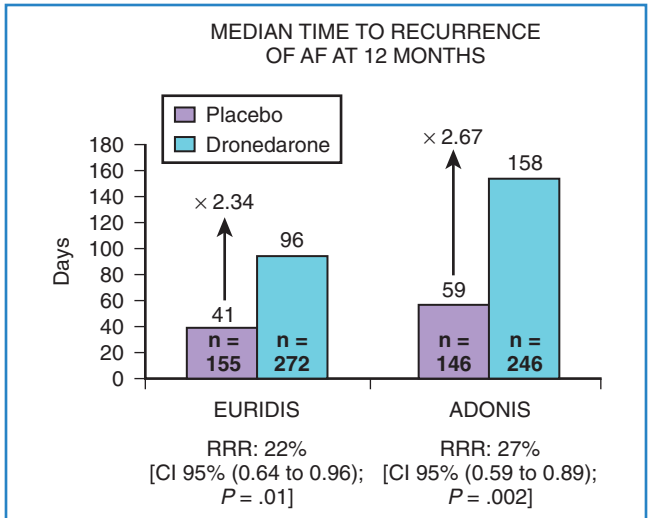

FIGURE 81-3 Clinical efficacy of dronedarone versus placebo in the European Trial in Atrial Fibrillation or Flutter in Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm (EURIDIS) and the Australian-American-African Trial with Dronedarone in Atrial Fibrillation or Flutter for the Maintenance of Sinus Rhythm (ADONIS). Note the marked increase in median time to atrial fibrillation *(AF)* recurrence in a follow-up period of up to 12 months. *CI,* Confidence interval; *RRR,* relative risk reduction.

twice daily, was safe and effective in preventing AF recurrences following conversion of persistent AF but was not very effective in the medical conversion of persistent AF.

Two pivotal phase III trials assessed the efficacy of dronedarone in the maintenance of sinus rhythm in patients with AF or atrial flutter: (1) The Australian-American-African Trial with Dronedarone in Atrial Fibrillation or Flutter for the Maintenance of Sinus Rhythm (ADONIS) and (2) the European Trial in Atrial Fibrillation or Flutter in Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm (EURIDIS).[5] These blinded, placebo-controlled trials randomized patients in a 2:1 ratio of either placebo or dronedarone 400 mg twice daily (Figure 81-3). Patients had a history of AF or atrial flutter in the previous 3 months and had to be in sinus rhythm for at least 1 hour before randomization. In the two trials, 1237 patients were randomized to either dronedarone or placebo (612 in the EURIDIS trial and 625 in the ADONIS trial). In the EURIDIS trial, dronedarone prolonged the median time to recurrence of AF or atrial flutter from 41 days in the placebo group to 96 days (relative risk [RR], 0.784; $P = .0138$). In ADONIS, the median time to recurrence increased from 59 days in the placebo group to 158 days in the dronedarone group (RR, 0.725; $P < .0017$). Dronedarone also significantly reduced symptomatic AF recurrences and significantly slowed the ventricular response rate by about 12 to 15 beats/min compared with placebo ($P < .001$) in those who had AF recurrence.

In the Efficacy and Safety of Dronedarone for the Control of Ventricular Rate During Atrial Fibrillation (ERATO) trial, in addition to other AV node–blocking agents, dronedarone had

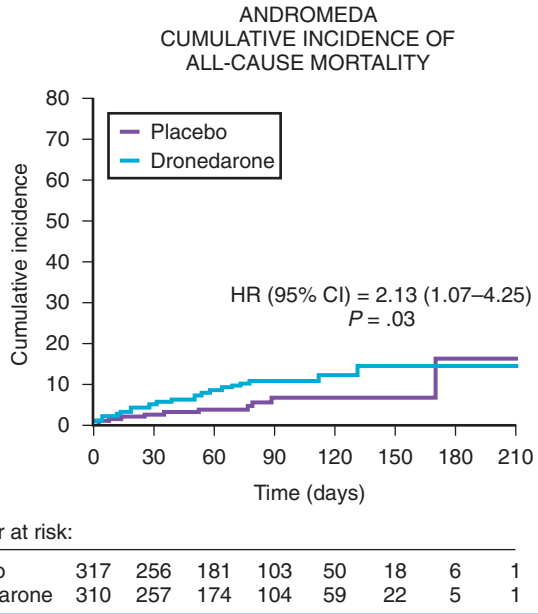

FIGURE 81-4 Cumulative incidence of all-cause mortality with dronedarone versus placebo in patients with unstable heart failure (class 2 or 3) or class 4 heart failure in the Antiarrhythmic Trial with Dronedarone in Moderate to Severe CHF Evaluating Morbidity Decrease (ANDROMEDA). *CI,* Confidence interval; *HR,* hazard ratio.

therapeutic use in further slowing ventricular response during permanent AF or atrial flutter as assessed by Holter monitoring and stress testing.[6]

As part of the European regulatory filing, the active control Randomized, Double-Blind Trial to Evaluate the Efficacy and Safety of Dronedarone (400 mg bid) Versus Amiodarone (600 mg qd for 28 Days, then 200 mg qd Thereafter) for at Least 6 Months for the Maintenance of Sinus Rhythm in Patients with AF (DIONYSOS), which compared dronedarone with amiodarone, was performed in 504 patients with persistent AF.[7] The primary endpoint of this trial was a composite of electrocardiographically documented AF recurrence or premature discontinuation of drug for lack of efficacy or adverse events. The trial had a short follow-up period (mean, 7 months) but was able to show that amiodarone was more effective in suppressing the recurrence of AF but tended to having more adverse events, including thyroid abnormalities and bleeding secondary to amiodarone-warfarin interaction problems.

The safety of dronedarone in moderate to severe congestive heart failure (CHF) was assessed in the Antiarrhythmic Trial with Dronedarone in Moderate to Severe CHF Evaluating Morbidity Decrease (ANDROMEDA) trial.[8] The ANDROMEDA trial was a double-blind, placebo-controlled study evaluating dronedarone (400 mg twice daily) in high-risk patients with CHF and ventricular dysfunction (Figure 81-4). The primary endpoint of the ANDROMEDA trial was the composite endpoint of all-cause mortality or hospitalization for heart failure. The ANDROMEDA trial focused on patients at the highest possible risk of major cardiovascular events and enrolled recently hospitalized patients having current symptomatic New York Heart Association (NHYA) class II to IV heart failure with at least one decompensation of heart failure (class III to IV) in the last month and a wall motion index (WMI) by echocardiography of 1.2 or less, which correlates to a left ventricular ejection fraction of 35% or lower. Except for the Danish Investigations of Arrhythmia and Mortality on Dofetilide (DIAMOND) trials with dofetilide, patients hospitalized for decompensated heart failure generally had not been enrolled in survival trials to evaluate the safety of antiarrhythmic drugs.[9] After enrolling 627 of the 1000 planned patients, the trial was stopped by the Data and Safety Monitoring Board because of the excess risk of death (risk ratio, 2.13) in patients treated with dronedarone. In a review of the cause of deaths in this trial, the majority of deaths were secondary to nonsudden death or worsening of heart failure in the dronedarone arm. The primary composite endpoint of mortality and cardiovascular hospitalization trended adversely for dronedarone but was not statistically different (hazard ratio [HR], 1.38; CI, 0.92 to 2.09). The most likely explanation is that the ANDROMEDA trial finding is a true finding that can be explained by the deleterious effect of dronedarone in NYHA class III to IV patients with left ventricular ejection fractions of less than 35% who also had a recent hospitalization for decompensated heart failure. Similar concern has been raised by the termination of the recent Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy (PALLAS) trial.

The 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 (ATHENA) trial was conducted to focus on patients at risk of AF recurrence who may or may not have had heart failure but who would not have been randomized in the ANDROMEDA trial.[10] Thus, key exclusion criteria for the ATHENA trial were pulmonary edema within 12 hours, cardiogenic shock requiring intravenous pressors, mechanical ventilation or class IV heart failure within 4 weeks, or all. The ATHENA trial was also performed for several other regulatory reasons: (1) to verify the post hoc result from the ADONIS and EURIDIS trials that dronedarone prospectively could reduce the composite endpoint of cardiovascular hospitalizations or death; (2) to create a large database to show that dronedarone would be safe in a large number of patients with structural heart disease; and, (3) to define a point estimate to show that this drug could be used safely in high-risk patients with AF or atrial flutter excluding the ANDROMEDA trial population.

The ATHENA trial demonstrated a statistical reduction in the composite endpoint of all-cause mortality or cardiovascular hospitalization in the dronedarone group (HR, 0.76; CI, 0.69 to 0.84; $P < .001$)] (Figure 81-5). Although dronedarone reduced cardiovascular hospitalization rates (HR, 0.75; CI, 0.67 to 0.82), no effect was seen on reducing hospitalizations for noncardiovascular reasons (HR, 0.98; CI, 0.87 to 1.11). The decrease in re-admission for cardiovascular hospitalization was mainly determined by the suppression of AF and other supraventricular disorders (HR, 0.62; CI, 0.53 to 0.71). All-cause mortality trended favorably in the dronedarone group with an HR of 0.84 (CI, 0.66 to 1.08); cardiovascular death relative risk was 0.70 (CI, 0.51 to 0.96). A retrospective analysis of the ATHENA trial reported that dronedarone reduced the incidence of stroke by 34% (HR, 0.66; CI, 0.46 to 0.96).[11]

Regulatory Affairs

In the United States, dronedarone's approved indication is for the reduction of cardiovascular hospitalization in patients similar to those in the ATHENA trial. The warning in the package insert

excludes patients with class IV heart failure and those recently hospitalized for heart failure within the past month from an acute decompensation. In Europe, dronedarone is approved for the suppression of AF recurrences and for rate control. The 2001 update of the ACC/AHA guidelines now includes dronedarone in the first tier of antiarrhythmic drug therapy for rhythm control (Figure 81-6).

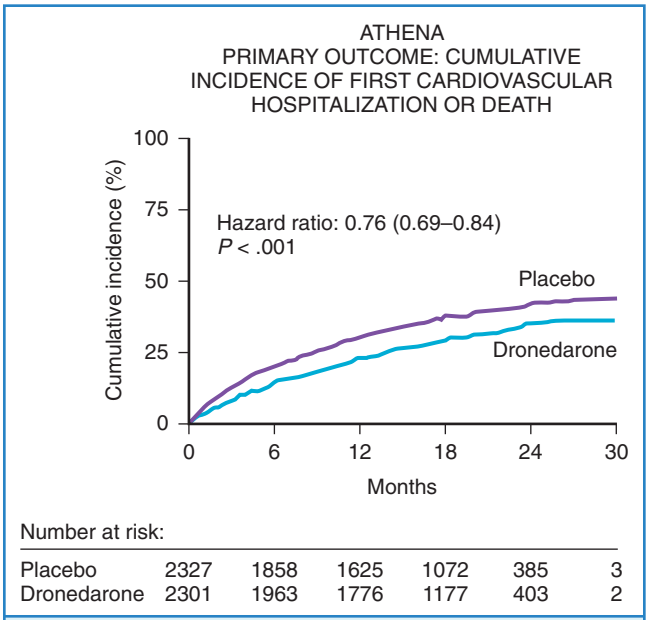

FIGURE 81-5 Clinical outcome of dronedarone therapy compared with placebo (rate control) in the Placebo-Controlled, Double-Blind Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg bid for the Prevention of Cardiovascular Hospitalization or Death from Any Cause in Patients with Atrial Fibrillation/Atrial Flutter (ATHENA). The primary endpoint was the cumulative incidence of first cardiovascular hospitalization or death.

Vernakalant (Kynapid, Brinavess)

Vernakalant is a new amino-cyclohexyl ether antiarrhythmic agent discovered by Cardiome Pharma. The drug has some selective atrial-channel–blocking properties that minimize QT prolongation and torsades de pointes.[12,13] Cardiome and Astellas Pharma are co-developing intravenous vernakalant for the acute termination of AF in the United States. Merck and Cardiome are developing the intravenous compound outside North America and developing the oral compound worldwide.

Electrophysiological Effects of Vernakalant

Vernakalant (RSD-1235) is an atrial selective (I_{KACh}, I_{Kur}) potassium channel blocker with little effect on ventricular repolarization and frequency-dependent and voltage-dependent I_{Na}–blocking activity (Table 81-1).[12,13] The combined effects of blockade of these channels include prolongation of atrial refractory periods and rate-dependent slowing of atrial conduction. Vernakalant also blocks the atrial expressed transient outward potassium current (I_{to}) carried by the Kv4.3 channels, which may prolong atrial refractoriness but has minimal effects on hERG. Vernakalant has been shown to be a rate-dependent blocker (fast onset, fast offset) of late I_{Na} which should attenuate any QT-prolonging effect from I_{Kr} inhibition.

In in vivo studies, vernakalant showed an increase in the left atrial effective refractory period and the QRS complex; however, it did not change the Q-T interval of the right ventricular effective refractory period and terminated AF.[13] In basic animal studies in which the clofilium or methhoxamine model was used, vernakalant has been shown to decrease dofetilide-induced action

Table 81-1 New Antiarrhythmic Agents for Managing Atrial Fibrillation

AGENT	MECHANISM OF ACTION	COMMENTS
Dronedarone	Vaughn Williams class I, II, III, and IV effects Inhibits I_{Kr}, I_{Ks}, $I_{Ca,L}$, I_{to}, I_{Na}, I_{Kl}, and I_{KACh} β_1–anti-adrenergic effects	Noniodinated benzofuran derivative of amiodarone Half-life of ~1 day Several large-scale phase III trials have been completed
Celivarone	As above	Noniodinated benzofuran analog of amiodarone Half-life of 7 hours Available in oral and intravenous formulations Currently in clinical development
Budiodarone (ATI-2042)	As above	Iodinated analog of amiodarone Half-life of 7 hours Currently in clinical development
Vernakalant HCl (RSD-235)	High affinity for I_{Kur} Lower affinity for I_{to}, I_{KACh}, and $I_{Ca,L}$	IV formulation: Several phase III trials have been completed (moderately effective for cardioversion of AF of <7 days; ineffective for atrial flutter; the U.S. Food and Drug Administration has issued an approval letter) Oral formulation: Several phase II trials have been completed (moderately effective for maintaining normal sinus rhythm)
Ranolazine	Strong inhibitor of the late I_{Na} current Weaker effect on peak I_{Na} current and on I_{NCX}, $I_{Ca,L}$, I_{Kr}, and I_{Ks} currents	Anti-anginal agent Has been evaluated for AF as part of the safety analysis of a trial in patients with acute coronary syndrome Basic studies suggest that the drug may be effective in AF

AF, *Atrial fibrillation.*

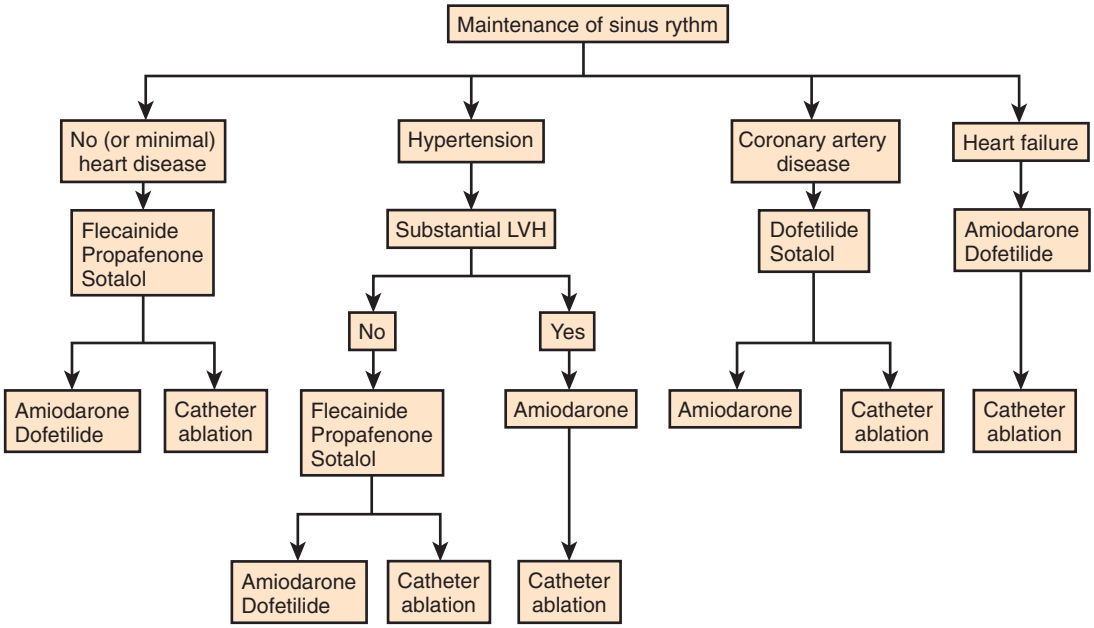

FIGURE 81-6 Antiarrhythmic drug therapy to maintain sinus rhythm in patients with recurrent paroxysmal or persistent atrial fibrillation. Within each box, drugs are listed alphabetically and not in order of suggested use. The vertical flow indicates the order of preference under each condition. The seriousness of heart disease increases from left to right; the selection of therapy in patients with multiple conditions depends on the most serious condition present. *LVH,* Left ventricular hypertrophy. (Modified from the 2011 ACCF/AHA/HRS Focused Updates Incorporated Into the ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation.)

potential duration and early after-depolarizations (EADs) and to prevent torsades de pointes. In humans, vernakalant appears to prolong the atrial effective refractory periods, with no significant effect on ventricular repolarization.

Pharmacokinetics and Dosing

Intravenous vernakalant demonstrates linear kinetics and follows a two-compartment model with rapid first-order elimination from the central compartment.[12,13] Mean plasma concentrations peak at the end of a 10-minute infusion. In the Atrial Arrhythmia Conversion Trial 1 (ACT 1) and ACT 3, vernakalant 3 mg/kg was intravenously infused over 10 minutes, followed by 2 mg/kg if AF persisted 15 minutes after the first infusion was completed.[12,14,15] Vernakalant is primarily metabolized by the cytochrome P450 system (CYP2D6). In poor metabolizers, the half-life is approximately 2.7 hours in normal volunteers and 8.5 hours in patients with AF. Two demethylated metabolites have some bioactivity, but these are rapidly conjugated, inactivated, and eliminated by renal excretion.

Because of the drug's short elimination half-life intravenously, a sustained-release formulation has been developed for long-term oral use. Oral bioavailability in healthy volunteers ranged from 58% to 71% with a maximum plasma concentration (C_{max}) of 1.8 to 1.9 μg/mL.

Clinical Efficacy: Intravenous Vernakalant for the Conversion of Atrial Fibrillation

Intravenous vernakalant was developed to be an effective therapy for the acute termination of recent-onset AF. In the Controlled Randomized Atrial Fibrillation Trial (CRAFT), a phase IIa dosing study, patients were randomized to placebo versus infusions of 2 + 3 mg/kg intravenous vernakalant.[16] This study demonstrated that vernakalant had a dose-related ability to terminate AF of 3 to 72 hours' duration. The subgroup given 2 mg/kg followed by 3 mg/kg of intravenous vernakalant showed superior results compared with the placebo group in termination of AF (61% vs. 5%, $P < .0005$), patients in sinus rhythm at 30 minutes (56% vs. 5%, $P < .001$) and 1 hour (53% vs. 5%, $P = .0014$), and median time to conversion (14 vs. 162 minutes, $P = .016$).

The efficacy of intravenous vernakalant for converting AF was studied in several prospective, placebo-controlled trials (Table 83-2). The ACT 1 trial compared intravenous vernakalant to placebo in 416 patients with AF onset of 3 hours' to 7 days' duration.[14] The primary endpoint was conversion to sinus rhythm within 90 minutes of injection, and 52% of the patients with recent-onset AF (duration of 3 hours to 7 days) converted to sinus rhythm compared with 4% of those in the placebo group ($P < .001$). However, in the subset of patients with AF duration of 3 hours to 45 days, only 38% of patients receiving intravenous vernakalant had their AF terminated compared with 3% of patients in the placebo group ($P < .001$). Of note, intravenous vernakalant was ineffective in converting atrial flutter.

The ACT 3 trial randomized 276 patients, and intravenous vernakalant converted 51% of those patients with recent-onset AF of 3 hours to 7 days to sinus rhythm compared with only 4% of the placebo group ($P < .001$). In the ACT 3 trial, only 7% of patients with atrial flutter receiving vernakalant converted to sinus rhythm compared with 0% of the placebo group. A pooled analysis of the ACT 1 and ACT 3 trials demonstrated that conversion rates with intravenous vernakalant were not affected by the concomitant use of β-blockers or calcium channel blockers and were numerically more efficacious in patients taking sotalol.

Table 81-2 Vernakalant: Clinical Trial Comparison of Conversion of Atrial Fibrillation*

	CRAFT†	ACT I	ACT III (AF ONLY)	ACT IV	ACT II† (AF ONLY)
Number of patients	36	220	170	167	150
Vernakalant conversion	9/17 (52.9%)	74/145 (51.0%)	44/86 (51.2%)	85/167 (50.9%)	47/100 (47.0%)
Placebo conversion	1/19 (5.3%)	3/75 (4.0%)	3/84 (3.6%)	NA	7/50 (14.0%)
P Value	.00147	<.0001	<.0001	NA	.0001

**>3 hours to ≤7 days to sinus rhythm.*[14-17]
†AF duration of 3 to 72 hours.
AF, *Atrial fibrillation.*
CRAFT: phase II, intravenous (IV) dosing; ACT I: phase III, IV dosing, conversion of AF to sinus rhythm; ACT II: phase III, IV dosing, conversion of post–cardiac surgery AF or atrial flutter to sinus rhythm; ACT III: phase III, IV dosing, conversion of AF or atrial flutter to sinus rhythm; ACT IV: 167-patient, open-label study.

The ACT 2 trial evaluated the efficacy and safety and intravenous vernakalant in 190 patients who developed AF or atrial flutter between 24 hours and 7 days following coronary artery bypass graft or valve replacement surgery (Figure 81-7).[17] In the AF group, 47% of patients dosed with intravenous vernakalant converted to sinus rhythm within 90 minutes compared with only 14% of the placebo group ($P = .0001$) (see Table 81-2). The median time to conversion was 12.3 minutes for the vernakalant responders. Similar to the other two ACT trials, no torsades de pointes was reported, and the drug was ineffective in the medical conversion of atrial flutter in 0 of 10 patients.

The ACT 4 trial, a phase III open-label study, evaluated the safety of intravenous vernakalant in the conversion of 236 patients with AF (<3 hours but ≤45 days).[12] Of these patients, 167 had AF of less than 3 hours but 7 days or longer. This subgroup had a 50.9% conversion rate, similar to the other ACT trials. In patients who converted within 90 minutes, the median time to conversion was 14 minutes.

The recent Superiority Study of Vernakalant vs. Amiodarone in Subjects With Recent Onset Atrial Fibrillation (AVRO) trial demonstrated that intravenous vernakalant was almost 10 times more effective than intravenous amiodarone in terminating recent-onset AF.

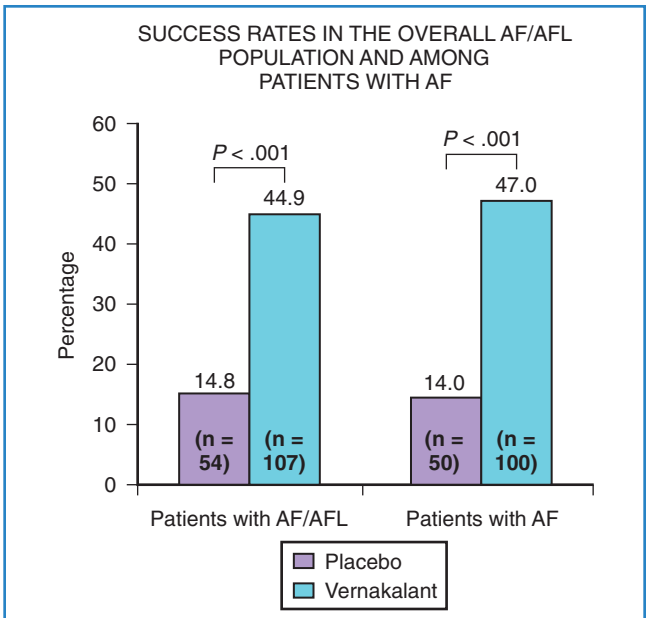

FIGURE 81-7 Efficacy of vernakalant in patients with atrial fibrillation *(AF)* after coronary bypass surgery (ACT 3 trial). *AFL,* Atrial flutter. (From Kowey et al: Vernakalant hydrochloride for the rapid conversion of atrial fibrillation after cardiac surgery, *Circulation* 2:652–665, 2009.

Clinical Efficacy of Oral Vernakalant

A phase IIa trial demonstrated that oral vernakalant at 300 mg and 600 mg twice daily was superior to placebo in maintaining sinus rhythm after cardioversion of persistent AF over a 28-day treatment.[12] In the 300-mg twice-daily group, 61% (33 of 54) of patients maintained sinus rhythm 28 days after cardioversion compared with 43% (24 of 56) of patients in the placebo group ($P = .048$) and 61% (30 of 49) in the 600-mg twice-daily group. A phase IIb, placebo-controlled trial of more than 670 patients measured the safety and efficacy of 150-mg, 300-mg, and 500-mg twice-daily oral vernakalant over a 90-day period after conversion of persistent AF. In this study, the 500-mg dose was most effective in suppressing recurrences of AF. Further phase II trials with the oral compound are planned.

Safety and Tolerability

Intravenous vernakalant has been associated with transient adverse effects, including dysguesia (28.3%), sneezing (17.1%), paresthesias (10.9%), nausea, cough, pruritus, bradycardia, and hypotension. Hypotension was more likely to occur in patients with a history of congestive heart failure (12.7%) than in patients without a history of congestive heart failure (4.1%). Drug-induced hypotension usually responded to drug discontinuation and intravenous fluids. Although vernakalant increases the maximal corrected Q-T interval, only rare cases of torsades de pointes have been reported. So far, the oral form of the drug appears to have a low incidence of subjective and proarrhythmic adverse effects.

Regulatory Affairs

Although the U.S. Food and Drug Administration cardiorenal panel recommended the approval of intravenous vernakalant by a 6-2 vote for the indication of rapid conversion of AF, concerns about the safety of the drug have delayed regulatory approval in the United States. Further studies to assess the

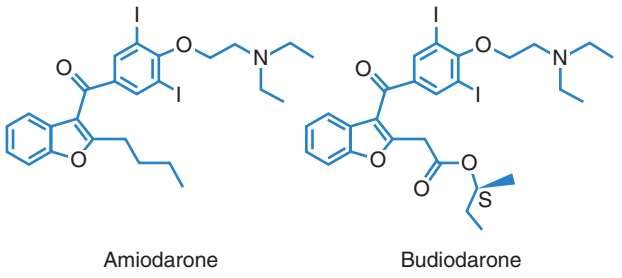

FIGURE 81-8 Chemical structure of budiodarone compared with amiodarone. Budiodarone is a benzofuran derivative with a sulfhydryl moiety. It has a smaller volume of distribution, shorter half-life of 7 hours, and achieves steady state in 2 to 3 days.

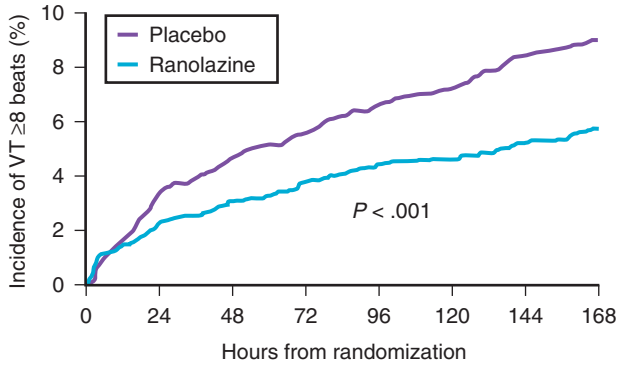

FIGURE 81-9 Effectiveness of ranolazine in the suppression of ventricular arrhythmias acutely after non–ST-elevation myocardial infarction. Kaplan-Meier estimated rates of the first occurrence of an episode of ventricular tachycardia *(VT)* lasting at least 8 beats. The incidence of VT was significantly lower in patients treated with ranolazine versus placebo at 24 hours after randomization (2.3% vs. 3.4%; relative risk, 0.67; 95% confidence interval, 0.50-0.90; $P = .008$) and 48 hours (3.1% vs. 4.7%; relative risk, 0.65; 95% confidence interval, 0.51-0.84; $P < .001$). (From Scirca et al: Effect of ranolazine, an antianginal agent with novel electrophysiological properties, on the incidence of arrhythmias in patients with non–ST-segment–elevation acute coronary syndrome, *Circulation* 116:1647–1652, 2007.)

efficacy and safety of intravenous vernakalant (ACT V) are ongoing. Intravenous vernakalant has been approved by European regulatory bodies.

Phase III prospective trials to assess the efficacy and safety of oral vernakalant in the maintenance of sinus rhythm in AF patients are planned.

Other Amiodarone Analog Compounds (Celivarone, Budiodarone)

Celivarone (SSR149744C), developed by Sanofi-Aventis, has electrophysiological effects similar to those of dronedarone, with a longer half-life of 28 to 35 hours, so the drug can be given once a day.[2] No iodine moieties are present in the celivarone molecule, and thus thyroid adverse effects should not be an issue. An early phase II human trial with oral celivarone reported no dose effect (50 mg, 100 mg, 200 mg, 300 mg once a day) in preventing the recurrence of persistent AF following cardioversion. The 50-mg once-daily dose had a recurrence rate of 52.1% at 3 months compared with 67.1% for the placebo group ($P = .055$). Celivarone holds some promise for suppressing implantable cardioverter-defibrillator discharges in patients.[2]

Budiodarone (ATI-2042), developed by ARYX, is an amiodarone-like compound (addition of a sec-butyl acetate side chain at position 2 of the benzofuran moiety) with a short half-life of 7 hours (Figure 81-8).[2] Budiodarone has multi-channel–blocking electrophysiological effects with increased effects on atrial refractory periods compared with amiodarone. Preliminary patient trials have shown that budiodarone twice daily is effective in suppressing the AF burden in a dose-dependent fashion, as assessed by pacemaker monitoring logs. Larger scale AF trials are needed to determine budiodarone's safety and efficacy.

Ranolazine (Ranexa)

Ranolazine is a piperazine derivative that is approved for the treatment of angina at a dose of 500 mg to 100 mg twice daily.[17] Ranolazine reduces calcium overload in the ischemic myocyte via late sodium channel blockade. The drug is extensively metabolized in the gut and liver (CYP3A4), and its elimination half-life is 7 hours. Steady state is reached after 3 days of twice-daily dosing. CYP3A4 inhibitors such as diltiazem and verapamil will increase ranolazine levels. Because ranolazine is a substrate of P-glycoprotein, inhibitors of P-glycoprotein such as verapamil may increase the absorption of ranolazine and increase plasma levels. In addition, ranolazine increases digoxin levels up to twofold probably through competition in the P-glycoprotein pathway in the intestine and kidneys. The most common adverse effects with ranolazine include dizziness, nausea, dyspepsia and headache.

In relation to its potential in suppressing AF, ranolazine inhibits I_{Kr} and late I_{Na}. Although ranolazine increases the Q-T interval in a dose-related manner, drug-induced torsades de pointes is uncommon via a protective effect similar to that of dronedarone and amiodarone, with no increase in the dispersion of repolarization. Basic studies have demonstrated that the inhibition of late I_{Na} mitigates the inhibition of I_{Kr}. In the Metabolic Efficiency with Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndromes (MERLIN) trial, the drug was shown to be safe for use in patients with acute coronary syndromes, and some antiarrhythmic effect was seen in the atria and ventricles (Figure 81-9).[19] Basic electrophysiological data suggest that ranolazine may be useful in suppressing AF and have shown that ranolazine can abolish ectopic activity from pulmonary vein sleeves as a result of re-entry, delayed after-depolarization, and late phase 3 EAD triggered activity.[20] The clinical efficacy of ranolazine in suppressing AF is documented in small patient trials and in the MERLIN study.[21] Further clinical trials will be required to establish ranolazine's effectiveness in suppressing AF.

Other Compounds

Although a number of compounds with atrial specificity and drugs that improve gap junction facilitation are being developed, these compounds have not yet been studied in clinical trials but may hold promise in the future.[2]

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CHAPTER 82

Non-antiarrhythmic Therapies for Cardiac Arrhythmias

Prakash Deedwania and Joel A. Lardizabal

Background

Heart disease in any form may predispose the patient to the development of ventricular arrhythmias, some of which are lethal and may lead to sudden cardiac death (SCD). As a major public health burden, SCD has an incidence of nearly a half-million cases every year in the United States.[1] Considerable effort has been invested in devising therapies specifically aimed at reducing the incidence of ventricular arrhythmias, particularly in the setting of ischemic heart disease and heart failure, where these fatal arrhythmias are exceedingly common. To date, however, the preponderance of evidence shows that the strategy of using antiarrhythmic drug therapy to directly suppress arrhythmias fails to improve morbidity or mortality outcomes. In ischemic heart disease, the Cardiac Arrhythmia Suppression Trial (CAST), the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT), and the European Myocardial Infarct Amiodarone Trial (EMIAT) found that antiarrhythmic therapy either increased mortality or failed to reduce it.[2-4] A similar observation was noted in the Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure (CHF-STAT) and the Antiarrhythmic Trial with Dronedarone in Moderate to Severe Congestive Heart Failure Evaluating Morbidity Decrease (ANDROMEDA) in the setting of heart failure.[5,6] The use of an implantable cardioverter-defibrillator (ICD), a form of nonpharmaceutical antiarrhythmic therapy, has been shown to be beneficial in the long term but has failed to improve survival in the early postmyocardial infarction period when the incidence of SCD is highest.[7]

Growing evidence, however, suggests that certain therapies that are not used primarily for antiarrhythmic intent can actually be effective in preventing the development of ventricular arrhythmias, reducing their recurrence, and decreasing SCD incidence. Among these so-called *non-antiarrhythmic* therapies are β-adrenergic blocking agents, calcium channel blockers (CCBs), statins, fish oil, and renin-angiotensin-aldosterone system (RAAS) antagonists, and others (Figure 82-1). These agents are thought to target the underlying disease processes and reverse the basic pathophysiological substrates that promote arrhythmogenesis; this is expected to result in long-term cardiac electrophysiological stabilization.

Sudden Cardiac Death and Ventricular Arrhythmias

SCD is the unexpected natural death from a cardiac cause a short time after onset of symptoms, defined epidemiologically as any cardiac death occurring out of the hospital or taking place in the emergency room. It accounts for 63% of all cardiovascular deaths, and 84% of SCDs are caused by ventricular arrhythmias, often starting as ventricular tachycardia, rapidly progressing to ventricular fibrillation.[8,9] Although not all instances of SCD are caused by arrhythmias, it is used by most investigations on cardiovascular outcomes as a surrogate marker for lethal ventricular arrhythmias. Crude and imprecise as it may be, SCD incidence still serves as an important indicator that helps measure the clinical effects of various antiarrhythmic therapies.

β-Blockers

The role of β-adrenergic blocking agents in the prevention of ventricular arrhythmia and SCD is well established, especially in the setting of ischemic heart disease and heart failure. Early observational studies showed that the β-blockers timolol, metoprolol, and propranolol reduced the incidence of SCD by 30% to 45% after myocardial infarction. In a large randomized study, the Clopidogrel and Metoprolol in Myocardial Infarction Trial: The Second Chinese Cardiovascular Study (COMMIT-CCS2) found a 17% relative risk reduction in the incidence of ventricular fibrillation with the early use of metoprolol in patients with myocardial infarction.[10] The Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial involving patients with myocardial infarction and heart failure also revealed that carvedilol was associated with a 77% reduction in the risk of malignant ventricular arrhythmias as well as a 23% reduction in overall mortality. In patients with heart failure, β-blockers were found to have a more pronounced and more consistent effect in reducing SCD than any other therapy, including angiotensin-converting enzyme (ACE) inhibitors. The Cardiac Insufficiency Bisoprolol Study II (CIBIS II) demonstrated that bisoprolol reduced SCD by 44% and total mortality by 34% in patients with severe symptomatic systolic heart failure. Similarly, β-blockers reduced SCD in heart failure by 43% in the Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure (MERIT-HF), in which long-acting metoprolol was used, and by 36% in the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial, in which carvedilol was used.[11] Some agents may have greater antiarrhythmic properties than others, as seen in the Carvedilol Or Metoprolol European Trial (COMET), where carvedilol reduced SCD incidence more than did metoprolol in patients with myocardial infarction.[12]

Although not used clinically as antiarrhythmics in the strict sense, β-blockers are known to have antiarrhythmic properties and are grouped as class II agents in the Vaughan-Williams

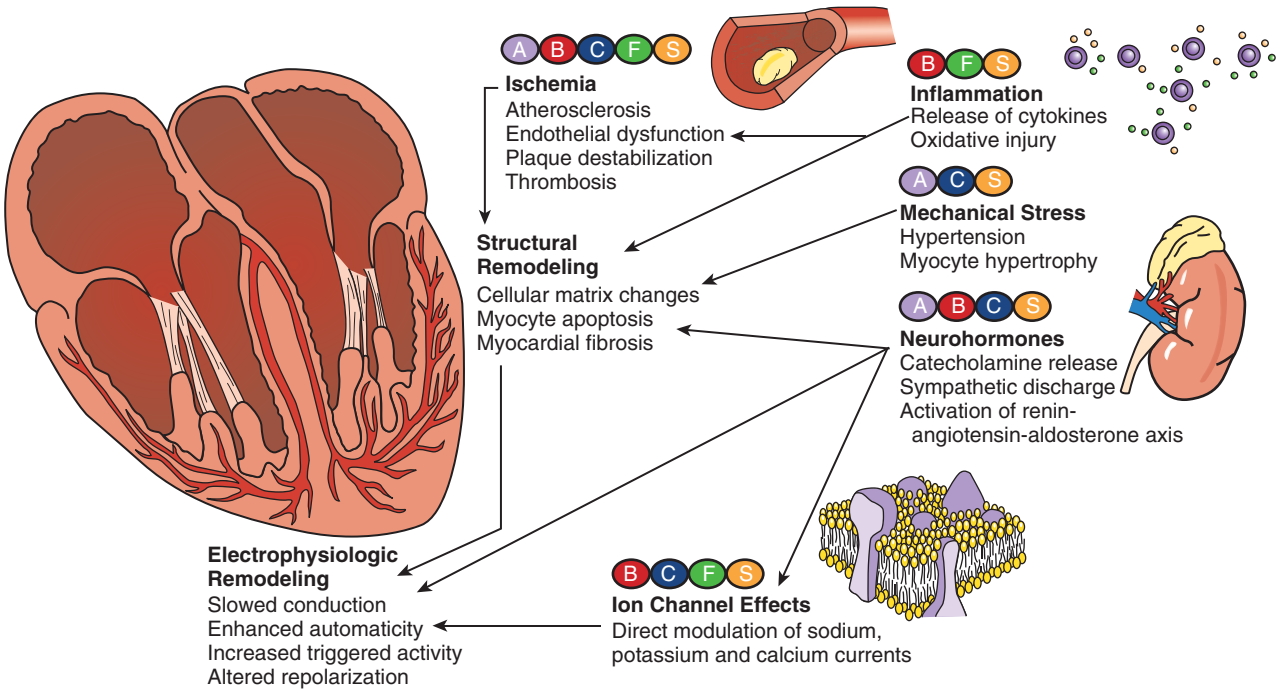

FIGURE 82-1 Possible pathophysiological mechanisms for ventricular arrhythmogenesis and proposed modes of action of the non-antiarrhythmic therapies. *A*, Renin-angiotensin-aldosterone antagonists; *B*, β-adrenergic blockers; *C*, calcium-channel blockers; *F*, fish oil; *S*, statins.

classification of antiarrhythmics. They differ from the "classic" antiarrhythmic agents in that β-blockers do not directly modify ion channel functions but, rather, prevent the arrhythmogenic actions of β-adrenergic stimulation. In addition to competitive antagonism of β-adrenergic subtype receptors (β_1 and β_2 being the most important), individual β-blockers may also exhibit intrinsic sympathomimetic activity, inverse agonism, vasodilating properties, and α_1-receptor antagonism.

In ischemic heart disease, β-blockers reduce myocardial oxygen demand, optimize diastolic filling, and improve coronary blood flow as a result of their negative chronotropic and inotropic effects. Areas of ischemic myocardium are particularly prone to arrhythmogenesis, and the suppression of ventricular arrhythmias by β-blockers may be partly attributed to their anti-ischemic properties. Myocardial infarction induces a state of heightened catecholamine discharge and autonomic dysfunction, both of which lower the threshold for ventricular fibrillation. Antagonism of this high cardiac sympathetic tone may also explain the protective effect of β-blockers against SCD. Antiproliferative and antiatherogenic mechanisms have also been proposed for some agents. Studies on animal models of myocardial ischemia further suggest that certain β-blockers may have sodium channel–blocking actions that could stabilize the myocyte membrane and suppress ventricular arrhythmias, similar to class I antiarrhythmic agents.[13] β-Blockers may even induce electrophysiological changes in action potential by blocking the L-type calcium current, the transient outward potassium current, and the rectifier potassium current, resembling the class III antiarrhythmic actions of amiodarone. Experimental models also postulate that specific β-blockers such as carvedilol could exert significant antioxidant activity that protects the myocardium from reperfusion arrhythmias through adenosine-mediated processes.[14]

In patients with heart failure, chronic catecholamine stimulation exerts long-term biologic effects that induce significant changes in the pattern of myocardial cell growth, apoptosis, and cellular matrix composition, also known as *mechanical remodeling*. These myocardial structural changes and fibrosis associated with cardiomyopathy and ventricular hypertrophy result in electrophysiological changes that can initiate and perpetuate lethal arrhythmias by altering refractoriness, increasing repolarization abnormalities, slowing conduction, enhancing automaticity, and increasing triggered activity. In chronic heart failure, β-blockade helps reverse these structural and electrophysiological remodeling processes through the modulation of gene expression as well as by direct inhibition of adrenergic stimulation. This is in addition to the previously described anti-ischemic, membrane-stabilizing, direct ion channel–blocking, and antioxidant properties of β-blockers that are also of benefit in the setting of heart failure.

Although β-blockers have been shown to significantly reduce ventricular arrhythmias and SCD, adverse events associated with this therapy, which include worsening heart failure and cardiogenic shock, have somewhat diminished their benefits on overall mortality and morbidity outcomes.

Statins

It is well established that lipid-lowering therapy using 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) is associated with reduction in cardiac and all-cause mortalities.

This is, perhaps, reflective of the known beneficial effects of statin therapy on coronary atherosclerosis. Evidence that statins significantly reduce lethal arrhythmias and SCD is also growing. Although reduction in SCD is expected with any therapy that reduces the initiation and progression of ischemic heart disease, clinical and experimental data suggest that statin therapy may have direct and indirect antiarrhythmic properties that are independent of its cholesterol-lowering effects.

In patients with atherosclerotic heart disease enrolled in the Antiarrhythmics versus Implantable Defibrillators (AVID) trial, lipid-lowering therapy was associated with a 40% relative risk reduction in ventricular tachyarrhythmias and cardiac mortality.[15] This significant benefit was expressed early in follow-up and is unlikely to be from the effects on cholesterol levels. In the Multicenter Automatic Defibrillator Implantation Trial (MADIT)-II involving patients with coronary artery disease and heart failure, statin use was associated with risk reductions of 28% for ventricular arrhythmias and 35% for SCD, with no significant effect on non-SCD.[16] In the setting of nonischemic cardiomyopathy, an analysis of the Defibrillators in Non-ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial showed that statin therapy was associated with an 86% reduction in arrhythmic sudden death, 22% reduction in ICD shocks from ventricular arrhythmias, and 78% reduction in mortality.[17] A meta-analysis of randomized controlled trials on pravastatin, simvastatin, atorvastatin, and fluvastatin showed that statin treatment decreased the risk of SCD by 19%.[18] The findings of these observational studies were further supported by small randomized trials in which patients with advanced heart failure treated with statins had significantly lower rates of SCD and all-cause mortality but not of pump failure.[19]

Statins have pleiotrophic effects that go beyond lipid lowering, including anti-inflammatory, anti-proliferative, anti-oxidative, and anti-thrombotic properties, which may as well explain their apparent antiarrhythmic effects. Myocardial ischemia is a potent trigger for lethal ventricular arrhythmias, and both atorvastatin and pravastatin have been shown to significantly reduce myocardial ischemia in the Study Assessing Goals in the Elderly (SAGE) and the Regression Growth Evaluation Statin Study (REGRESS).[20,21] Proposed mechanisms include inhibition of luminal narrowing, restoration of endothelial function, plaque stabilization, anti-inflammatory effects, as well as modification of hemostatic processes that ultimately lead to improvement in myocardial perfusion and amelioration of ischemia-driven reperfusion injury. Ischemic heart disease is associated with cardiac electrophysiological remodeling leading to the formation of anatomic barriers, regions of slow conduction, and prolonged repolarization. In animal models of myocardial infarction and heart failure, successful inhibition of myocardial remodeling has been demonstrated with simvastatin and fluvastatin.[22,23]

Aside from their anti-ischemic properties, statins may also exert antiarrhythmic effects through various structural, neurohormonal, and electrophysiological mechanisms. The bilayer phospholipid structure of the membranes, as well as its functions, can be altered by changes in the dietary distribution of fatty acids.[24] At least in theory, it may be possible for statins to exert direct antiarrhythmic effects by changing the lipid environment of the myocyte cell or organelle membranes, which results in altered channel protein function and ionic currents. Cardiomyocyte hypertrophy usually follows myocardial infarction and contributes to ventricular remodeling that, in turn, predisposes to ventricular arrhythmias. Pravastatin has been shown to decrease such hypertrophy in animal studies, probably by decreasing the secretion of endothelin-1. Dysfunctional intramyocardial calcium handling results in ventricular action potential abnormalities. By inhibiting intracellular calcium mobilization and transmembrane currents, statin therapy could stabilize ventricular repolarization and decrease the risk of arrhythmia.[25] Overexposure of the myocardium to cathecholamines, in addition to worsening ischemia, also directly stimulates arrhythmogenesis. In experimental models, lipid-lowering therapy has been shown to normalize autonomic function and decrease sympathetic tone, as well as increase the cardiac response to parasympathetic stimulation.[26,27] Diminished heart rate variability, an electrophysiological marker of endothelial dysfunction, is a known predictor of susceptibility to arrhythmias and SCD. Rosuvastatin and simvastatin have been shown in animal models to improve heart rate variability, likely through the modulation of nitric oxide synthase function.[28] Increased QT variability, another marker of vulnerability to lethal arrhythmias, has been shown to improve with atorvastatin and fluvastatin therapy.[29]

Despite its well-established beneficial effect on cardiovascular mortality and evidence of reduction of SCD, the antiarrhythmic role of statins is still under debate because of conflicting reports. In the setting of myocardial ischemia, high-dose atorvastatin did not reduce the rates of resuscitated cardiac arrest in the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) and Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trials.[30,31] In patients with stable coronary artery disease, statin therapy similarly did not reduce the incidence of resuscitated cardiac arrest with the use of atorvastatin in the Treat to New Targets (TNT) trial and simvastatin in the Scandinavian Simvastatin Survival Study (4S).[32,33] In fact, the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) showed a trend toward a higher incidence of malignant arrhythmias with atorvastatin in high-risk hypertensive patients.[34] The small number of patients who presented with life-threatening arrhythmias in these negative studies may explain disparities in outcomes, but large randomized trials that address the issue directly are still lacking. For now, statin use for prevention of ventricular arrhythmias seems only to benefit patients who had acute myocardial infarction, those who underwent revascularization procedures, and those who received ICDs.

Fish Oil

Epidemiologic data, including that of the U.S. Physicians Health Study, indicate that ingestion of very-long-chain n-3 polyunsaturated fatty acids (n-3 PUFA), found in fish or fish oil, is associated with reduced cardiovascular mortality.[35] This was further reinforced by clinical investigations, including the Diet and Reinfarction Trial, which showed that consumption of fatty fish was associated with a 30% reduction in all-cause mortality.[36] This was largely thought to result from the stabilization of the atherosclerotic plaque by n-3 PUFA through its lipid-lowering, anti-thrombotic, and anti-inflammatory properties. The GISSI-Prevenzione trial found a 45% reduction in SCD in patients with previous malignant ventricular arrhythmias who consumed 1 g of n-3 PUFA daily.[37] In this trial, the beneficial effect of n-3 PUFA was thought to be unrelated to its effects on the lipid profile because the reduction in SCD appeared very early, and no effect was observed on the rate of myocardial infarction. This finding was reaffirmed in the Cardiovascular Health Study, which noted that frequent fish consumption was associated with a 58% reduction in

arrhythmic death without changing the risk of myocardial infarction.[38] This led to the theory that n-3 PUFA acids may have antiarrhythmic and antifibrillatory properties that are independent of their antiatherosclerotic and anti-thrombotic effects.

Such hypothesis is also supported by animal and experimental evidence. In an animal model of ischemia-induced SCD, infusion of n-3 PUFA emulsion prior to coronary artery ligation prevented ventricular fibrillation by 75%.[39] Long-term feeding studies in primate models showed that n-3 PUFA supplementation and successful incorporation of the fatty acids into the myocardial membrane significantly reduced myocardial vulnerability to arrhythmic stimuli induced by ischemia.[40] Dietary n-3 PUFA also reduced drug-induced repolarization abnormalities and abolished ventricular arrhythmias in a rabbit model.[41] These cardioprotective effects have been attributed specifically to eicosapentaenoic and docosahexaenoic acids, which make up the majority of n-3 PUFA in fish-derived fats.

Ultrastructural, metabolic, electrophysiological, and autonomic mechanisms have been proposed to explain the antiarrhythmic effects of n-3 PUFA. The metabolic effects of n-3 PUFA may be able to modulate biochemical processes that promote ventricular arrhythmias through their actions on cardiac voltage-gated sodium channels, on inositol-mediated cell signaling, and on eicosanoid-mediated inflammatory reactions. Direct electrophysiological stabilization of the cardiomyocyte by n-3 PUFA was thought to be largely caused by the modulation of fast, voltage-dependent sodium currents, and the L-type calcium channels in the myocyte membranes that mediate the final common pathway affecting the excitability of the heart cell. Other possible modes of action include their inhibition of the delayed-rectifier potassium channel current and suppression of the sodium-calcium exchanger, which ultimately mediate aberrations in ventricular repolarization. These sodium, calcium, and potassium currents in the myocyte membrane are also actively involved in autonomic regulation. In cultured myocytes, n-3 PUFA were able to attenuate sympathetically induced arrhythmias, independent of confounding hormones and neurotransmitters.

The consistent reduction of cardiac mortality and SCD with n-3 PUFA in observational human studies and experimental investigations has brought to light a major role of fish oil in cardiovascular therapy. However, randomized controlled trials have so far failed to demonstrate a clinically relevant antiarrhythmic effect. The Fatty Acid Antiarrhythmia Trial randomized patients at high risk for fatal ventricular arrhythmias to supplementation with either fish oil or placebo and found a trend toward reduced risk of arrhythmic events with n-3 PUFA, but this did not reach statistical significance.[42] A multicenter, double-blind study in the United States that randomized patients with recent malignant ventricular arrhythmias to fish oil or placebo showed that n-3 PUFA supplementation did not prevent episodes of ventricular tachycardia or fibrillation.[43] In fact, a trend toward increased ventricular arrhythmia occurrence was seen, which suggests a proarrhythmic effect of fish oil. The Study on Omega-3 Fatty Acids and Ventricular Arrhythmia (SOFA), a similar multicenter, randomized, placebo-controlled study conducted in Europe, also found no evidence of a strong protective effect of n-3 PUFA against ventricular arrhythmia.[44] It did, however, establish that fish oil treatment does not cause harmful proarrhythmic effects. Meta-analysis of randomized trials involving nearly 33,000 patients found that fish oil supplementation was associated with a significant (20%) reduction in cardiac death, but it had no effect on arrhythmias or overall mortality.[45] Proposed explanations for the inconsistent data in clinical trials include differences in study protocols, lack of standardized dosing, and inconsistencies in duration of supplementation, among a host of other confounders. Since most of the benefits were seen in the setting of early ischemic heart disease, it is conceivable that the antiarrhythmic utility of n-3 PUFA may be confined only to prevention of ventricular arrhythmia in patients with recent myocardial infarction, when the amount of scar tissue is still limited.

Renin-Angiotensin-Aldosterone System Antagonists

The benefit of ACE inhibitors in reducing cardiovascular and overall mortality in the setting of heart failure and ischemic heart disease is firmly established. A favorable effect on SCD was also noted, suggesting possible antiarrhythmic properties of ACE inhibitors. In patients with chronic heart failure, the Vasodilator Heart Failure Trial II (V-HEFT-I) demonstrated that enalapril reduced ventricular arrhythmias by 27% and SCD by 52%.[46] Post hoc analyses of the Survival and Ventricular Enlargement (SAVE) trial and the Studies of Left Ventricular Dysfunction (SOLVD) trials also showed a trend toward reduced arrhythmic events and SCD, albeit not statistically significant.[47,48] In patients with acute myocardial infarction, however, the Acute Infarction Ramipril Efficacy (AIRE) trial found that ramipril not only reduced total mortality but also decreased the incidence of SCD by 30%.[49] Even in patients without heart failure, the Heart Outcomes Prevention Evaluation (HOPE) trial demonstrated that ramipril was able to cut arrhythmic death by 21%.[50] Analyses of the Chinese Cardiac Study (CCS-1), the Cooperative New Scandinavian Enalapril Survival Study (CONSENSUS)-II, the Fourth International Study of Infarct Survival (ISIS-4), and the Survival of Myocardial Infarction Long-Term Evaluation (SMILE) trial also showed a trend toward reduced arrhythmic events and SCD, but none achieved statistical significance.[51-54]

Depressed left ventricle (LV) systolic function and ventricular dilatation are the most important predictors for developing ventricular arrhythmias. ACE inhibitors are thought to reduce SCD primarily because of their beneficial effect in reversing LV remodeling and improving systolic function. Electrophysiological remodeling also accompanies these myocardial fibrosis and structural changes, leading to slow conduction, early afterdepolarization (EAD), and other proarrhythmic repolarization abnormalities. ACE inhibitors have been shown to reduce the degree of ventricular dispersion of repolarization by maintaining myocyte sodium and pH homeostasis, acting analogously as a class I antiarrhythmic agent.[55] ACE inhibitors are also hypothesized to exert antiarrhythmic effects through antiatherosclerotic, anti-thrombotic, and neurohormonal mechanisms. Stabilization and regression of atherosclerotic plaque has been shown to be associated with ACE inhibitor therapy.[56] Angiotensin-II is a vasoactive peptide that can activate inflammatory cytokines, promote ultrastructural myocardial fibrosis, modulate myocyte ion channels, induce release of endogenous cathecholamines, decrease gap junction conduction, and increase transmural dispersion of refractoriness in the ventricles.[57] These effects substantially increase the propensity for arrhythmogenesis and SCD but can be effectively attenuated with ACE inhibitor or angiotensin receptor blocker (ARB) therapy.

Although observational and small prospective randomized studies point toward a modest reduction in ventricular arrhythmias, strong evidence to confirm the long-term antiarrhythmic benefit of ACE inhibitors is currently lacking.[58] It was postulated

that ACE inhibitors only have a modest effect on ventricular arrhythmias and SCD because of incomplete blockade of angiotensin II. In the Evaluation of Losartan in the Elderly (ELITE) study comparing the ARB losartan and the ACE inhibitor captopril in patients with heart failure, a 46% risk reduction in total mortality was seen with losartan compared with captopril, primarily because of a 64% risk reduction in SCD.[59] This difference in SCD and mortality outcomes, however, was no longer seen in the subsequent ELITE-II trial. In the Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan (OPTIMAAL) of patients with acute myocardial infarction, losartan was associated with a 19% risk reduction in SCD compared with captopril, although there were fewer cardiovascular deaths with captopril.[60] ARBs were thought to exert a more complete inhibition of angiotensin II, especially at the tissue level, and this may explain its apparent advantage over ACE inhibitors. The Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) trial showed that the ARB candesartan, when added to standard heart failure therapy that includes ACE inhibitors (with or without β-blockers and aldosterone-antagonists), improves mortality and morbidity outcomes, perhaps because of a more comprehensive inhibition of the RAAS.[61] Like ACE inhibitors, regression of left ventricle hypertrophy (LVH) is seen with ARB therapy, which can explain a large part of its perceived antiarrhythmic effects. The Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) trial found that regression of LVH with losartan was associated with a 30% reduction in SCD, independent of blood pressure reduction and other cardiac risk factors.[62]

Aldosterone can induce arrhythmogenesis through mechanisms similar to that of angiotensin-II, including detrimental effects on LV structural and electrophysiological remodeling, myocardial fibrosis, endothelial dysfunction, platelet activation, and sympathetic tone. In patients with chronic heart failure, the aldosterone antagonist spironolactone was associated with a significant reduction in SCD by 29% and total mortality by 30% in the Randomized Aldactone Evaluation Study (RALES).[63] In patients with myocardial infarction, the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) found a 21% reduction in SCD and 15% reduction in overall mortality with the selective aldosterone blocker eplerenone.[64] Eplerenone reduced SCD by 37% within 30 days when given early (7 days average) after myocardial infarction.[65] Concerns have been expressed, however, regarding the safety of aldosterone antagonist therapy because of significant increase in hyperkalemia-related morbidity after publication of the RALES study.[66]

Nondihydropyridine Calcium Channel Blockers

CCBs comprise the class IV antiarrhythmics of the Vaughan-Williams system. However, only two agents that are predominantly cardioselective—the nondihydropyridine verapamil and diltiazem—are used primarily for antiarrhythmic intent, exerting their electrophysiological effects by inhibiting the slow calcium channel that deloparizes both the sinoatrial and atrioventricular nodes. The more widely used dihydropyridine CCBs are selective for blood vessels at therapeutic doses, relaxing arteriolar smooth muscles without clinically detectable myocardial depression.

Analyses of landmark studies in hypertension indicated a favorable effect of nondihydropyridine CCBs on SCD, suggesting possible significant antiarrhythmic properties. In the Systolic Hypertension in Europe Trial, successful antihypertensive therapy using nitrendipine, with the possible addition of enalapril or hydrochlorothiazide, significantly reduced SCD by 26% and total mortality by 24%.[67] The Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial of hypertensive patients found that the addition of amlodipine to ACE inhibitor therapy increased the rate of resuscitation after sudden cardiac arrest by 75% and reduced cardiac mortality by 20% when compared with combination ACE inhibitor-thiazide therapy.[68] In high-risk hypertensive patients with diabetes and coronary artery disease, long-acting nifedipine was found to be as effective as ACE inhibitors in reducing cardiovascular events, with a trend toward better SCD outcomes.[69] In the setting of chronic heart failure, the Prospective Randomized Amlodipine Survival Evaluation (PRAISE) trial showed that the addition of amlodipine to standard heart failure therapy was associated with a 21% reduction in sudden cardiac death, which was much higher than the reduction in other modes of cardiac death, pointing to a possible antiarrhythmic mechanism for this particular CCB.[70]

Nondihydropyridine CCBs are known to have antianginal and anti-ischemic effects, and this might partially explain some of their antiarrhythmic properties. In animal models of myocardial ischemia, nondihydropyridine CCBs were shown to reduce ventricular arrhythmias from reperfusion injury, possibly related to their attenuation of cardiac sympathetic nerve activity.[71] Subgroup analysis of the PRAISE trial, however, found a 38% reduction in SCD with amlodipine in patients with heart failure caused by nonischemic etiologies, and it appears to have no effect on cause-specific mortality in ischemic cardiomyopathy. The apparent antiarrhythmic properties of nondihydropyridine CCBs may just be a reflection of their beneficial effects on regression of LV hypertrophy and remodeling, which are independent predictors of SCD.[72] Hypertension, in itself, is associated with development of complex ventricular arrhythmias; thus control of hypertension with effective agents, including CCBs, is expected to have a favorable impact on SCD.[73]

Other Therapies

Ranozaline, a piperazine, is the first among a novel class of agents that exert antianginal effects by enhancing myocardial relaxation and reducing diastolic dysfunction. In addition to its anti-ischemic effects, ranozaline therapy was also shown by the Metabolic Efficiency With Ranolazine for Less Ischemia in Non ST-Elevation Acute Coronary Syndrome Thrombolysis in Myocardial Infarction (MERLIN-TIMI)-36 trial to be associated with a significant 36% reduction in ventricular arrhythmias in patients with acute coronary syndrome.[74] Its anti-ischemic properties could be attributed to the inhibition of the late phase of the inward sodium current, which is responsible for cytosolic calcium accumulation that ultimately leads to impaired myocardial mechanical relaxation. The increased concentration of intracellular calcium also produces electrical instability and repolarization abnormalities that promote ventricular arrhythmogenesis, a process which ranozaline can potentially modulate. In experimental models, ranozaline was shown to induce ion channel alterations similar to that of amiodarone, leading to suppression of EADs and reduction in spontaneous ventricular arrhythmias.[75] In spite of its favorable effects on ventricular arrhythmias, however, ranozaline has not yet been shown to reduce mortality or major adverse cardiovascular events, and data on SCD are lacking.

Practice Guidelines

The current guidelines on management of ventricular arrhythmias and prevention of SCD, published jointly by the American College of Cardiology (ACC), American Heart Association (AHA), and European Society of Cardiology (ESC), consider β-blockers to be the mainstay of antiarrhythmic therapy because of their safety and proven efficacy.[76] The current guidelines also recognize the antiarrhythmic properties of statins and fish oil, and their potential role in SCD prevention. However, no definite recommendations were made on their utility because of conflicting clinical data on their effectiveness.

Non-antiarrhythmic Therapy of Atrial Fibrillation

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice, with a prevalence of over 2.2 million in the United States alone. This figure continues to rise to epidemic proportions, given the steady incidence of AF in the setting of an aging global population, in which more and more people survive to an age when this condition predominates. AF, a major risk factor for stroke, is associated with considerable morbidity and mortality, especially in association with other conditions such as heart failure.

The concept of AF cardioversion and maintaining patients on sinus rhythm is appealing, given the theoretical benefit on improved hemodynamics. However, multiple landmark trials in AF (including the AFFIRM, PIAF, RACE, STAF, and HOT-CAFÉ studies) repeatedly failed to demonstrate any long-term advantage of a rhythm-control strategy over the rate-control approach.[77] Even in the setting of heart failure, where antiarrhythmic therapy was thought to have the greatest impact, the Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial found no clear evidence to recommend a routine rhythm-control approach.[78] In fact, some of these studies even point toward worse morbidity outcomes with the use of pharmacologic antiarrhythmic agents.

With the disappointing track record of conventional antiarrhythmic drugs in AF management, attention has turned toward non-antiarrhythmic therapeutic alternatives. In addition to β-blockers, a growing body of evidence suggests that RAAS antagonists, statins, n3-PUFA, antioxidants, and anti-inflammatory agents can favorably alter the natural course of AF by modulating the underlying structural, electrophysiological, and neurohormonal substrates that fuel atrial arrhythmogenesis.

β-Blockers in Atrial Fibrillation

The utility of β-adrenergic blocking agents for rate control in AF is well established. However, their role in preventing the development of AF and in maintaining sinus rhythm is less well defined. Such a role has been most documented in the setting of cardiac surgery as prophylaxis against postoperative AF. Metoprolol was associated with a 20% reduction in postoperative AF after elective cardiac surgery, while carvedilol was associated with a 15% lower incidence of AF after coronary artery bypass grafting.[79,80] The excessive adrenergic stimulation wrought by cardiac surgery is thought to promote postoperative atrial arrhythmogenesis, a process β-blockers could effectively attenuate. Pericardial inflammation and oxidative injury also are known triggers for postoperative AF, and these can be modulated by the antioxidant actions of certain β-blockers, carvedilol in particular.[81] In patients with heart failure, in addition to their known benefits on mortality and morbidity rates, the use of β-blockers was associated with 27% risk reduction in AF incidence.[82]

Small randomized controlled trials found that patients with AF taking metoprolol had significantly lower relapse rates compared with those on placebo after successful cardioversion and repeated cardioversion to sinus rhythm. However, nearly half of the subjects on this β-blocker still had AF relapse after 6 months of follow-up.[83,84] Some evidence suggests that β-blockers only have significant antiatrial fibrillatory effects in those with hypertension.[85] Even in hypertensive patients, however, the LIFE trial demonstrated that atenolol was inferior to losartan in preventing new-onset AF and stroke.[86]

Renin-Angiotensin-Aldosterone System Antagonists in Atrial Fibrillation

The various effects of angiotensin-II and RAAS activation on myocyte fibrosis and electrophysiological remodeling, which are known to promote ventricular arrhythmias, also affect the atria, creating substrates for supraventricular arrhythmogenesis. The ability of ACE inhibitors and ARBs to reverse this maladaptive process could explain most of their antifibrillatory effects seen in the clinical setting.

Retrospective analyses of large randomized trials point to a possible desirable effect of ACE inhibitors on AF pathogenesis. Trandolapril was associated with a 47% reduction in the incidence of new-onset AF in patients with systolic dysfunction after myocardial infarction who were enrolled in the Trandolapril Cardiac Evaluation (TRACE) study.[87] Similarly, in the SOLVD trial, enalapril was found to be the most powerful predictor for AF risk reduction in patients with systolic dysfunction, accounting for a 78% decrease in AF incidence compared with placebo.[88]

A similar observation was noted in the post hoc analyses of ARB trials. Losartan was associated with a 33% risk reduction in new-onset AF compared with atenolol in hypertensive patients enrolled in the LIFE study, which translated to lower adverse cardiac events and stroke rates. Hypertensive patients in the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial had a 32% reduction in the incidence of persistent AF when treated with amlodipine. Patients with heart failure in the Val-HEFT study who were treated with valsartan had a 37% reduction in AF incidence.[89] A more modest benefit was seen in the CHARM trial, where candesartan was associated with an 18% reduction in AF incidence compared with placebo in patients with symptomatic heart failure.[90]

In small prospective trials, the addition of ACE inhibitors or ARBs to amiodarone resulted in lower AF recurrence rates after cardioversion compared with amiodarone treatment alone.[91,92] Meta-analyses of RAAS antagonist trials suggest that both ACE inhibitors and ARBs appear effective in preventing AF but may only be limited to patients with LV dysfunction or to those undergoing cardioversion.[93]

More recent randomized trials, however, provide contradictory data on the antifibrillatory effect of RAAS antagonists. Analysis of the HOPE trial showed that the ACE inhibitor ramipril did not reduce the incidence of AF compared with placebo.[94] Similarly, the Telmisartan Randomised Assessment Study in ACE-intolerant Subjects with Cardiovascular Disease (TRANSCEND)

found no effect of the ARB telmisartan on the incidence of new-onset AF compared with placebo in patients with high-risk cardiovascular diseases.[95] The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) demonstrated a weak trend toward a lower incidence of new-onset AF with telmisartan compared with ramipril, as well as minimal reduction in new-onset AF with combination telmisartan-ramipril therapy compared with either treatment alone, but these differences were statistically insignificant.[96]

Lipid-Lowering Agents in Atrial Fibrillation

Evidence exists to support the claim that inflammation, marked by increased cross-reactive protein (CRP) levels, is involved in the arrhythmogenesis and perpetuation of AF.[97] Statins have been shown to reduce CRP levels independent of lipid-lowering, and it is plausible that statins exert clinically significant antifibrillatory properties because of their anti-inflammatory and antioxidant effects.[98] Atorvastatin, in particular, has been shown to decrease the recurrence of AF after cardioversion, in part because of reduction in CRP levels.[99] The Atorvastatin for Reduction of Myocardial Dysrhythmia after Cardiac Surgery 3 (ARMYDA-3) trial also found that elevated postoperative CRP levels were associated with a twofold increase in the risk of developing AF after cardiac surgery and that atorvastatin therapy started 1 week prior to surgery was associated with a 61% reduction in postoperative AF.[100] Analysis of the ADVANCENT Registry of patients with LV systolic dysfunction demonstrated that statin therapy was associated with a 31% reduction in the prevalence of AF, which is larger than that seen in β-blockers and ACE inhibitors.[101] This effect on AF was independent of lipid profile, suggesting possible anti-inflammatory and antioxidant mechanisms. Furthermore, experimental data suggest a significant interaction between RAAS and cholesterol homeostasis. Oxidized low-density lipoprotein was shown to upregulate the expression of ACE and angiotensin II. This neurohormonal "cross-talk," which appeared to be attenuated with simvastatin treatment, was thought to be implicated in AF pathogenesis.[102]

In addition to their beneficial effects on lipid profile, fish oils also exert anti-inflammatory properties, as evidenced by the reduction in CRP and cytokine levels.[103] Because of this anti-inflammatory effect, n3-PUFA may have clinical utility in AF therapy, similar to that seen with statins. A small randomized trial found that n3-PUFA treatment was associated with a significant 54% reduction in the incidence of postoperative AF in patients who underwent coronary artery bypass grafting (CABG).[104] Observational data also suggest that dietary consumption of broiled or baked fish was associated with lower incidence of AF in an almost linear fashion.[105] This finding, however, was refuted by larger epidemiologic studies that could not show a beneficial effect of fish consumption on atrial arrhythmias.[106,107]

Other Non-antiarrhythmic Therapies in Atrial Fibrillation

Because inflammation occupies a central role in the pathogenesis of AF, direct suppression of inflammation using corticosteroids has been explored. Prednisone has been shown to prevent experimentally induced AF and atrial flutter in animal models.[108,109] A small prospective study demonstrated that prophylactic administration of steroids was associated with reduced incidence of postoperative AF in patients undergoing CABG, but this was associated with higher complication rates.[110] In another small series, low-dose methylprednisolone therapy was also shown to successfully cut the incidence of recurrent AF through reduction of CRP levels.[111] However, analysis of the Rotterdam study found that high-dose corticosteroid therapy was actually a strong risk factor for the development of AF.[112] Safety issues associated with steroid therapy currently limits its use in AF management.

The AF burden may be associated with increased atrial oxidative stress and peroxynitrite formation, processes that can be attenuated by vitamin C, which possesses antioxidant and anti-inflammatory properties.[113] Some data suggest that vitamin C supplementation might reduce postoperative AF in patients undergoing CABG and also reduce the recurrence of AF after cardioversion.[114,115] More reliable clinical evidence, however, is lacking at this time.

Non-antiarrhythmic Practice Guidelines in Atrial Fibrillation

The current guidelines on AF management, published jointly by the ACC, the AHA, and the ESC, describe β-blockers not only as rate-control agents (their primary role in AF) but also as possible first-line treatment in maintaining sinus rhythm in patients with myocardial infarction, heart failure, and hypertension.[116] Although β-blockers may reduce subacute recurrences of AF after cardioversion, no further recommendations were made because they are unlikely to enhance the success of cardioversion or to suppress immediate or late recurrences of AF. The current guidelines also recognize the potential role of ACE inhibitors, ARBs, and statins in the long-term maintenance of sinus rhythm in high-risk patients; however, further clarification in randomized clinical trials is required before they can be routinely recommended.

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CHAPTER 83

Anticoagulation in Atrial Arrhythmias: Current Therapy and New Therapeutic Options

Pamela S.N. Goldman and Michael D. Ezekowitz

Atrial fibrillation (AF) is an independent risk factor for stroke and the direct cause of 15% to 20% of all strokes.[1] Anticoagulation reduces the relative risk by 68% and all-cause mortality by 33%.[2] In the United States, approximately 500,000 people have strokes each year.[3]

Economics of Stroke

The economic costs of stroke are from direct costs for stroke-related morbidity and mortality, estimated at $17 billion per year. Indirect costs from lost income are $13 billion.[3] Institutional care is the bulk of post-stroke care cost and varies according to the type of stroke and long-term disability.[4] The costs of anticoagulation with warfarin therapy include frequent laboratory monitoring and hospitalization for bleeding complications, including the need for blood transfusions.

Risk Factors for Stroke

Risk markers for a first stroke can be classified according to their potential for modification (nonmodifiable, modifiable, or potentially modifiable) and the strength of evidence (well documented or less well documented) for prevention. Nonmodifiable risk factors include age, gender, low birth weight, race or ethnicity, and genetic factors. Well-documented modifiable risk factors include hypertension, exposure to cigarette smoke, diabetes, AF and certain other cardiac conditions, dyslipidemia, carotid artery stenosis, sickle cell disease, postmenopausal hormone therapy, poor diet, physical inactivity, and obesity and body fat distribution. From the Framingham data, Wang et al found obesity—or, more specifically, body mass index—to be a risk factor for the development of AF.[5]

Stroke Risk Stratification

Determination of the need for anticoagulation and the appropriate therapy choice are based on various strategies, focusing on risk factors. Tools such as the $CHADS_2$ score and the more-detailed strategy, CHA_2DS_2-VASc, with major and minor risk factors, are valuable for determining the need for anticoagulation for the prevention of stroke.

$CHADS_2$

The $CHADS_2$ score is the primary risk stratification scheme and was used for the 2006 American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) guidelines for nonvalvular AF.[6] The following risk factors are allotted values that guide the administration of anticoagulation: congestive heart failure (CHF), 1; hypertension, 1; age 75 years and older, 1; diabetes mellitus, 1; and stroke or transient ischemic attack (TIA), 2. For a score of 0 or 1, which indicates low risk or no risk of stroke (lone AF), aspirin therapy (81 or 325 mg) is recommended. For a score of 1 or 2, which indicates intermediate risk, an oral anticoagulant therapy should be recommended if the patient has no contraindications. A score of 3 or greater indicates a high risk for stroke, and oral anticoagulant therapy is recommended (Table 83-1).

CHA_2DS_2-VASc

The CHA_2DS_2-VASc score, recommended by the 2010 ESC guidelines for use by cardiology professionals for the determination of stroke risk, accounts for major and nonmajor stroke risk factors.[7] Major risk factors, scored with 2 points, include previous stroke, TIA or systemic embolism, and age 75 years and older. Minor risks, scored with 1 point each, include CHF with impaired left ventricular function (left ventricular ejection fraction [LVEF] <40%), hypertension, diabetes mellitus, vascular disease, female gender, and age 65 to 74 years. A score of 0 indicates very low risk, and either no therapy or aspirin therapy (75 or 325 mg) is recommended. A score of 1 shows a benefit to the use of oral anticoagulant therapy or aspirin therapy. For a score greater than 2, an oral anticoagulant is recommended. Patients with paroxysmal AF should be treated with anticoagulants, as are those with persistent or permanent AF (Table 83-2).

Transthoracic Echocardiography

Transthoracic echocardiography is used in risk stratification by evaluating left ventricular function as an indicator of stroke risk. For moderate to severe left ventricular dysfunction, the stroke relative risk is 2.5 times greater than in patients with mild or normal function. By analysis with transthoracic echocardiography, 38% of patients determined to be in a low-risk group were re-categorized to a high-risk group on the basis of findings

Table 83-1 $CHADS_2$ Score Stroke Rates and Recommended Therapy

$CHADS_2$ SCORE	STROKE RISK % (95% CI)	RECOMMENDATION
0	1.9 (1.2–3.0)	Aspirin therapy (81 or 325 mg daily)
1	2.8 (2.0–3.8)	Oral antithrombotic therapy or aspirin therapy
2	4.0 (3.1–5.1)	Oral antithrombotic therapy
3	5.9 (4.6–7.3)	Oral antithrombotic therapy
4	8.5 (6.3–11.1)	Oral antithrombotic therapy
5	12.5 (8.2–17.5)	Oral antithrombotic therapy
6	18.2 (10.5–27.4)	Oral antithrombotic therapy

Data from Gage BF, Waterman AD, Shannon W, et al: Validation of clinical classification schemes for predicting stroke: Results from the National Registry of Atrial Fibrillation, JAMA *285(22):2864–2870, 2001.*

Table 83-2 CHA_2DS_2-VASc Stroke Rate and Recommended Therapy

CHA_2DS_2-VASC SCORE	ADJUSTED STROKE RATE (% PER YEAR)	RECOMMENDATION
0	0	No therapy (or aspirin)
1	1.3	Oral anticoagulant (or aspirin)
2	2.2	Oral anticoagulant
3	3.2	Oral anticoagulant
4	4.0	Oral anticoagulant
5	6.7	Oral anticoagulant
6	9.8	Oral anticoagulant
7	9.6	Oral anticoagulant
8	6.7	Oral anticoagulant
9	15.2	Oral anticoagulant

Data from Lip GY, Nieuwlaat R, Pisters R, et al: 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 *137:263–272, 2010.*

pertaining to left ventricular function.[8] Transesophageal echocardiography (TEE) is not recommended for risk stratification.

Challenges of Anticoagulation

Anticoagulation therapy confers a reduced stroke rate but it has its challenges, including time in therapeutic range (TTR), frequent monitoring of international normalized ratio (INR), and bleeding risk. Interactions with vitamin K antagonist (VKA) therapy drug-drug interactions for competing metabolism in the CYP 2C9, drug-food interactions in vitamin K–containing foods, and genetic mutations that make it a challenge to increase TTR, all occur frequently.[9]

TTR is essential for the prevention of stroke; the ideal frequency of testing of INR values is determined by multiple factors, such as comorbid conditions, diet changes, medication changes, and variable dose response.[10] INR values within therapeutic range increased from 48% to 89% when monitoring occurred every 4 days by point-of-care device versus every 28 days in patients with mechanical valves.[11] New therapeutic options boast a longer TTR, offering better protection against stroke.[12]

Current Therapy

Warfarin

Warfarin, a VKA, has been used for the prevention of stroke in the United States since the 1950s. It is an effective anticoagulant that has been proven to reduce the risk of stroke associated with AF. Warfarin reduces stroke relative risk by 62%.[12] For primary prevention, the absolute risk reduction with dose-adjusted warfarin was 2.7% per year; for secondary prevention, the absolute risk reduction was 8.4% per year. Aspirin reduced stroke rates by 22%, showing warfarin to be superior to aspirin in the reduction of stroke.[13] Warfarin has been standard of care for stroke prevention until an update of the 2006 ACC/AHA recommendations in February 2011, which recommended the use of dabigatran as an acceptable alternative to warfarin therapy in the prevention of stroke in nonvalvular AF.

Aspirin and Clopidogrel

Antiplatelet therapy with aspirin and clopidogrel were compared with anticoagulant therapy in the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE W) study to evaluate the efficacy of each therapy for stroke prevention. The study showed oral anticoagulants to be superior to antiplatelet therapy, with a higher annual event rate with aspirin and clopidogrel compared with warfarin (3.93% vs. 5.64%; $P < .001$). For patients with contraindications for anticoagulant therapy, the ACTIVE A trial showed a reduction in stroke rates with combined aspirin and clopidogrel verses aspirin alone.[12]

Dabigatran

Dabigatran (Pradaxa) is the first new oral anticoagulant in more than 50 years approved by the U.S. Food and Drug Administration for the reduction of stroke risk and systemic thromboembolism in nonvalvular AF. Benefits of dabigatran include prevention of thromboembolism without the need for monitoring. Dabigatran has no food interactions and limited drug interactions. A warning to avoid the use of rifampin, a P-glycoprotein (P-gp) inducer, is included in the FDA label. Interactions with the P-gp inhibitors ketoconazole, amiodarone, verapamil, and quinidine do occur, but no dose adjustments are needed.[14]

Dabigatran has been evaluated in two major clinical trials, the Prevention of Embolic and Thrombotic Events in Patients with Persistent Atrial Fibrillation (PETRO) study (and the extension study PETRO-EX) and the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study (and the continuation study RELY-ABLE). In the phase II PETRO study, dabigatran (300 mg, 150 mg, and 50 mg twice daily) was compared with

dose-adjusted warfarin or aspirin.[15] Major bleeding events occurred most often in the highest dose (300 mg) group of patients who concurrently took aspirin (stopped during the study), and inadequate thromboembolic prevention was seen in the lowest dose (50 mg) group.[16] This trial proved pivotal in choosing the correct doses for the evaluation of the drug in the definitive phase III trial.

RE-LY showed the 150 mg twice-daily dose to be superior in the prevention of stroke or systemic embolism in patients with nonvalvular AF compared with the warfarin 150 mg twice-daily dose (hazard ratio [HR], 0.65; 95% confidence interval [CI], 0.52 to 0.81, $P = .0001$) and 110 mg twice-daily dose (HR, 0.72; 95% CI, 0.58 vs. 0.90; $P = .004$).[14] The 150-mg dose of dabigatran had fewer stroke and systemic thromboembolism rates compared with warfarin and lower rates of hemorrhagic stroke compared with warfarin.[14]

TEE is not recommended for risk stratification purposes. However, it is useful before cardioversion to evaluate for clots in the left atrial appendage. Anticoagulation is recommended before cardioversion for the prevention of potential complications by thromboembolism. According to the 2010 ESC guidelines, anticoagulation with warfarin is recommended for at least 3 weeks before cardioversion. If no clots are seen in the left atrial appendage on TEE, the time frame can be shortened. Anticoagulation is recommended for 4 weeks to life after cardioversion, depending on stroke risk factors.[17] Eighty percent of thromboembolic events occur within 3 to 10 days after cardioversion. In instable AF, cardioversion should be performed without delay.[17] In the case of emergency cardioversion, low-molecular-weight heparin is not recommended. Unfractionated heparin should be used and should be followed by 4 weeks of post-cardioversion warfarin administration.[18]

Use of dabigatran in cardioversion was analyzed from the RE-LY data. The rates of stroke and systemic embolism at 30 days after cardioversion following the recommended 3 weeks of pre-cardioversion anticoagulation were 0.8% ($P = .71$ vs. warfarin) for the 110-mg dose, 0.3% ($P = .40$ vs. warfarin) for the 150-mg dose, and 0.6% for warfarin. Major bleeding event rates were similar in the 150-mg group (1.7%) and warfarin group (0.6%), whereas the 110-mg group had more events (0.6%; $P = .06$ vs. warfarin). Rates of stroke and systemic embolism were low compared with those of warfarin. As Nagarakanti et al have concluded, dabigatran is an alternative to warfarin for cardioversion anticoagulation.[19]

RE-LY also evaluated the rates of stroke and systemic embolism in VKA-naïve patients compared with the two dose groups (110 mg twice daily and 150 mg twice daily). Being "VKA naïve" was defined as 62 days or less of lifetime VKA exposure. Stroke and systemic embolism rates per year for the 110-mg, 150-mg, and warfarin groups were 1.57%, 1.07%, and 1.69%, respectively. The 150-mg dose was found to be superior to warfarin ($P = .005$) and the 110-mg dose similar to warfarin ($P = .65$). Major bleeding rates in VKA-naïve patients were similar in the dose groups compared with warfarin. Intracranial bleeding rates for the 110-mg, 150-mg, and warfarin groups were 3.11%, 3.34%, and 3.57% per year, respectively, with the 110-mg and 150-mg groups having a lower rate than the warfarin group ($P < .001$ and $P = .005$, respectively). In the VKA-experienced 110-mg, 150-mg, and warfarin groups, the stroke and systemic embolism rates were 1.51%, 1.15%, and 1.74% per year, respectively, with 110 mg being similar to warfarin ($P = .32$) and 150 mg superior ($P = .007$). Major bleeding rates were lower in the 110-mg group and similar to warfarin in the 150-mg group ($P = .003$ and $P = .41$, respectively). Intracranial bleeding rates were lower in both groups of dabigatran compared with the warfarin group ($P < .001$). RE-LY showed that prior VKA exposure did not alter the benefit of dabigatran.[20]

Stroke rate, broken down by subtype, either ischemic or hemorrhagic, was evaluated in RE-LY. In the 150-mg twice-daily dose group, the HR, compared with the warfarin group, for all stroke events was 0.64 (95% CI, 0.51 to 0.81), 0.75 (95% CI, 0.58 to 0.97) for ischemic stroke, and 0.26 (95% CI, 0.14 to 0.49) for hemorrhagic stroke. The HR of systemic embolism was 0.61 (95% CI, 0.30 to 1.21) versus warfarin. Dabigatran 150 mg twice daily reduced stroke occurrence compared with warfarin.[14]

On the basis of the evidence of the RE-LY trial, the ACC/AHA/Heart Rhythm Society (HRS) published a focused update on management of patients with nonvalvular AF that recommended the use of dabigatran for the prevention of stroke.[21] Dabigatran is dosed at 150 mg twice daily and 75 mg twice daily for creatinine clearance of 15 to 30 mL/min. It is not approved for patients with creatinine clearance less than 15 mL/min.

Anticoagulants

Other anticoagulant medications are in development at various targeted sites of the coagulation cascade (Figure 83-1 and Table 83-3).[22]

Vitamin K Antagonist

VKAs, such as warfarin, work by preventing γ-carboxylation of factors II, VII, IX, and X. Tecarfarin (ATI-5923) is a VKA similar to warfarin but without the CYP-P450 metabolism, which provides a more reliable dose response compared with warfarin. Initial studies with tecarfarin showed a mean of 71.4% of TTR; however, further study is needed.[23-25]

Factor Xa Inhibitors

Apixaban

Excretion of apixaban is primarily hepatobiliary, and the drug requires twice-daily dosing (half-life of 12 hours). Initial phase II trials evaluated the drug against warfarin in deep venous thrombosis patients for the prevention of thromboembolism. Bleeding events and liver transaminase elevation were similar in both the warfarin and apixaban groups. Phase III trials are ongoing to evaluate the efficacy of apixaban in stroke prevention in nonvalvular AF. Apixaban is being compared with both warfarin therapy (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation [ARISTOTLE]) and aspirin therapy (Apixaban Versus Acetylsalicylic Acid to Prevent Strokes [AVERROES]). ARISTOTLE is a phase III trial comparing apixaban with warfarin in more than 18,000 patients; results are expected in late 2011. The recently completed AVERROES study showed apixaban to be superior to aspirin in patients with AF for the reduction of stroke, myocardial infarction, systemic embolism, and vascular death. Additional concurrent studies comparing apixaban with warfarin for deep vein thrombosis, unstable angina, myocardial infarction, and advanced metastatic disease are ongoing.[26]

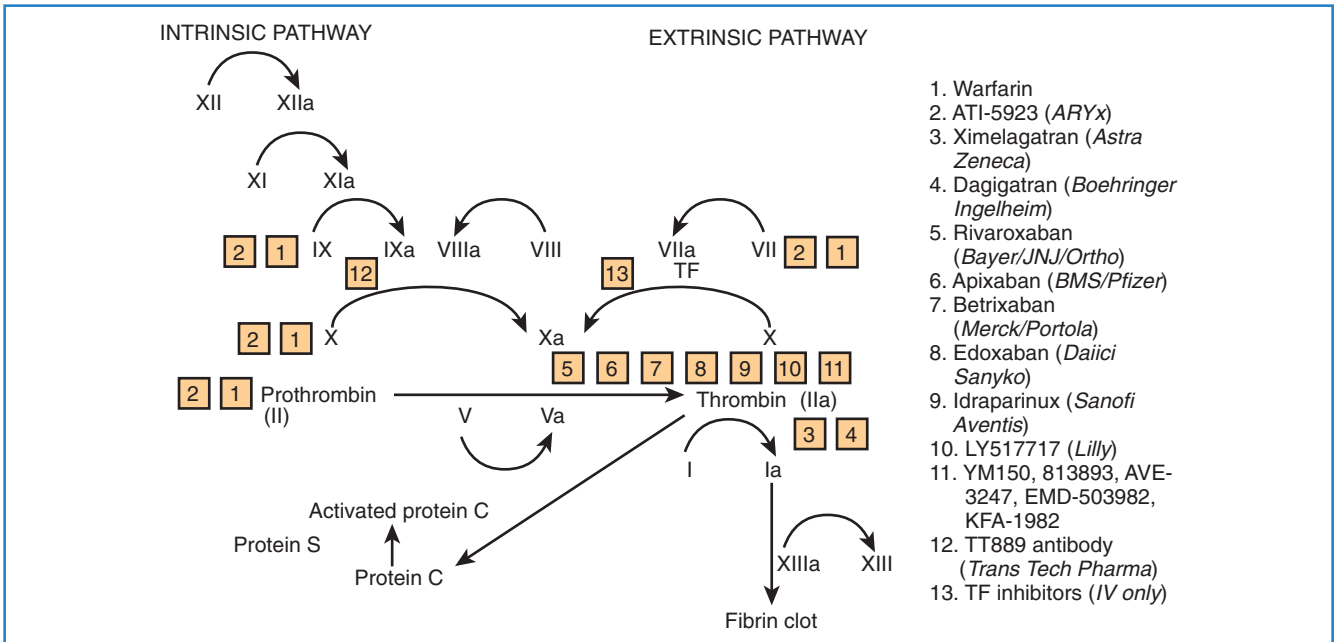

FIGURE 83-1 Targeted therapy on the coagulation cascade. *(From Goldman PSN, Ezekowitz MD: Principles of anticoagulation and new therapeutic agents in atrial fibrillation,* Card Electrophysiol Clin *2[3]:479–492, 2010.)*

Table 83-3 Anticoagulant Phases of Development

AGENT	MECHANISM AND SITE OF ACTION	PHASE OF DEVELOPMENT*
Warfarin (Coumadin)	VKA (Factors II, VII, IX, X)	Established therapy
Dabigatran (Pradaxa)	Direct thrombin inhibitor	FDA approval October 2010
ATI-5923 (ARYx)	Novel VKA (Factors II, VII, IX, X)	Phase II complete
Ximelagatran	Direct thrombin inhibitor	Phase III complete; suspended by FDA due to liver toxicity
Apixaban	Factor Xa inhibitor	Phase III ongoing
Betrixaban	Factor Xa inhibitor	Phase II complete
Edoxaban	Factor Xa inhibitor	Phase III ongoing
Idraparinux	Factor Xa inhibitor	Phase III; terminated
LY517717	Factor Xa inhibitor	Phase II
Rivaroxaban	Factor Xa inhibitor	Phase III ongoing
GW813893 AVE-3247 EMD-503982 KFA-1982	Various	Various stages
Tissue factor inhibitors	Tissue factor inhibition at the initiation site	Preclinical models

VKA, *Vitamin K agonist.*
**As of publication date of this text.*
Data from Goldman PSN, Ezekowitz MD: Principles of anticoagulation and new therapeutic agents in atrial fibrillation, Card Electrophysiol Clin *2(3):479–492, 2010.*

Betrixaban

Betrixaban is distinct from other factor Xa inhibitors in that it has been developed with an antidote. The phase II study has been completed, and the results presented in March 2010 at the ACC meeting have shown that once-daily betrixaban reduces major and clinically relevant nonmajor bleeds in patients with AF and at least one other stroke risk factor compared with dose-adjusted warfarin. The phase III trial is being planned.[27]

Edoxaban

Edoxaban directly and specifically inhibits factor Xa. It is excreted through the kidneys. The phase III study, Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thromboembolism in Myocardial Infarction 48 (ENGAGE-AF TIMI 48), a double-blind, double-dummy study, is ongoing. It compares prevention of stroke with warfarin and two doses of edoxaban (30 mg and 60 mg daily). The phase II trial findings determined that the rate of bleeding events with the 30-mg and 60-mg daily doses to be comparable with that of warfarin.[28]

Rivaroxaban

Rivaroxaban, an inhibitor of both free and clot-bound factor Xa in addition to prothrombinase, has shown predictable pharmacokinetics and pharmacodynamics in early studies.[29,30] Rivaroxaban has renal and hepatobiliary excretion, with increased absorption when taken with food. Rivaroxaban interacts with CYP3A4 inhibitors (macrolide antibiotics, ketoconazole, etc.).[31,32] Rivaroxaban is being evaluated in Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF), a phase III double-blind study comparing rivaroxaban with warfarin in patients with nonvalvular AF and one additional stroke risk factor. Results of the ROCKET-AF trial were

presented at the AHA 2010 Scientific Session and showed that rivaroxaban was not inferior to warfarin in the prevention of stroke and noncentral nervous system embolism (HR, 0.79; 95% CI, 0.66 to 0.96; $P < .001$). On intention-to-treat analysis, it was not found to be superior to warfarin.[33]

Other Factor Xa Inhibitors

Other factor Xa inhibitors in clinical development have been studied for venous thromboembolism (VTE) prevention in both orthopedic surgery and AF. Oral formulations in phase II trials include LY517717 and YM 150. LY517717, evaluated in a phase II trial, showed comparable efficacy and safety at three doses (100, 125, and 150 mg daily) compared with enoxaparin for the prevention of VTE in patients receiving total hip or total knee replacements.[34] This compound is metabolized by the liver and safe for patients with renal insufficiency.[35] The phase II YM 150 study on patients with hip arthroplasty was completed in 2010. The study found that the tested doses, 30 to 120 mg, were as efficacious and safe as enoxaparin, which is the current recommended therapy.[36] Additional compounds being developed include GW813893, AVE-3247, EMD 503982, and KFA-1982.

Table 83-4 Clinical Trial Summary

AGENT	CLINICAL TRIAL	COMPARISON
Apixaban	ARISTOTLE	Stroke and VTE prevention vs. warfarin
ATI-5923 (ARYx)	Phase II	Time in therapeutic range vs. warfarin
Betrixaban	Phase II	Less bleeding vs. warfarin
Dabigatran	PETRO	Stroke and VTE prevention vs. warfarin
	PETRO-Ex	Study drug only
	RE-LY	Noninferiority to warfarin
	RE-LY-ABLE	Study drug only
Edoxaban	ENGAGE AF-TIMI 48	Stroke and VTE prevention vs. warfarin
Idraparinux	AMADEUS	Stroke and VTE prevention vs. warfarin
	BOREALIS-AF	Noninferiority of biotinylated drug vs. warfarin
Rivaroxaban	ROCKET-AF	Stroke and VTE prevention vs. warfarin
Tissue factor inhibitors	Preclinical models	Human suitability and bioavailability
TTP889 antibody	FIXIT	Proof-of-concept of drug over placebo: failed
Ximelagatran	SPORTIFF III	Stroke and VTE prevention vs. warfarin
	SPORTIFF V	

VTE, *Venous thromboembolism.*
Data from Goldman PSN, Ezekowitz MD: Principles of anticoagulation and new therapeutic agents in atrial fibrillation, Card Electrophysiol Clin *2(3):479–492, 2010.*

New Concepts

Factor IX Antibody: TTP889

Factor IX plays a role in clot formation by creating an interaction of activated factor IX and platelets. Factor IX antibodies (IXia) provide selective inhibition between factor IX and platelets by competitively binding to platelet surface membranes.[37,38] TTP889 is the only oral agent found to be as effective as heparin without an increased frequency of bleeding events.[39] The Factor IX Inhibition in Thrombosis Prevention (FIXIT) trial compared TTP889 with placebo in the prevention of VTE in hip replacement. It has not been evaluated in AF. This trial did not show superiority of TTP889 over placebo (32.1% vs. 28.2%; $P > .5$).[40]

Tissue Factor Inhibitors

Tissue factor inhibitors work by inhibiting the initiation of the proteolysis that causes the formation a thrombus and are believed to inhibit neointimal proliferation.[41,42] Inhibiting coagulation at the initial step of thrombus formation creates fewer hemorrhagic complications (Table 83-4).[43]

Summary

Anticoagulation with warfarin (a VKA) or dabigatran (a direct-thrombin inhibitor) is recommended for all patients with nonvalvular AF and one or more risk factors for thromboembolism. Aspirin therapy or no therapy is recommended for patients with lone AF. Many new therapeutic options that use targeted therapy at alternative sites of the coagulation cascade show promise with regard to easier compliance, fewer drug-drug and drug-food interactions, and decreased economic burden.

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CHAPTER 84

Implantable Cardioverter-Defibrillators: Device Technology and Implantation Techniques

Sanjeev Saksena and Nandini Madan

Introduction

The implantable cardioverter-defibrillator (ICD) has emerged as the primary therapeutic option for the treatment of patients at risk for sudden cardiac death (SCD) caused by ventricular tachyarrhythmias.[1-4] ICD devices were originally developed for the secondary prevention of SCD in patients with malignant ventricular arrhythmias and in survivors of SCD. Increasingly, ICDs are used for the primary prevention of SCD in an ever-expanding list of at-risk patient subgroups, which are discussed in this chapter. In addition, ICD systems have undergone a rapid technologic evolution to improve functionality and decrease the morbidity and mortality associated with implantation. These refinements in ICD lead and generator technology have led to a progressive expansion in their use. However, optimal device performance and follow-up require an intimate knowledge of these devices and their operations as well as the clinical electrophysiology of the arrhythmia being managed. This chapter summarizes current ICD technology and insertion techniques for ICD systems when used for SCD prevention.

Implantable Cardioverter-Defibrillator Technology: Evolution and Status

ICD device technology has evolved since the 1980s from a nonprogrammable generator requiring epicardial lead implantation by thoracotomy or at cardiac surgery to a multi-functional therapeutic and monitoring device that uses anatomically distinct transvenously implanted lead systems for atrial and ventricular pacing, defibrillation, and monitoring. Typical ICD systems consist of a pulse generator and one or more ICD leads connected to the generator. Developments in this technology have encompassed generator systems as well as lead refinements. The original ICD generators delivered shock therapy alone; pacing for bradycardia prevention and tachycardia termination was later added. Subsequent generations have included capabilities for atrial pacing, rate-responsive pacing and, most recently, atrial anti-tachycardia pacing and defibrillation. Complex new algorithms for the detection and discrimination of supraventricular and ventricular tachyarrhythmias as well as those for prevention of arrhythmias are now available. In the same period, diagnostic and monitoring capabilities of the device have expanded. Devices can now evaluate their own component functions and permit automated testing functions for system performance, record spontaneous arrhythmic events, deliver interventional therapies, and store information relative to patient or arrhythmia status. ICD generator longevity has improved, with most devices rated for 4 or more years depending on the current drain for activated features. In this regard, the monitoring functions constitute a significant current drain. With the multitude of features and the multi-functional nature of the device, the pivotal features of optimal ICD function need to be clearly defined. ICD technology can be classified in two categories: (1) technology related to ventricular defibrillation and (2) technology related to combined atrial and ventricular defibrillation. Specific component features of devices are discussed for each category.

Implantable Cardioverter-Defibrillator Pulse Generators

ICD generators must be capable of providing low-energy current output for monitoring and pacing as well as high-energy current pulses for shock delivery for defibrillation. ICD generators house several key components of the ICD system. These include the following:

1. Battery to power the generator
2. Capacitor(s) and a charging circuit to provide the high-voltage pulse for shocking the heart
3. Microprocessor-based control systems and electronic circuitry to provide precise delivery of electronic pulses for pacing, sensing, and monitoring functions
4. Sense circuits and amplifiers for cardiac electrical signals

The essential elements and principles of these components are detailed in this section. A schematic diagram showing these components is shown in Figure 84-1, *A*.

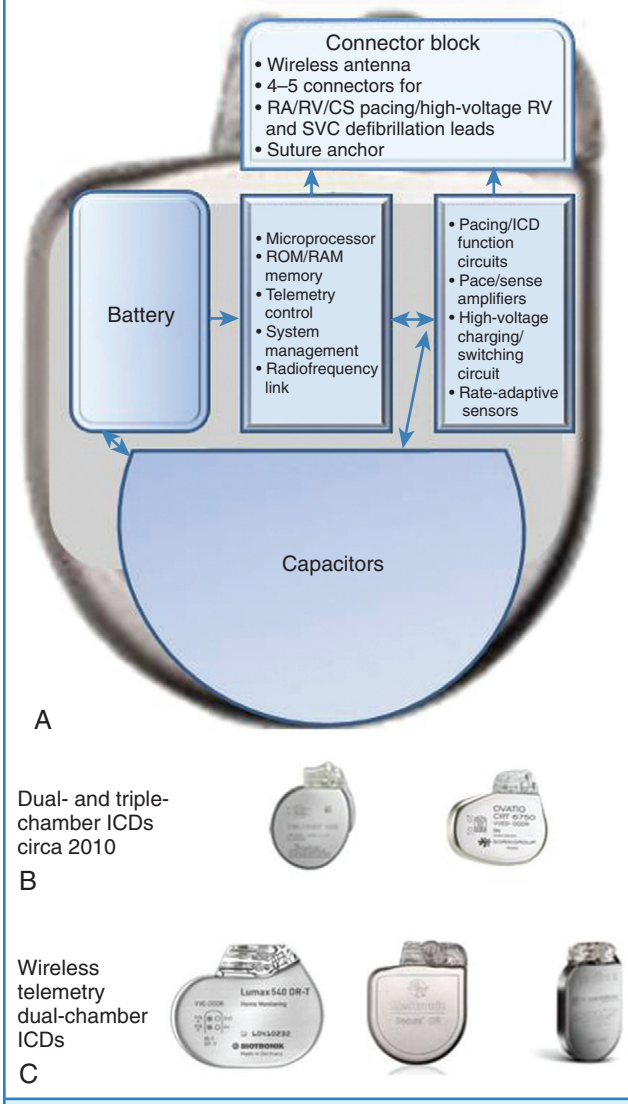

FIGURE 84-1 A, Schematic diagram of major components of an implantable cardioverter-defibrillator (*ICD*) generator. **B,** Decreasing ICD generator size with progressive technologic advances. Current ICDs have broken the 30-cm^3 volume barrier and are markedly smaller than early devices. **C,** Wireless telemetry units require a larger header for the radiofrequency antenna and are now available as single-, dual-, and triple-chamber pacing defibrillation devices.

Batteries

Batteries, in essence, convert chemical energy into electrical energy, which can be stored or made available for use, as needed. This requires a chemical reaction that can be managed and modulated for the designed purpose. The chemical reaction used typically involves interaction of inorganic elements (constituted or embedded in the cathode and anode of the battery) to produce a compound at a lower energy state. The difference in energy state is converted to electrical energy rather than heat, with electrons being directed to an external circuit to perform the work. Batteries for implantable devices, therefore, comprise three components: (1) a positive electrode called an *anode*, (2) a negative electrode referred to as a *cathode*, and (3) an intervening electrolyte, which can be a conductive solution or a solid chemical. The anode is typically a metal plate that furnishes the electrons in the reaction, and the cathode receives them via an external circuit (e.g., the lead).

ICD batteries have several requirements. These include, among others, availability of different voltage levels for pacing and monitoring functions versus defibrillation therapy, substantial longevity, mechanical and electrical durability, and patient safety. In typical ICD batteries, a lithium metal plate serves as the anode, and a silver vanadium oxide plate serves as the cathode (see Figure 84-1). The electrolyte is a solution of a lithium compound in a highly conductive organic solvent or solvents. Multiple layers of the anode and cathode are present in an ICD battery. The battery's electrode and electrolyte are contained within a hermetically sealed metal case. These two elements immediately interact, and the electrons released from the lithium anode enter the external device circuit. The cathode accepts electrons from the external circuit. Progressive and uncontrolled charge buildup on the anode and cathode is prevented by the ionic nature of the electrolyte.

Typical lithium pacemaker batteries charge rapidly on contact of the elements to 2.8 V. With the development of the lithium iodide layer, the reaction is slowed, which permits a long, stable plateau phase of battery voltage in the life of the pacemaker battery. Defibrillator batteries differ from pacemaker batteries in their construction and in some elements of their behavior. The ICD battery has one voltage level when normal sensing and pacing functions are in progress without any tachyarrhythmia therapy. This background voltage is reported in ICD interrogations and starts out at about 3.25 V at beginning of service life, decreases to approximately 3.15 V when 30% discharged, and maintains a long, stable period at approximately 2.6 V until it is 85% discharged. Then it declines at a more rapid rate, triggering an elective replacement indicator. During high-voltage charging for shock therapy, a "load" voltage is available and is indirectly measured by charge time measurements. Load voltage behavior varies with ICD models and programming. In general, load voltage declines gradually until the end of service life, at which point the load voltage accelerates. Internal impedance in the cell also changes over time, increasing after 50% of service life, though some modifications in anodal materials can defer this increase. Correspondingly, charge time gradually increases over the battery life, but this also accelerates at a much faster pace as impedance rises or when the battery approaches end of life. The ICD battery's end of life must be assessed by a review of both background voltage and charge times. Thus charge times over 15 seconds on repeated charge tests performed at least 10 minutes apart are generally undesirable. Combination materials are now being used for higher power needs for advanced ICD generator capabilities, which require increasing memory, data storage, and advanced pacing such as ventricular and atrial resynchronization therapy. Rechargeable lithium ion batteries may have a role in ICD devices with increased longevity and potential for outpatient recharging. They may supplement or even replace the primary ICD battery. Promising new developments in rechargeable lithium-ion batteries include nanocrystalline intermetallic alloys, nanosized composite materials, carbon nanotubes, and nanosized transition-metal oxides as new anode materials. Nanosized lithium cobalt oxide, lithium ferrous phosphate, and lithium manganese oxide show higher capacity and better cycle life as cathode materials than their usual larger particle equivalents. Nanosized metal-oxide

powders, when added to polymer electrolytes, improve performance of lithium rechargeable batteries.

High-Voltage Shock Therapy

High-voltage capacitors store and deliver the high-energy pulses needed to cardiovert and defibrillate tachyarrhythmias (see Figure 84-1). Capacitors, in essence, consist of two conductors, insulated from each other by a di-electric material, that charge via a charging circuit connected to the battery. During charging, these conductors assume equal but opposite charges that discharge through the lead system to deliver a high-voltage, high-energy shock. Voltage delivered in the shock decays in an exponential waveform, and the actual delivered energy is usually less than the stored energy. Thus measures of both are available for ICD devices. Capacitor size is a major determinant of overall ICD generator size. High-energy density minimizes capacitor size. ICD capacitors use aluminum or tantalum electrode either as foils, which are etched to increase surface area, or as porous pellets. Tantalum capacitors have a smaller size but a greater mass.

A metal oxide film is grown to lower the capacitance and increase the voltage storage capacity. An electrolyte of organic solvent with conductive salts is used to connect the metal oxide di-electric with the cathode. A series of capacitors is needed to achieve the voltage for defibrillation. Capacitors are susceptible to loss of metal oxide film, a process known as *deformation*. This film must be regrown by using additional energy to fill in the losses. Thus a substantial energy loss may occur. Modern ICDs incorporate a programmable regular maintenance charge schedule to prevent this deformation. It is still being debated whether this schedule is as efficient and whether more frequent charging is really needed but is not feasible because of battery life considerations. Current leakage after charging and internal capacitor resistance can also influence capacitor pulse voltage. Thus prolonged delay between capacitor charging and shock delivery can erode it if, for example, tachycardia reconfirmation is delayed or other sensing issues are present. In examining causes of failed defibrillation in clinical practice and potential device-based failure as a contributing factor, these issues must be considered.

A transformer is required to generate the high voltage stored by the capacitor. A direct-current to direct-current (DC-to-DC) converter with transformer coils wound around a core magnet and complex switching circuit for primary and secondary capacitors meets this need. Highly specialized output circuits with very low impedance permit more efficient energy conservation in the battery. Output circuits modulate the shock duration and amplitude permitting multi-phasic output pulses and varying shock waveforms.

Microprocessor-Based Circuitry

Integrated circuits using microchips are used in ICD generators. These consist of interconnected electronic components such as transistors and resistors that are etched or imprinted on a tiny chip. These circuits serve as the "controller" of the defibrillator function providing the memory, microprocessing needs, and logic that control the device function. One or two integrated circuits may be present in a single device. Microprocessors have markedly reduced size and current drain for the circuitry used in ICD devices. These new circuit designs have allowed implementation of new therapy and detection algorithms, enhanced memory for storage of diagnostic data, and more complex software needed to implement these sophisticated ICD algorithms. Two types of memory are used: (1) read only (ROM) and (2) random access (RAM). The former is used to store the device software, whereas the latter can be used for programming, diagnostic information and, in some instances, software. RAM memory may be susceptible to corruption by external interference such as power supply interruption or atmospheric particle radiation. Error correction routines are incorporated to reduce the risk of corruption of RAM memory. External upgrades and programming may be needed in some instances to address this issue.

Sense Amplifiers and Sensing Circuits

Accurate sensing of input signals and their analysis are important challenges for ICD devices. Near-field and far-field signals are often present in the signal presented by the lead or leads connected to the generator. The amplitude of the signal is measured against a comparator set by the sensing threshold value. However, the tachycardia and fibrillation signal can be highly variable with respect to amplitude on a beat-to-beat basis, along with changing slew rates and morphology. To address this challenge, an important technical feature of ICD sensing circuits is the automatic adjusting signal amplifier "autogain" feature. This feature compensates for variable amplitudes of electrograms during the arrhythmia. The signal amplitude can vary as much as 10 times during a single episode of ventricular fibrillation (VF). Variability in electrocardiogram (ECG) amplitude during VF has also been observed to be a cause for redetection failure.[5] The sense amplifier must be able to respond to the widely varying cardiac signals and does so by changing the sensing threshold on a beat-to-beat basis. It is initially set to a fraction of the signal amplitude, and then the threshold decays over time, depending on programming on the threshold and delay. Raising gain for low-amplitude signals can increase oversensing, resulting in oversensing of T waves and "double counting" of fragmented potentials or skeletal myopotentials, leading to inaccurate detection. The autogain feature adjusts sensitivity on the basis of the amplitude of recently sensed signals. The autogain feature of some devices increases sensitivity when a rapid rhythm is detected to sense VF. It also increases sensitivity during bradycardia pacing so that low-amplitude signals from VF will not be interpreted as bradycardia.

Generator Header

The ICD header is typically made of a clear plastic material, usually silicone, to allow visual verification of complete insertion of the lead connector pin within the header and connect the sealed internal device circuitry to the lead system. The header also contains insulation for all wires, seal plugs, and setscrews. Setscrews are used to fasten the lead pin in the defibrillator header. To lock the lead in place, setscrews are inserted into the threaded holes in connector blocks and tightened down against the contact areas on the proximal lead terminal. Seal plugs keep the setscrews in connector blocks, prevent their backing or falling out, and also ensure a reliable seal from body fluids. Seal plugs are made of silicon and have a pre-slit center depression to allow a torque wrench access to the setscrews. The slit reseals after withdrawal of the torque wrench. Spring contacts are used to complete the electrical connection between the pacing terminal pins and the device.

Developments in Device Material Technology

One major limitation placed by device materials is the ferrous content of lead and generator elements, which causes interactions with magnetic fields and the magnetic imaging techniques in clinical practice. Recent studies have attempted to shield the devices from such fields, and these techniques have been used as temporary measures to allow imperative imaging procedures. One new initiative is to use nonferrous materials in device system construction. Clinical trials with such a system have been encouraging, and approvals are pending in many countries.

Implantable Cardioverter-Defibrillators for Ventricular Defibrillation

Technological developments in the original ICD device have now improved its functionality. The transition from an epicardial lead system to wholly nonthoracotomy placement occurred in 1987, with the inclusion of a left extra-thoracic patch lead that permitted a larger electrode surface area combined with a new left-to-right shock current vector for successful endocardial defibrillation.[6] In the original version, a three-electrode configuration permitted two simultaneous shock vectors, left-to-right and right-to-left, for bi-directional current delivery to improve defibrillation thresholds (DFTs). Refinements to both generator and lead systems in the past decade have simplified the implementation of endocardial defibrillation with wholly transvenous implantation. This included use of a biphasic shock waveform as the standard defibrillation shock waveform, which helped reduce defibrillation energy and reduced the need for multiple electrodes for optimal energy transfer to the myocardium.[7] New lead configurations have permitted reliable transvenous defibrillation within the maximal leading edge shock voltage (750 to 800 V), available in most ICD generators, in more than 98% of all patients.[8] The device can now serve as an integral component of the shock energy delivery system—becoming an active pectoral lead replacing left thoracic patch electrode insertion in the original systems.[7] ICD generator size has consistently been reduced, with device volumes now well under 40 cm^3 (see Figure 84-1). Although sub-30-cm^3 devices are a reality (e.g., the 29-cm^3 Sorin Ovatio CRT ICD; Sorin Group, Milan, Italy), the trade-off between generator size and the surface area needed for optimal DFTs is now becoming an issue (see Figure 84-1). Wireless telemetry is now incorporated in three devices currently available in the United States (Biotronik Lumax [Berlin] Medtronic Secura series [Minneapolis, MN], and St Jude Current Promote RF [St Paul, MN]). Because of this feature, the header size increases with overall increase in generator volume (see Figure 84-1).

Single-Chamber Ventricular Implantable Cardioverter-Defibrillator Technology

Device Insertion

In its simplest iteration, the ICD device has capabilities for the detection of lethal ventricular tachyarrhythmias and permits ventricular pacing and monitoring of ventricular rhythms alone. This requires insertion of a single, combined ventricular pacing and defibrillation lead via cephalic or subclavian vein placement with a pectoral generator site—the generator being an active defibrillation shock electrode (Figure 84-2, *A*). The defibrillation lead includes a large surface area electrode in the right ventricle, integrated or true bipolar sensing, and an active or passive fixation mechanism.[9] The shock current is transmitted between the right ventricular electrode and the generator, since a right-to-left shock vector reduces defibrillation threshold energy. Left-sided placement of the generator is therefore preferred, whenever feasible, although right-sided placement is possible. In studies on human DFTs with different lead configurations, the mean energy for defibrillation varies with electrode configuration and location. In

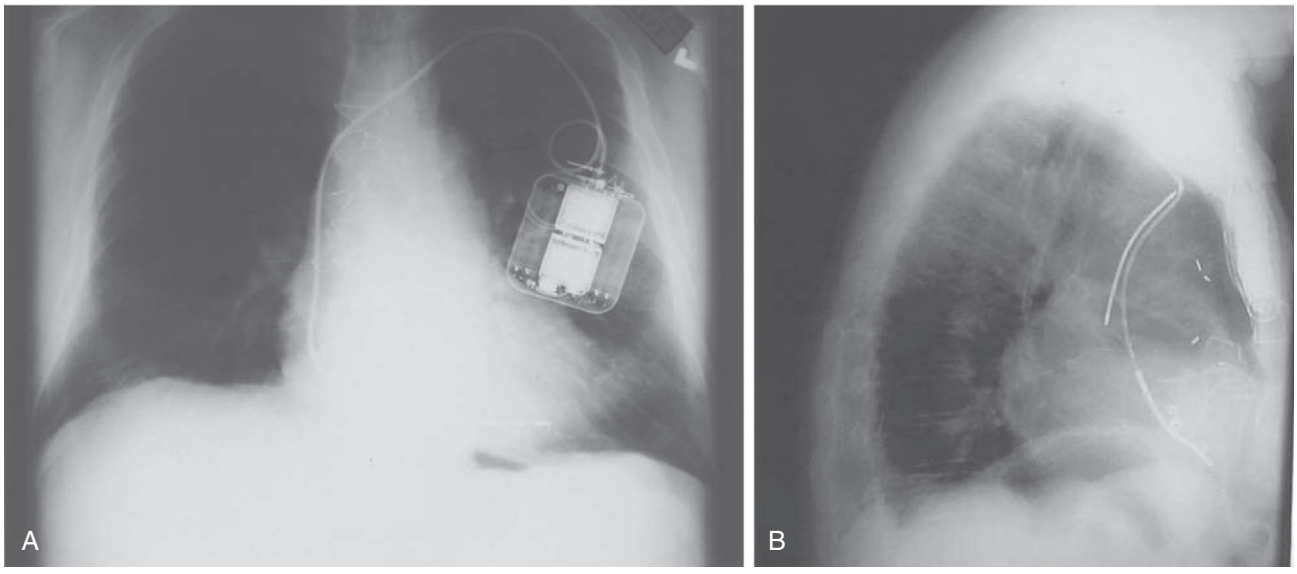

FIGURE 84-2 A, Chest radiograph (posteroanterior view) of a single-chamber ventricular implantable cardioverter-defibrillator (ICD) with single right ventricular pacing and defibrillation lead. **B,** Chest radiograph (lateral view) of single-chamber ventricular ICD with additional defibrillation lead in the superior vena cava. Today, dual-coil leads avoid the need for this additional lead.

addition, the electrode surface area is a critical determinant of current and voltage requirements for defibrillation by virtue of its effects on the electrode-myocardium interface and shock energy vector. Thus DFTs vary in inverse proportion to the electrode surface area, with defined boundaries for such effects in either direction. The addition of a third SVC or right atrial electrode permitted bi-directional shock vectors, which may reduce mean DFTs by 10% to 20%, as shown in some studies, and by larger increments in individual patients. Initially, a second superior venocaval electrode was used for this purpose (see Figure 84-2, *B*), but now dual-electrode catheters with variable spacing of the two defibrillation coils obviate the need for an additional lead. Similarly, reversal of shock polarity may not reduce DFTs in population studies but can alter thresholds in specific patients. Both these maneuvers are of value in patients with high DFTs. Several endocardial defibrillation leads routinely include two defibrillation electrodes for right ventricular and SVC locations, resulting in a bi-directional shock configuration. Reduction in generator size for cosmetic acceptability and implant simplicity may require attention to optimal generator location for successful and low DFTs. In our early studies on left-sided electrode location for defibrillation, the lowest DFTs were achieved with left axillary locations in the anterior to midaxillary line in the vicinity of the fourth intercostal space, with slightly higher values in the left infraclavicular location in the second intercostal space.[10] Currently, this latter location is most commonly used for generator placement. Axillary locations can reduce DFTs, but are not widely used because of arm movement issues; however, they remain an option in some patients. Highest thresholds are obtained with an apical placement in the left midclavicular line at the fourth or fifth intercostal space. Thus the thoracic site of placement or relocation of a generator can have an impact on DFTs, which should be considered by an implanting physician.

Tachyarrhythmia Detection

Ventricular rhythm detection in these systems is based on the ventricular electrogram rate, regularity, morphology, and patterns of electrogram interval changes. Initial detection in all devices is based on absolute ventricular rate, with most devices allowing up to three zones for distinguishing different tachyarrhythmias. In general, a minimum of two-zone programming is usually performed for distinguishing monomorphic ventricular tachycardia (VT) from VF. When empiric programming is sought, we prefer to establish three zones for "slow" VT, "fast" monomorphic ventricular tachyarrhythmias, and VF, as illustrated in Figure 84-3.[11-12] Such distinction is useful for both clinical and therapeutic purposes. The slowest zone is usually associated with nonsyncopal rhythms, which are often responsive to anti-tachycardia pacing. The second zone has symptomatic rhythms, but early anti-tachycardia pacing or cardioversion with a lower energy shock with rapid charge times may abort the syncope. Very rapid anti-tachycardia pacing can be considered in this zone. Finally, ventricular fibrillation is usually syncopal in many patients and requires a highly effective shock for immediate termination based on threshold determination. Although nominal detection rate values are provided by manufacturers, it is important to individualize these values on the basis of the patient's sinus rhythm mechanism, its chronotropic competence, exercise response and activity level of the patient, and the presence of coexisting supraventricular tachyarrhythmias and their ventricular rates. It is generally preferable to ensure a difference of 15 to 20 beats/min between the maximal sinus rate or supraventricular arrhythmia rate and the initial threshold rate for VT detection, provided the latter arrhythmia rate falls above this value by at least 10 to 15 beats/min. If this level of distinction is not possible on the basis of rate alone, and overlapping rates are present between supraventricular tachycardias (SVTs) and VTs, other algorithms are available in most devices to help identify the arrhythmia.

All devices offer sudden onset criteria, which identify an abrupt cycle length change in the ventricular cycle, to discriminate a pathologic tachycardia from sinus tachycardia. In addition, electrogram morphology in supraventricular and ventricular tachyarrhythmias may be matched to the sinus rhythm template. In the absence of intraventricular conduction abnormalities, supraventricular rhythms can often be identified by similar ventricular electrogram morphology. The duration of the ventricular electrogram as a discriminating factor, although used often, is less valuable. Ventricular electrogram duration may increase in ventricular tachyarrhythmias because of slower intraventricular conduction without the use of the specialized conduction system (Figure 84-4). However, few systematic data validate this belief, and "narrow" complex VTs are surprisingly common. Most devices consider sustained high-rate events as ventricular in origin for patient safety and trigger a therapeutic strategy. In many patients, ventricular tachyarrhythmia rates can be variable, particularly with changing autonomic tone and antiarrhythmic drug therapy. Presentation with a monomorphic tachycardia rarely predicts subsequent freedom from VF. In fact, in clinical studies, the mortality and event rates in patients with hemodynamically "stable" VT were comparable with those in patients who had sustained a cardiac arrest.[13]

Device Therapies

Anti-tachycardia Pacing or Cardioversion

Tachyarrhythmia and bradyarrhythmia therapies are available in these devices. Ventricular demand pacing with or without rate response is present. Ventricular pacing output can be altered for specific situations such as anti-tachycardia pacing or post-shock bradycardia pacing. Tachyarrhythmia therapies include anti-tachycardia pacing for termination of monomorphic VT, and low- and high-energy programmable shock therapies for cardioversion of VT and defibrillation of VF.[4,15] Anti-tachycardia pacing is most effective in the termination of monomorphic VT, especially with rates below 180 beats/min, although individual episodes with rates above this may respond to this therapy.[1,15-17] In slow VT, the excitable gap is large; therefore anti-tachycardia pacing can easily interrupt the tachycardia. When the tachycardia is fast, the excitable gap is shorter, and anti-tachycardia pacing interruption may be more difficult. Pacing termination of rapid VT is discussed below.

Several types of anti-tachycardia pacing are available in these devices. It is not uncommon for several attempts or different algorithms to be deployed during such efforts at tachycardia termination in an individual patient. Allowances for these repetitive efforts must include the hemodynamic stability of the patient during anti-tachycardia pacing programs. These algorithms include burst pacing, which may be rate adaptive or fixed rate, and low-energy cardioversion shocks (Figure 84-5). In rate-adaptive algorithms, the pacing rate is determined by the tachycardia rate and is generally a percentage of that rate. Commonly used adaptive algorithms use adaptive rates, which can vary from 95% to 70% of the tachycardia rate, for a given number of pacing

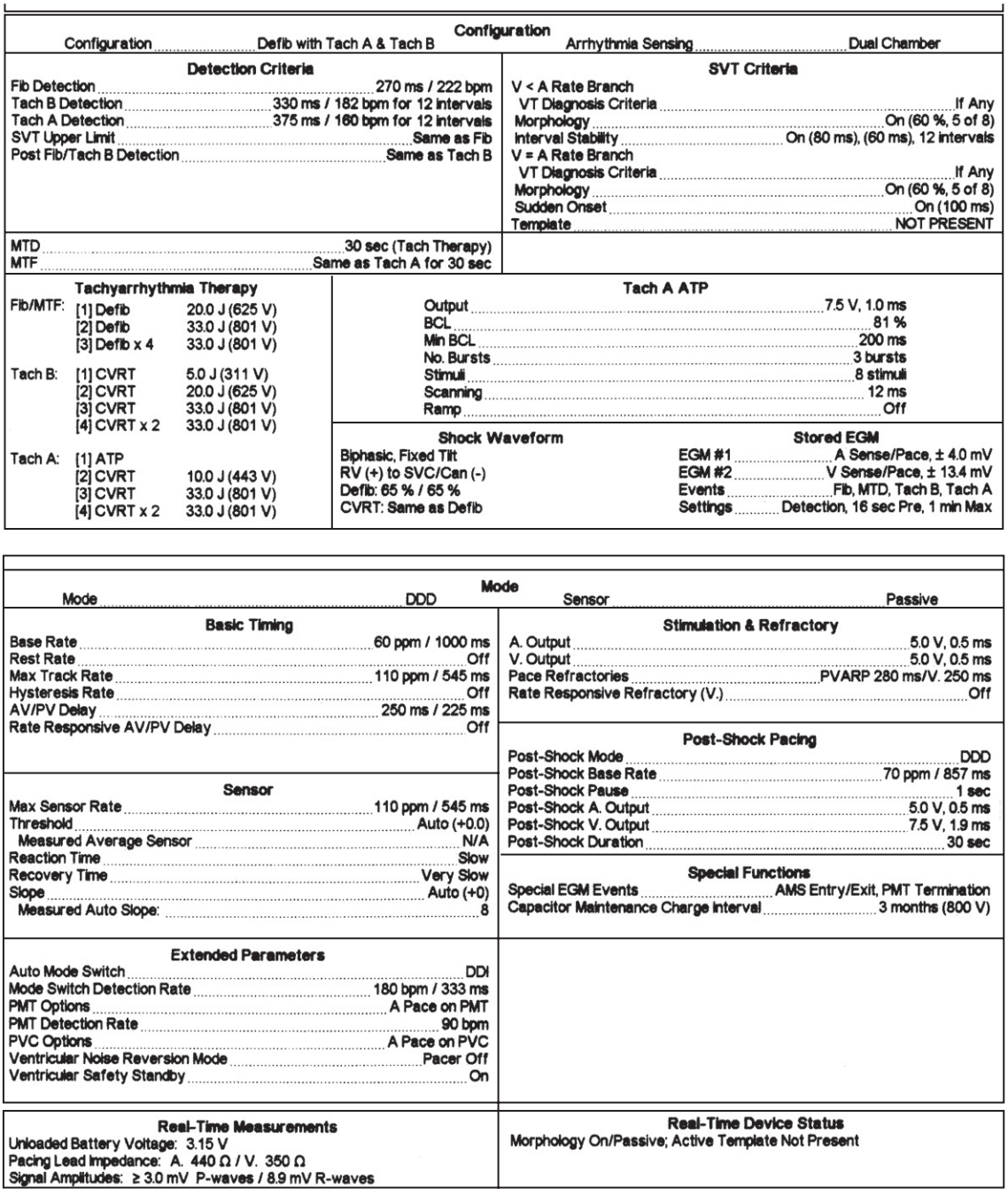

FIGURE 84-3 Three-zone tachyarrhythmia programming for discrimination and treatment of slow and fast ventricular tachycardias and ventricular fibrillation. Dual-chamber pacing is also programmed.

stimuli.[15] Most commonly used adaptive rates for efficacy vary between 75% and 90% with 3 to 20 delivered pacing stimuli. Ramp pacing modes vary the intervals during a burst to an accelerating (positive) or decelerating (negative) ramp. Other algorithms use scanning programmed extrastimuli, usually on the basis of electrophysiology study (EPS) or ramp or burst pacing with terminal programmed scanning extrastimuli.[18] In general, burst or ramp pacing, or variations thereof, provide the greatest likelihood of efficacy, especially if extensive EPS is not used for pace-termination windows and algorithms. Randomized comparative studies suggest similar efficacy for both modes.[11]

Clinical studies have documented a reduction in the need for defibrillator shocks with anti-tachycardia pacing from its early application to the present.[18,19] The Pain Free 1 and 2 trials evaluated the use of anti-tachycardia pacing in rapid VT and its clinical impact.[16,17] Anti-tachycardia pacing was performed with a predetermined adaptive pacing train at 91% of a rapid VT cycle for eight beats (Figure 84-6) to successfully terminate the episode (see Figure 84-6, *A*). In Pain Free 1, 32% of all VT events were in the rapid VT zone, whereas 58% were in the slow VT zone; 85% of all rapid VT events with a cycle length less than 320 ms were terminated by the initial pacing algorithm (see Figure 84-6, *B*), another 4% were

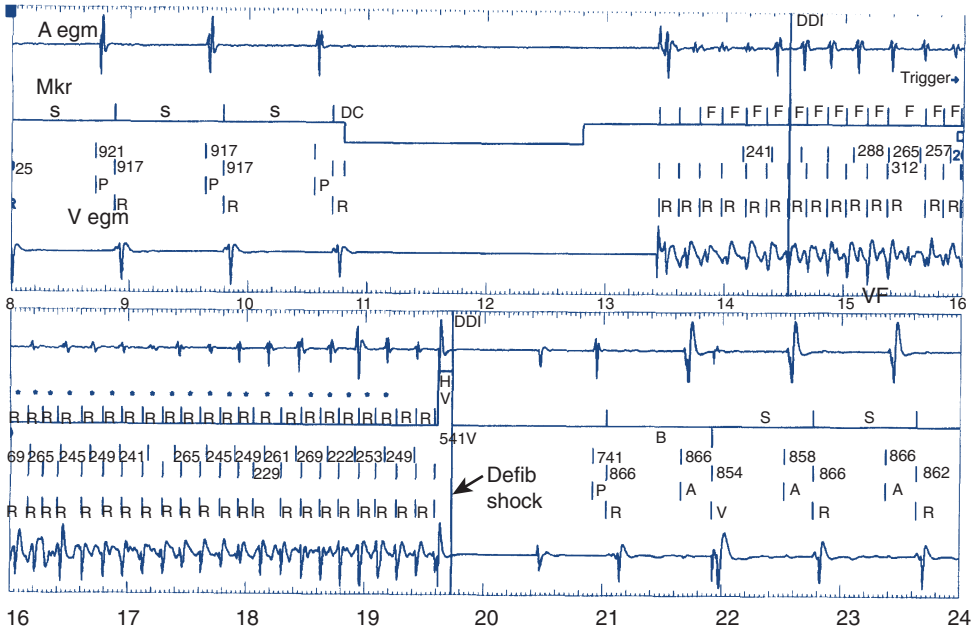

FIGURE 84-4 Duration of ventricular tachycardia with a T-wave shock. Note the ventricular electrogram duration is not prolonged. Termination by a high-voltage 311-V shock results in wider V electrograms. *Top trace*, Intracardiac atrial electrogram (*A egm*). Marker (*Mkr*) channel P-P and R-R intervals. *Bottom trace*, Intracardiac ventricular electrogram (*V egm*). *CV*, Cardioversion.

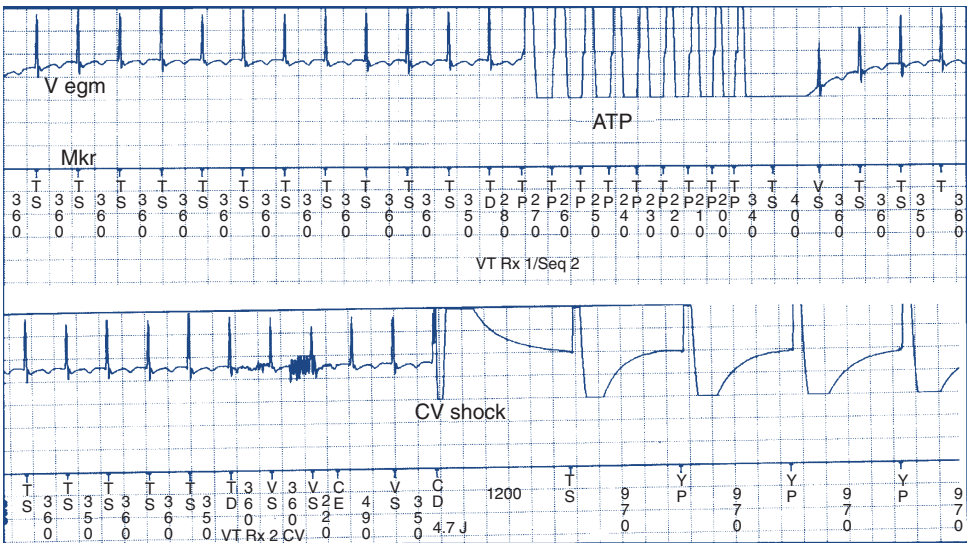

FIGURE 84-5 Failure of termination of ventricular tachycardia with anti-tachycardia pacing (*ATP*) and subsequent cardioversion by a low-energy shock (*CV shock*). *V egm*, Ventricular electrogram; *Mkr*, marker channel with intervals in milliseconds; *TS*, tachycardia sense.

terminated by subsequent algorithms, and only 10% of patients proceeded to shock therapy. A marked improvement was seen in quality of life measures of physical and mental functioning. These results indicate that anti-tachycardia pacing can be effective for treating fast VT and preventing painful shocks and secondary rehospitalizations. Multiple shocks for incessant VT have been shown to reduce battery longevity. Current-generation ICD devices provide anti-tachycardia pacing train delivery during charging.

The recent trend is a more intensified use of empirical ICD programming.[18,19] However, these algorithms merit significant device testing to ensure efficacy. We prefer to establish a greater than 80% likelihood of efficacy for pace termination before final programming of the algorithm, particularly in slow VT. At a minimum, 10 episodes of induced tachycardia should be tested in the laboratory for pace termination; higher standards have been previously advocated.

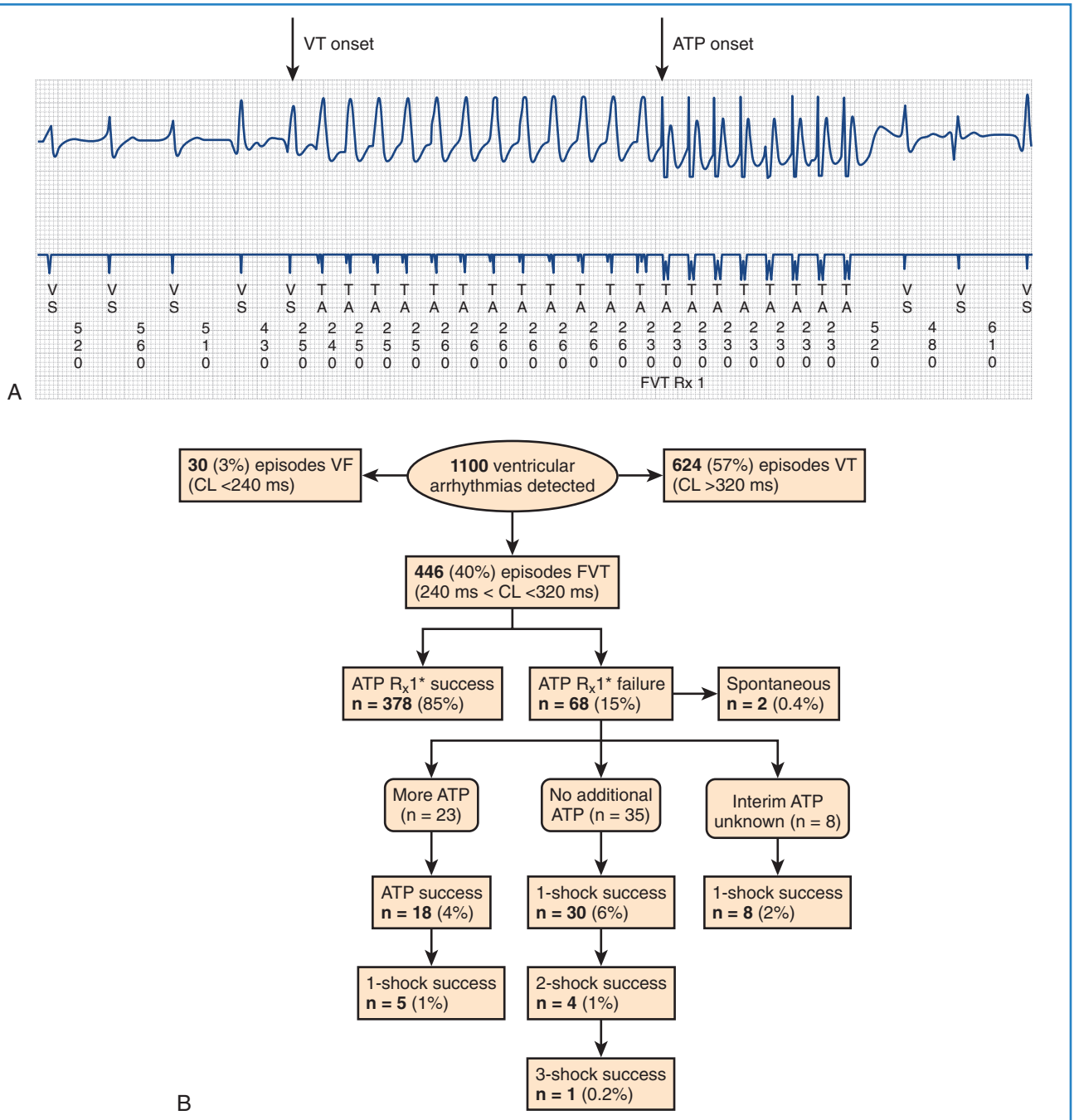

FIGURE 84-6 Clinical outcomes in the Pain Free 1 study. **A,** Anti-tachycardia pacing (*ATP*) termination of fast ventricular tachycardia (*FVT*) episode with a cycle length (*CL*) of 24 to 250 ms. Empiric programming in the Pain Free 1 study is shown with termination with pacing treatment 3. **B,** Flow diagram showing outcomes after programming of anti-tachycardia pacing in the fast VT or ventricular fibrillation zones in the Pain Free 1 study.

Defibrillation Therapies and Threshold Testing

Initial defibrillation energy programming is based on the DFT. This threshold is not a fixed value and is a probabilistic value in an individual patient at a specific moment. The defibrillation efficacy curve has been well demonstrated in human and animal studies to be sigmoid in nature, with the threshold being at the superior but still rising end of the curve. The principles and mechanisms of defibrillation are discussed in Chapter 14. Thus the objective of reliable and reproducible defibrillation in a patient requires objective determination of defibrillation efficacy during testing and the use of initial shock energies that are highly likely to be successful. This mandates the use of energies at, or close to, this threshold. Repeated efficacy of the lowest successful energy is needed to place the shock near the threshold, with three successive or repeated successful terminations needed to place the shock energy at this level of efficacy. Another approach is to statistically predict the likelihood of success with a maximal energy shock and limit the testing. Thus two successful shocks at 10 J or less or a single successful shock at 5 J is highly likely to predict success with a 30-J shock. In unstable patients in whom testing is

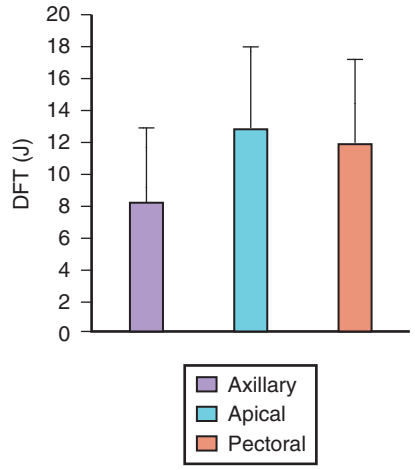

FIGURE 84-7 Defibrillation thresholds (*DFT*) with differing thoracic electrode locations. (*Modified from Saksena S, DeGroot P, Krol RB, et al: Low-energy endocardial defibrillation using an axillary or a pectoral thoracic electrode location,* Circulation *88:2655–2560, 1993.*)

to be limited by clinical imperatives, knowledge of defibrillation protocols is invaluable in defining an optimal testing protocol. Step-down DFT testing is used in our laboratory commencing at the mean value for a particular electrode configuration to minimize the number of induced VF episodes. This is most often 10 J for left-sided pectoral devices and 15 J for right-sided implants (Figure 84-7).[8] Induced VF is obtained by using the noninvasive induction sequences available in the device. The initial shock energy or voltage is tested and based on outcome when subsequent inductions are performed. If the initial shock is unsuccessful, rescue high-energy, device-based or external defibrillation should be used. After hemodynamic stability is restored and 3 to 5 minutes elapse, further testing is performed in step-down decrements if the initial shock was successful; step-up increments are used if it failed for the initial shock efficacy. Other techniques use a binary protocol with an up-down approach for minimizing shocks and arrhythmia episodes. Once the lowest successful shock energy or voltage is identified, we recommend two additional attempts to confirm reproducible efficacy. Three successful terminations at this level or three out of four such attempts place the shock at or above 90% of the DFT.

When patient stability issues intrude and abort extensive testing, reproducibility of a single energy level is sought. In either instance, a 10-J safety margin is programmed above the successful shock energy to ensure efficacy. The second and subsequent defibrillation shocks can, and should, be programmed to maximal shock energy for the potential rise in defibrillation energy that is observed with prolonged VF events. This usually supervenes when such events exceed 30 seconds in clinical studies. Reversal of successive shock polarity may improve efficacy in some situations, although the optimal shock polarity should be determined at implant testing. An increasing amount of information suggests that DFT testing is not associated with improved outcomes.[20-22] Significant controversy has been ignited with the suggestion that DFT testing is associated with a potentially greater implant risk.[22] There clearly is a need to define the patients who would be at risk with such testing. Evidence suggests that DFT testing can be safely avoided in many patients but concerns exist, particularly for patients with high DFTs. With an increasing trend to limit implant testing, lack of knowledge of defibrillation energy requirements may compromise the ability to safely introduce new drugs or maintain confidence in the device's ability to defibrillate when intercurrent clinical scenarios such as heart failure or ischemia potentially raise DFTs.

Device-Based Monitoring

Monitoring and testing functions in these devices have improved ease of use and device performance and have provided more automated device-based testing with expanded capabilities, which include continuous arrhythmia detection and noninvasive EPS. Many of these features are present in current pacemakers and have been simply extended to the ICD. These include battery status, lead impedance measurement on a frequent (even daily) basis, pacing thresholds, and extent of pacing. Diurnal pacing rates, rate response, and hysteresis rates are present in many devices. Additional features specific to defibrillators include the capacitor charge time to maximal shock delivery. This was once a key manual test performed at follow-up, but now it can be automatically initiated by the device at prespecified intervals of time. Charge times in excess of 12 seconds merit close attention and frequent follow-up, and suggest the impending end of battery life. We routinely recommend battery replacement if charge times exceed 15 seconds because this prolonged interval permits longer arrhythmic episode continuation before intervention. This can approach intervals in which defibrillation energy requirements can rise, substantially increasing the likelihood of failure and also predisposing patients to syncope prior to intervention. Tachyarrhythmic events are logged with a time-and-date stamp and their duration recorded (Figure 84-8). In most devices, recorded ventricular electrograms are available for a segment of the event. Recording capabilities for such digitized graphics require substantial device memory, which has been rapidly expanding with more than 120 seconds available in some newer devices. These monitoring capabilities also contribute to substantial current drain on the battery and, if used indiscriminately, can limit longevity. During follow-up evaluations, the patient's arrhythmia history since the last visit or even since implantation is readily available.

Device-Based Testing

Noninvasive EPS has been available for device-based testing for tachycardia induction and termination in ICD devices. During such testing, noninvasive communication with the device is established by a hand-held wand and driven by a software-based external programmer. The present day ICD device can be temporarily programmed to a ventricular stimulation mode for VT induction. VF induction is achieved by using shocks delivered in the vulnerable period on the T wave during ventricular pacing, 50-Hz pacing bursts, or standard high-rate ventricular pacing bursts (Figure 84-9). This permits testing of the pre-programmed tachyarrhythmia detection algorithm and selected therapy for appropriate function of the device.

Tachycardia Detection in Implantable Cardioverter-Defibrillators

Reliable detection algorithms for arrhythmias are just as important as the circuitry in ICDs. The general idea is to deliver a life-saving shock when in doubt rather than withhold the shock. Current ICDs have improved detection algorithms but still deliver

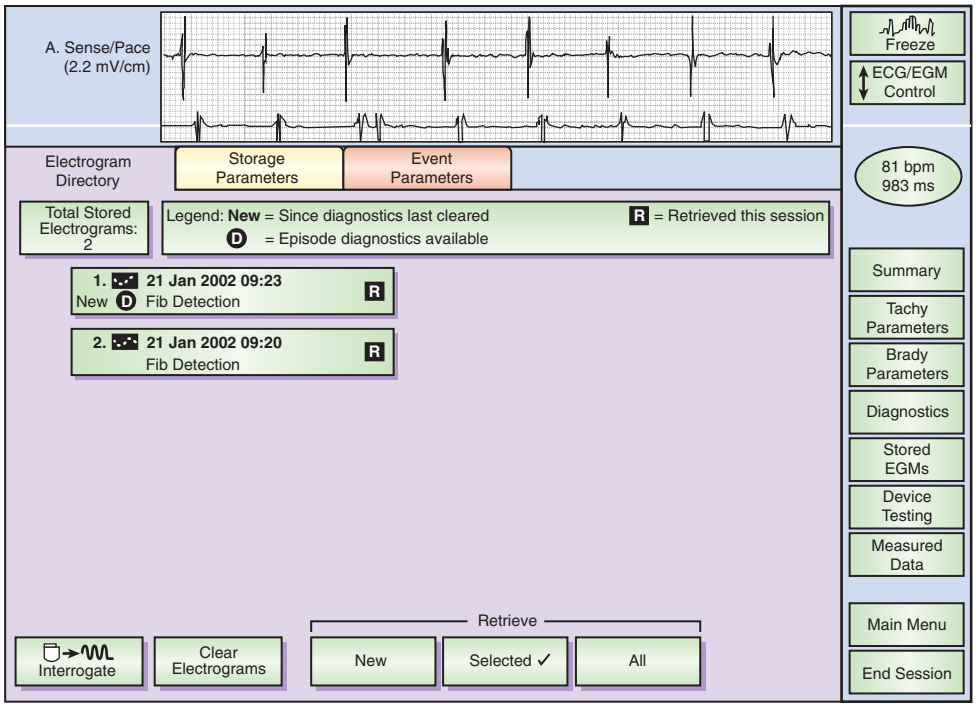

FIGURE 84-8 Arrhythmia event log in the device memory of an implantable dual-chamber cardioverter-defibrillator. *Right,* A categorization of programmable device functions. Telemetered atrial and ventricular electrograms are seen in the two traces (*top*).

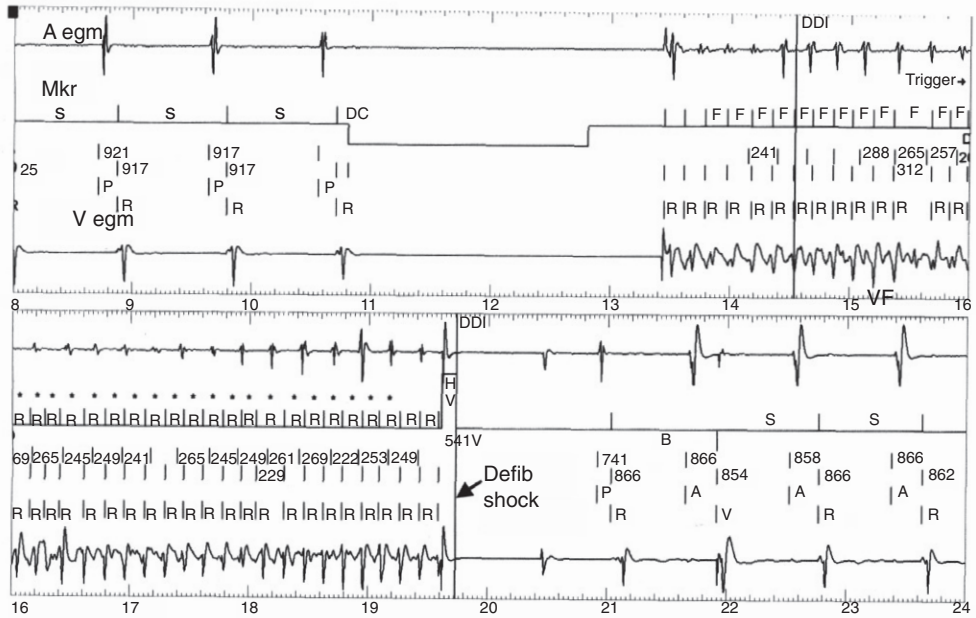

FIGURE 84-9 Induction of ventricular fibrillation (VF) with high-frequency direct current and termination by high-energy defibrillation shock (*Defib shock*) with device-based testing. Electrograms of device-based defibrillation threshold testing demonstrate induction of VF and termination by shock. *Top trace*, Intracardiac atrial electrogram (*A egm*). Marker (*Mkr*) channel P-P and R-R intervals. *Bottom trace*, Intracardiac ventricular electrogram (*V Egm*).

inappropriate shocks 10% to 40% of the time. In Multicenter Automatic Defibrillator Implantation Trial II (MADIT II), inappropriate shock therapy was delivered in 20% of patients by 3.5 years (Figure 84-10), and overall clinical trial experience suggests that this can comprise one third of all shocks.[23]

Inappropriate shocks are painful both physically and emotionally; they also reduce battery life and can be proarrhythmic. To prevent false shocks, detection techniques have been developed using sensing in the atrium and the ventricle and computing interval measurements, such as measurement of atrioventricular (AV) and ventriculoatrial (VA) intervals. The ICD detects tachycardia when the ventricular rate exceeds a pre-programmed rate. This detection algorithm lacks specificity and interprets atrial arrhythmias as ventricular tachyarrhythmia and delivers a shock therapy. To minimize overdetection of VT, current tiered therapy devices have optional detection algorithms than can enhance the specificity of the diagnosis of VT. Selection of an onset criterion excludes gradually accelerating rhythms such as sinus tachycardia and the programming rejected sinus acceleration 98% of the time. However, onset criteria programmed at a ratio of 87% caused underdetection of 0.5% of VT episodes. The stability criterion, designed to exclude irregular rhythms such as atrial fibrillation (AF), reduced detection of induced AF by 95%, paroxysmal AF by 95%, and chronic AF by 99%. Undersensing of VF did not occur because the enhancement algorithms do not apply to that arrhythmia.

Another important technical feature of ICDs is the automatic adjusting signal amplifier autogain. This feature compensates for variable amplitudes of electrograms during arrhythmia. The signal amplitude can vary as much as 10 times during a single episode of VF. Variability in ECG amplitude during VF has also been observed to be a cause for redetection failure.[5] Also, a high gain for low-amplitude signals can increase sensing and oversense T waves "double counting" skeletal myopotentials, leading to inaccurate detection. The autogain feature adjusts sensitivity on the basis of the amplitude of recently sensed signals. Autogain feature of some devices increases sensitivity when a rapid rhythm is detected or to sense VF. It also increases sensitivity during bradycardia pacing so that low-amplitude signals from VF will not be interpreted as bradycardia.

Although a variety of approaches have been used to improve the specificity of tachycardia detection and device therapy, a recent clinical trial—Primary Prevention Parameters Evaluation (PREPARE)—modified the detection time in an effort to reduce device therapies for nonsustained tachycardias in a primary prevention defibrillator population.[24] No increase was observed in patient mortality with increased detection time to seconds. Figure 84-11 shows event rates of appropriate and inappropriate shock therapy in the study. A significant reduction in both shocks for VT and supraventricular tachyarrhythmias is observed, with a minimal increase in arrhythmic syncope events. A reduction in proportion of patients receiving all-cause shock therapy (from 16.9% to 8.5%) and shocks for ventricular tachyarrhythmias (from

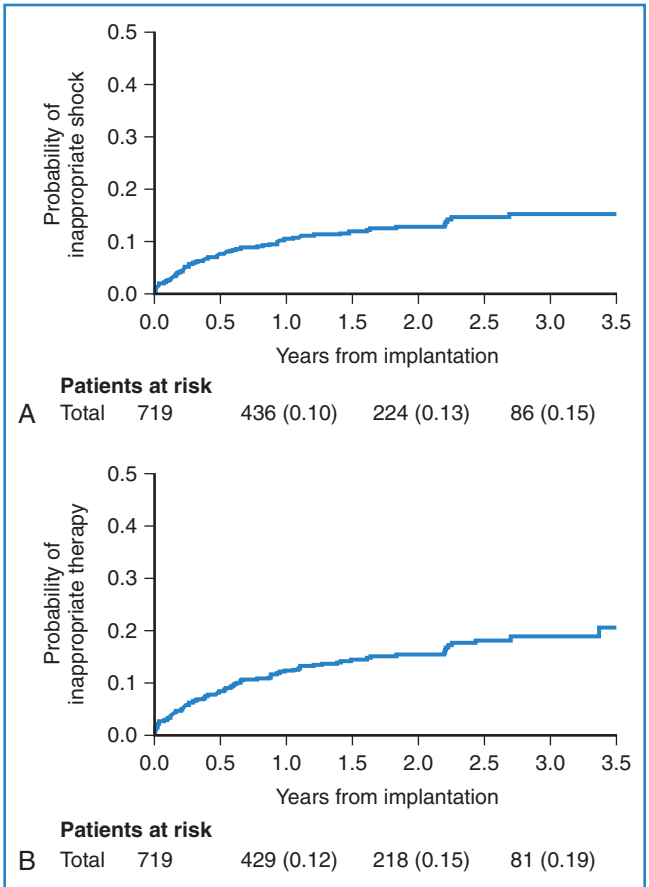

FIGURE 84-10 Probability of inappropriate patient shocks (**A**) and all inappropriate tachyarrhythmia therapy (**B**) in the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II). Inappropriate interventions progressively affect an increasing proportion of implantable cardioverter-defibrillator recipients over a period of 3 years, though some plateauing of new patient recruitment is seen over time. (*Courtesy American Heart Association.*)

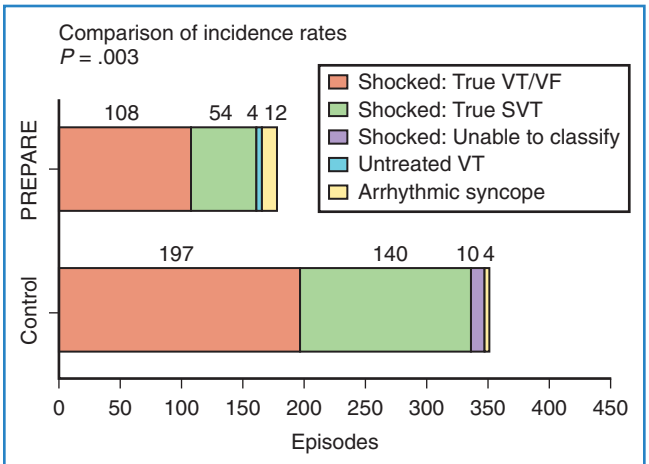

FIGURE 84-11 Clinical use of implantable cardioverter-defibrillator therapy in the Primary Prevention Parameters Evaluation (PREPARE) study algorithm compared with control programming. Note the marked reduction in inappropriate and appropriate interventions, suggesting that current algorithms favor interventions at the expense of specificity and limiting spontaneous arrhythmia event terminations. *VT/VF*, Ventricular tachycardia/ventricular fibrillation; *SVT*, supraventricular tachycardia. (*Wilkoff BL, Williamson BD, Stern RS, et al: Strategic programming of detection and therapy parameters in implantable cardioverter-defibrillators reduces shocks in primary prevention patients: Results from the PREPARE (Primary Prevention Parameters Evaluation) study,* J Am Coll Cardiol *52[7]:541–550, 2008.*)

9.4% to 5.4%) was seen. A significant improvement was observed in the morbidity index related to device-based therapy in the PREPARE patient cohort.

Dual-Chamber and Triple-Chamber Ventricular Implantable Cardioverter-Defibrillator Technology

Conventional dual-chamber pacing has been available in ICD devices for more than 10 years, and their programmability has gradually expanded. These devices require the insertion of an additional bipolar atrial pacing lead in the right atrium, similar to a conventional pacemaker (Figure 84-12, *A*). The device header size is minimally enhanced with an additional port for this lead. Electrode spacing on this lead has been reduced to avoid far-field R-wave sensing, and lead placement in a high lateral right atrial location has been advised for the same reason. Inappropriate atrial lead placement can seriously impair the tachyarrhythmia functions of this device.

The ability to perform atrial pacing has provided AV synchronous pacing or, simply, atrial demand pacing, which may be particularly valuable in patients with impaired ventricular function. It has also allowed improved arrhythmia detection and new algorithms for discrimination based on atrial and ventricular electrograms. Pacing capabilities now approach conventional

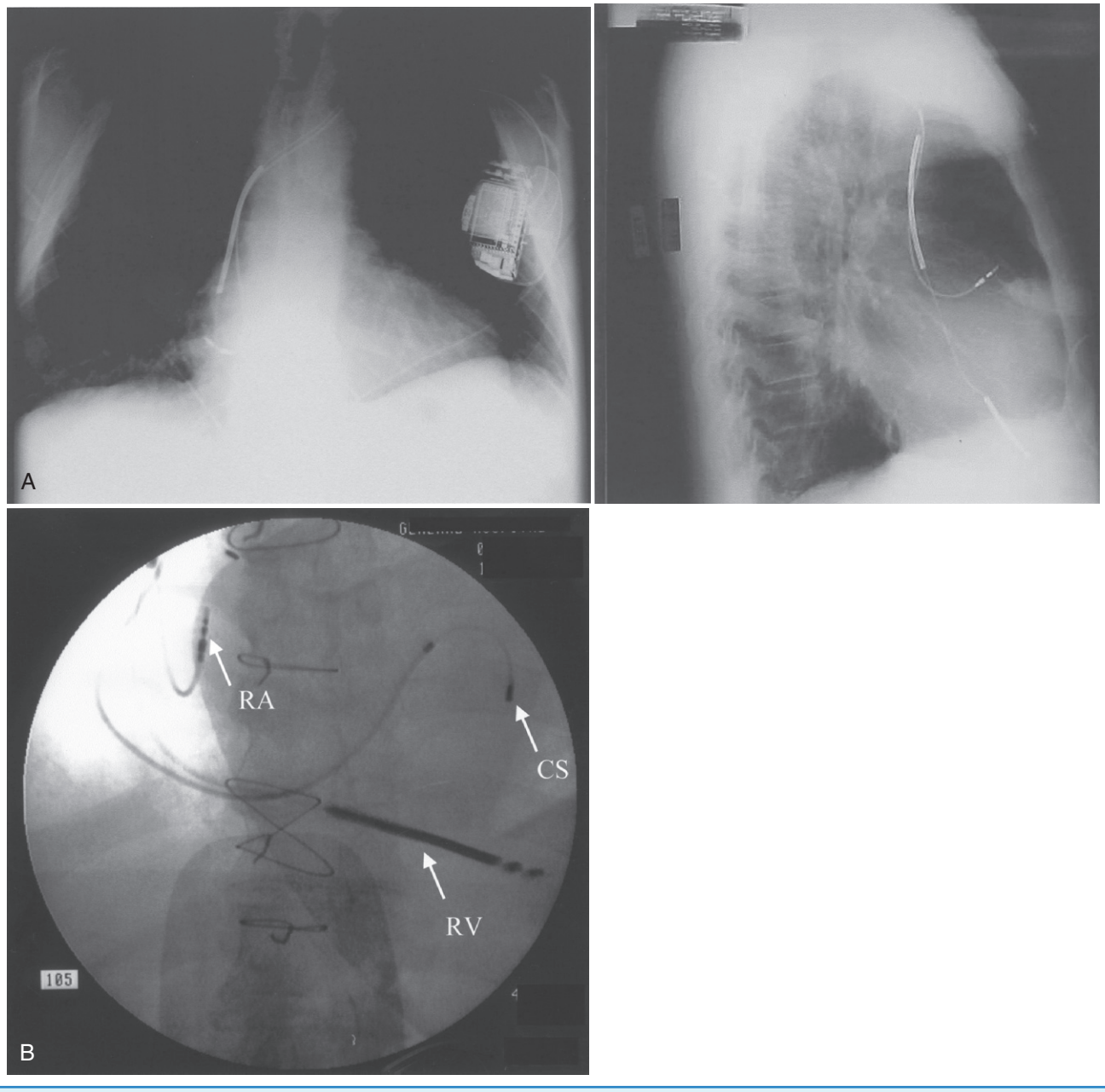

FIGURE 84-12 Different types of dual-chamber implantable cardioverter-defibrillator (ICD) systems. **A,** Posteroanterior and lateral chest radiographs of dual-chamber ICD with right atrial pacing and sensing lead and right ventricular pacing and defibrillation lead. **B,** Fluoroscopic view of biventricular ICD demonstrating pacing lead in coronary sinus (*CS*) in addition to right atrial (*RA*) and right ventricular (*RV*) pacing, defibrillation leads, or both.

dual-chamber pacemakers. Rate response is usually present, but the range of upper rate programmability is usually more limited than in dual-chamber pacemakers. This is usually caused by the potential for conflict with tachycardia detection, although models that are more recent have overcome such software conflicts. Rate response is usually based on an activity sensor alone, and multisensor devices are still awaited. Future sensors could include ischemia, oxygen, or pressure hemodynamic sensors.

Triple-chamber pacing is now available with biventricular pacing ICDs (see Figure 84-12), which are discussed fully in Chapter 85 with indications and implantation techniques. These ICDs are devised to treat drug refractory congestive heart failure (CHF) populations with ventricular dyssynchrony.

Tachycardia discrimination in these devices now uses traditional rate-based detection algorithms in both chambers, overlaid with pattern analysis of atrial and ventricular electrogram relationships (see Figure 84-9). Rate detection alone can easily differentiate rapid and unrelated atrial activity such as that seen in AF or ectopic atrial tachycardia (AT) with varying block from ventricular tachyarrhythmias. Difficulties remain when AV relations are fixed and have identical rates.[14] In such situations, VT with 1:1 retrograde atrial conduction is hard to differentiate from an atrial tachyarrhythmia with antegrade 1:1 conduction. This could include AT or atrial flutter (AFL) for 1:1 conduction. Rules for discrimination have been established in device logic and are highly individualized for each device. For example, the initial PR logic algorithm in the Medtronic Gem device series used a rule for the timing of the atrial event in the ventricular cycle, with the midpoint discriminating antegrade and retrograde atrial activations. This rule was subsequently discarded with the recognition that AV conduction intervals can vary and prolong substantially in very rapid atrial arrhythmias, reducing algorithm efficiency. In contrast, the PARAD algorithms in the Sorin devices examine the onset relationship of the atrium and the ventricle and note the chamber showing initial acceleration, which is then used as an important determinant of tachycardia origin. Whereas atrial triggers can initiate a ventricular tachyarrhythmia in an occasional patient, this algorithm has proved to be quite robust in clinical practice. Finally, the most recent devices provide retrieval of both atrial and ventricular electrograms on the basis of operator-selected parameters for arrhythmic episodes. These provide important discriminatory information with respect to device detection and therapy. More importantly, new device intervention–induced tachyarrhythmias are now more commonly detected, as are successive distinct arrhythmias in an individual patient (Figure 84-13).

Current indications for dual-chamber ICD insertion in patients with ventricular arrhythmias include standard indications for dual-chamber pacing such as sinus node dysfunction with conduction system disease or when AV nodal blocking drugs are concomitantly administered, in advanced AV block when physiological pacing is desired, or in patients with left ventricular dysfunction.[4] They are particularly desirable in patients with coexisting atrial and ventricular tachyarrhythmias for discrimination of the two rhythms.

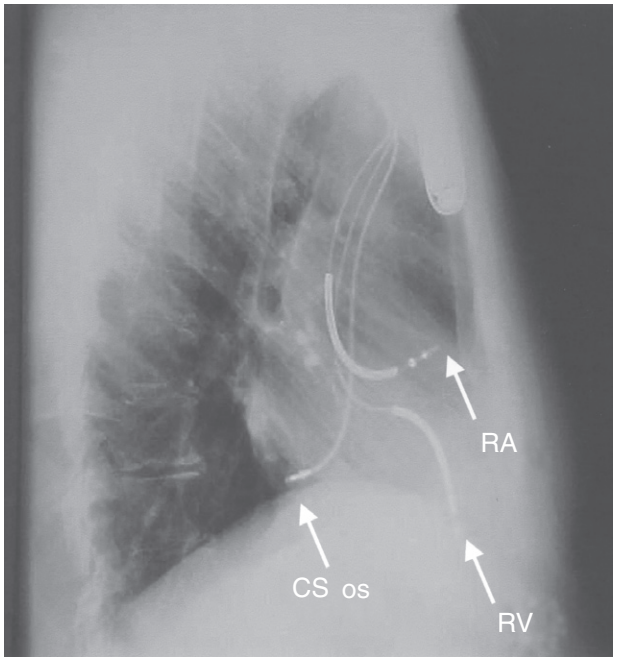

FIGURE 84-13 Chest radiograph, lateral view of dual-chamber atrioventricular implantable cardioverter-defibrillator with dual atrial leads. Note the additional atrial pacing lead at the coronary sinus ostium (*CS os*) to right atrial (*RA*) and right ventricular (*RV*) pacing or defibrillation leads.

Dual-Chamber Atrioventricular Implantable Cardioverter-Defibrillator Technology

The first generation atrial defibrillation device has been replaced by a commercially available dual-chamber AV defibrillator as illustrated in Figure 84-13.[25-29] The technology permits individualized atrial and ventricular anti-tachycardia therapies to be delivered, extending the device population beyond discrimination of coexisting atrial and ventricular tachyarrhythmias in the same patient.[27-29] Initial studies have been conducted in patients with AF who may or may not have coexisting lethal ventricular tachyarrhythmias.[27-29] Because the population pool of AF is very large and atrial cardioversion is a commonly used procedure, the chances of this technology being available in a hybrid therapy format is likely to increase. Stand-alone atrial defibrillation devices, which have been evaluated in a prototype form, have significant limitations in clinical capability, application, and safety and have been largely discarded.[29] Dual-chamber defibrillators are approved for use in patients with drug-refractory and symptomatic AF and in patients with coexisting symptomatic atrial and ventricular tachyarrhythmias.

The atrial channel now permits classification and zone-based therapy of atrial tachyarrhythmias in a manner quite similar to the single-chamber ventricular ICD. It requires insertion of an additional atrial defibrillation electrode. This electrode can be mounted on separate and distinct pacing and defibrillation leads placed in the right atrium and extending into the superior vena cava (SVC) for pacing, detection, and shock delivery. Alternatively, the SVC electrode on a conventional ventricular defibrillation lead can provide the atrial defibrillation electrode and a conventional pacing lead used in the atrium. The use of coronary sinus defibrillation leads was widely advocated initially because of modestly lower DFTs.[18-26] However, the reduction in thresholds had few clinical advantages, except in the management of the patient with high atrial DFTs.[26] Energy thresholds were still too high for patient tolerance for repeated use. Many clinical disadvantages with the existing technology have limited the use of this

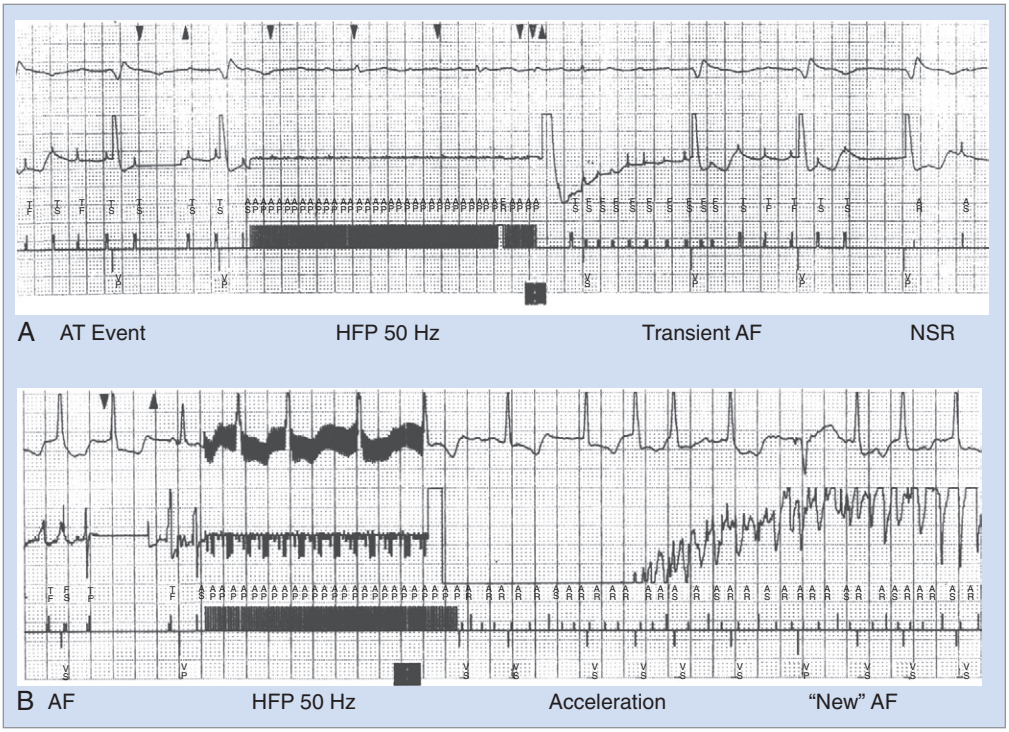

FIGURE 84-14 A, Termination of atypical atrial flutter (AFL) by high-frequency burst at 50 Hz. This converts AFL to transient atrial fibrillation (*AF*) that terminated spontaneously. **B,** High-frequency pacing accelerating atypical AFL to AF in the AF zone. *AT*, Atrial tachycardia.

approach. These include difficult lead insertion, with prolonged procedure times, sensing, and pacing issues from the coronary sinus. The use of such leads can require highly specific and sophisticated algorithms to avoid cross-talk with the ventricular channel and pose significant risks in lead extraction. These issues become particularly important when the AF population has coexisting ventricular tachyarrhythmias.

Atrial tachyarrhythmia detection is based on a two-zone rate stratification structure, with a monomorphic tachycardia zone for ATs and AFL categorization and a fibrillation detection zone. Cycle lengths in these two zones are selected on the basis of spontaneous or induced arrhythmias, and therapies are individualized for each zone. Anti-tachycardia pacing, using burst, ramp, or 50-Hz trains, is available in the tachycardia zone. The efficacy of the former two has been proved in prior experiences with anti-tachycardia atrial pacemakers and in laboratory testing.[27] Burst pacing and ramp pacing have been effective in both intra-atrial re-entrant tachycardia and common AFL, with a lower efficacy rate in non–isthmus-dependent atypical AFL. Trains of 50 Hz for 1 to 4 seconds have been demonstrated to be effective—the latter arrhythmia with repetitive application, with efficacy rates of up to 60%.[30] Back-up shock therapy is used if pacing therapies are ineffective with programmable shocks from 0.1 to 27 J. In the AF zone, 50-Hz pacing and shock therapy alone are available. The efficacy of 50-Hz trains in this zone is based on the categorization of very rapid monomorphic arrhythmias in the zone (Figure 84-14, *A*). It can also accelerate these rhythms into AF (see Figure 84-14, *B*). Established AF rarely responds to this modality. Atrial defibrillation shocks have similar principles of efficacy to ventricular defibrillation. A sigmoid defibrillation efficacy curve exists and thresholds vary widely with lead configuration. Inclusion of a coronary sinus electrode with a right atrial to coronary sinus vector provides lower thresholds compared with right-sided shocks using right atrial to right ventricle, or SVC to right ventricle, or configurations with a can or left pectoral electrode.[31]

In clinical studies, reliable atrial defibrillation has been obtained with shock energies of up to 27 J with the Medtronic Jewel AF device.[27-29] Newer iterations of these devices include pacing prevention algorithms such as continuous atrial pacing for AF prevention. Enhanced monitoring capabilities of these devices include atrial and ventricular arrhythmia detection and categorization and electrogram detection in either chamber as programmed. Noninvasive electrophysiological stimulation is available in both the atrium and the ventricle. This permits testing of detection and therapies for both atrial and ventricular tachyarrhythmias. Finally, a handheld patient activator is available for delivery of shock therapy on demand by the patient or the physician. This device can activate shock therapy as programmed by physician prescription. Thus symptoms and duration of AF as determined by the user can be used in deciding cardioversion shock delivery.

Implantation of Implantable Cardioverter-Defibrillator Systems

The first generation of ICD systems used epicardial leads placed surgically via a transthoracic approach.[32] In 1988, the first non-thoracotomy implantation involving transvenous leads and a submuscular patch was described.[6] This permitted a right-to-left shock vector with successful defibrillation using monophasic

shock waveforms. Further technologic advances in the last decade resulted in the use of biphasic shock waveforms in conjunction with endocardial defibrillation leads.[33] This further reduced the energy requirements for defibrillation, allowing smaller sized pulse generators. The reduction in generator size, coupled with the replacement of patch leads with active generator can electrodes, permitted pectoral rather than abdominal implantation of ICD systems. The use of the epicardial approach is now limited to very few patients such as those with complex congenital heart lesions that do not permit transvenous lead placement or patients who lack vascular access required for lead placement. Even in patients undergoing routine cardiac surgery for any other indication, a postoperative transvenous implantation is preferred over intraoperative epicardial device placement. This is a result of the superior lead performance and durability associated with transvenous leads. The following section will provide a detailed description of the transvenous implantation technique. Epicardial placement techniques are briefly summarized, but the reader is referred elsewhere for a more detailed description of that procedure.[33]

Implantation Facility

Implantation of internal defibrillators requires a dedicated team consisting of an implanting physician (either surgeon or electrophysiologist), a fully trained electrophysiologist (if not the implanting physician), surgical nursing support, and technical support staff for ICD implantation and testing. At the present time, defibrillator system implantations are performed either in the operating room or in properly equipped electrophysiology or catheterization suites.[34,35] Limited data suggest that no significant differences exist in complication rates between procedures performed in the operating room environment and in the electrophysiology laboratory.[36] Regardless of the site, the implanting location should be equipped with general anesthesia capabilities, appropriate air filtering, surgical scrub areas, surgical sterilization and lighting, and high-quality fluoroscopy. Electrocardiographic and hemodynamic equipment permitting arterial pressure monitoring and intracardiac signal recording should be available in the suite as necessary. ICD procedures should be performed in hospitals with electrophysiology programs and rapid access to cardiac surgical services to be able to respond to the potential complications of the procedure.

Preoperative Assessment

The preceding sections have described in detail the advances in ICD technology that have taken place since the 1980s. An important part of the preoperative assessment is to ascertain which system is appropriate for a particular patient on the basis of patient status as well as future needs. This is based on the recognition that each new generation of devices is associated with increased complexity of implantation and follow-up procedures as well as accelerated battery drainage. Thus it is important to establish that the device and the patient are the best possible fit.

An integral part of the preoperative assessment is the evaluation of the patient for the presence of any chest deformities, thickness of subcutaneous tissue, presence of any skin lesions in an anticipated implant region, presence of any physical or laboratory signs of active infection, and body and heart sizes, as well as general body habitus. All these factors may influence the technique of system insertion, including the selection of the pulse generator (based on size and its energy output), and lead system (size and length).

Patient preparation commences before entering the operating suite with the removal of cutaneous hair, followed by cleaning of the proposed insertion site. Before the procedure, adhesive cutaneous pacing and defibrillation electrodes are placed to enable electrocardiographic monitoring and external defibrillation, and an arterial line is usually placed for hemodynamic monitoring. A prophylactic dose of an appropriate broad-spectrum antibiotic is administered intravenously.

Implantation Technique

Implantation of any ICD system involves insertion and positioning of the leads, followed by testing of their pacing and sensing functions. The generator pocket is then created and the leads connected to the generator. This is followed by DFT testing as outlined earlier and final modifications to the programming. The wound is then closed. The implantation procedure for a single-chamber ICD is described below. The modifications of the implantation technique required for the more advanced devices is discussed later.

Single-Chamber Ventricular Implantable Cardioverter-Defibrillator Implantation

ICD implantations are generally performed in the left pre-pectoral area to establish a left-to-right defibrillation shock vector. The generator is placed in a pre-pectoral pocket, and the leads are inserted transvenously from the cephalic veins, the subclavian veins, or both. With standard sterile technique, a pre-pectoral incision is performed suitable for cephalic or subclavian access (Figure 84-15, *A*). The initial incision is usually below the clavicle. The right pectoral region may be used in selected left-handed patients or if local abnormalities, infection, or venous access preclude using the standard technique. Transvenous lead insertion is then performed via either the cephalic route or the subclavian route, as described below.

The cephalic vein access for transvenous lead insertion is preferred over subclavian vein puncture because the latter can be associated acutely with a small risk of pneumothorax and arterial complications and in the long term with subclavian crush injury to the leads.[37] Subclavian crush occurs when leads inserted via the subclavian vein are trapped within the costoclavicular complex or under the subclavius muscle. This phenomenon, which is almost never seen with the cephalic vein access, is more common with large-diameter defibrillating electrodes than with pacemaker leads.[37] Dissection in the delto-pectoral groove is used to isolate the cephalic vein. The vein is controlled proximally and distally to the site of venous entry with ligatures. The vein is opened with a small incision. The pacing and defibrillator electrodes are then introduced and advanced via the subclavian vein into the right side of the heart into the pulmonary artery under fluoroscopic guidance (see Figure 84-15, *B*). The lead is withdrawn and fixed in the right ventricular apex. If the cephalic vein or the venous valves do not allow lead insertion, a guidewire can be passed into the right atrium. A split-sheath introducer is advanced over the wire permitting lead insertion. Ong and Barold described a modified cephalic vein guidewire technique for the introduction of one or more electrodes.[38] In this technique, insertion of the guidewire into the cephalic vein is followed by insertion of the introducer

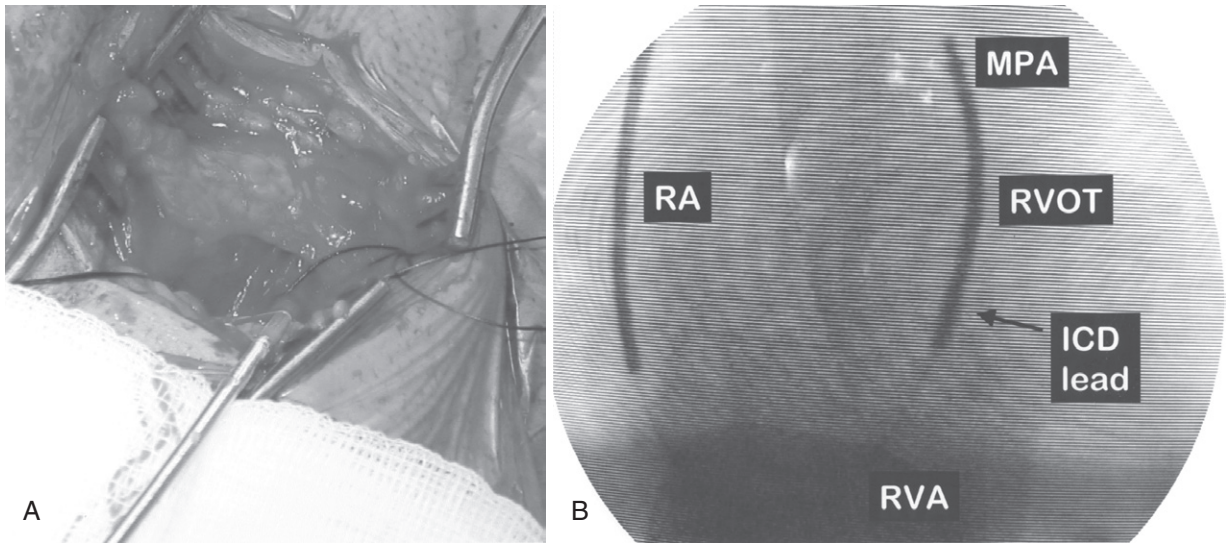

FIGURE 84-15 A, Cephalic vein dissection for lead insertion. Note the vein in the delto-pectoral groove has been opened with lead introduction. **B,** Fluoroscopic defibrillation lead positioning in the pulmonary artery before withdrawal to right ventricle. *ICD*, Implantable cardioverter-defibrillator; *MPA*, main pulmonary artery; *RA*, right atrium; *RVA*, right vertebral artery; *RVOT*, right ventricular outflow tract.

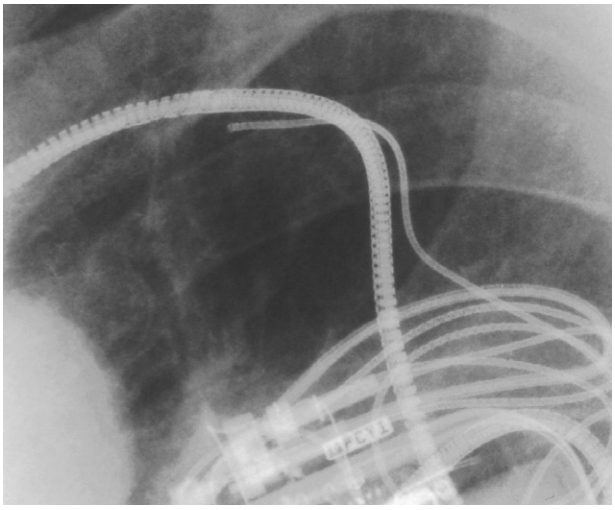

FIGURE 84-16 Subclavian crush fracture of defibrillation electrode in the superior vena cava. The fractured lead remnant is seen below the clavicle.

and invagination into extra-thoracic segment of the subclavian vein with sacrifice of the cephalic vein.

If a subclavian puncture is required for the placement of the lead, it should be performed as far lateral as possible to minimize the risks of subclavian crush syndrome (Figure 84-16).[39] Before vein puncture, the patient is placed in a Trendelenburg position, thus distending the vein, facilitating puncture, and avoiding air embolism. Fluoroscopy, with or without contrast venography using peripheral injection of 20 to 30 mL of contrast, can assist in localizing the vein.[40] In rare instances, when both the cephalic and subclavian venous accesses cannot be obtained, the internal jugular, external jugular, or the axillary vein can be used. These alternative approaches require dissection that is more extensive and lead tunneling to reach the pectoral pocket.

Pacing and defibrillator leads are of larger diameters (approximately 9 Fr) and greater stiffness than pacemaker leads. Downsizing of lead diameters has occurred in the past few years with varying degrees of change in lead performance. The 7-Fr Medtronic Sprint Fidelis lead was associated with an increased incidence of lead fracture, especially at the tip, and has been discontinued (see Chapter 85 for more details). The 7-Fr St Jude pacing and defibrillation Durata lead model 7020 has had acceptable survival rates in the initial years of its introduction. Great care must be taken to avoid damage to the leads as well as the surrounding vascular structures during lead insertion. A curved stylet is inserted into the lead, and the lead is carefully advanced across the tricuspid valve into the right ventricular outflow tract and the pulmonary artery. Retracting the stylet to soften the lead tip can facilitate crossing of the tricuspid valve. The curved stylet is replaced with a straight stylet, and the lead is slowly withdrawn until it drops down toward the right ventricular apex. It is then gently advanced to the right ventricular apex, preferably with the stylet slightly withdrawn from the tip. The lead position chosen should place the defibrillation coil electrode in proximity to the inferior right ventricular myocardium. After optimal lead placement has been achieved, active fixation leads are anchored at the apex. The lead is then evaluated for stability with deep inspiration and after coughing. Pacing thresholds and diaphragmatic stimulation with pacing are assessed.

In patients with high DFTs, the insertion of additional leads may be necessary to attempt to increase the active area of the defibrillation electrodes and improve current distribution. Commonly used leads are an additional SVC coil electrode positioned at the atrial junction, a coronary sinus defibrillation lead, or a subcutaneous patch or array. The subcutaneous patch is usually positioned below the axilla, in the second to fourth intercostal space posterior to the midaxillary line. This requires a separate incision, formation of a subcutaneous pocket, and tunneling of

the lead connector to the pectoral pocket. If the generator header cannot accept three or more leads, the additional lead is connected to the generator via a Y-connector, which is placed in the pre-pectoral pocket. After demonstrating satisfactory lead positioning, electrogram stability, and acceptable pacing and sensing parameters, the lead is fixed at the venous entry site. Silk sutures are used to anchor the sleeve to the lead and muscular fascia surrounding the lead.

A subcutaneous pre-pectoral pocket is used for generator location. This is usually on the medial aspect anterior to the plane of the pectoral fascia. It may be developed at different points in the implantation procedure. It is generally more desirable to develop it after vascular access has been obtained to avoid unnecessary surgery if vascular issues emerge during the procedure precluding device implantation. The generator is placed inferior to the clavicle to prevent restriction of shoulder motion and medial to avoid interference with arm motion. The pocket should be appropriate for the size of the device. A tight pocket can lead to generator erosion, whereas an oversized pocket may permit migration, seroma formation, and "twiddler syndrome." The leads are connected to the generator header. Tissue blood or other fluids should not be interposed between the leads and the header ports. It is important to verify that the leads are inserted into the correct ports and securely connected. The pocket is irrigated with antibiotic solution, and the generator is placed in the pocket. Excess lead length is looped under the device to avoid lead injury during future operations at this site. Testing of pacing, sensing, and DFT is now performed. After demonstration of satisfactory device function, the pocket is closed, and sterile adhesive strips can be applied to ensure incision apposition.

A small number of physicians routinely perform submuscular implantations below the pectoralis major muscle in the same region, citing similar complication rates to subcutaneous implantations. We generally do not recommend this as routine practice. Special circumstances, such as in children, wasted or thin individuals with limited subcutaneous tissue, or those with prior history of device erosion, can lead to the preferential use of this approach. Several concerns exist with the use of this approach on a routine basis. Most importantly, limitations in pectoralis muscle function, atrophy, and fibrosis are long-term issues. Device replacement procedures are more difficult and promote more muscle injury. Recently, device header disruption has been reported in a few Teligen ICD devices (Boston Scientific, personal communication, 2009). Alternatives such as submammary and axillary implant locations for devices have been proposed and should be considered in selected patients.

After device system implantation, the implanting physician should demonstrate that VF can appropriately be detected by the device and reproducibly terminated by using the lead configuration and energy capabilities of the device. Although very rare complications of defibrillation testing have been documented, patients who may be inappropriate for such testing should be identified on the basis of clinical status and parameters. Small clinical trials have demonstrated the effectiveness of untested systems. However, the efficacy of device function must be ascertained to demonstrate the appropriate function of the entire system and to provide psychological reassurance to the patient regarding device efficacy. In earlier days, patients were asked to undergo a test shock to be more prepared as to the nature of shock therapy. The use of deep anesthesia during testing often precludes this. Although device-based measurement of system integrity is always performed for pacing and shock impedances and pacing thresholds, this should not be a substitute for arrhythmia induction and reversion. This testing can be performed in a formal fashion with DFT determination or limited shock efficacy testing. DFT testing, which has been described previously, is performed with the patient under deep sedation (e.g., with propofol or etomidate) or sometimes general anesthesia. Alternatively, a fixed-shock energy level is tested repetitively for efficacy. Typically, a 15- or 20-J shock is tested for three successful reversions. A safety margin of 10 J above DFT is usually programmed in the first shock therapy. Many maneuvers can be used to lower the threshold. These include reversing the shock polarity and changing pulse duration or electrode configuration. If these programming options fail to provide an adequate safety margin, it may be necessary to add another lead to the system or to reposition the ventricular electrodes, the SVC electrodes, or both. Finally, a pulse generator with a higher energy output may be used to obtain satisfactory defibrillation. In critically ill or unstable patients, defibrillation efficacy testing can be deferred till the patients have stabilized to avoid risks of exacerbation of heart failure, ischemia, or incessant ventricular arrhythmias.

On the basis of the results of DFT testing, final programming of the device is then performed, and the pocket is closed. Postoperatively, the patient's arm is placed in a sling, and an intravenous antibiotic is administered. A chest radiograph is obtained immediately after the implantation to define lead location and to exclude complications such as pneumothorax. Posteroanterior and lateral radiographs should be obtained before discharge for future reference. Patients are usually discharged within 24 hours of implantation. Predischarge ICD testing is recommended for final programming for VT and VF detection and therapy. In addition, patients may undergo a device shock or pacing therapies to facilitate psychological adjustment to device function. Figure 84-17 illustrates a typical checklist of postoperative orders for patients after ICD implantation at our institution.

Dual-Chamber Ventricular Implantable Cardioverter-Defibrillator Insertion

These devices incorporate conventional dual-chamber pacing capabilities along with defibrillation. The initial steps in device placement are similar to those with a single ventricular lead. However, these devices require insertion of an additional atrial lead, which is similar to the leads used in conventional pacemakers. The atrial lead should be placed following the insertion of the ventricular lead and, to avoid cross-talk, should be placed in the high right atrium or in the superior aspect of the atrial appendage. Pacing and sensing thresholds are tested as in conventional pacemakers. During DFT testing, cross-talk between atrial stimuli and ventricular detection circuits should be assessed. Programming of algorithms to differentiate supraventricular and ventricular tachyarrhythmias can be performed at this time or at a later point in follow-up device management. This is encouraged before discharge in patients with a history of atrial tachyarrhythmias.

Dual-Chamber Atrioventricular Defibrillation Devices

These devices incorporate atrial pacing and defibrillation algorithms in patients with combined AF with VT, VF, or both. The atrial defibrillation shock is delivered via an atrial and ventricular defibrillation electrode. The atrial defibrillation coil is mounted on a combined atrial pacing and defibrillation lead (see Figure 84-11) or incorporated in the ventricular defibrillation lead, with

POSTOPERATIVE PACEMAKER OR ICD IMPLANT ORDERS	
ONLY CHECKED ITEMS WILL BE IMPLEMENTED	
PROCEDURE: DATE:	
PHYSICAN: ALLERGIES:	
☐ **DIET**:	
☐ **ACTIVITY**:	
☐ **WOUND CARE**:	
☐ **ABDOMINAL IMPLANT**: Maintain supine position ¥ _____ hrs.	
☐ **PECTORAL IMPLANT**: Apply arm sling to affected side ¥ _____ days.	
☐ Initial surgical dressing to be removed by physician	
☐ Cleanse surgical site daily with normal saline. Apply Bacitracin ointment and dry sterile dressing	
☐ **LABORATORY AND DIAGNOSTIC STUDIES**:	
☐ Stat portable chest x-ray	
☐ Stat ECG	
☐ Chest x-ray PA and Lateral in AM	
☐ Other:	
☐ **MEDICATIONS**:	
☐ Ancef 1gm IV q8hrs ¥ 3 doses followed by Keflex 500mg PO TID ¥ _____ days.	
☐ Other:	
IF PATIENT IS PENICILLIN ALLERGIC:	
☐ Vancomycin 500mg IV q12hrs ¥ 2 doses followed by Erythromycin 500mg PO TID ¥ _____ days.	
☐ Other:	
☐ Percocet 1 tablet (5/325mg) PO q4hrs PRN for moderate pain	
☐ Tylenol 2 tablets PO q4hrs PRN for mild pain	
☐ Anticoagulation:	
☐ Other:	

FIGURE 84-17 Postoperative orders for implantable cardioverter-defibrillator management after system insertion.

a separate atrial pacing lead being inserted in the patient. Atrial defibrillation threshold testing can be performed analogous to ventricular defibrillation. Commonly used shock configurations are similar to ventricular defibrillation, with a coronary sinus electrode being used on rare occasions. Insertion techniques are similar to those of dual-chamber ICD leads. The atrial defibrillation coil is usually located in the SVC or the high right atrium. It is important to maximize atrial sensitivity during device testing to accurately detect AF. This is best accomplished by reducing atrial sensitivity to 0.3 mV. These devices are infrequently used in patients with AF alone but are more useful in patients with both AF and ventricular tachyarrhythmias.

Postoperative Management

After device insertion, device behavior and limitations on specific physical activity should be reviewed with the patient. Immobilization of the ipsilateral arm in a sling for a short period after implantation is desirable. Prolonged immobilization can affect shoulder range of motion. Recent guidelines recommend restrictions on driving for secondary prevention ICD indications for a minimum of 3 months and preferably 6 months to determine pattern of recurrent VT or VF events.[39] Patients with primary prevention implants are frequently allowed to drive, because the time to first event remains uncertain. Other limitations include magnetic resonance imaging, although methods for device shielding and devices with nonferrous metallic construction that will permit such imaging are being developed. Device interactions with electromagnetic sources, environmental issues, and antibiotic prophylaxis for device infections should also be discussed. ICD recipients should be encouraged to carry proper device identification documents at all times. Avoidance of prolonged exposure to electronic sensor systems should be emphasized. Patients receiving these devices can experience transient or sustained behavioral disturbances, including depression and anxiety.[40,41] Education and psychological support before, during, and after ICD insertion are highly desirable and can improve the patient's quality of life.[42,43]

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CHAPTER 85

Implantable Cardioverter-Defibrillators: Indications, Management of Complications, and Device Follow-up

Sanjeev Saksena, Rangadham Nagarakanti, Nandini Madan, and Mark Preminger

The widespread use of implantable cardioverter-defibrillators (ICDs) worldwide has resulted in the rapid evolution of device indications, crystallized techniques for device management after implantation, and highlighted the complications associated with this therapy, all of which are discussed in this chapter. However, continuous revision of these areas is the norm, and the reader is referred to practice guidelines from major cardiology organizations for updates.

Indications for Implantable Cardioverter-Defibrillator Therapy

Indications for ICD therapy, as established in 2009–2010, include patients with manifest ventricular tachyarrhythmic events (referred to as *secondary prevention indications*) or those at risk for sudden, symptomatic ventricular tachyarrhythmias (*primary prevention indications*) that could potentially result in sudden cardiac death (SCD). Updated guidelines for the use of ICDs in ventricular tachyarrhythmias were most recently published in 2008 by the expert panel from the American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) Joint Task Force.[1] Of note, these guidelines, compared with earlier versions released, reflect significant changes in our understanding of the mechanisms and risks of SCD in high-risk subpopulations with coronary diseases, nonischemic heart diseases, and primary electrical diseases of the heart. Because of the overlap between primary and secondary SCD prevention indications, the recommendations have been simplified into a single list. The primary prevention indications for nonischemic cardiomyopathies have been updated to include data from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) (i.e., ischemic and nonischemic cardiomyopathies with left ventricular ejection fraction [LVEF] ≤35% and New York Heart Association [NYHA] class II to III).[2] As new clinical trials continue to expand the primary prevention applications with regard to SCD, the guidelines are updated to include inherited arrhythmia syndromes and select nonischemic cardiomyopathies. In accordance with clinical practice, the primary prevention guidelines continue to expand, but the guidelines for secondary prevention remain relatively stable.

The new guidelines, again, place emphasis on the application of primary prevention ICD recommendations only in patients who meet prespecified screening criteria:

1. Optimal medical therapy
2. A reasonable survival expectancy, with good functional capacity for more than 1 year
3. Independent risk assessment, including patient preference

The guidelines address programming at the device's end of life. The LVEF criteria of the current primary prevention ICD recommendations are based on the entry criteria of the randomized clinical trials that showed the benefit of such indications (e.g., Multicentre Automatic Defibrillator Trial II [MADIT-II], SCD-HeFT).[2,3]

These guidelines divide the recommendations into the following major classes:

Class I: Benefit is greater than risk. ICD therapy is indicated on the basis of evidence and should be performed.
Class IIa: Benefit is greater than risk. Additional studies with focused objectives are needed. ICD therapy is a reasonable therapeutic option.
Class IIb: Benefit is greater than risk. Additional studies and registries are needed. ICD therapy may be considered.
Class III: Risk is greater than benefit. Clinical situations exist in which the use of ICD therapy is generally not justified and may be harmful.

The levels of evidence for these recommendations are classified as follows:

Level A: Data have been derived from multiple randomized clinical trials or meta-analyses. Multiple populations have been evaluated.
Level B: Data have been derived from a single randomized trial or from nonrandomized studies. Limited populations have been evaluated.
Level C: Only consensus of expert opinions, case studies, or standard of care exist. Very limited populations have been evaluated.

Box 85-1 summarizes the ACC/AHA/HRS 2008 practice guideline indications for ICD therapy. For convenience, the use of ICDs in the secondary and primary prevention of ventricular arrhythmias and SCD are discussed separately.

Box 85-1 Indications for Implantable Cardioverter-Defibrillator Therapy

CLASS I

1. ICD therapy is indicated in patients who are survivors of cardiac arrest caused by ventricular fibrillation (VF) or hemodynamically unstable sustained ventricular tachycardia (VT) after evaluation to define the cause of the event and to exclude any completely reversible causes. (Level of Evidence: A)
2. ICD therapy is indicated in patients with structural heart disease and spontaneous sustained VT, whether hemodynamically stable or unstable. (Level of Evidence: B)
3. ICD therapy is indicated in patients with syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced at electrophysiological study. (Level of Evidence: B)
4. ICD therapy is indicated in patients with left ventricular ejection fraction (LVEF) less than 35% caused by prior myocardial infarction (MI), who are at least 40 days post-MI and are in New York Heart Association (NYHA) functional class II or III. (Level of Evidence: A)
5. ICD therapy is indicated in patients with nonischemic dilated cardiomyopathy (DCM), who have an LVEF less than or equal to 35% and who are in NYHA functional class II or III. (Level of Evidence: B)
6. ICD therapy is indicated in patients with left ventricular dysfunction caused by prior MI, who are at least 40 days post-MI, have an LVEF less than 30%, and are in NYHA functional class I. (Level of Evidence: A)
7. ICD therapy is indicated in patients with nonsustained VT caused by prior MI, LVEF less than 40%, and inducible VF or sustained VT at electrophysiological study. (Level of Evidence: B)

CLASS IIA

1. ICD implantation is reasonable for patients with unexplained syncope, significant left ventricular dysfunction, and nonischemic DCM. (Level of Evidence: C)
2. ICD implantation is reasonable for patients with sustained VT and normal or near-normal ventricular function. (Level of Evidence: C)
3. ICD implantation is reasonable for patients with hypertrophic cardiomyopathy (HCM) who have 1 or more major risk factors for sudden cardiac death (SCD). (Level of Evidence: C)
4. ICD implantation is reasonable for the prevention of SCD in patients with arrhythmogenic right ventricular dysplasia (ARVD)/C who have 1 or more risk factors for SCD. (Level of Evidence: C)
5. ICD implantation is reasonable to reduce SCD in patients with long QT syndrome who are experiencing syncope, VT, or both while receiving β-blockers. (Level of Evidence: B)
6. ICD implantation is reasonable for non-hospitalized patients awaiting transplantation. (Level of Evidence: C)
7. ICD implantation is reasonable for patients with Brugada syndrome who have had syncope. (Level of Evidence: C)
8. ICD implantation is reasonable for patients with Brugada syndrome who have documented VT that has not resulted in cardiac arrest. (Level of Evidence: C)
9. ICD implantation is reasonable for patients with catecholaminergic polymorphic VT who have syncope, documented sustained VT, or both while receiving β-blockers. (Level of Evidence: C)
10. ICD implantation is reasonable for patients with cardiac sarcoidosis, giant cell myocarditis, or Chagas disease. (Level of Evidence: C)

CLASS IIB

1. ICD therapy may be considered in patients with nonischemic heart disease who have an LVEF of less than or equal to 35% and who are in NYHA functional class I. (Level of Evidence: C)
2. ICD therapy may be considered for patients with long QT syndrome and risk factors for SCD. (Level of Evidence: B)
3. ICD therapy may be considered in patients with syncope and advanced structural heart disease, in whom thorough invasive and noninvasive investigations have failed to define a cause. (Level of Evidence: C)
4. ICD therapy may be considered in patients with a familial cardiomyopathy associated with SCD. (Level of Evidence: C)
5. ICD therapy may be considered in patients with left ventricular noncompaction. (Level of Evidence: C)

CLASS III

1. ICD therapy is not indicated for patients who do not have a reasonable expectation of survival with an acceptable functional status for at least 1 year, even if they meet ICD implantation criteria specified in the class I, IIa, and IIb recommendations above. (Level of Evidence: C)
2. ICD therapy is not indicated for patients with incessant VT or VF. (Level of Evidence: C)
3. ICD therapy is not indicated in patients with significant psychiatric illnesses that may be aggravated by device implantation or that may preclude systematic follow-up. (Level of Evidence: C)
4. ICD therapy is not indicated for NYHA class IV patients with drug-refractory congestive heart failure who are not candidates for cardiac transplantation or cardiac resynchronization therapy. (Level of Evidence: C)
5. ICD therapy is not indicated for syncope of undetermined cause in a patient without inducible ventricular tachyarrhythmias and without structural heart disease. (Level of Evidence: C)
6. ICD therapy is not indicated when VF or VT is amenable to surgical or catheter ablation (e.g., atrial arrhythmias associated with the Wolff-Parkinson-White syndrome, right or left ventricular outflow tract VT, idiopathic VT, or fascicular VT in the absence of structural heart disease). (Level of Evidence: C)
7. ICD therapy is not indicated for patients with ventricular tachyarrhythmias caused by a completely reversible disorder in the absence of structural heart disease (e.g., electrolyte imbalance, drugs, or trauma). (Level of Evidence: B)

Modified from Epstein AE, DiMarco JP, Ellenbogen KA, et al: ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: American College of Cardiology/American Heart Association Task Force on Practice Guidelines, J Am Coll Cardiol *51:1–62, 2008.*

Implantable Cardioverter-Defibrillators for the Secondary Prevention of Ventricular Arrhythmias

Sustained Symptomatic Ventricular Tachycardia and Survivors of Cardiac Arrest

The first established indication for the use of the ICD was in patients who had had spontaneous sustained and symptomatic ventricular tachycardia (VT) or ventricular fibrillation (VF) or who were survivors of a cardiac arrest. In these patients, ICD devices have terminated sustained ventricular tachyarrhythmias with either anti-tachycardia pacing or shock therapy. Various studies have documented pace termination of VT in 89% to 91% of all episodes, with the residual events being converted by shock therapy.[4,5] Programmed ICD therapy has also successfully converted VF in more than 98% of episodes.[4,5] Failure to induce VT or VF at electrophysiological study (EPS) occurs in up to 40% of all SCD survivors.[6] However, VT, VF, SCD, or all recur in 8% to 50% of these patients, and more than half of them die at the time of recurrence.[6-8] In a large body of cumulative experience, the

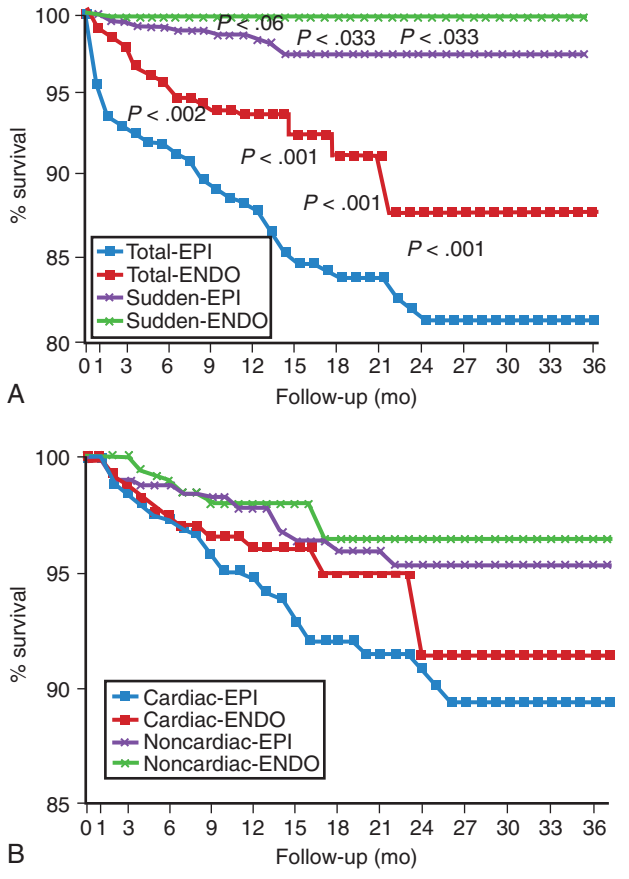

FIGURE 85-1 Survival in the Medtronic PCD trial for implantable cardioverter-defibrillators with epicardial (*EPI*) and nonthoractomy (*ENDO*) lead systems. Sudden cardiac death survival (**A**) and total survival (**B**) are improved with nonthoracotomy lead systems. *(From Saksena S: For the PCD Investigator Group: Clinical outcome of patients with malignant ventricular tachyarrhythmias and a multiprogrammable cardioverter-defibrillator implanted with or without thoracotomy: An international multicenter study,* J Am Coll Cardiol *23:1521–1530, 1994.)*

Table 85-1 Frequency of Implantable Cardioverter-Defibrillator Complications in the First 539 Implantations in the Antiarrhythmics Versus Implantable Defibrillators (AVID) Trial

TYPE OF COMPLICATION	NO. OF PATIENTS (%)
Lead fracture	15 (2.8)
Infection	14 (2.8)
Bleeding/hematoma	8 (1.5)
Lead dislodgment	8 (1.5)
Pneumothorax with chest tube	6 (1.1)
Thrombosis	2 (0.4)
Cardiac perforation	2 (0.4)
Generator migration/erosion	3 (0.6)
Generator failure*	4 (0.7)
TOTAL	62 (11.5)

**An additional six patients had their generators recalled.*
Modified from Kron J, Herre J, Renfroe EG, et al: Lead- and device-related complications in the Antiarrhythmics Versus Implantable Defibrillator trial, Am Heart J *141:92–98, 2001.*

SCD rate reported with device therapy has been in the range of 1% to 2% (Figure 85-1) per year, with a cumulative incidence of less than 10% at 5 years and a significant projected survival benefit compared with untreated populations.[4,5,9,10] Thus data from large multi-center, randomized trials comparing ICD therapy with various drugs for the secondary prevention of SCD in patients with VT or VF consistently indicate that device therapy is superior to guided or empiric medical therapy for these patients. In the original three trials addressing this subject—the Antiarrhythmics versus Implantable Defibrillator (AVID) trial, the Cardiac Arrest Study of Hamburg (CASH), and the Canadian Implantable Defibrillator Study (CIDS)—the total mortality rate showed an average 30% relative risk (RR) reduction in the ICD arm of the study.[11-13] Individual patient groups have often varied among trials. The AVID trial excluded patients with sustained but minimally symptomatic or hemodynamically well-tolerated VT and syncope with induced sustained VT. Inclusion required the presence of hemodynamic instability or left ventricular dysfunction with VT. In contrast, CIDS included many of these subgroups. Subsequent analyses of the AVID registry data, which tracked excluded subgroups, showed that mortality rates without device therapy in patients with hemodynamically well-tolerated VT were comparable with those of other groups included in the study. In the current guidelines, all these subgroups are considered to have indications for device therapy. Also, left ventricular dysfunction as an important determinant of the benefit of defibrillation therapy in patient survival continues to be highlighted.[14]

In analyzing recommendations for device therapy, procedural risk and longer term complications must be factored in the equation. These and other large clinical trials have shown that the implant risk with current ICD systems is less than 0.5%.[4,5,11] Table 85-1 provides the complications observed in the ICD arm in the AVID study.[12] The most common clinical complication observed has been inappropriate device therapy, typically occurring in patients with atrial fibrillation (AF) with rapid ventricular response. This occurs in approximately 5% to 11% of all patients and most often in combination with appropriate device activations in the same patients in these studies.[14] Careful device follow-up, operator training and experience, and refinements in technology have minimized device-related complications. A more recent report from the National Cardiovascular Data Registry (NCDR) assessed ICD implantation risks as ranging from 3.5% for electrophysiologists to 4% for thoracic surgeons and 5.8% for other implanting physicians.[15] Patient outcomes improve with higher volume operators and implant centers.[16] Thus, given the low perioperative mortality, limited morbidity, and overwhelming evidence for survival benefit, the latest guidelines classify cardiac arrest and sustained VT or VF as class I indications for ICD therapy.

Syncope with Inducible Sustained Ventricular Tachycardia

In patients with recurrent syncope, EPS may reveal inducible sustained VT, which may be the mechanism of syncope (Figure 85-2). In CIDS, patients were included with this presentation and derived similar benefits from ICD therapy as did other groups.[10] These patients are considered as having symptomatic cardiac syncope and are included in the secondary prevention group. In

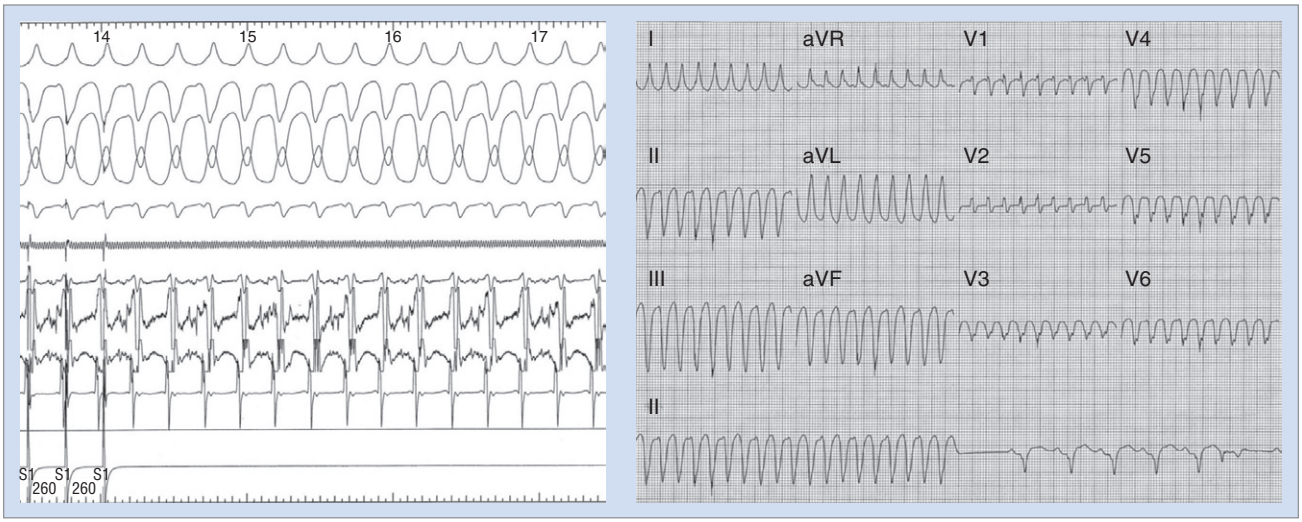

FIGURE 85-2 Induction of ventricular tachycardia in an older patient with syncope and coronary artery disease. *Left*, Induction of rapid monomorphic ventricular tachycardia with burst pacing at 260 ms. The patient became syncopal and hypotensive. *Top to bottom*, Surface leads I, II, III, aVL, and V1 are displayed followed by high right atrium (disabled), three bundle of His recordings, and a right ventricular apical electrogram and the stimulation channel. *Right*, A 12-lead electrocardiogram of induced ventricular tachycardia showing rapid ventricular tachycardia with a left axis and a self-terminating left bundle branch block morphology, resulting in syncope.

general, they have underlying organic heart disease, often with compromised left ventricular function or regional wall motion abnormalities supporting a substrate for the tachyarrhythmia.

Implantable Defibrillators for the Primary Prevention of Ventricular Arrhythmias

Several patient subgroups have been or are being actively evaluated for the primary prevention of malignant ventricular tachyarrhythmias. These include several indications now listed in classes I and II of the ACC/AHA/HRS guidelines. Coronary artery disease (CAD) is the most common underlying condition in ICD recipients. Because survival rates after cardiac arrest are dismal, varying from 1% to 25%, with many large cities reporting less than 10% survival rates, a sustained effort has been made to identify high-risk patients before cardiac arrest for prophylactic device insertion or "primary prevention" of SCD. In patients with CAD, risk stratification is performed by using clinical and electrophysiological markers to identify those who would benefit from ICD implantation. Other noncoronary indications or high-risk clinical syndromes have been included on the basis of recent clinical trial data or expert consensus. More categories are under study and are briefly mentioned in the following discussion.

Specific Clinical Syndromes and Disease States with Indications for Implantable Cardioverter-Defibrillator Therapy

Coronary Artery Disease

Patients with CAD comprise the majority of patients receiving ICDs in most reports.[4,5,11-13] Device implantation is widely accepted as improving the outcomes of these patients. Patients with reduced left ventricular function may receive greater benefit with ICD therapy than with drug therapy.[3,17] Risk stratification may be appropriate to avoid device insertion in patients with a relatively low risk of arrhythmic events. These patients can be identified by the absence of spontaneous ventricular arrhythmias, late potentials on signal-averaged electrocardiogram (ECG), T-wave alternans (TWA) on exercise testing, and absence of inducible VT or VF on programmed electrical stimulation. This is discussed in more detail in other chapters in this text. Implantation of an ICD also requires careful assessment of other comorbidities that could limit survival. Patients with advanced noncardiac disease (e.g., renal disease requiring dialysis or end-stage pulmonary disease) derive little or no survival benefit with ICD therapy. Once a decision has been made to proceed with ICD insertion in patients with significant coronary disease, ischemic status should be assessed with stress testing, coronary angiography, or both. In well-selected patients, appropriate defibrillation or cardioversion shocks have been effective in prolonging survival and have been documented in device datalogs (Figure 85-3).

To limit risk to the patient during defibrillation efficacy testing, the presence of active ischemia should be determined before proceeding with device implantation. Furthermore, optimal antiischemic treatment further enhances quality of life as well as survival. Ventricular function should be assessed before device implantation, although depressed function is not a contraindication to device therapy. However, uncontrolled heart failure increases the risks associated with implantation. To prevent deterioration of functional status, defibrillation threshold testing should be minimized in patients with elevated pulmonary capillary wedge pressure or severely compromised cardiac output.[18]

Nonsustained Ventricular Tachycardia with Coronary Artery Disease and Left Ventricular Dysfunction

This patient group is the first primary prevention category adopted as a consequence of the MADIT-I.[19] This subgroup has long been recognized to have a high propensity for SCD and

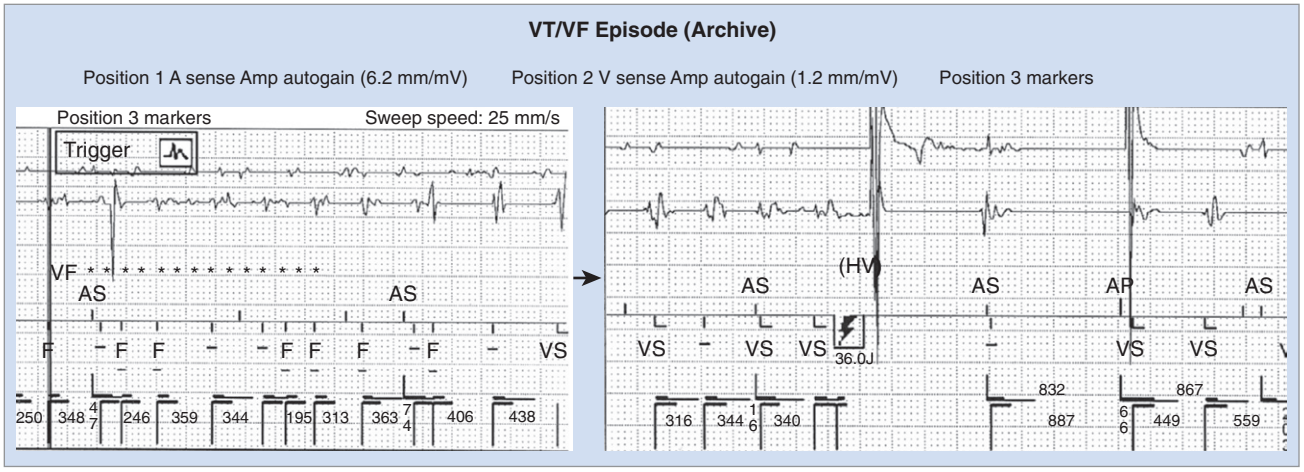

FIGURE 85-3 Appropriate implantable cardioverter-defibrillator therapy in a patient with ischemic dilated cardiomyopathy, atrial fibrillation, and refractory heart failure with no prior history of symptomatic ventricular tachyarrhythmias and severe left ventricular systolic dysfunction with an implanted dual-chamber defibrillator. *Left*, Onset of detection of spontaneous ventricular tachycardia with occasional double sensing of ventricular fragmented or double potentials. *Right*, Delivery of high-voltage shock that terminates ventricular tachycardia and converts the patient to sinus rhythm with frequent atrial premature beats. Electrograms and marker channels are shown with the atrial electrogram (*top position*), ventricular electrogram (*position 2*), marker channel (*position 3*), and timing intervals (*position 4*).

inducible sustained VT. In early studies, Wilber and colleagues recognized that electrophysiological provocation was capable of stratifying the risk of SCD in this population with the induction of sustained VT.[20] The investigators of MADIT-I hypothesized that ICD therapy would improve survival in this high-risk population. They demonstrated a 54% reduction in the relative risk of death in these patients compared with that of conventional drug therapy such as amiodarone. The study was prematurely terminated, and the indication has now been widely adopted. It has been estimated that approximately 3% to 7% of survivors of acute myocardial infarction (MI) in different series will eventually be stratified into this subgroup. Implantation experiences have confirmed the MADIT data that virtually 50% of these patients have a sustained ventricular tachyarrhythmia after prophylactic ICD implantation within 18 months, confirming the original hypothesis.[21] Cost-effectiveness analyses have been very favorable, with an estimated $27,000 per life-year saved with transvenous implantation. Recent trends with declining device costs and shorter hospitalizations in these patients are likely to further improve the cost effectiveness of this therapy.

Syncope in Coronary Artery Disease

Patients with CAD and syncope of undetermined etiology in whom clinically relevant VT or VF is induced at EPS may be candidates for ICD therapy. In these patients, the induced arrhythmia is presumed to be the cause for syncope.[22,23] Follow-up studies of these patients have established that their annual cardiovascular mortality rate averages 20%, with a large proportion of sudden, presumably arrhythmic, deaths.[23] In this patient subset, ICD therapy is often applied with results comparable with those obtained in patients with sustained VT.[12] ICD therapy currently is a class I indication for patients with syncope of unknown etiology and inducible VT or VF.[1]

Prophylaxis After Acute Myocardial Infarction

SCD is a devastating but increasingly infrequent complication after acute MI. Delayed VT or VF was originally linked to post-infarction ventricular arrhythmias, poor left ventricular function, impaired heart rate variability, and other risk factors.[24] Two large clinical trials, Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) and Immediate Risk Stratification Improves Survival (IRIS), have studied post-infarction populations with risk factors for potential benefits of ICD therapy.[25,26] In DINAMIT, patients had reduced left ventricular function (mean, 28%) and impaired autonomic function (depressed heart rate variability or an elevated average 24-hour heart rate ≥80 beats/min on Holter monitoring), whereas in IRIS risk factors included reduced left ventricular function (mean, 35%) and a heart rate of 90 beats/min or higher or nonsustained VT at a heart rate of 150 beats/min or higher on Holter monitoring with any LVEF.[26] Neither trial demonstrated the benefits of ICD therapy in the immediate post-infarction period, defined as 6 to 40 days in DINAMIT and less than 30 days (mean, 13 days) in IRIS.[23,24]

Nonischemic Dilated Cardiomyopathy

Nonischemic dilated cardiomyopathy (DCM) is associated with a high mortality rate within 2 years of diagnosis, with a minority of patients surviving 5 years. Approximately half of these deaths are sudden and unexpected.[27] The combination of poor left ventricular function and frequent episodes of nonsustained VT in these patients is associated with an increased risk of SCD.[28] Unlike in ischemic heart disease, the value of EPS is limited.[29] The efficacy of drug therapy is low in the presence of impaired left ventricular systolic function and is difficult to predict on the basis of invasive or noninvasive testing. ICD implantation may be preferred in the management of symptomatic patients with this condition as well as VT or VF. ICD therapy can also be used as the bridge to

orthotopic heart transplantation in many of these patients. The Cardiomyopathy Trial (CAT) was undertaken as a pilot study to evaluate the potential benefit of prophylactic ICD implantation on all-cause mortality in patients with DCM. The trial was terminated early because no appreciable benefit of ICD implantation was observed. However, the trial group was small, the event rate was extremely low, and the follow-up was abbreviated. In contrast, in the AVID study, these patients derived benefits similar to those derived by patients with CAD and had similar event rates. The optimal management of idiopathic DCM, especially the role of ICD in the primary prevention of SCD, has been defined by recently completed large trials (Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation [DEFINITE], SCD-HeFT). These trials enrolled patients with DCM and moderate left ventricular systolic dysfunction (ejection fraction <35%) with or without ventricular arrhythmias. Although DEFINITE showed no overall mortality benefit with the ICD, a large subgroup (NYHA class III patients) showed a favorable trend to survival improvement with the ICD ($P = .06$).[31] The SCD-HeFT population showed survival benefit with the ICD.[2] These data support the prophylactic use of ICD therapy in nonischemic DCM with moderately impaired systolic left ventricular function.

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is a diverse group of disorders that have, as a common feature, primary hypertrophy of the left ventricle. Their prevalence has recently been estimated to be as high as 1 in 500, making this group of diseases the most common genetically transmitted cardiovascular diseases.[32] SCD, which may be the first manifestation of the disease in an asymptomatic individual, has been reported annually in up to 4% of these patients.[33] Malignant ventricular tachyarrhythmias have been described as a mechanism for SCD in adults with this condition.[33,34] Risk factors for SCD include syncope, a very young age at presentation, extreme degrees of ventricular hypertrophy, a strong family history of SCD from cardiac causes, and nonsustained VT.[32-33] Studies of patients resuscitated from cardiac arrest indicate that many patients will have another event. In contrast to other cardiomyopathies, EPS may be of prognostic significance because some studies have shown that inducible sustained ventricular arrhythmias appear to be associated with cardiac arrest and syncope.[35] Pharmacologic therapy, in the form of β-blockers or calcium channel antagonists, has frequently been used. Although outflow tract gradients may diminish with medical therapy, it has, at best, marginal efficacy in preventing SCD. The empirical use of amiodarone has been recently reported to be associated with improved survival.[34] However, risk stratification and the prediction of drug efficacy remains difficult and controversial. High-risk patients with HCM and SCD survivors should be considered for ICD therapy instead of, or in conjunction with, drug therapy.[1]

The limited efficacy of medical therapy combined with compliance issues associated with long-term drug administration in young patients makes device therapy an attractive option. Maron and associates published a multi-center retrospective study of the efficacy of ICD therapy in 128 HCM patients thought to be at high risk for SCD.[36] Thirty-four percent of these patients had ICDs implanted for secondary prevention after cardiac arrest, whereas 66% had devices implanted for primary prevention because of the presence of risk factors listed earlier. During a mean follow-up of 3 years, appropriate therapy was delivered in 23% of patients. Two patients died suddenly despite ICD therapy. On a cautionary note, a significant rate of complications was associated with ICD therapy, with inappropriate therapy being delivered to 25% of patients. ICD therapy is indicated in patients with HCM for secondary prevention after sustained VT or VF.[1] Primary prevention is considered a class IIb indication for ICD implantation. The results of ICD therapy in HCM should lead to greater use of device therapy in high-risk patients.[36] Future directions of research include better characterization of the specific myosin gene mutations associated with shorter life expectancy, which may target candidates for primary prevention with early use of amiodarone, defibrillator therapy, or both.[37]

Heart Failure Populations

In the secondary prevention studies, the role of left ventricular dysfunction as an important determinant of the survival benefit of defibrillator therapy was highlighted.[14,38,39] Survival of ICD recipients is strongly influenced by left ventricular systolic function. Patients with LVEF less than 30% have inferior survival rates at 3 years of follow-up compared with those with better left ventricular function. However, both populations appear to derive a significant survival benefit from ICD implantation. In an early analysis, we demonstrated that patients with LVEF less than 36% derived the benefit of defibrillator therapy over drug therapy.[17] Similar data were noted in the CIDS and MADIT-I studies. The MADIT-II study evaluated the hypothesis that patients with CAD and MI who had an LVEF less than 30% would have improved survival with defibrillator therapy compared with conventional heart failure therapy.[3] The trial demonstrated a 31% reduction in relative risk, which was estimated to decline from a projected 19% 2-year mortality rate to an actual 12% mortality rate with defibrillator insertion. Both appropriate and inappropriate shock deliveries have been noted during follow-up (see Figure 85-3). However, analyses have identified the subgroup deriving the most benefit. These appear to be patients with prolonged QRS duration and left ventricular dysfunction. However, a recent analysis suggests that patients in the ICD arm have similar rapid VT or VF events detected by the ICD, whether or not the QRS duration was above or below 140 ms.[40] SCD-HeFT compared survival after ICD insertion or empiric amiodarone with placebo in patients with ischemic or nonischemic NYHA classes II and III heart failure and LVEF below 35%.[2] The overall mortality rate in the placebo arm (7.2% annually) was not altered by amiodarone therapy but was greatly reduced by ICD insertion (hazard ratio [HR], 0.77; $P = .007$). This effect was more obvious in class II patients (HR, 0.54), with LVEF less than 31%, and prolonged QRS duration (HR, 0.67). The Comparison of Medical Therapy, Pacing and Defibrillator Trial (COMPANION) demonstrated improved survival in NYHA classes III and IV heart failure patients with a prolonged QRS, LVEF less than 35%, and a left ventricular diameter greater than 60 mm with a biventricular ICD compared with pacing or conventional heart failure drug therapy.[41] A 43% reduction in mortality rate was observed with biventricular ICD insertion as prophylaxis for SCD. The recently completed MADIT CRT and RAFT trials, reviewed in detail in Chapter 83, provide strong evidence to support improved survival in patients with left ventricular systolic dysfunction, ventricular dyssynchrony demonstrated by wide QRS on electrocardiogram, and class I or II heart failure symptoms.[41,42] The recently released update to the European Society of Cardiology (ESC) guidelines for cardiac resynchronization therapy now accepts the use of a cardiac

resynchronization therapy (CRT) device, including ICD therapy, in patients with NYHA class II heart failure, QRS duration of 150 ms or greater, and left ventricular systolic dysfunction manifested as an EF of 35% or less.[43]

Familial Syndromes with High Risk of Sudden Cardiac Death

The guidelines recognized several small but important patient groups that have familial or acquired diseases that predispose them to SCD and malignant VTs. In most of these categories, small clinical series or pilot data and expert consensus led to the adoption of the indication. This includes high-risk patients with congenital long QT syndrome (LQTS) or Brugada syndrome, HCM, and arrhythmogenic right ventricular dysplasia (ARVD). A family history of SCD is a key element in the selection of the ICD as a primary prevention therapy. Patients with prior symptomatic sustained VT or cardiac arrest are considered to qualify and would be included in secondary prevention. LQTS represents a spectrum of electrophysiological disorders characterized by the propensity for the development of malignant ventricular arrhythmias, especially torsades de pointes (TdP).[44,45] Younger patients also manifest a more malignant form of LQTS.[44] Because this is a primary electrical disorder, usually with no evidence of structural heart disease or left ventricular dysfunction, effective control of malignant arrhythmias can ensure an excellent long-term prognosis. Most asymptomatic or minimally symptomatic patients can be effectively treated with β-blockers, permanent pacing, or left cervico-thoracic sympathectomy.[44] Device therapy is recommended for selected patients in whom recurrent syncope, sustained ventricular arrhythmias, or SCD occur despite drug therapy.[1] However, the use of the ICD as primary therapy should be considered in a subgroup of patients such as those with a familial history of SCD, those with compliance issues or intolerance for drugs, or those who prefer defibrillator therapy.[45] In addition, as genotypic and molecular analyses permit increasingly accurate risk stratification of these patients, higher risk subgroups will be identified, and ICD therapy may be considered in the primary prevention of SCD in selected individuals even in the absence of a sentinel event.

Other primary electrical diseases such as LQTS, idiopathic VF with repolarization abnormalities, and ARVD are infrequent indications for ICD implantation in adolescents and in younger and middle-aged patients.[1,46-50] Risk stratification based on clinical and laboratory testing is needed to identify high-risk individuals who are potential candidates for ICD therapy. For example, in patients with ARVD, symptoms such as syncope, exercise-induced arrhythmias, evidence of delayed potentials on ECG (ε-waves) or signal-averaged ECG, inducible VT at EPS, significant fatty infiltration of the ventricular myocardium, and family history of malignant arrhythmias can influence ICD therapy use. It has been estimated that 10% of young patients, despite extensive evaluation, do not reveal an etiology for VF.[49] EPS in these patients with idiopathic VF usually reveals polymorphic VT or VF, which is often suppressible with class Ia drugs such as quinidine or mexiletine.[51] However, the long-term efficacy of drug therapy remains unknown. Given the guarded prognosis, even with supposedly effective drug therapy (annual rate of SCD estimated to be as high as 11%), the limited clinical data appear to support the use of ICDs in such patients.[52,53] However, inappropriate device therapy is particularly common in these young, active individuals with familial SCD syndromes. The device programming must be individualized to suit the activity levels of the patient, and stress testing is recommended to assess the risk of sinus tachycardia triggering anti-tachycardia therapy and to guide tachycardia detection programming (Figure 85-4).

Implantable Cardioverter-Defibrillator Therapy as a Bridge to Cardiac Transplantation or Left Ventricular Assist Device Implantation for Drug-Refractory Heart Failure

Clinical data from cardiac transplantation centers have long documented an inordinately high risk of SCD in individuals awaiting cardiac transplantation after their candidacy has been established by screening. In these individuals, pilot data have shown appropriate ICD prevention of malignant VTs. Recently, left ventricular assist devices are being increasingly used as a bridge to transplantation and perhaps as destination therapy for heart failure.[54,55] Because this small subgroup is unlikely to be suitable for clinical trial, expert consensus has supported the application of the ICD in these patients.

Clinical Practice in Implantable Cardioverter-Defibrillator Therapy

The availability of ICD guidelines since the early 1990s with the evolution of indications has influenced clinical practice. In the United States, the NCDR now includes data on ICD recipient profiles, implanting physicians, implant sites, and outcomes.[54] In the most recent iteration, 339,076 patients were included from 2006 to 2008. Mean age was 68 years, 74% were male, 83% were white, 12% were African American, and 4% were Hispanic. Of the implantation procedures, 78.2% were performed for primary prevention indications, and 25% of procedures were performed for replacement or revision of devices or leads. Two thirds of all implantations were performed in patients with CAD; the average LVEF of ICD recipients was 28%, and 82% were NYHA class II to III. The lower rate of implantation frequency in women continues to be investigated.

Complications of Implantable Cardioverter-Defibrillator Systems

Complications with ICD implantation are divided into procedure related and non–procedure related.[54-58] The majority of procedure-related complications are seen very early after implantation. They are most commonly related to the insertion technique and subsequent infections. Serious complications of peri-procedural death or systemic infections have become rare (<1%) with nonthoracotomy ICD insertion techniques. According to the NCDR, complications at the time of device implantation and before hospital discharge in the case of new ICD implants occurred in 3.36% and included procedure-related, in-laboratory death in 0.02%, hematoma in 0.97%, and lead dislodgment in 1.07%. Total complications related to new implants have decreased over time from 3.78% in 2006 to 3.01% in 2008. Complications are also related to the type of ICD generator and lead system implanted. Specific lead systems have had high failure rates and may need to be evaluated in that light.[59,60] Combination devices with CRT require an additional lead (in the coronary sinus) and have much longer procedure times. Operator training, implantation procedure volume, and

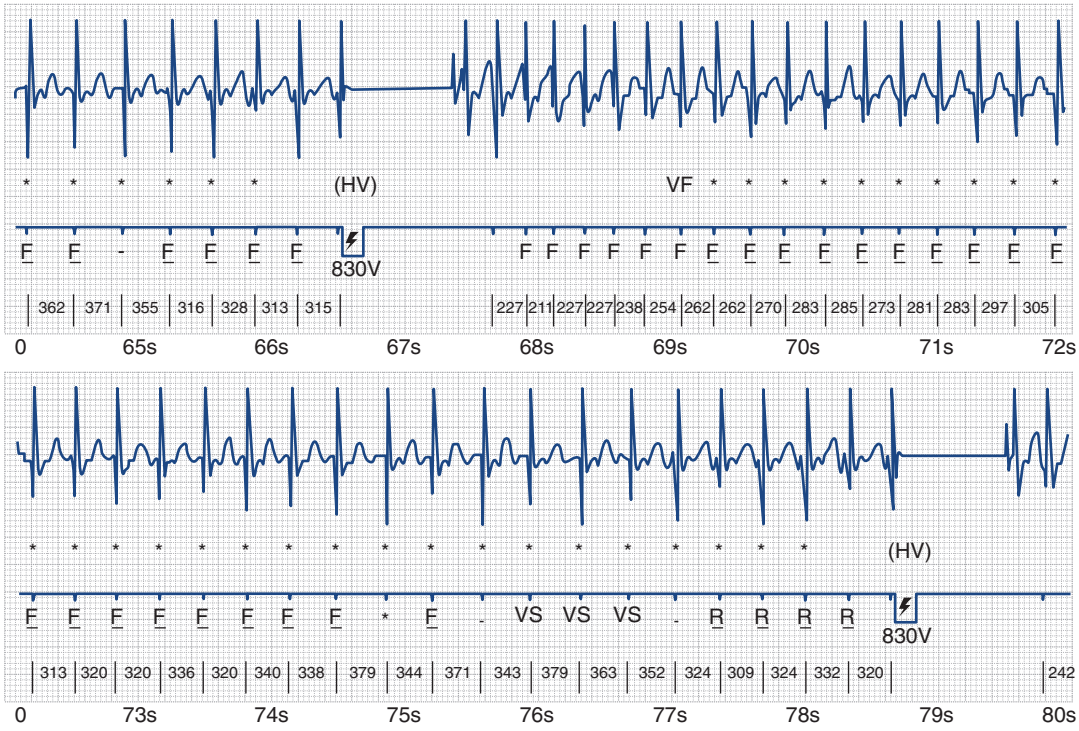

FIGURE 85-4 Inappropriate shock delivery in a young patient with long QT syndrome during strenuous exercise, resulting in sinus tachycardia and repeated high-voltage (*HV*) shock delivery by a single-chamber defibrillator programmed to a single ventricular fibrillation detection zone. Ventricular electrograms (*top position*), marker channel (*position 2*), and timing cycles (*position 3*) are shown. *Top*, An HV shock is delivered, and sinus tachycardia continues with initial irregular conduction but regularizes. *Bottom,* A second shock is delivered. No significant change in ventricular electrogram morphology is observed before or after the shocks.

implantation institution volume have also been correlated with outcomes. Procedural complications are lowest with electrophysiologist implanters and high-volume implanters and centers and when complex CRT/ICD devices are more frequently implanted by electrophysiologists.[16,17] The majority of nonprocedural complications are reported during the long-term follow-up period and are mostly related to device and lead system malfunctions.

Bleeding, infection, cardiac tamponade, pneumothorax, and lead dislodgment occur soon after implantation. Bleeding complications include hematomas or bleeds that require surgery or transfusion. Pneumothorax is most common with the subclavian approach (1%) and requires chest tube insertion. Coronary sinus perforation is common with combination bi-valve ICDs (2%). Stroke is a rare complication in patients with chronic AF who are not adequately anticoagulated. The majority of lead dislodgments occur within the first postoperative month and are more common with dual-chamber or bi-ventricular ICDs (0.12% to 2.0%) and less common with single-chamber ICDs (0.3% to 4%).[5,57-62] Infections of ICD systems can have devastating effects and can result in potentially fatal complications. Cellulitis at the generator pocket incision, if detected early, can be effectively treated with aggressive and prolonged antibiotic therapy. Once evidence of significant pocket or lead infection and systemic dissemination is present, explantation of the device system is mandatory. Generator pocket aspiration should be avoided unless strictly necessary. The likelihood of introducing infection into a sterile hematoma exceeds the diagnostic yield obtained by performing this procedure in cases with diagnostic uncertainty. Other techniques such as gallium scanning, echocardiography, and repeated blood cultures can assist in the diagnosis. The detailed methods of device and lead explantation procedures are beyond the scope of this chapter and are discussed in other chapters in this text. However, larger caliber pacing and defibrillation leads are more difficult to remove by mechanical methods. Specialized techniques such as laser lead extraction may be required. After system explantation, the pocket should be allowed to heal fully, if feasible. In some instances, a new system can be inserted on the contralateral side after a few days or weeks if resolution of the active septic process is evident. Long-term antibiotic therapy is necessary to achieve proper healing of the previously explanted site and to prevent seeding of the new location of the system.

The major predictors of procedure-related complications in some reports were the route of ICD insertion and the use of periprocedural antibiotics. Insertion via the subclavian route resulted in more complications than the cephalic vein route (14% vs. 4%, $P = .005$), as did the abdominal versus pectoral generator site (13% vs. 6%, $P < .02$). The complications most commonly associated with subclavian route are pneumothorax (1%) and lead fractures. Failure to use perioperative antibiotics significantly increases the risk of device or pocket infection ($P = .001$).[54-57]

Nonprocedural generator- or lead-related complications requiring system explantation and replacement are more commonly seen during long-term follow-up. Manufacturer recalls (4%) and prolonged charging periods (2%) account for most generator-related complications. With increasing age of the transvenous lead systems, a growing number of lead fractures and

Table 85-2 Major and Minor Complication Rates in Patients Receiving Replacement Implantable Cardioverter-Defibrillator Devices

DEVICE	MAJOR COMPLICATIONS (%)	MINOR COMPLICATIONS (%)
All ICDs	6.0	8.4
Single-chamber ICDs	5.0	8.9
Dual-chamber ICDs	4.9	7.5
CRT-Ds	8.0	9.1

ICDs, *Implantable cardioverter-defibrillators;* CRT-Ds, *cardiac resynchronization therapy defibrillators.*

insulation defects have to be expected. Necessity for operative revision is reported as 6% within 1 year of initial implantation and up to 15% during 4 years.[55] Recent data from Canadian and U.S. national registries demonstrated that the rate of major complications during ICD replacement procedures varies between 4.2% and 5.8%.[57,59,60] The majority (two thirds) of these major complications included pocket infections requiring device extraction and hematomas leading to reoperation (Table 85-2). New complications of wireless telemetry systems are now being identified. They are related to interference with other medical devices, security and integrity of the data transmitted, and the resultant less frequent direct patient cardiovascular examinations. In the instance of other device implants such as left ventricular assist devices, telemetric frequency overlap has been a concern for some devices as described in isolated cases.[61] Shielding of the assist device before programming the ICD is necessary in some instances.

Follow-up Techniques for Patients with Implantable Cardioverter-Defibrillators and Device Systems

Follow-up Program

All patients with ICDs require periodic and meticulous follow-up to ensure patient safety and optimal device performance because the consequences of device failure are potentially catastrophic.[1] The goals of ICD follow-up include monitoring device system function; optimizing performance for maximal clinical effectiveness and system longevity; minimizing complications; anticipating replacement of system components; ensuring timely intervention for clinical problems; patient tracking, education, and support; and maintenance of records related to the ICD system. The need for device surveillance and management should be discussed with patients before ICD insertion. Compliance with device follow-up is an important element in establishing the appropriate candidates for device therapy and obtaining the best long-term results. In general, device programming is initiated at implantation and should be reviewed at predischarge or during subsequent postoperative EPS. The follow-up of a patient with an ICD must be individualized in conjunction with the clinical status of the patient. ICD follow-up is best achieved in an organized follow-up program at outpatient clinics analogous to pacemaker follow-up.[1,62] Routine follow-up includes a wound check shortly (1 to 2 weeks) after ICD implantation. Patients should be seen 1 to 2 weeks postoperatively, at 1 month, and every 3 to 4 months thereafter. Clinical patient evaluation during visits should include history taking, review of systems, and physical examination. Chest radiographs should be obtained before hospital discharge, at 6 months, and then as needed (e.g., annually) to confirm lead integrity radiographically. The risks of lead dislodgment are highest within the first few days after implantation. The risks of early lead displacement and changes in device function test results may warrant noninvasive ICD testing with VT as well as VF induction in the electrophysiology laboratory soon after implantation. Patients with device activation with or without therapy delivery should be evaluated shortly after the event until a regular, acceptable pattern of patient symptomatology during, and tolerance for, such events is established. Furthermore, device behavior must be deemed reliable, safe, and effective. Devices should be periodically monitored with the exact frequency, depending on the device model and the clinical status of the patient. Transtelephonic follow-up should always be supplemented with clinic visits at a minimum of 3- to 4-month intervals for patient and device evaluation.[1] More frequent evaluation is needed when elective replacement indicator values are being reached. Manufacturer guidelines for device follow-up vary with individual models and should be reviewed.

Institutions performing implantation of ICDs should be able to locate and track patients who have received ICD devices or have entered the follow-up program. Such facilities should obtain and maintain the equipment for implant monitoring and follow-up support monitoring for all devices used at that facility. The facility should be staffed or supported by a fully trained clinical cardiac electrophysiologist who may work in conjunction with trained associated professionals.[1,63,64] Ideally, access to these services should be available on both a regularly scheduled basis and an emergent 24-hour basis.

Elements of an Implantable Cardioverter-Defibrillator Follow-up

ICD follow-up involves routine surveillance visits in the case of asymptomatic or minimally symptomatic patients and troubleshooting in the case of patients with suspected device malfunction, symptoms, or deterioration of clinical status. Routine outpatient ICD follow-up should follow a logical sequence aimed at assessing the unit's functions and lead integrity as well as evaluation of any problems that may have arisen in the interim period. The interval history should be reviewed for symptoms suggestive of arrhythmias and for other illnesses such as the onset or progression of heart failure. The latter may have resulted in alteration of ventricular function or the institution of a medical regimen, which may affect device therapy. Changes in antiarrhythmic therapy may have important consequences because these agents can change defibrillator thresholds and slow tachycardia cycle lengths. The lower cutoff limits for tachycardia detection may need to be reprogrammed to ensure appropriate device therapy. Antiarrhythmic drugs may also cause significant sinus bradycardia and chronotropic incompetence that can lead to pacemaker syndrome in patients with single-chamber ICDs.

Clinical examination should include careful evaluation of the ICD generator site for signs of infection or device erosion. These complications are infrequent. However, early detection can lead to appropriate intervention that would result in a reduction in morbidity and mortality (Figure 85-5). An ECG is performed at all follow-up visits to determine the baseline rhythm. It is also

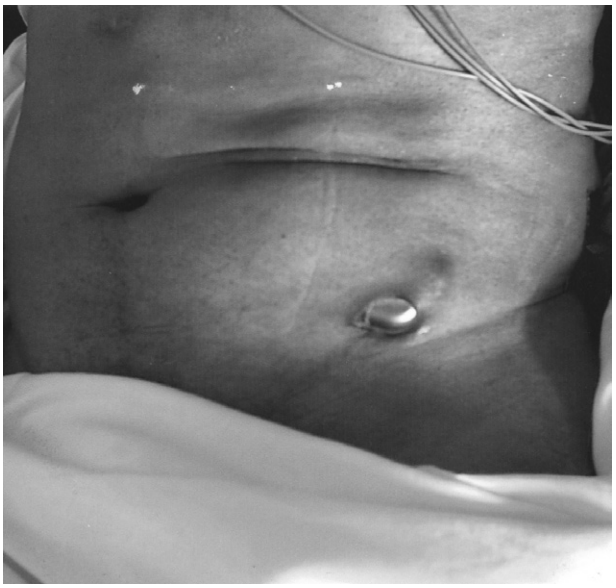

FIGURE 85-5 Postoperative wound infection in an abdominal device pocket resulting in device erosion.

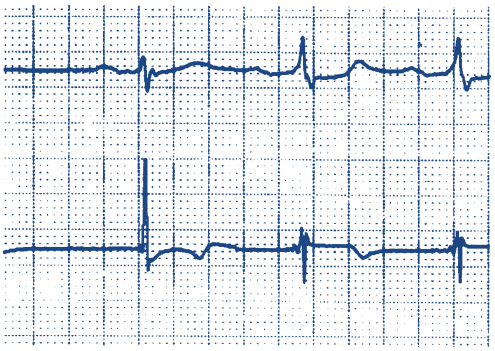

FIGURE 85-6 Changes in intracardiac ventricular electrogram amplitudes with the development of bundle branch block. *Top*, Surface electrocardiogram tracing. *Bottom*, Telemetered intracardiac ventricular electrogram tracing.

reviewed for potential toxic effects of concomitant antiarrhythmic therapy and to confirm the appropriate pacing and sensing functions of the device.

An overpenetrated chest radiograph should periodically be performed in these patients. Transvenous lead fractures can sometimes be seen but are often subtle and difficult to detect. Complications associated with epicardial systems, such as patch fractures and "crinkling," can often be detected radiologically. These complications affect defibrillation efficacy and result in failure of therapy.

Evaluation of Implantable Cardioverter-Defibrillator Function

The device is interrogated to evaluate tachycardia and bradycardia functions as well as patient and device monitoring data. Particular attention should be given to reviewing sensing parameters, programmed defibrillation and pacing therapies, device activations, and event logs. Technical elements requiring review include battery status, lead system parameters, and end-of-life markers. Electrogram amplitudes (P, QRS, and T waves) should remain stable. However, these can change with the development of bundle branch block (Figure 85-6), and some patients demonstrate a small but progressive diminution in electrogram amplitude over time, resulting in sensing dysfunction. The assessment of pacing lead impedances is also important. The current generation of devices uses sub-threshold stimuli to measure high-voltage lead impedance and thus the integrity of the shocking lead circuit. A fall in R-wave amplitude, coupled with a significant fall in pacing lead impedance (e.g., >200 ohms), suggests the possibility of lead insulation failure. Reprogramming the initially selected parameters either in the outpatient clinic or during EPS often is necessary. Reprogramming therapies in the outpatient setting should be done with great caution. Changes in tachycardia detection rates can only be performed with the knowledge of the cycle lengths of the clinical tachycardia as well as those induced at previous electrophysiological testing. Of note, clinical tachycardia, especially in patients receiving antiarrhythmic medications, tends to be slower than that seen on baseline electrophysiological testing. Thus the lowest VT detection rate should be set at least 50 ms below the slowest detected VT cycle length to ensure an adequate safety margin. It is not wise to empirically program the VT detection rate upward in response to inappropriate therapy for supraventricular tachycardia. Finally, it is imperative to incorporate a meticulous, easily accessible record-keeping system documenting ICD history, programming data, and characteristics of tachycardia into any successful ICD follow-up program.

Evaluation of Implantable Cardioverter-Defibrillator Therapy

Approximately 50% to 75% of patients will receive a shock within the first 2 years after ICD insertion. The occurrence of a single shock does not require evaluation. However, patients should be evaluated after their first ICD discharge if they remain symptomatic following the shock, if they receive multiple shocks, or if they have severe anxiety after the shock. When evaluating shock therapy, it is important to obtain a history of the clinical events surrounding the shock and then interrogate the device. The advent of stored electrograms has improved the accuracy of diagnosis of the rhythm that resulted in the delivery of therapy.[65,66] Dual-chamber ICDs can provide both atrial and ventricular electrical activity during the event (see Figure 85-3). A combination of diagnostic information, including the onset interval, the stability and rate of the tachycardia, individual R-R intervals singly or tabulated in a graphic form, and the morphology of the stored ventricular electrograms allow an accurate diagnosis in most instances. Evaluation of "rate sensing" or "shock surface" electrograms can be effective in providing an accurate reflection of the rhythm leading to the delivery of therapy. Each of these modalities when used alone can provide 90% diagnostic accuracy; however, when the device stores both atrial and ventricular electrograms the diagnostic accuracy is very high.[66,67]

Troubleshooting

See Table 85-3.

Table 85-3 Troubleshooting Implantable Cardioverter-Defibrillator Function: Inappropriate Therapy

CAUSE	ANALYSIS
Asymptomatic tachyarrhythmia	Analysis of event EGM including atrial channel if available (R-R interval and morphology) SVT, slow VT, and outcome of shock
Sinus tachycardia	Analysis of event EGM with particular respect to event onset and morphology Exercise test, if indicated T and P waves Analysis of marker channel at different oversensing heart rates Re-evaluate leads for fractures, insulation failure, and R-wave signal stability Oversensing Analysis of marker channel during a 100% pacemaker-paced event at maximal pacemaker spikes or double output and analysis of ECG along with counting QRS intracardiac EGM marker channel Electromagnetic History combined with analysis of event interference or EGM for high-frequency signal myopotentials Re-create activities that initiate shocks

ECG, *Electrocardiogram;* EGM, *electrogram;* SVT, *supraventricular tachycardia;* VT, *ventricular tachycardia.*

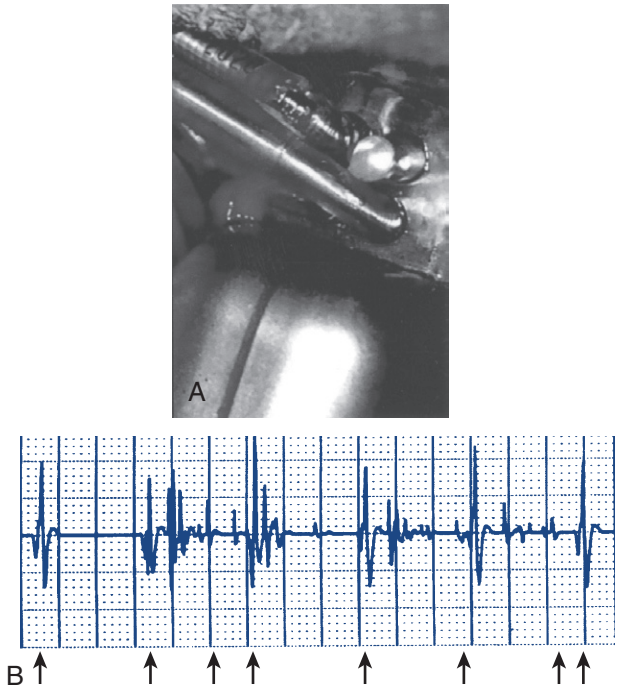

FIGURE 85-7 Oversensing of myopotentials (**B**) on ventricular sensing channel due to disruption of lead insulation in an ICD system (**A**). *Arrows* show ventricular potentials and myopotentials sensed by the device during sinus rhythm.

Inappropriate Therapy

In some instances, ICD therapy can be delivered in response to arrhythmias or detected electrical signals unrelated to ventricular arrhythmias. Studies have documented that as many as 40% of patients may be asymptomatic before an appropriate ICD discharge.[66,67] However, up to 30% of all ICD shocks may be inappropriate in select patient populations.[67] In general, single shocks, whether preceded by symptoms or not, are most often caused by the appropriate detection and treatment of a ventricular tachyarrhythmia (see Figure 85-3). Conversely, multiple ICD discharges often result from the detection of other arrhythmias or signals that are inaccurately classified as a ventricular tachyarrhythmia (see Figure 85-4). Thus ICD therapy often is inappropriately delivered for sinus tachycardia or other supraventricular tachycardias with rapid AV conduction. Stored ICD diagnostic data including electrograms usually provide adequate information to enable accurate detection of these rhythms. It may be necessary, at times, to perform exercise testing to ensure that the maximal sinus rate during exercise is below the programmed detection rate to avoid inappropriate shocks.

Therapies delivered in the absence of documented arrhythmias are most often related to oversensing of noise leading to inappropriate detection by the device (Figure 85-7). Disruption in the silicone or polyurethane insulation surrounding the lead can result in inappropriate detection of myopotential artifacts and inappropriate shocks (Figure 85-8). These can result from pressure damage caused by an overlying device or lead, by an acute angle made by the lead as it leaves the header, or by inadvertent laceration at the time of initial implantation. Insulation leaks often are accompanied by falls in the measured electrogram amplitudes

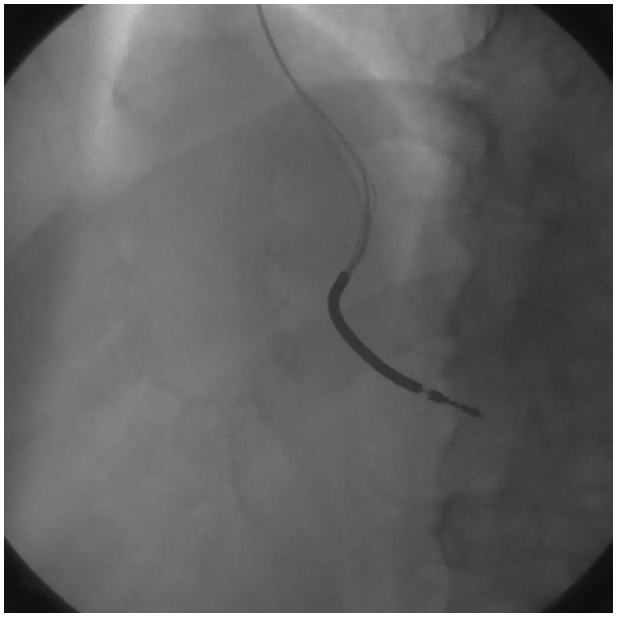

FIGURE 85-8 Fluoroscopic video image showing lead body disruption in a patient with multiple inappropriate defibrillator shocks. The left anterior oblique view shows lead insulation disruption with conductors outside the main lead body.

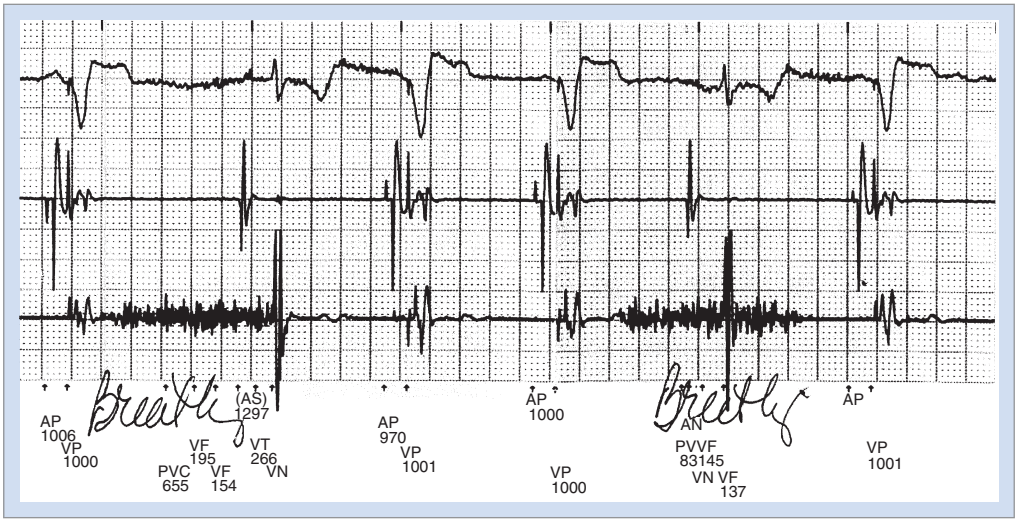

FIGURE 85-9 Oversensing of noise on the ventricular sensing channel during breathing from myopotentials. Note that the counters record electrical signals with markedly shortened intervals (less than 100 ms) and in the ventricular fibrillation zone (*top*). Surface ECG (*middle*) shows atrial and ventricular electrograms. *Bottom*, Atrial- and ventricular-sensed events.

and lead impedance. Inappropriate sensing of diaphragmatic muscle activity can initiate ICD therapy that, for example, may occur while straining during a bowel movement or a coughing paroxysm (Figure 85-9). Stored electrograms from the sensing lead generally show the noise artifacts, and marker channels can confirm the origin of these signals. However, if the device lacks electrogram storage capabilities, it may become necessary to record real-time electrograms while manipulating the pocket and to have the patient simulate the activities of daily living that trigger device activation.

Environmental noise is another, although relatively infrequent, cause of inappropriate device activation. Electronic surveillance systems can sometimes trigger inappropriate shocks, although inhibition of demand pacing is a more common problem.[68-70] In the operating suite, the use of electrocautery can also cause inappropriate shocks. "Phantom shocks" are therapies perceived by the patient in the absence of actual device activation. This phenomenon has been reported both by patients anticipating their first shock as well as by those who recently received multiple shocks. Interrogation of the device to confirm the absence of device activation, followed by reassurance and patient education about device function, usually results in alleviating these symptoms and the associated anxiety.

Box 85-2 Major Causes of Failure to Deliver Appropriate Therapy

Device inactivated or battery depleted
Failure to sense ventricular EGM
- Low amplitude signal with arrhythmia or following a failed high-energy discharge
- Lead or generator malfunction

Inappropriate programming
- Inappropriately high rate for detection of ventricular tachyarrhythmias
- Failure to satisfy multiple criteria before delivering therapy
- Ineffective anti-tachycardia pacing algorithms (change in threshold) or inappropriately low programmed shocks for VT
- Failure to recognize drug- or disease-induced rise in DFT

Mechanical failure
- ICD component failure resulting in failure to deliver appropriate therapy

EGM, *Electrogram;* VT, *ventricular tachycardia;* DFT, *defibrillation threshold;* ICD, *implantable cardioverter-defibrillator.*

Failure of Implantable Cardioverter-Defibrillator Therapy

Failure of ICD therapy may be related to failure to deliver therapy or actual failure to generate electrical therapy (Box 85-2). Device interrogation in cases of failure to deliver therapy should confirm the proper programming of detection parameters after implantation and exclude accidental device deactivation during interval interventions. At each surveillance visit, it is imperative to evaluate the sensing parameters because sensing failure is not usually documented in stored electrogram data. Sudden loss of sensing during episodes may herald the problem. Lead fracture may manifest as failure to pace, rise in impedance, and changing pacing artifact (Figure 85-10). The "subclavian crush" injury is particularly important for large-caliber defibrillation electrodes, multiple-lead systems, and patients with narrow costoclavicular angles. This can result in failure to defibrillate or a rise in defibrillation thresholds with changes in high-voltage shock impedance (Figure 85-11). If device interrogation during sinus rhythm fails to pinpoint the source of the problem and radiographic lead integrity is confirmed, it may be necessary to induce VF and repeat testing in some patients. Pacing thresholds may rise over time, resulting in exit block and failure of anti-tachycardia pacing. Drug therapy may reduce the VT rate, resulting in detection failure and failure to deliver appropriate therapy.[70] In addition, drugs may raise the defibrillation threshold, resulting in failed defibrillator shocks, particularly if the initial defibrillation safety margin was low.[71,72] Defibrillation thresholds can also be raised by myocardial ischemia and acute heart failure. Mechanical system failure may lead to failure to deliver therapy or in ineffective therapy.

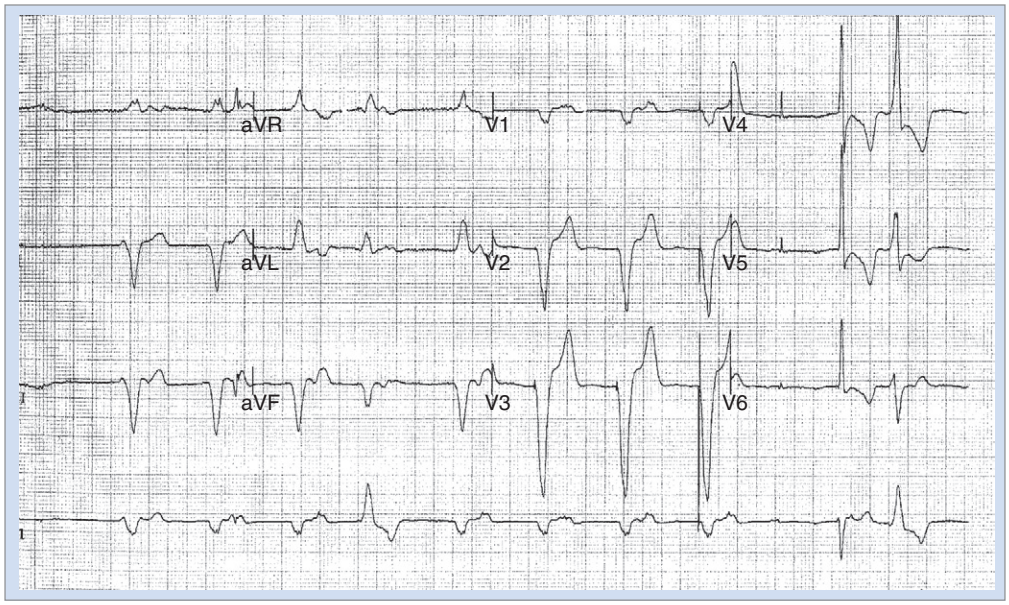

FIGURE 85-10 A 12-lead electrocardiogram showing intermittent pacing failure with varying pacing amplitudes and a rise in lead impedance identified a fractured pace or sense lead in this patient.

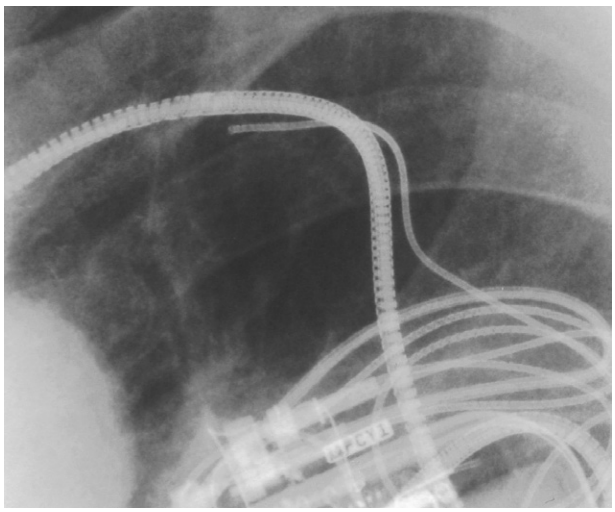

FIGURE 85-11 Subclavian crush fracture of defibrillation electrode. The fractured lead remnant is seen below the clavicle.

Migration, folding, or wrinkling of epicardial or subcutaneous patches can significantly increase the defibrillation threshold, as can migration or dislodgment of transvenous defibrillating electrodes. Treatment may require lead replacement, with removal of the fractured leads and the possible addition of other leads, patch electrodes, or both. It is important to recognize that lead malfunction may be intermittent and may not be detected unless extensive testing is undertaken. Generator failure, although rare, is not unknown. Component failures, especially in the capacitors, can lead to failed shock delivery. Immediate reoperation and generator replacement are indicated in such cases.

Remote Monitoring of Implantable Cardioverter-Defibrillators

More recently, Internet-based remote data management and monitoring systems have become available to simplify device data management. These approaches reduce the load imposed on overwhelmed ambulatory services and optimize patient care. Four major ICD manufacturers have their own version of the remote patient monitoring system (Table 85-4).[73] All these ICD device versions are equipped with a micro-antenna, which communicates with a small external device, commonly known as the *transmitter* or *patient device*. The transmitters are able to interrogate programmed parameters and the diagnostic data stored in the ICD's memory either with the active participation of the patient (via a wand) or automatically (wandless) at preset intervals. Once the encrypted data have been collected from the ICD and transferred to the patient device, they are uploaded via standard analog telephone lines or via cellular phone transmission to a secure central database or data-processing facility set up by the manufacturer. Alerts or event messages to the patient are generally announced with an audible signal (beep) or vibration from the ICD. In some systems, these alerts are used to instruct the patient to initiate a manual transfer of data from the transmitter to a central database.[73] A more detailed discussion of this subject is available in Chapters 87 and 88.

Depending on the clinical urgency of the event, data processing facilities at central databases may trigger a quick alert to the physician via email, text messaging, fax, or telephone call, whereas the report details are simultaneously posted on a secure Web site to be viewed by the physician or other authorized medical reviewer at their convenience. Most remote monitoring systems transmit device and patient data via standard telephone lines weekly or bi-weekly. With any system, a wide variety of device and patient information can be continuously monitored

Table 85-4 Current Remote Implantable Cardioverter-Defibrillator Patient Monitoring and Management Systems

	BIOTRONIK: HOME MONITORING	MEDTRONIC: CARELINK NETWORK	BOSTON SCIENTIFIC: LATITUDE	ST. JUDE: HOUSECALL PLUS
Name(s)	CardioMessenger	PatientLook, SentryCheck (in OptiVol)	Latitude Communicator	Housecall Plus
Characteristic	Portable, simple	Stationary, simple	Stationary, interactive	Stationary, voice interaction
Long-range telemetry	4-band GSM, GPRS mobile, landline	Landline	Landline	Landline
Transmission	Daily FU, event messages (automatic)	Scheduled FU, event messages (patient initiated)	Scheduled FU, event messages (patient initiated)	Patient initiated (manual)
Patient reminder for transmission or to take action	Automatic CardioMessenger call-back light	Audio	Audio	Vibration
Information channels by events	Fax, email, text message	Email, text message	Fax, phone	Fax, Internet, EMR
Data storage	Long term	Long term	Long term	Long term
IEGM or real-time Holter transmission	Event-triggered IEGM (up to 45 seconds)	Holter, 10 seconds IEGM strip on request	Holter	NA
Cognitive interpretation	Physician	Raytel partnership	Raytel partnership	Mednet, Raytel, other partnership
Impact of daily monitoring on battery longevity	Low	High	High	NA

IEGM, *Intracardiac electrogram;* FU, *follow-up;* NA, *not available;* EMR, *electronic medical record.*

in vivo. The level of patient involvement during transmission varies depending on the device manufacturers. Variables that are typically monitored include battery status, lead integrity (occasional painless test of the defibrillation coil and pacing lead impedance) and function, detected arrhythmias, delivered therapies, mean heart rate, and patient activity. Importantly, the remote monitoring of ICD includes the recording of silent events, which may be clinically relevant. For instance, lead fracture or insulation defect, elective replacement time indicator caused by battery depletion, ineffective delivery of pacing stimuli, repetitive anti-tachycardia pacing, onset of asymptomatic AF, and worsening heart failure status are potentially important silent events. The event-triggered reports may include intracardiac electrograms (IEGMs) with marker channels and respective far-field or near-field signals.

Figure 85-12 shows an online IEGM recorded at the time of detection of VF onset as displayed on the physician's computer screen. No special report or status update is transmitted as long as the ICD functions normally and the patient remains without symptoms. In general, the transmitted parameters of different remote monitoring systems are programmable and adaptable to individual patients. The physician can program specific alert conditions based on the patient's particular disease characteristics. Remote monitoring reports are typically generated and sent with different alert levels, enabling the caregiver to respond according to the urgency of the alert. For instance, the physician may wish to be alerted during adjustments of antiarrhythmic drug therapy about VT occurring in recipients of ICDs implanted for primary prevention but not in all ICD recipients. Recent studies by Lazarus and Nielson et al demonstrated that remote monitoring of ICDs is feasible and associated with an early detection of medical and technical events.[74,75] The remote follow-up for ICD therapy in patients meeting MADIT-II criteria was investigated to find out whether remote home monitoring data reduced the follow-up burden and associated costs and improved the clinical outcome and quality of life of the patients compared with the standard ICD follow-up.[76-78] The study showed that the number of visits was reduced by 63.2% in the remote monitoring group, but there was no significant difference in patients' hospitalization and mortality rate between the two arms.[76]

According to the Heart Rhythm Society Task Force on Device Performance Policies and Guidelines, the primary goal of remote ICD monitoring is to identify abnormal device behavior as early as possible and to limit the under-reporting of device malfunctions by frequently and accurately verifying the functional status of an implanted device.[79] Remote monitoring is indicated when the patient's medical condition is stable and no device reprogramming is required—close follow-up at the approach of elective device replacement and, in case of a safety alert, when close monitoring may detect a ICD malfunction. Because remote ICD monitoring does not allow a direct cardiovascular examination, remote monitoring follow-up should be scheduled at least at 6-month intervals.[77]

The Lumos-T Reduces Routine Office Device Follow-up (TRUST) study has shown that remote monitoring is more likely to achieve early detection of ICD system or patient health issues.[78]

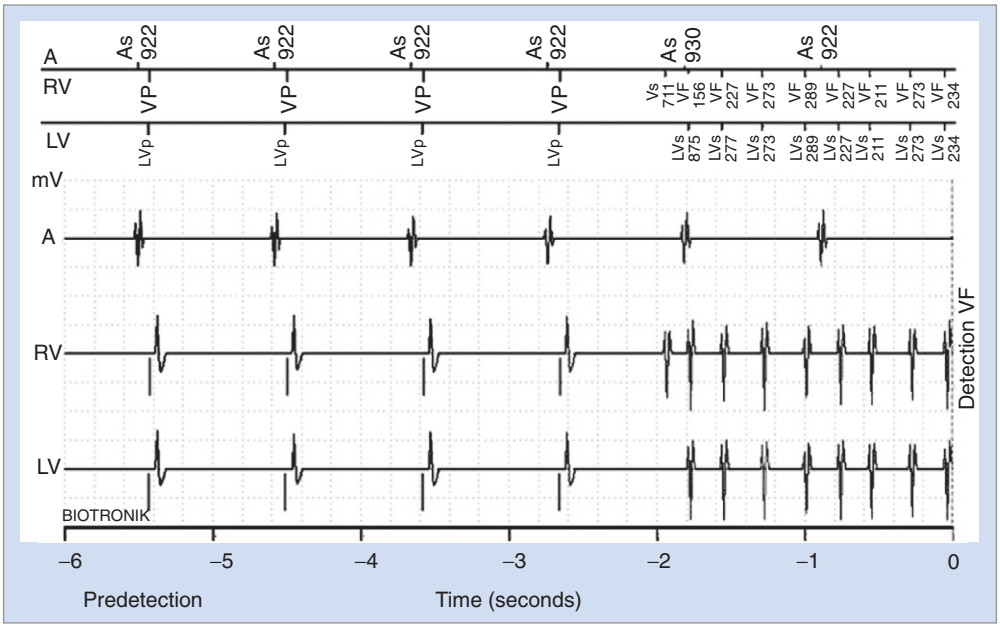

FIGURE 85-12 Intracardiac electrogram recorded by remote monitoring at the time of ventricular fibrillation detection as displayed on the physician's computer screen.

In this study, 1339 patients were randomized to remote monitoring or conventional follow-up. Follow-up checks occurred at 3, 6, 9, 12, and 15 months after implantation. Only remote monitoring was used, with office visits as necessary. Conventional patients were evaluated with office visits only. Remote monitoring reduced total in-hospital device evaluations by 45% without affecting morbidity; 85.8% of all 6-, 9-, and 12-month follow-ups were performed only remotely. Median time to evaluation was reduced for arrhythmic events to 2 days in the remote monitoring group compared with 36 days in the conventional group. Future prospective trial outcomes and development of medical guidelines will result in an exponential growth in capabilities in the implementation of remote monitoring of ICDs, supplementing and replacing in-clinic and, perhaps, in-hospital patient management with remote management.[79]

Future Directions

ICD therapy will be used increasingly for the primary prevention of SCD in high-risk populations based on improved methods of risk stratification (e.g., genotype and heart rate variability analyses). New indications have been approved by the ESC on the basis of the recent report of the MADIT-CRT trial.[43,80] This will extend device therapy for heart failure, including defibrillation capability to patients with NYHA class II heart failure, LVEF less than 36%, and QRS duration longer than 150 ms. A new goal for the next generation of ICDs will be to provide preventative interventions before arrhythmia onset to avoid electrical therapy. This may be achieved through electrical pacing therapy, for example, to avoid long-short coupling or multi-site stimulation, intermittent antiarrhythmic therapy, or CRT to improve hemodynamics. Innovations need to be coupled with a decrease in device cost, making device therapy more cost effective in a variety of health care environments worldwide.[81]

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CHAPTER 86

Cardiac Resynchronization Therapy for Congestive Heart Failure: Physiological Basis, Technology, Indications, and Management

Sanjeev Saksena, Bharat K. Kantharia, Angelo Auricchio, and Helmut Klein

Over the past decade, treatment of heart failure has markedly improved with progress in pharmacologic treatment modalities.[1-5] Rates of death from pump failure and sudden cardiac death (SCD) caused by ventricular tachyarrhythmic events have significantly declined.[5,6] Hospitalizations for severe symptoms of heart failure have decreased after the use of angiotensin-converting enzyme inhibitors, β-blockers, diuretics, and spironolactone became more frequent. Heart transplantation is considered the therapy of choice for end-stage heart failure, but the limited availability of donor organs and the unresolved issue of tissue rejection after transplantation have stimulated research in other nonpharmacologic approaches to symptomatic heart failure, such as multi-site cardiac pacing and left ventricular assist device therapy.

Electrical Dyssynchrony and Heart Failure

A common pathophysiological finding in the failing heart is a delay in the spread of ventricular activation. This can be caused by structural abnormalities of the myocardium leading to asynchronous ventricular contraction, referred to as *cardiac dyssynchrony*.[6] Cardiac dyssynchrony can result in inefficient ventricular performance (discussed later) and may be prevalent in 25% to more than 60% of patients with congestive heart failure.[7] These structural changes can also provide an electrophysiological substrate that can support potentially life-threatening ventricular tachyarrhythmias. Ventricular conduction delay has been shown to be an independent risk marker for the development of heart failure and increased mortality rates.[8-10]

Devices such as cardiac pacemakers, which can potentially correct delayed cardiac electrical activation, or defibrillators with pacing capabilities, which can also prevent SCD, have the potential to be effective tools in heart failure therapy. Our current understanding of bi-ventricular pacing therapy for heart failure indicates that dyssynchronous contraction seen in ventricles is corrected in some measure by this therapy. For this reason, it is more appropriate to use the term *cardiac resynchronization therapy* (CRT). This approach accomplishes atrial-synchronized RV and LV (bi-ventricular) pacing for the treatment of heart failure.

Pathophysiological Concepts Underlying Resynchronization Therapy

Electrical and Mechanical Abnormalities in Heart Failure

Abnormalities of electrical function in heart failure can occur singly or in combination in either atrioventricular (AV) conduction or interventricular or intraventricular conduction. Prolongation of the A-V interval is associated with impaired atrial contribution to ventricular filling and reduced diastolic ventricular filling. Intraventricular as well as interventricular conduction delays prolong the pre-ejection time and reduce the global and regional ventricular ejection fraction (EF) because of dyssynchronous mechanical contraction and relaxation patterns. This mechanical dysfunction interferes with mitral valve function and permits mitral regurgitation.[11-14] One electrical indicator for delayed asynchronous ventricular contraction is the presence of a left bundle branch block (LBBB) pattern on the surface electrocardiogram (ECG). Ventricular conduction abnormalities, especially LBBB, may be responsible for the unequal regional distribution of ventricular work and wall stress.[15-17] At the beginning of ventricular systole, the region of earliest ventricular activation (usually the interventricular septum) contracts against minimal workload because the remaining ventricular myocardium (usually the lateral and posterolateral left ventricular regions) is still in the relaxation period or in a nonactivated phase. The regions of early ventricular activation waste contraction energy because no effective intraventricular pressure can develop. In contrast, the delayed depolarized regions, that is, the lateral and posterolateral ventricular regions, must contract against a pre-existing stiffened portion of the ventricular wall (the septum). This generates increased wall stress with increased cardiac work. These changes in regional wall stress can contribute to myocyte damage, production of fibrous tissue, and development of regional hypertrophy and may induce regional apoptosis. The mechanical contractile dysfunction caused by asynchrony or dyssynchrony can be assessed by standard echocardiographic indexes, but greater precision is obtained with tissue Doppler imaging and magnetic resonance imaging.[12,15-17]

Mechanical synchrony between the atrium and the ventricle can also be disturbed when AV conduction is pathologically

prolonged. A prolonged electromechanical A-V interval can be assessed by measuring the onset of the P wave of the surface ECG to the aortic valve closure. The mechanical A-V interval is always longer than the electrical A-V interval. This interval can be prolonged even in the absence of a prolonged P-R interval on the surface ECG. Prolongation of AV conduction reduces the active ventricular filling phase and shortens the passive diastolic filling, creating a ventriculoatrial (VA) gradient causing presystolic mitral regurgitation.[13,14] A prolonged mechanical A-V interval is frequently found in patients with heart failure, even with an almost normal electrical A-V interval.[18]

Cardiac Resynchronization Using Pacing Techniques

LBBB causes delayed electrical activation and mechanical contraction of the lateral left ventricular wall, whereas the ventricular septum itself exhibits a paradoxic movement.[19-22] Pacing electrode placement becomes a critical component of the extent of effective resynchronization achieved by CRT. For example, pre-excitation of the left lateral ventricular wall with atrio–bi-ventricular pacing in hearts with LBBB resynchronizes the ventricular contraction pattern by bypassing the conduction delay, resulting in improved ventricular contraction pattern and performance.[20-23] It is conceivable that differing patterns of intraventricular conduction delay may also produce regional wall motion abnormalities that could be addressed with CRT. Optimizing AV synchrony is a critical element in obtaining good hemodynamic outcomes in these patients.

Atrioventricular Synchrony During Physiological Pacing

Programming the AV delay appropriately is essential for the improvement of hemodynamic performance with CRT. A very long AV delay will not support ventricular resynchronization because the atrial electrical impulse will follow the same route as during sinus rhythm without pacing. A very short AV delay, in contrast, will cause early depolarization at the site of left ventricular stimulation, leaving the ventricle partially or totally refractory by the time the regularly conducted impulse reaches this region. An AV delay between these two extremes causes a collision of two activation wavefronts: one coming from the regular His-Purkinje system and the other from the pre-excited ventricular activation. The region of collision depends on individual intraventricular and interventricular conduction properties and the left ventricular pacing site (Figure 86-1). Therefore appropriate timing with respect to the AV delay, as well as the left lateral ventricular stimulus, is crucial for achieving the hemodynamic benefits of the resynchronized ventricular contraction pattern in a failing heart.[24,25] A nonphysiological short electrical A-V interval must be used with AV sequential bi-ventricular pacing to avoid AV asynchrony and to reduce presystolic mitral regurgitation. The discrepancy between electrical and mechanical AV sequences is most likely caused by a prolonged intraventricular conduction time. In patients with LBBB, the onset of the electrical depolarization of the left ventricular free wall is significantly delayed. This causes delayed mechanical onset of the left ventricular systole. Consequently, AV sequential pacing with a shortened AV delay is able to restore an adequate mechanical AV synchrony.[24,25] Maximal hemodynamic benefit is achieved when the peak of the atrial pressure curve coincides with the onset of the mechanical ventricular systole (Figure 86-2).

Effect of Bundle Branch Block and Pacing Electrode Location on Efficacy of Resynchronization Therapy

In early experimental studies, Verbeek et al demonstrated that the induction of LBBB produced mechanical dyssynchrony, which could be improved by bi-ventricular pacing.[26] In normal or rapid pacing–induced failing canine hearts, Helms et al performed either left ventricular pacing or left bundle ablation and CRT using a fixed right ventricular pacing site and randomly selected left ventricular pacing sites covering the entire free wall (see Figure 86-1, *B*).[27] Cardiac stroke volume was measured with a conductance catheter, and mechanical synchrony was evaluated by using magnetic resonance imaging tagging. In this model, right bundle branch block (RBBB) was associated with a lesser degree of cardiac dyssynchrony compared with LBBB. Three-dimensional maps showed that optimal CRT was achieved from lateral left ventricular wall sites, which were slightly more anterior than posterior and more apical than basal (see Figure 86-1).[27] Left ventricular sites yielding a 70% or greater increase in dP/dT_{max} covered approximately 43% of the left ventricular free wall. In this model, their distribution and size were similar in both normal and failing hearts. Controversy has swirled around the benefits of left ventricular pacing alone versus bi-ventricular pacing in LBBB. In some clinical studies, the concept of tailored CRT has been advanced, but better imaging approaches such as three-dimensional echocardiography, intracardiac echocardiography, or other methods may be needed in clinical practice to prove this concept.[28-30]

Effect of Resynchronization Therapy on Mitral Regurgitation

Patients with symptoms of heart failure and a dilated left ventricle (LV) often demonstrate moderate or even severe mitral regurgitation. This is often seen in patients with LBBB. The delay in regional ventricular activation caused by intercellular fibrosis enhances mechanical asynchrony between different ventricular regions and can involve both papillary muscles.[25] Geometric distortion in the dilated LV and delayed left ventricular free wall activation further decrease the timely closure of mitral leaflets along with an increased tethering of the mitral apparatus.[23,25]

Pacing from the left lateral wall, especially from the proximity of the posterior papillary muscle, diminishes conduction delay and decreases mitral regurgitation. Mean capillary wedge pressure drops significantly with left ventricular free wall pacing, whereas systolic blood pressure rises. The altered ventricular geometry of the dilated failing ventricle results in incomplete closure of the mitral valve at the onset of ventricular contraction causing early systolic mitral regurgitation. Therefore, shortening of the A-V interval during AV sequential pacing, along with left ventricular pre-excitation by left ventricular pacing, diminishes or even abolishes mitral regurgitation.[31]

Clinical Results of Cardiac Resynchronization Therapy

Short-Term Results

Acute hemodynamic testing has demonstrated that the type of intraventricular conduction block and the pacing site location are the primary determinants of hemodynamic benefits. In addition, short-term data suggest a dichotomous behavior in patients who

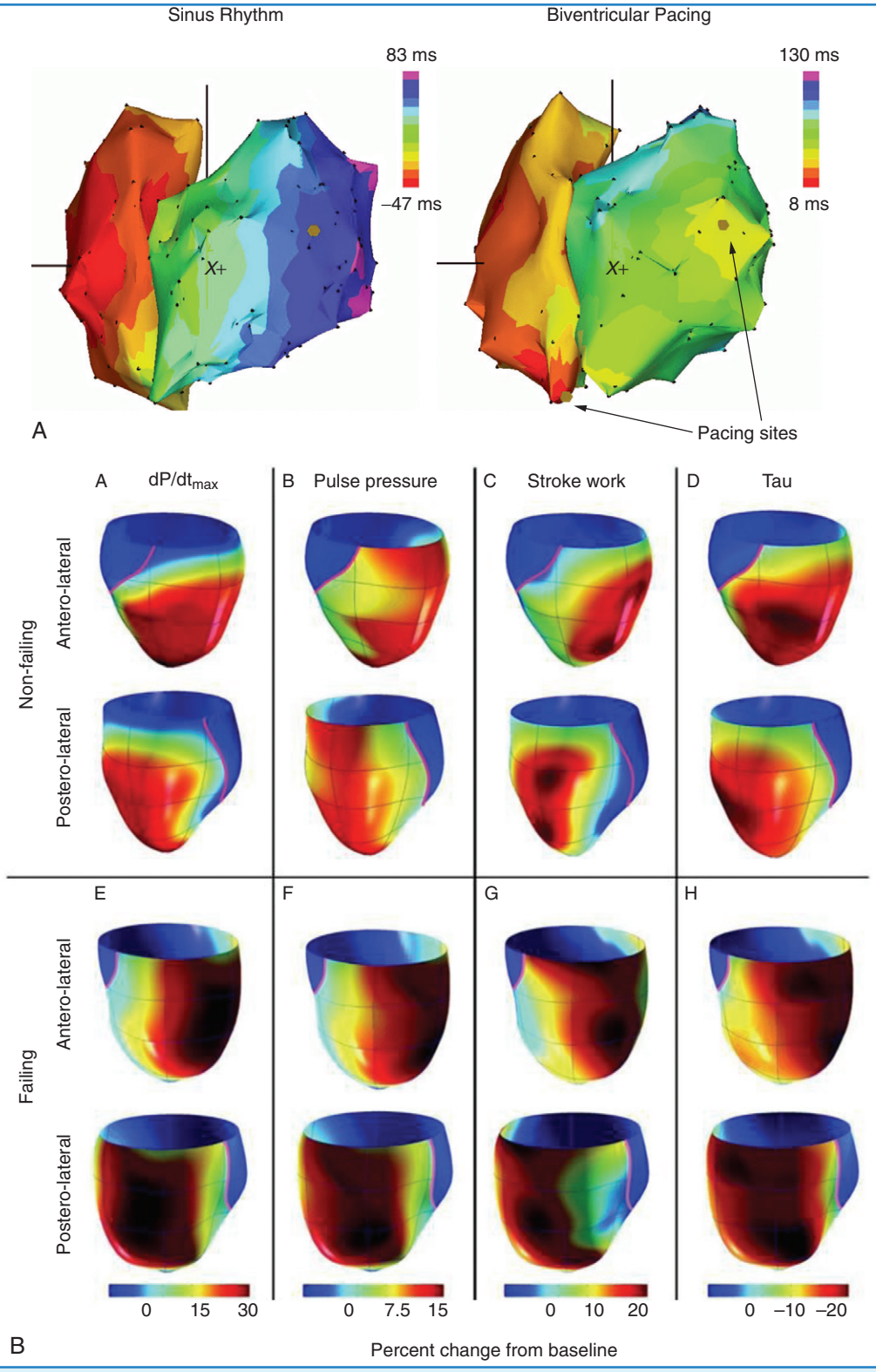

FIGURE 86-1 A, Three-dimensional electroanatomic, nonfluoroscopic mapping in a patient with dilated cardiomyopathy during sinus rhythm and during biventricular stimulation. In sinus rhythm (*left*), the earliest ventricular activation (*red*) is located at the anterolateral wall of the right ventricle. After about 60 ms, the activation breaks through into the left ventricle and slowly proceeds (cell-to-cell conduction) from the septum to the lateral and posterolateral wall. The simultaneous pacing from the apex of the right ventricle and lateral wall restored a more homogeneous electrical activation of both ventricles. **B,** Representative functional maps showing change in various systolic and diastolic measures induced by cardiac resynchronization therapy (CRT) as a function of the left ventricular stimulation site. *Top*, Results for a nonfailing heart; *bottom*, results for a failing heart. Each set has two orientations (*top*, anterolateral; *bottom*, posterolateral) to display the optimal sites more clearly. Color coding reflects the percent change in a given hemodynamic variable referenced to the dyssynchronous baseline, with dark orange/red regions indicating most optimal CRT. The region of optimal left ventricular pacing was fairly similar among function parameters and between nonfailing and failing hearts.

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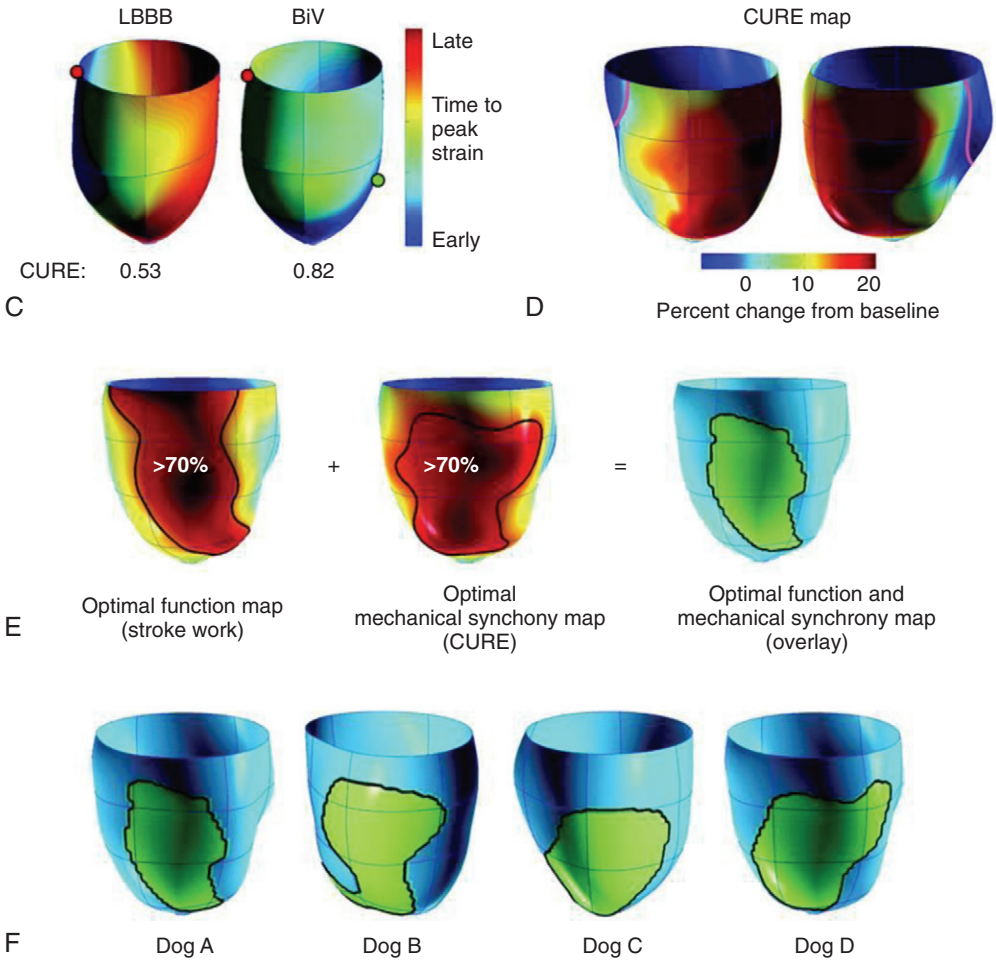

FIGURE 86-1, cont'd C, Three-dimensional plot of relative mechanical activation time (time from QRS to peak circumferential strain) in a dyssynchronous failing heart (left bundle-branch block) and during bi-ventricular pacing. The *green dot* shows the left ventricular stimulation site. **D,** Synchrony indexed by circumferential uniformity ratio estimate (*CURE*) was calculated as a function of varying left ventricular pacing site and plotted on three-dimensional maps. The *red region* denotes the territory in the lateral wall that achieved optimal mechanical resynchronization. **E,** Full maps derived for ventricular stroke work and synchrony (CURE) were determined in four failing hearts, and the territories producing optimal responses (≥70% maximal) for both were calculated and are displayed in *green* (*far right*). This region was somewhat smaller and located in the midlateral (midapical) wall. **F,** Overlay maps generated for all four animals revealing similarly sized, shaped, and localized co-optimal regions. Dogs A and B had right ventricular free wall stimulation during bi-ventricular pacing; dogs C and D had right ventricular apical pacing during bi-ventricular pacing. *(From Helm RH, Byrne M, Helm PA, et al: Three-dimensional mapping of optimal left ventricular pacing site for cardiac resynchronization,* Circulation *115[8]:953–961, 2007.)*

present with a QRS duration between 120 and 150 ms.[23] Patients with a QRS duration of greater than 150 ms showed the largest hemodynamic benefit. The Pacing Therapies for Congestive Heart Failure (PATH-CHF) trial results and data from Kass and colleagues suggest that patients with LBBB and diffuse intraventricular conduction delay tend to benefit more from bi-ventricular pacing than from right ventricular pacing.[21,23] Atrial synchronous left or bi-ventricular stimulation at a nominal AV delay is significantly more beneficial than is right ventricular pacing alone. Parameters of acute systolic function significantly improved during pacing of the left ventricular free wall alone or synchronously with the right ventricle (RV) but not by pacing the right ventricular apex or septum alone. Pressure-volume loops of the LV show that in patients with LBBB, left ventricular pacing but not right ventricular pacing, increased the stroke volume while minimally affecting the end-diastolic volume. Pulmonary capillary wedge pressure dropped significantly with left ventricular pacing and bi-ventricular pacing but not with right ventricular pacing alone. Resynchronization of ventricular contraction improves mechanical performance with a net decrease in myocardial energy consumption.[22] Acute benefits of resynchronization therapy depend on the A-V interval for each ventricular pacing site, with the shortest and longest AV delays being suboptimal.[23] In general, a range of AV delay around 100 ms produced the most beneficial hemodynamic effect. However, a large variability was present in the optimal AV delay during sequential right ventricular pacing, ranging from 50 to 120 ms, and during bi-ventricular stimulation, ranging from 100 to 150 ms.[32]

Intermediate-Term Results

In the short term, hemodynamic results of bi-ventricular or left ventricular pacing alone clearly demonstrate hemodynamic improvement, but it is necessary to show that this translates into

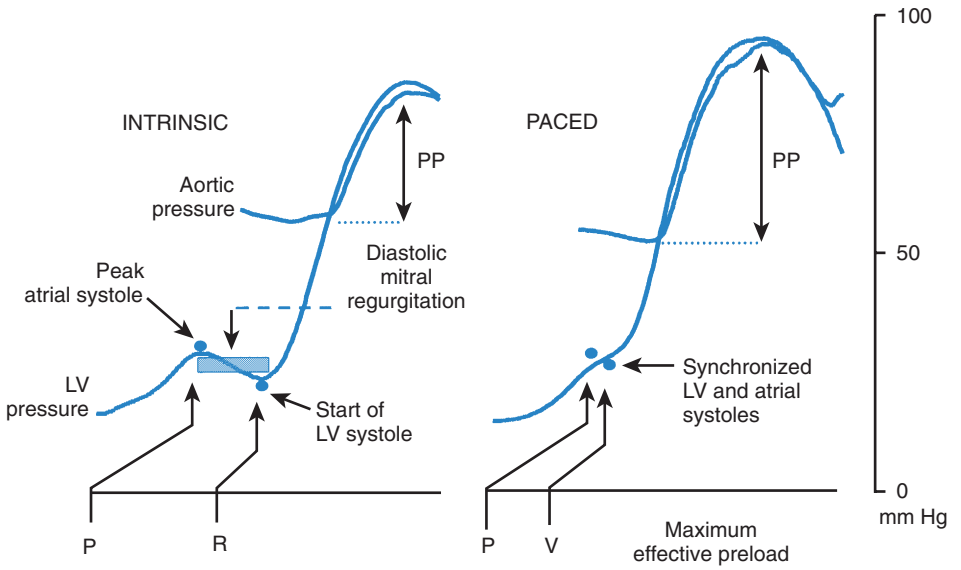

FIGURE 86-2 Schematic representation of the hemodynamic benefit obtained when the maximum of the atrial contraction curve is coincident with the onset of the mechanical ventricular systole *LV*, Left ventricular.

Table 86-1 First-Generation Trials and Registries of Cardiac Resynchronization Therapy

TRIALS	YEAR CONCLUDED	NO. PATIENTS ENROLLED	NO. RANDOMIZED PATIENTS (%)	PRIMARY ENDPOINTS	SECONDARY ENDPOINTS
PROSPECTIVE, CONTROLLED, RANDOMIZED TRIALS					
PATH-CHF I	1999	42	41 (98)	VO_2, 6MW	QOL, NYHA, HF
MUSTIC (sinus rhythm)	2000	67	58 (87)	6MW	VO_2, QOL, NYHA, HF
MUSTIC (atrial fibrillation)	2000	65	48 (74)	6MW	VO_2, QOL, NYHA, HF
MIRACLE	2001	285	266 (93)	6MW	VO_2, QOL, NYHA, CE
Contak-CD	2001	581	490 (84)	HF, VT/VF	VO_2
PATH-CHF II	2001	101	90 (89)	VO_2, 6MW	QOL, NYHA, HF
REGISTRIES					
InSync	1999	110	NYHA		
Contak	2000	1000	NYHA		

CE, Composite endpoints; HF, hospitalization frequency; NYHA, New York Heart Association (functional classification); QOL, quality of life (by Minnesota Living with Heart Failure Questionnaire); VO_2, oxygen consumption; 6MW, six-minute walk test; VT/VF, frequency of ventricular tachycardia/fibrillation.

symptomatic improvement and eventually survival benefit.[33-40] Data from several prospective randomized studies on CRT pacing (CRT-P) and on CRT with defibrillator therapy (CRT-D) (Table 86-1) and large patient registries have been very encouraging in the intermediate term. The majority of patients enrolled in these randomized studies had severely impaired functional capacity (New York Heart Association [NYHA] heart failure classes III to IV), left ventricular systolic dysfunction (EF <35%), a wide QRS complex (>120 ms) and, in most cases, LBBB. None of the patients had conventional indications for pacing therapy. The Multi-site Stimulation in Cardiomyopathy (MUSTIC) study, the Contak-CD trial, and the Multicenter InSync Randomized Chronic Evaluation (MIRACLE) study exclusively assessed the role of bi-ventricular stimulation in patients with heart failure. The PATH-CHF I study was performed to address the question of whether acutely optimized atrial-synchronous ventricular stimulation (right ventricular, left ventricular, or bi-ventricular stimulation based on acute hemodynamic evaluation) reduces heart failure in patients with intraventricular conduction defects. In these studies, CRT increased exercise tolerance, improved quality of life, and reduced hospitalization (Table 86-2).[23,25,33-35] Oxygen consumption at maximal exercise capacity increased, on average, from 11 to 12 mL/kg/min before pacing to 15 to 16 mL/kg/min after 3 to 6 months of pacing (see Table 86-2). The 6-minute walk test, a

Table 86-2 Summary of Early North American Long-Term Clinical Studies Evaluating Cardiac Resynchronization

	MIRACLE	CONTAK	MIRACLE-ICD	MUSTIC-CD
QOL	+++	+++	+++	+++
NYHA classification	+++	+++	+++	+++
Six-minute walk test	+++	+++	+	+++
Peak VO_2	+++	+	+++	+++
Exercise time	+++		+++	
LVEDD	+++		+++	+++
Ejection fraction	+++	+	+	+
MR jet area	+++	+		
Freedom from hospitalization, IV inotropes	+++	+	+	

+, *Showed improvement with cardiac resynchronization without achieving clinical significance;* +++ *showed clinically significant improvement with cardiac resynchronization.*
IV, *Intravenous;* LVEDD, *left ventricular end-diastolic diameter; MR, mitral regurgitant;* NYHA, *New York Heart Association;* QOL, *quality of life.*

generally accepted parameter of physical exercise capacity, increased on average by 10% to 15%, and patients showed a positive improvement in quality of life. Nearly two thirds of patients who underwent bi-ventricular therapy improved to NYHA class I or II from class III or IV. Patients in whom the CRT device was turned on were hospitalized less frequently and needed fewer days in the hospital for worsening of heart failure.

Objective assessment of autonomic and neurohormonal systems has shown the beneficial effects of CRT. Changes in heart rate variability (HRV) and resting heart rate reflect changes of the autonomic nervous system. The PATH-CHF I study showed that resting heart rate was significantly reduced after 3 months of pacing. HRV increased during CRT, whereas during the CRT-off phase, an almost complete reversion to baseline values was observed. In the Vigor in Congestive Heart Failure (VIGOR-CHF) study, a significant reduction of the norepinephrine plasma level after 16 weeks of continuous bi-ventricular stimulation was seen, which also confirmed the positive effect of CRT on neurohumoral activation.[36]

The Contak-CD study, which is considered one of the first-generation CRT-D studies, differed from many other studies of CRT by including patients with NYHA class I indication for an implantable cardioverte-defibrillator (ICD).[34] A reduction of 21% occurred in the overall combined endpoint in Contak-CD, which was not statistically significant ($P = .17$). This may be attributed to the fact that the relatively large proportion of patients in NYHA class II enrolled in Contak-CD did not show a mortality benefit from CRT-D. Nevertheless, CRT-D in the Contak-CD trial was associated with fewer deaths (23% relative risk [RR] reduction), a lower hospitalization rate (13% RR reduction), and a smaller proportion of patients with worsening heart failure (26% RR reduction). Ventricular tachyarrhythmias were only modestly reduced in some studies of patients receiving CRT.[34,40] All patients showed a significant increase in peak oxygen consumption. Patients in an advanced functional class (NYHA class III or IV) showed double the average increase of oxygen consumption. Longer term outcomes of CRT in the ICD subpopulations are available from the recently completed Multicenter Automatic Defibrillator Implantation Trial (MADIT)-CRT and Resynchronization/Defibrillation for Ambulatory Heart Failure Trial (RAFT) studies (discussed later).[37,38]

Although the effect of CRT on the diseased myocardial structure is still not completely understood, it is now well accepted that CRT can lead to reverse remodeling with a significant reduction of left ventricular diameters within 6 to 12 months. CRT is able to reduce abnormal myocardial strain distribution and induce reverse remodeling with a significant decrease of left ventricular volume within the first 6 months after initiation of CRT.[39] These effects may be attributed to a direct reduction of regional wall stress or a reduction of increased oxygen demand of the asynchronously contracting ventricles. It is possible, however, that at a critical size of the left ventricular end-diastolic or end-systolic volume, reverse remodeling cannot be achieved. A beneficial effect is also achieved with a decrease in mitral regurgitation.

Many patients with heart failure are not candidates for CRT; the current indications for CRT are limited to patients who fulfill the disease and selection criteria outlined in the practice guidelines, which are largely based on clinical trials. The type of conduction delays, typically RBBB or LBBB or nonspecific intraventricular conduction delays, may play an important role in predicting a beneficial effect of pacing. Although morphologic ECG features may be similar in patients with either RBBB or LBBB, left ventricular electrical activation sequences may differ. The precise spread of activation may only be assessed with detailed high resolution invasive electroanatomic mapping.[41] This, however, is difficult to perform in daily practice. In some cases, it may, indeed, help to select the optimal left ventricular pacing site by accurately detecting the region(s) of delayed left ventricular activation that may be optimal left ventricular pacing sites for CRT. Another approach that has been recently proposed uses intracardiac echocardiography intraoperatively to guide left ventricular pacing to maximize acute improvement in left ventricular EF (LVEF) with varying left ventricular lead position and AV interval programming. Reduction in nonresponder rates has been suggested with this approach, but a large clinical trial is awaited.[30]

Long-Term Clinical Outcomes of Cardiac Resynchronization Therapy

Second-generation prospective, randomized, controlled studies have examined the effect of CRT and CRT-D on clinical outcomes, morbidity, and disease progression.[42-45] Several have examined the effect of CRT-P (exclusively bi-ventricular pacing) and CRT-D (bi-ventricular pacing with ICD) therapy on outcome and morbidity. The Comparison of Medical Therapy, Pacing and Defibrillation in Chronic Heart Failure (COMPANION) trial was a multi-center trial evaluating the effect of CRT on mortality, morbidity, and exercise performance in symptomatic heart failure patients without ICD indications.[43] The study randomized patients in NYHA class III or IV with an LVEF of less than 35% and a prolonged QRS duration (>120 ms) and left ventricular dilation (left ventricular end-diastolic diameter >60 mm). This trial showed that CRT reduced the composite endpoint of death or hospitalization for major cardiovascular event by 12%. However, significant mortality reduction was achieved only in the CRT-ICD arm. Similarly, Cardiac Resynchronization in Heart Failure (CARE-HF) was a mortality and morbidity trial that included patients with NYHA class III or IV heart failure, an LVEF of less than 35%, and a prolonged QRS duration (>150 ms or >120 ms with echocardiographic criteria of dyssynchrony on optimal medical therapy).[43] CRT plus optimal pharmacologic treatment was compared with pharmacologic treatment alone. Over a mean follow-up of 29 months, the CARE-HF study showed significant reduction of 37% for the composite endpoint of death or hospitalization for a major cardiovascular event, and a 46% reduction in SCD. CRT-P also reduced mortality rate from 30% in the medical therapy group to 20% in the CRT-P group (hazard ratio [HR], 0.64; $P < .002$). Reductions in mortality rate from heart failure (HR, 0.55; $P = .003$) and SCD (HR, 0.54; $P < .006$) were seen compared with medical therapy. Compared with the control group, the CRT group showed significant improvements in indexes of left ventricular function, symptoms, and quality of life. Longer term follow-up in this study has confirmed long-term benefits in both mortality and morbidity.[44]

The impact of CRT on ventricular remodeling and function was assessed in the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) study.[39,45] At 12 months, the clinical composite response endpoint, which measured disease progression, rose by 16% with CRT-on compared with 21% in CRT-off ($P = .10$). However, the patients assigned to CRT-on experienced a greater improvement in left ventricular end-systolic volume index ($-18.4 + 29.5$ mL/m^2 vs. $-1.3 + 23.4$ mL/m^2; $P < .0001$) and other measures of left ventricular remodeling. Time to first heart failure hospitalization was significantly delayed in CRT-on (HR, 0.47; $P = .03$).

The MADIT-CRT study evaluated the additional beneficial effect of CRT on the occurrence of heart failure or death in patients with moderate to severe left ventricular systolic dysfunction, with minimal or no symptoms of heart failure and a QRS width of 130 ms (Table 86-3).[37] Patients with CRT-D were compared with those receiving ICD-only therapy. CRT provided an additional 34% risk reduction in the primary endpoint after a mean follow-up of 2.4 years. The benefit of CRT was mainly attributable to a 41% reduction of heart failure. Patients with LBBB and women showed the most benefit, whereas patients with RBBB and intraventricular conduction delay demonstrated no benefit. Patients with ischemic and nonischemic cardiomyopathy derived similar benefits. Evidence of left ventricular reverse remodeling was evident as marked reduction in left ventricular volumes and an increase in LVEF with CRT-D. Overall mortality rate was not significantly reduced, which may be a result of follow-up duration. Similar findings were observed in RAFT. (see Table 86-3).[38] This trial had a longer follow-up of the enrolled patients and reported a reduction of overall mortality rate. These trials suggest a potential for an early role of CRT in the prevention of progression of heart failure.

Cardiac Resynchronization Therapy with Defibrillator Therapy

Controversy has swirled on the need for defibrillation therapy in patients receiving CRT therapy. Death in patients with heart failure can result from a variety of causes other than mechanical pump failure. SCD in heart failure is a catastrophic event. The incidence increases from 2% to 6% per year in patients with NYHA class II symptoms and up to 24% per year for patients with class III or IV symptoms.[46] Mechanisms of SCD can include ventricular tachycardia,ventricular fibrillation, bradycardia- or

Table 86-3 Trials of Cardiac Resynchronization Therapy Alone and with Defibrillator Therapy

TRIAL/PATIENTS	TYPE OF TRIAL/ FOLLOW-UP DURATION	INCLUSION CRITERIA	ENDPOINTS	RESULTS
Cardiac Resynchronization in Heart Failure (CARE-HF), N = 813	RCT of CRT + optimal medical therapy vs. optimal medical therapy alone; mean, 29 months	NYHA class III or IV, LVEF ≤35%, QRS >150 ms or QRS ≥120 ms + echocardiographic criteria of dyssynchrony; stable optimal medical therapy	All-cause mortality, all-cause mortality or HF hospitalization, NYHA class, QOL, echocardiographic left ventricular function, neurohormone levels, economic impact	Improvements in morbidity and mortality/ cardiovascular hospitalization by CRT
Comparison of Medical Therapy Pacing and Defibrillation in Heart Failure (COMPANION), N = 1520	Randomized, three-arm study to compare optimal drug therapy + CRT or drug therapy + CRT; median, 12-16 months	NYHA class III or IV, LVEF ≤35%, QRS ≥120 ms, PR >150 ms, no indication for pacemaker or ICD, HF hospitalization in the past year	Combined all-cause mortality and all-cause hospitalization, QOL, functional capacity, peak exercise performance, cardiac morbidity	Early termination of the trial; CRT showed to reduced all-cause mortality and hospitalization with CRT; reduced all-cause mortality with CRT-D

Continued

Table 86-3 Trials of Cardiac Resynchronization Therapy Alone and with Defibrillator Therapy—cont'd

TRIAL/PATIENTS	TYPE OF TRIAL/ FOLLOW-UP DURATION	INCLUSION CRITERIA	ENDPOINTS	RESULTS
Contak-CD Bi-Ventricular Pacing Study, N = 501	Started as a 3-month crossover between BiV CRT and no CRT; modified to 6-month parallel, double-blind trial between CRT and no CRT, starting 1 month after implantation; mean, 4.5 months	NYHA class II-IV, LVEF ≤35%, QRS ≥120 ms, ICD indication; stable optimal medical therapy	Composite endpoint of all-cause mortality, HF-related hospitalization, or VT/VF resulting in device therapy; peak VO_2, QOL, 6MWD, NYHA class, echocardiographic parameters, neurohormone levels	Improvements in peak VO_2, 6MWD, QOL, and NYHA functional class in class III-IV patients with CRT
Multicenter InSync Randomized Clinical Evaluation (MIRACLE)	Prospective randomized, double-blind, parallel, controlled trial	NYHA class III-IV, LVEF ≤35%, LVEDD ≥55 mm, QRS ≥130 ms; patients with pacing indication not admitted; stable optimal medical therapy	NYHA class, 6WMD, QOL, echocardiography indexes, peak VO_2, death, hospitalization, QRS duration, neurohormone levels	Improvements in NYHA class, 6MWD, QOL, LVEF; ventricular volumes, mitral regurgitation, peak VO_2; reduced hospitalizations
Multicenter In Sync ICD Randomized Clinical Evaluation (MIRACLE-ICD)	Prospective randomized double-blind parallel, controlled trial evaluating safety and efficacy of CRT in patients with HF and indication for ICD	NYHA class III-IV, LVEF ≤35%, LVEDD ≥55 mm, QRS ≥130 ms; ICD indication	QOL, NYHA class, 6MWD, peak VO_2 exercise duration, HF composite (death, HF, hospitalization, NYHA class, and patient global self-assessment), safety of CRT-D	Improvements in QOL, NYHA class, and clinical composite endpoints; CRT-D safe to use
Multisite Stimulation in Cardiomyopathy Sinus Rhythm (MUSTIC SR)	Prospective, randomized, single-blind crossover study	NYHA class III, LVEF <35%, LVEDD >60 mm, QRS ≥200 ms, 6MWD <450 m	6MWD, peak VO_2, QOL, NYHA class, hospitalization, patient treatment preference, all-cause mortality, echocardiographic indexes	Improvements in 6MWD, peak VO_2, QOL, and NYHA class; reduced hospitalizations; patients preferred CRT
Multisite Stimulation in Cardiomyopathy Atrial Fibrillation (MUSTIC AF)	Prospective randomized, single-blind crossover VVIR-BiV study	NYHA class >III, LVEF <35%, LVEDD >60 mm, paced QRS ≥200 ms during ventricular pacing, 6MWD <450 m	6MWD, peak VO_2, QOL, NYHA class hospitalization, patient treatment preference, all-cause mortality, echocardiographic indexes	Improvements in 6MWD, peak VO_2, QOL, NYHA class; reduced hospitalizations; patients preferred CRT
Pacing Therapies in Congestive Heart Failure (PATH-CHF)	Longitudinal study of CRT with second placebo control phase; first and third periods crossovers between left ventricular and BiV	NYHA class III-IV, QRS >120 ms, sinus rate ≥55 beats/min, PR ≥150 ms	Peak VO_2, 6MWD, NYHA class, QOL	Improvements in exercise capacity, functional status, and QOL
PATH-CHF II	Crossover randomized trial of no CRT vs. CRT in LV only; 2 patient groups: QRS 120-150 ms and QRS >150 ms	NYHA class II-IV, LVEF ≤30%, QRS ≥120 ms, optimal therapy, for HF; patients with ICDs may be included	Peak VO_2, peak VO_2, AT, 6MWD, QOL, NYHA class, hospitalization	In group with QRS 120-150 ms, no improvement in group with QRS >150 ms, improvements in VO_2, AT, 6MWD, and QOL
Resynchronization-Defibrillation for Ambulatory Heart Failure Trial, N = 1798	RCT of CRT-D vs. ICD; mean, 40 months	NYHA class II-III, LVEF<30%, QRS >120 ms, paced QRS >200 ms	All-cause mortality, HF-related hospitalization	CRT-D reduced rates of death and HF hospitalization
REVERSE Trial, N = 610	RCT of CRT or CRT-D on vs. CRT-off; mean, 24 months	NYHA class III-IV, QRS ≥120 ms, LVEF ≤40%	HF clinical composite response endpoint	Left ventricular function improved and left ventricular dimensions decreased
MADIT CRT, N = 1820	RCT of CRT-D vs. ICD; mean, 2.4 years	NYHA class I-II, LVEF ≤30%, QRS ≥130 ms	All-cause mortality, nonfatal HF event	CRT-D decreased the risk of HF events

AT, Anaerobic threshold; AV, *atrioventricular;* BiV, *biventricular;* CRT, *cardiac resynchronization therapy;* D, *defibrillator;* HF, *heart failure;* ICD, *implantable cardioverter-defibrillator;* LVEDD, *left ventricular end-diastolic diameter;* LVEF, *left ventricular ejection fraction;* NYHA, *New York Heart Association;* QOL, *quality of life;* RCT, *randomized controlled trial;* VO_2, *oxygen uptake;* VF, *ventricular fibrillation;* VT, *ventricular tachycardia,* 6MWD, *6-minute walk distance.*

tachycardia-dependent polymorphic ventricular tachycardia, primary bradyarrhythmias, and conduction disturbances resulting in asystolic cardiac arrest and electrical mechanical dissociation or pulseless electrical activity. Early ICD trials did not systematically select patients with advanced heart failure despite observational data and clinical trial subgroup analyses that suggested major benefits accruing with appropriate ICD use in patients with severe left ventricular dysfunction.[47-52] In the Antiarrhythmics Versus Implantable Defibrillators (AVID) study, ICD survival benefit was restricted to patients with an EF below 35%.[50] The survival benefit in the MADIT I study was almost entirely confined to the ICD group with an EF below 26%.[51] The Canadian Implantable Defibrillator Study (CIDS) showed the greatest benefit was derived by patients in the highest risk quartiles, that is, those with a low EF and a poorer NYHA functional classification.[52]

In early CRT studies, SCD rates ranged from 33% to 47%. In examining modes of death in the CRT-only group in the CARE-HF study, SCD was observed in 32 of 101 deaths during the extended follow-up, and a certain proportion of these deaths would be deemed preventable by ICD therapy.[43,44] The Multicenter Longitudinal Observational Study (MILOS) group reported their analysis of the long-term outcomes of 1303 patients treated with CRT alone, CRT-P, or CRT-D.[53] The cumulative event-free survival rates were 92% and 56% at 1 and 5 years, respectively; and the cumulative incidence rates of death from heart failure and SCD were 25.1% and 9.5%, respectively. CRT-D was associated with a 20% decrease in mortality rate, and its protective effect against SCD was highly significant ($P < .002$).

Dual-chamber ICD devices have traditionally been used in these patients, but some pacing features may be deleterious. Data from the Dual Chamber and VVI Implantable Defibrillator (DAVID) study suggest that adverse physiological effects and outcomes result from chronic right ventricular apical pacing.[54] CRT can be considered when intraventricular conduction disturbances, as previously discussed, are present. However, the use of CRT in ICD devices is primarily based on the assumption that prevention of SCD in heart failure populations will provide survival benefits not seen with pacing alone. Table 86-3 summarizes the experience with CRT-D therapy in multi-center clinical trials in this population. Initial experience with an ICD incorporating ventricular resynchronization therapy was assessed in a prospective study using the InSync model 7272 ICD (Medtronic Inc., Minneapolis, MN).[55] Significant improvement of heart failure symptoms and left ventricular dimensions were seen in these patients, particularly those in NYHA classes III and IV. Patients showed improvement in the 6-minute walk test at 3 and 6 months. All ventricular tachyarrhythmias were correctly identified, and double counting of sensed QRS events did not occur. In the Contak-CD trial, patients with class I indication for ICD therapy and NYHA class II or more heart failure had a 21% reduction of overall mortality rate (nonsignificant).

Table 86-3 summarizes the long-term outcomes of major CRT trials. In the COMPANION study, CRT alone improved NYHA class and quality of life and reduced hospitalizations for heart failure. However, significant mortality rate reduction was achieved only in the CRT-ICD arm. These data are consistent with the original pacing trials in this population, which suggested that SCD can limit the benefits achieved with CRT and challenges the notion that CRT, per se, reduced SCD. However, the delayed separation (after 9 months) of mortality curves ($P = .12$) between the pacing and medical therapy arms in this study raises the possibility of ventricular remodeling trending to improving survival. This is supported by long-term follow-up in CARE-HF. Over a mean follow-up of 29 months, CRT reduced mortality rates from 30% in the medical therapy group to 20% in the CRT group (HR, 0.64; $P < .002$), with a reduction in SCD rates (HR, 0.54; $P = .005$).[44]

Indications for Cardiac Resynchronization Therapy

CRT was originally recommended as heart failure therapy to reduce mortality and morbidity in patients with class III and IV heart failure with markers of ventricular dyssynchrony. For clinical practice purposes, early patient selection criteria are enumerated in Box 86-1. It is important to state that CRT is adjunctive therapy to medical therapy for heart failure and requires careful monitored prescription to achieve benefit. CRT is not a "stand alone" therapy or a "replacement" therapy for medical therapy in patients with heart failure. CRT should always be an additional step in therapy when drug therapy is unable to relieve symptoms or improve quality of life. Medical therapy of heart failure, as it is currently recommended in various guidelines, should be thoroughly tried before CRT is initiated. A careful titration—lasting over months—of angiotensin-converting enzyme inhibitors, β-blocking agents, and diuretic compounds, including aldosterone antagonists, is mandatory and should be continued after initiating CRT. The currently accepted American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) guidelines for CRT device implantations in patients with heart failure are given in Box 86-2.[56]

The recently updated European Society of Cardiology (ESC) guidelines now recommend the use of CRT-D in patients with NYHA class II heart failure, in sinus rhythm, and with QRS duration greater than 150 ms and an LVEF less than 35% to reduce morbidity and prevent disease progression.[57] In patients with atrial fibrillation (AF), CRT should be considered to reduce morbidity in those with NYHA class III or IV heart failure, an LVEF less than 35% on optimal medical therapy, and QRS duration greater than 130 ms, and in those with a slow ventricular rate or in whom AV junctional ablation has been performed to create pacemaker dependency. In patients with indications for pacemaker therapy, CRT is recommended to reduce morbidity in those with class III or IV heart failure, an LVEF less than 35%, and a QRS duration greater than120 ms. It may be considered in patients without a prolonged QRS interval (class IIa indication, but level C evidence).

As currently practiced, CRT is associated with improvement in a majority of properly selected patients. However,

Box 86-1 Patient Selection for Resynchronization Therapy in 2004

Drug-refractory New York Heart Association class III and IV heart failure
Optimal medical treatment with angiotensin-converting enzyme inhibitors, β-blockers, diuretics, and aldosterone antagonists
Ischemic and nonischemic cardiomyopathies
Intraventricular or interventricular conduction abnormality, including left bundle branch block with a QRS duration 130 ms
Left ventricular ejection fraction <35%
Left ventricular end-diastolic diameter 55 mm
Stable sinus rhythm

Box 86-2 Indications for Cardiac Resynchronization Therapy

CLASS I

1. For patients with an LVEF ≤35%, a QRS duration ≥0.12 seconds, and sinus rhythm, CRT with or without an ICD is indicated for the treatment of NYHA functional class III or ambulatory class IV heart failure symptoms with optimal recommended medical therapy.

CLASS IIA

1. For patients with an LVEF ≤35%, a QRS duration ≥0.12 seconds, and AF, CRT with or without an ICD is reasonable for the treatment of NYHA functional class III or ambulatory class IV heart failure symptoms with optimal recommended medical therapy.
2. For patients with LVEF ≤35% and NYHA functional class III or ambulatory class IV symptoms who are receiving optimal recommended medical therapy and who have frequent dependence on ventricular pacing, CRT is reasonable.

CLASS IIB

1. For patients with LVEF ≤35% and NYHA functional class I or II symptoms who are receiving optimal recommended medical therapy and who are undergoing implantation of a permanent pacemaker, ICD, or both with anticipated frequent ventricular pacing, CRT may be considered.

CLASS III

1. CRT is not indicated for asymptomatic patients with reduced LVEF in the absence of other indications for pacing.
2. CRT is not indicated for patients whose functional status and life expectancy are limited predominantly by chronic noncardiac conditions.

nonresponder rates persist in the 30% to 40% range in many series. Methods to improve response include careful optimization of lead position and A-V and V-V interval programming, additional left ventricular lead placement and, in some instances, left ventricular endocardial lead placement. The role of the underlying disease causing heart failure and influencing the outcome of CRT has also been debated. Current data suggest that the use of CRT in coronary artery disease can be as effective as in patients with idiopathic dilated cardiomyopathy of nonischemic origin. More importantly, patient outcome depends on inherent progression of the basic disease process and comorbidities such as diabetes or renal failure.

Cardiac Resynchronization Therapy in Atrial Fibrillation Populations with Heart Failure

The complex association between AF and heart failure, with relationships to both cause and effect, makes this a challenging patient population for CRT therapy. Right ventricular pacing can be deleterious in the AF population, as also seen in the heart failure population, with an increase in AF recurrences as well as in atrial and ventricular dilatation.[58,59] AF prevents normal sequential AV relationships, and rapid intrinsic AV nodal conduction can result in inconsistent delivery of CRT therapy. Thus the true benefits of CRT may not be evident or appreciated in patients with AF. However, the benefits of CRT in this population have been achieved in several studies, as suggested by a recent metanalysis.[60-63] One consistent feature of these studies is achieving a high percentage of bi-ventricular pacing with rate control. Reversion to sinus rhythm or rhythm control with atrial pacing and antiarrhythmic therapy should also be attempted. In MUSTIC-AF, a single-blind, randomized, controlled, crossover study, significant improvement was observed in the 6-minute walk distance (9.3%) and peak oxygen uptake (13%) in patients treated with bi-ventricular pacing compared with those treated with conventional single-chamber ventricular demand (VVIR) pacing. Furthermore, hospitalization decreased by 70% and 85%, respectively, in the two groups during the bi-ventricular pacing period, with patients preferring this mode based on symptoms.[60] AV junction ablation may provide control of ventricular rate for CRT. In clinical trials, the strategy of AV nodal ablation and CRT provided greater benefit in patients with depressed left ventricular function and prevented further deterioration of left ventricular systolic function compared with conventional pacing.[61] AV nodal ablation was independently associated with survival benefit from death (HR, 0.13; 95% confidence interval [CI], 0.03 to 0.58; P = .007) and from combined death, heart transplantation, and left ventricular assisted device (HR, 0.19; 95% CI, 0.06 to 0.62; P = .006) after CRT.[62] The 2010 ESC update and ACC/AHA/HRS guidelines have included CRT therapy for patients with AF and class III or IV refractory heart failure and interventricular conduction delay greater than 130 ms.[57]

Cardiac Resynchronization Therapy in Recipients of Implantable Cardioverter Defibrillators

Prior and current guidelines for ICD implantation in patients with severely depressed ventricular function are also applicable to candidates for CRT.[64,65] Standard ICD indications (secondary or primary prevention of SCD) can also be applied once the patient has become a candidate for CRT. The incremental benefits of CRT-D therapy in candidates for each therapy have been individually debated. Some large clinical trials have looked at these issues. Most recently, the need for early CRT therapy in patients with ICDs has been evaluated by the MADIT-CRT and RAFT studies. Both studies provide evidence of favorable effects of CRT in this population on heart failure events, left ventricular function and, in the RAFT trial, mortality benefits. These benefits were most evident in patients with a QRS duration of greater than 150 ms regardless of the etiology of the cardiomyopathy.

Cardiac Resynchronization Therapy in Patients with Heart Failure and Normal QRS Complex

CRT has now been applied in patients with mechanical dyssynchrony without ventricular conduction delay.[66] Evidence of a consistent beneficial role of CRT in patients with narrow QRS complexes is not evident, despite the observation that some of these patients can have mechanical dyssynchrony. Several small trials and a meta-analysis of some of these trials suggested that CRT resulted in significant improvement in the parameters of NYHA heart failure class, LVEF, and 6-minute walk distance in patients with heart failure, mechanical dyssynchrony, and narrow QRS complexes.[67-72]

However, the Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS (ReThinQ study) did not substantiate the role of CRT in this population.[73] In this large randomized, controlled study, patients who had a standard indication for ICD (ischemic or nonischemic cardiomyopathy with LVEF <35%), NYHA class III symptoms, a QRS duration of less than 130 ms, and evidence of mechanical dyssynchrony measured on echocardiography were enrolled. No improvement was observed with CRT in the endpoints of improvement in peak oxygen consumption, Minnesota Living with Heart Failure

Questionnaire score, 6-minute walk test distance, left ventricular volumes, or LVEF at 6 months.

Cardiac Resynchronization Therapy in Patients with Right Bundle Branch Block

CRT therapy has been attempted in patients with RBBB. Detailed high-resolution invasive electroanatomic mapping of RV and LV activation patterns in the presence of RBBB and LBBB has shown a similar degree of left ventricular activation delay in patients with heart failure and LBBB or RBBB.[41] Patients with RBBB have a larger degree of right-sided conduction delay compared with patients with LBBB. Based on this premise, CRT has been advocated in patients with RBBB and heart failure.[74-76] Earlier data from a single center indicated that only patients with RBBB associated with echocardiographically detected left-sided intraventricular dyssynchrony of a major degree may respond to CRT. In the MIRACLE study, CRT showed functional benefits in patients with RBBB, most of whom also had left anterior hemi-block. A pooled analysis from the MIRACLE and Contak-CD trials demonstrated significant benefit of CRT in patients with RBBB with respect to NYHA class at 6 months. However, concern regarding inconsistent response to CRT in these patients remains and is an area of active investigation.

Technical Aspects of Cardiac Resynchronization Therapy

The complexity of heart failure, which is now seen as an electromechanical disease with neurohormonal features, in patients with intraventricular conduction defect needs unique and alternative technologies for both leads and generators to optimize CRT. New CRT lead technologies and CRT generators, which have been specifically designed for patients with heart failure, have integrated monitoring features and new sensor technologies and require more complex implant procedures and management for optimal benefit. A short description of the principles of CRT device system insertion and technology follows.

Implant Technique

The implantation technique for CRT devices does not differ from the currently used technique for standard pacemakers or ICDs (see Videos 86-1 to 86-6 on the Expert Consult site accompanying this text). The right or left subclavian or cephalic vein approach is used for the insertion of a conventional right atrial and right ventricular lead. An additional lead is required for pacing of the LV. Initially, the left ventricular lead was positioned on the epicardial surface of the left ventricular wall via a small left lateral thoracotomy. Alternative percutaneous techniques have been developed to insert the lead via the coronary sinus into the coronary veins. The left lateral wall is currently stimulated epicardially from the coronary vein. The anatomy of the coronary vein is therefore crucial for correct positioning of the left ventricular lead to achieve the most beneficial effect of resynchronization. The sequence of insertion of the three leads is not standardized and is based on personal experience. However, as most patients requiring CRT devices have significant His-Purkinje dysfunction, including LBBB, they are at a risk of developing complete heart block with catheter and sheath manipulation. In general, we prefer, and recommend, insertion of the active fixation pacing lead with or without defibrillation electrodes in the RV as the initial lead. For placement of the left ventricular lead, a preshaped long introducer or guiding catheter, which stabilizes the lead while introducing it into the coronary sinus, is necessary.[28,32,77-79] Severe dilation of the atrial or ventricular chambers may modify the usual position of the coronary sinus os and its anatomic course, so extensive and prolonged manipulation of the guiding catheter or different approaches may be required.

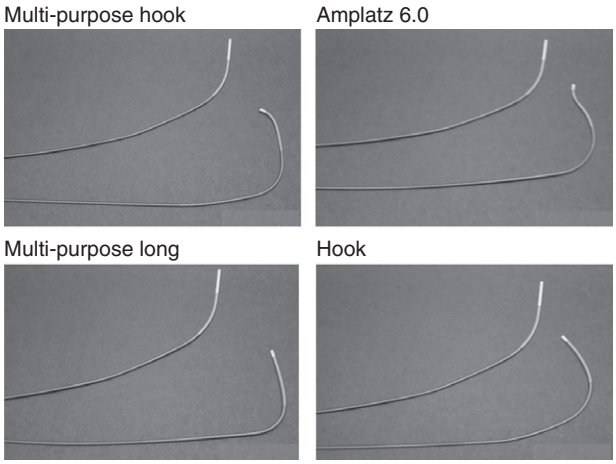

FIGURE 86-3 Guiding catheters specifically designed for insertion into the coronary sinus. A large variety of curves can be appreciated.

We preload the guiding catheter with a flexible 0.038-inch coated guidewire (e.g., Terumo guidewire), which is used for exploring the inferoseptal portion of the right atrium and facilitates the atraumatic insertion of a large (8 to 10 Fr) guiding catheter into the coronary sinus. A series of guiding catheters with different shapes is available to adapt to the anatomic variation of the coronary sinus (Figure 86-3). Other investigators preload the guiding catheter with a steerable catheter used for electrophysiological study (EPS). These catheters have deflecting tips to shape different curves and have been shown to reduce the time to coronary sinus cannulation.[80]

Major obstacles for cannulating the coronary sinus may be a severely dilated right atrium, a thick lamina cribrosa, or a large eustachian valve. We have occasionally seen narrowing of the body of the coronary sinus, usually in patients after previous open heart surgery (e.g., mitral valve surgery). Once the guiding catheter is inserted, occlusive angiography by an inflated large balloon catheter is highly recommended for better evaluation of the coronary vein anatomy (Figure 86-4; see Videos 86-1 and 86-2). Particular attention should be paid when performing balloon occlusion retrograde angiography of the coronary sinus and coronary vein. Inappropriate sizing of the balloon or inflation of the balloon at the most proximal portion of a side vein can produce endothelial damage or extensive intimal lesions, or even rupture of the coronary vein. These dramatic complications are rare—in the range of 1% to 3%. Radiographic examination from at least two different plane views should be performed (right anterior oblique 30 degrees and left anterior oblique 30 to 40 degrees; see Videos 86-3 to 86-6). Additional radiographic examinations (right anterior oblique 25 degrees, caudal 25 degrees, or anteroposterior view) are suggested when a tortuous or small lateral coronary vein

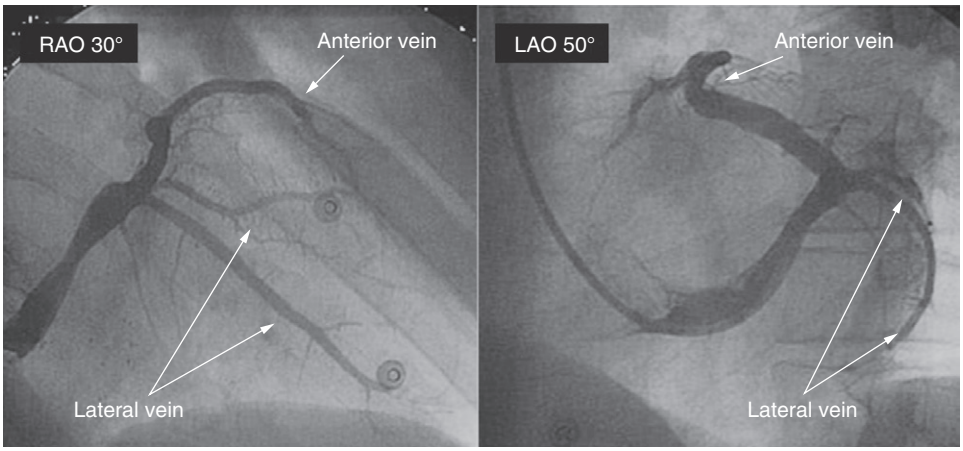

FIGURE 86-4 Selective occlusive angiography of the anterior and lateral coronary vein. *LAO*, Left anterior oblique; *RAO*, right anterior oblique.

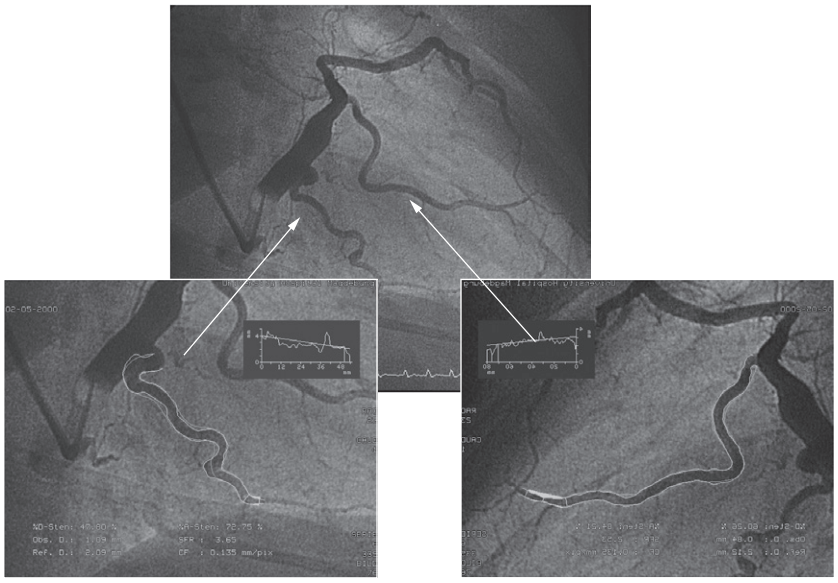

FIGURE 86-5 A tortuous coronary vein anatomy of two lateral veins (*arrows*) can here be appreciated. The sharp take-off of both veins prevented any possibility of inserting either a guidewire or a coronary vein lead.

(<2.5 mm in diameter) is noted (Figure 86-5). If the occlusive balloon is placed more distally in the body of the coronary sinus, it may be necessary to run longer cine loops to adequately visualize the branches (e.g., the middle cardiac and interventricular veins) that drain close to the os. In any instance, multiple views are needed to obtain anatomic delineation with standard techniques.

Alternative methods for performing coronary venography include high-speed rotational angiography. Using one of these methods, a strategy for left ventricular electrode placement should be developed and implemented at the procedure. The ESC has developed a classification for lead placement (Figure 86-6).[28] This classification identifies the location of the left ventricular lead and provides a basis for standardized reporting. Careful examination of coronary vein anatomy often reveals one or more large left ventricular lateral or posterolateral veins. These are the target veins for permanent lead implantation. Investigative interest in left ventricular endocardial pacing is currently growing.[81,82] Hemodynamic advantages have been demonstrated acutely compared with epicardial left ventricular pacing in humans.[81] Improved systolic performance and cardiac output have been noted, and efforts at long-term lead placement are now being reported. However, this technique remains in development for general clinical use at this time.

Lead Technology

Early attempts to pace from the coronary veins were done by using either standard endocardial leads, which were modified for coronary venous placement by removing the tines or used for other coronary sinus techniques.[31,83,84] It was soon realized that specifically designed pacing catheters were necessary to better navigate the coronary sinus and to insert leads into the coronary veins long term. To achieve this, innovative coronary venous lead systems that could incorporate components, accessories, and elements patterned after angioplasty devices were designed (Figure 86-7).

The most promising approach for long-term stimulation of the LV is an over-the-wire pacing lead. This lead has an open lumen lead that tracks over a standard 0.014-inch or 0.010-inch

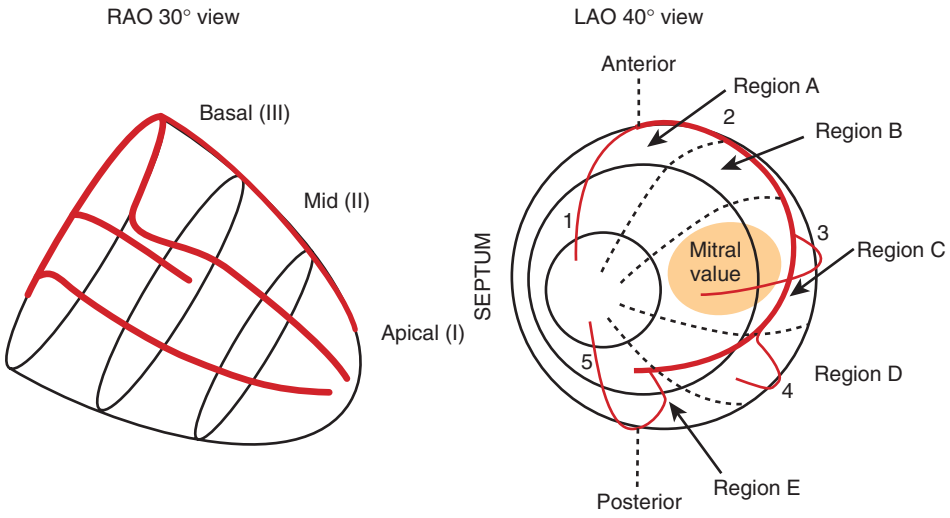

FIGURE 86-6 Proposed classification scheme of left ventricular pacing sites. *Left,* The three segments (apical, mid, and basal) of the left ventricle are shown. *Right,* The left anterior oblique (LAO) view presents the possible venous tributaries of the coronary sinus: *1,* anterior; *2,* anterolateral; *3,* lateral; *4,* posterolateral; and *5,* posterior (middle cardiac vein). Coronary sinus venous anatomy allowing left ventricular lead tip should usually be positioned in a basal/mid-basal lateral (*Region C*) or basal/mid-basal posterolateral (*Region D*) location, avoiding apical regions (too close to the right ventricular lead). (Modified from Vardas PE, Auricchio A, Blanc JJ, et al: Guidelines for cardiac pacing and cardiac resynchronization therapy: The Task Force for cardiac pacing and cardiac resynchronization therapy of the European Society of Cardiology, *Eur Heart J* 28:2256–2295, 2007.)

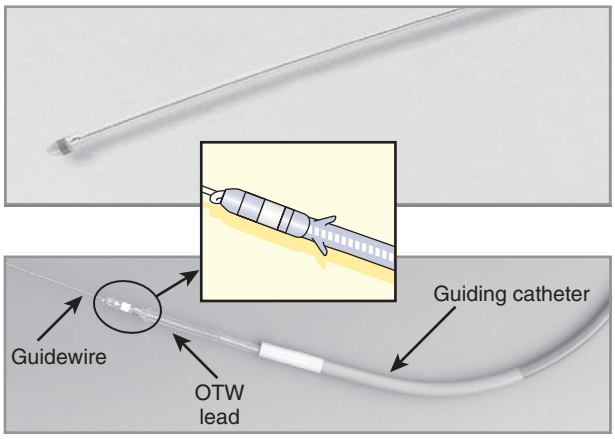

FIGURE 86-7 Two over-the-wire (*OTW*) permanent coronary vein leads.

guidewire to allow access to any coronary vein. Guidewire technology has evolved over the years to provide safe, atraumatic navigation through sharp angles and changes in direction within coronary vessels. As in coronary angioplasty procedures, the implanting physician can select a host of available guidewires to obtain the ideal combination of stiffness, torque, stability, and flexibility required for the individual patient's coronary vein anatomy. The lead incorporates a number of characteristics that allow smooth and safe placement in select vein branches. Because of their particular design, over-the-wire leads usually require a deeper insertion—wedge position—into the coronary vein for a stable chronic implantation.

Extensive experience has now accumulated with over-the-wire lead systems, which are commercially available from most major manufacturing companies (Medtronic, Minneapolis, MN; Boston Scientific, Natick, MA; St Jude Medical, St Paul, MN; and Biotronik, Erlangen, Germany). Successful placement of the coronary vein lead is now possible in the majority of patients within a reasonable time. The over-the-wire design allows a 95% implantation success rate, even when particularly challenging vein anatomy is present (e.g., stenosis of target vein requiring coronary venoplasty) or when repositioning in a second vein is needed.[83,84] If attempts to place a left ventricular lead through the coronary sinus fail, other approaches can be considered. A surgical approach, either minimally invasive or robotically assisted, is usually considered, but in patients who are not candidates for such intervention, a left ventricular endocardial lead placement with a trans-septal approach may be considered.[81,82] In nonresponders to CRT therapy, a second left ventricular lead has been implanted with some success.[85,86] Left ventricular lead dislodgement is an important cause of failed CRT. This may be related to technical factors (e.g., vein-lead size mismatch) or excess lead body slack in the right atrium. It is best detected by a change in the paced QRS morphology and emphasizes the need for a 12-lead ECG during follow-up visits. Lead impedance changes or threshold rise may also herald dislodgement. Programming to retain capture can be attempted if a significant margin of output and threshold for phrenic nerve stimulation are present. Lead repositioning can be attempted, as can the use of a different lead, perhaps with better sizing, or a different vein can be considered, as troubleshooting options.

For sensing, the mean R-wave amplitude at the left ventricular free lateral wall is usually comparable with that achieved in the RV. Pacing impedance and threshold are frequently higher than in the right ventricular apex. Sensing amplitude, pacing threshold and impedance varies from lead to lead, but additional factors such as myocardial viability, fat tissue around the coronary vein, and scar tissue after myocardial infarction affect electrical stability. Unipolar and bipolar stimulation modes have been used, with the latter becoming more prevalent. Thresholds are highly dependent on epicardial contact and electrode configuration, and minor

relocation of the lead may seriously modify thresholds. On occasion, one of two bipolar electrodes may have better thresholds and can be preferentially used.

Monitoring Features of Cardiac Resynchronization Therapy Devices

The monitoring features of pacemakers and ICDs are mainly focused on device-related parameters such as pacing threshold, impedance, and R-wave amplitude. In addition, storage of intracardiac electrograms has been implemented. In addition to these features, hemodynamic monitoring parameters are now available in CRT devices.

Monitoring of Hemodynamic Parameters and Heart Rate

Hemodynamic parameters can be either directly or indirectly monitored via the implanted devices. Specific sensors have been placed on right ventricular leads to detect the maximal positive dP/dT.[87] The accuracy of monitoring long-term hemodynamic changes in patients with heart failure has been evaluated in observational studies and clinical trials.[88,89] Hemodynamic changes can also be indirectly assessed by monitoring heart rate and HRV. Heart rate at rest and during exercise as well as HRV depend on a variety of autonomic mechanisms such as baro-receptor reflex, autonomic feedback, and contractility. Changes in heart rate or HRV can indirectly track spontaneous hemodynamic changes as well as those induced by CRT.

Patients with heart failure present with a significantly reduced HRV and high resting heart rate. Reduced standard deviation measured over the standard deviation of normal-to-normal intervals index has been shown to be associated with left ventricular dysfunction and increased mortality. Because pacemakers and ICDs can measure the intrinsic heart rate and perform beat-to-beat analysis, it is possible to monitor the daily, weekly, or monthly changes of mean heart rate, minimal heart rate, and HRV. A combined plot includes heart rate, HRV, and frequency count, and provides more information than each parameter alone. The automatic, permanent, long-term monitoring capability of one or all of these parameters is helpful in assessing the efficacy of certain medications and for evaluating the therapeutic influence of changes in pacing device programming. It is conceivable that in the future these parameters will allow us to automatically titrate parameters such as AV delay and pacing site and mode that determine the efficacy of CRT. One available device for CRT incorporates three-dimensional plots of heart rate, HRV, and frequency count. Initial experience showed significant changes during the first 12 weeks after the implantation compared with the preimplantation status (Figure 86-8). Whether changes in HRV really reflect improvement in patients with heart failure and whether they are associated with lower overall mortality rates remain to be determined.

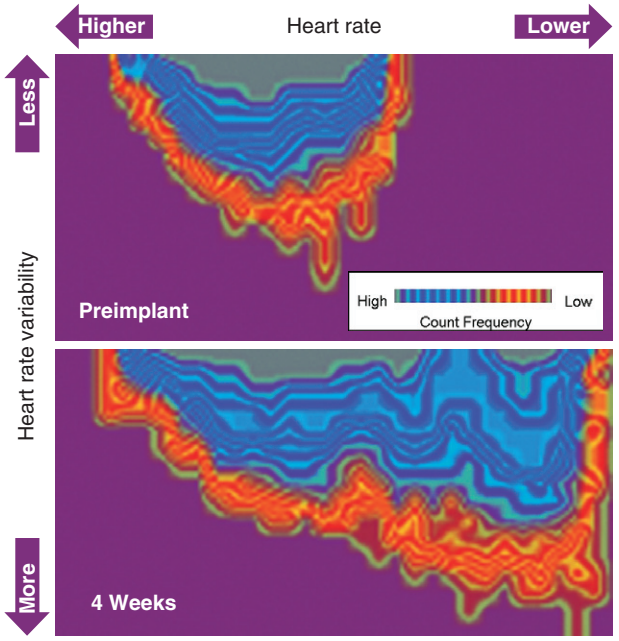

FIGURE 86-8 Three-dimensional plot of heart rate variability and heart rate before implantation of a cardiac resynchronization therapy (CRT) device and after 12 weeks of continuous pacing. At baseline, a markedly depressed heart rate variability was noted as well as a high resting heart rate. After CRT, the heart rate variability largely increased and the heart rate was greatly reduced, thus leading to a rightward shift of the plot.

Pulse Generators in Cardiac Resynchronization Therapy

The introduction of sophisticated sensors, new monitoring features, and innovative lead technology required substantial changes in the software and hardware of devices specifically designed for providing CRT. All the currently available CRT systems from different manufacturers have independent pacing outputs for each of the paced chambers, and some even provide independently programmable AV delay for the RV and the LV along with variable interventricular delay (VV timing).

Programmable features such as negative hysteresis allow the device to shorten the paced AV delay upon detection of conducted rather than bi-ventricular paced beats and enhance CRT pacing. Similarly, new pacing algorithms such as ventricular rate regularization (VRR) allow the device to override intrinsic rhythm through faster but regular ventricular pacing to enable continuous and uninterrupted bi-ventricular pacing during AF.[90,91]

Follow-up and Programming Issues

The follow-up of patients with a CRT device is more complex and time intensive than a standard pacemaker or ICD check-up.[92] The follow-up visit of the patient with heart failure includes testing of each of the three leads, careful evaluation of the AV delay, guarantee of a high percentage of CRT therapy delivery, and assessment of the maximal tracking rate. Correlation with patient symptoms, heart failure status, and device-monitored event data is important to a comprehensive follow-up. The use of new hybrid CRT-D devices initially posed special technologic challenges. In the first generation of CRT devices (Contak-TR, Guidant Corporation, Minneapolis, MN; and InSync, Medtronic), the two ventricular outputs were electrically connected (i.e., parallel pacing of the RV and LV was present). All electrical parameters (i.e., pacing threshold and R-wave sensing) were the algebraic sum of each of the two ventricles. Pacing threshold was indirectly measured by monitoring the ECG signals and changes in the axis orientation as well as the QRS duration (Figure 86-9). Because the LV often presents with a higher pacing threshold, a sudden change of the axis orientation from a superior rightward orientation to a

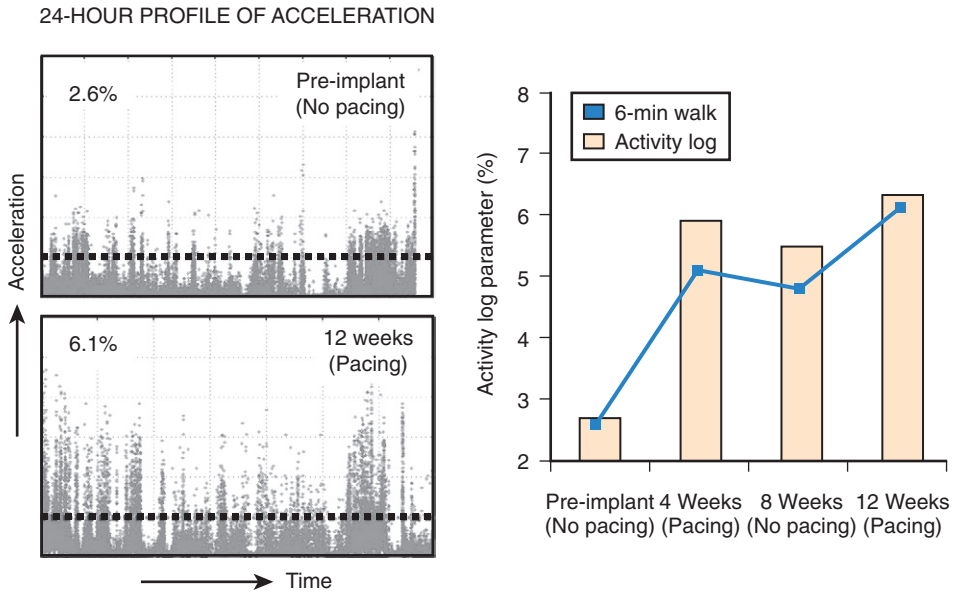

FIGURE 86-9 Changes in the activity log index in a patient with a cardiac resynchronization therapydevice. The changes in the activity log index correlated well with distance walked during 6 minutes of testing.

superior leftward rotation with only right ventricular pacing can be noted (see Figure 86-9). A change in the duration of the QRS complex is easy to recognize. Programming the pacing output to at least twice pacing threshold is strongly recommended because a rise of left ventricular pacing threshold is not unusual during the first few weeks after implantation. The most recent generation of devices for CRT has independently programmable ventricular and atrial channels so that most of these technical issues have been solved (Figure 86-10). The new-generation devices yield separate output programming for each of the three leads and also automatically perform continuous electrical measurements. A high percentage of CRT therapy requires greater than 85% left ventricular pacing, biventricular pacing, or both. This information is generally available in device datalogs.

Atrioventricular and Interventricular Delay Optimization

To achieve the full benefit of CRT, it is necessary to improve left-sided AV synchronization, which can also reduce concomitant existing mitral regurgitation. Thus it is preferable that the patient can maintain sinus rhythm or an atrial-paced rhythm. Atrial pacing also may be necessary because of the use of high-dose β-blocker therapy in these patients. However, programming the optimal AV delay during atrial pacing in patients with heart failure has not been fully investigated. Cardiac resynchronization is achieved with either atrial synchronous bi-ventricular pacing or left ventricular pacing and leads to early hemodynamic and long-term functional improvement in patients with moderate to severe systolic heart failure. An important issue for VV delay optimization during follow-up visits is whether narrowing of the QRS complex during bi-ventricular pacing alone should be pursued. Some early reports indicated a relationship between narrowing QRS and clinical benefit. Acute hemodynamic data and limited electrophysiological evaluations, however, do not support this observation. A good example of this still unresolved controversy is given by the abnormal QRS duration, usually larger than the baseline, and the positive short- and long-term effects (comparable with bi-ventricular pacing) during left ventricular pacing alone.

Echocardiographic measurements of the most suitable AV delay are usually performed. Preload optimization methods, such as evaluation of the relationship of the E and A waves with respect to ventricular systolic contraction, may not be necessarily as precise as once thought. Improvement of systolic pump function in patients receiving a CRT device is both preload (AV optimization) and non-preload dependent (improvement of ventricular synchrony), the echocardiographic optimization of the AV delay may lead to the selection of an AV delay that is longer than the AV delay, resulting in the maximal pulse pressure that can be achieved. Continuous adjustment of the AV delay is rarely required over the follow-up for patients with QRS duration greater than 150 ms. This is caused by the flat increase of pulse pressure while changing the AV delay within the range of 70 to 150 ms. Minor adjustment, however, may not be relevant in this specific subgroup of patients, and A-V interval optimization may be performed by echocardiographic methods of preload (E and A waves). In contrast, in patients with a narrow QRS complex (120 to 150 ms), the hemodynamically determined optimal AV delay is very close to the intrinsic value. For this reason, optimization methods that use preload-dependent parameters only may not be effective. It may be more suitable to optimize the degree of ventricular resynchronization (A-V and V-V intervals) by following changes in either left ventricular volumes and EF or tissue Doppler imaging of ventricular wall motion synchrony, rather than measuring preload.[28,30] Recently, intracardiac echocardiography has been used to guide this with the use of global LVEF measured on two-dimensional imaging.[30] Three-dimensional echocardiographic assessment of ventricular stroke volume and chamber volumes may hold promise in this regard.

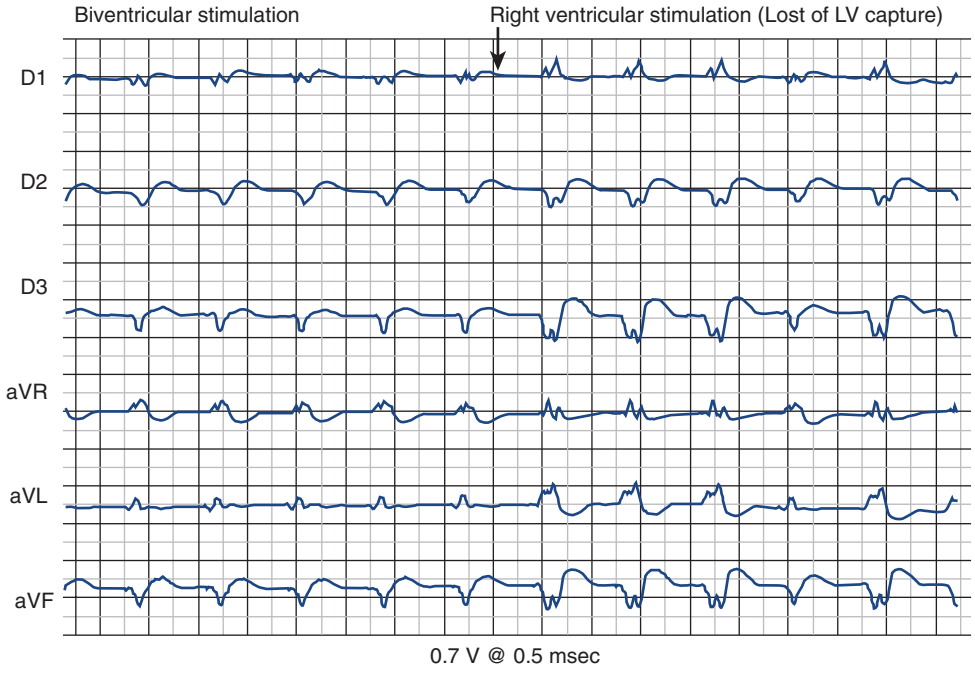

FIGURE 86-10 Evaluation of the pacing threshold in a patient with a first-generation cardiac resynchronization therapy (CRT) device. In this device (Contak-TR, Guidant Corporation), the ventricular outputs are electrically connected in parallel in the header of the device. There is no other way to determine the pacing threshold of each chamber than to progressively reduce the output while recording the electrocardiogram. The sudden loss of left ventricular (*LV*) capture is characterized by a change in the QRS duration and axis orientation.

Evaluation of the Maximal Tracking Rate of Physical Activity

Patients with heart failure have a significantly reduced exercise capacity because of limited pump efficacy, impaired systemic hemodynamics, altered muscular activity, and alteration of metabolic demand. The 6-minute walk test has been used to assess the submaximal exercise capacity of patients with heart failure.[93] Although the walk distance in patients with heart failure has been shown to predict overall mortality and the need for hospitalization, the walking distance can be monitored only periodically and may be influenced by several factors, including patient motivation, coaching, familiarity with the test, and physical limitations.[94] Variabilities in the walking distance between two subsequent tests are not unusual in patients with heart failure.[95] A more objective measurement of the functional capacity that is continuous, unbiased, and based on activities of daily living will be necessary in the future. In this regard, continuous recording of accelerometer signals, reflecting the patient's physical activity, is already used in pacemakers and ICDs. Experience with recording of patient activity tracked by accelerometer has shown that activity monitored by accelerometers or activity log index (ALI) is highly sensitive and specific in detecting the patient's physical activity.[96] Studies have demonstrated that the ALI increased substantially when CRT was applied in a blinded fashion. The magnitudes of ALI change significantly and correlate with the change in the walking distance measured with 6-minute walk testing (Figure 86-11).

To provide continuous resynchronization therapy at rest as well as during exercise, careful assessment of heart rate during physical activity above the anaerobic threshold is important during the follow-up of patients with CRT. We perform a symptom-limited exercise testing before and 1 month after the implantation of a CRT device in all patients. Almost all patients with severe heart failure demonstrated a high resting heart rate and chronotropic incompetence, with a markedly reduced heart rate reserve during exercise. CRT increases both maximal and submaximal exercise capacities and improves ventilation efficiency and heart rate adaptation during physical activity. When the patient's heart rate overrides the maximal tracking rate of the device, an immediate loss of pre-excitation of the left ventricular lateral wall, together with a drop in stroke volume, can be measured (Figure 86-12). A loss of CRT leads to dyspnea and fatigue. Thus sudden loss of CRT during exercise may prevent the patient from otherwise beneficial physical activity.

Assessment of Device Datalogs

Current-generation devices provide a large body of data that should be interrogated and assessed at follow-up. In the recently completed Program to Access and Review Trending Information and Evaluate Correlation to Symptoms in Patients with Heart Failure (PARTNERS-HF) study, routine device diagnostics were evaluated for their value in prevention of heart failure hospitalizations.[97] A combined diagnostic algorithm based on eight elements (trans-thoracic impedance, activity status, AF, ventricular rate during AF, heart rate, HRV, CRT, and shock delivery) was used. Development of abnormalities in two or more of these parameters was highly predictive of subsequent heart failure hospitalizations (HR, 4.8). Increasing patient inactivity, impedance changes beyond prespecified threshold values, and reduced HRV were important trends in predicting events. More frequent assessment

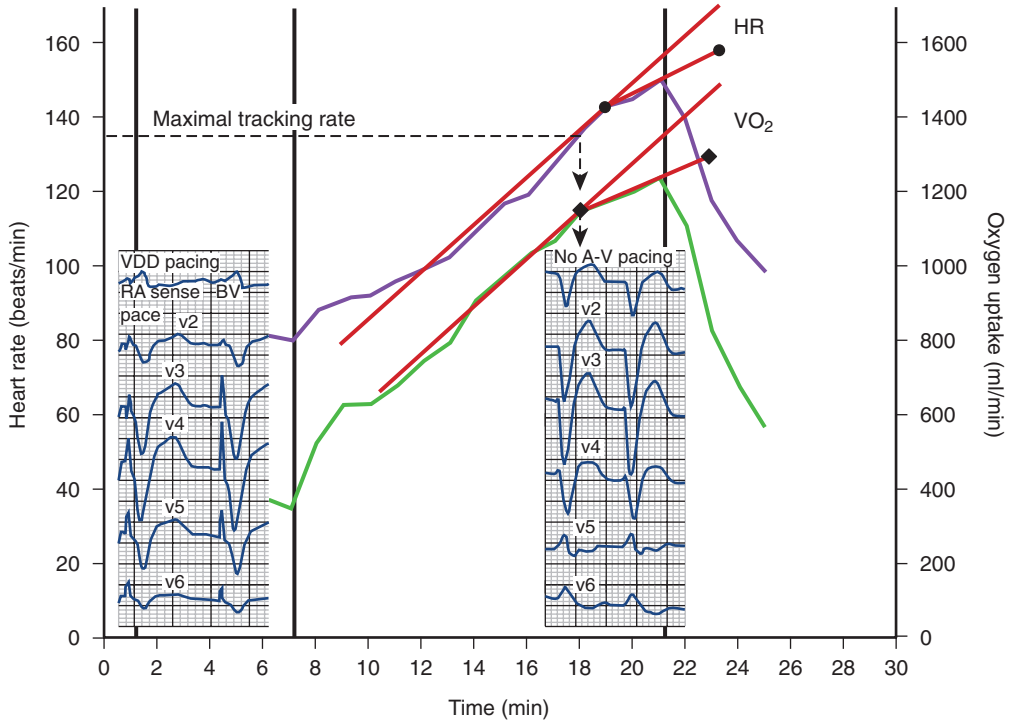

FIGURE 86-11 Loss of cardiac resynchronization therapy (CRT) at the maximal atrial tracking rate (135 beats/min) of the device causes an immediate drop in the continuous increase of heart rate and oxygen pulse in a patient with dilated cardiomyopathy. A 1:1 atrioventricular bi-ventricular stimulation (atrium sensed both ventricles paced) is attained throughout the exercise testing. Note the parallel increases of both heart rate and oxygen consumption. As soon as the sensed atrial rate reaches the maximal tracking rate of the device (*dashed line,* 135 beats/min in this patient), no CRT is evident as demonstrated by absence of the ventricular spike with sudden prolongation of the P-R interval and QRS duration. The oxygen consumption immediately dropped (*continuous thick line*). Also, the increase of heart rate (*continuous thin line*) was less pronounced than before the 1:1 synchrony. Drops of the systolic and diastolic blood pressure levels were also observed within several seconds. The exercise testing had been stopped within a few minutes after the loss of the 1:1 AV tracking sequence because of sudden onset of dyspnea and fatigue.

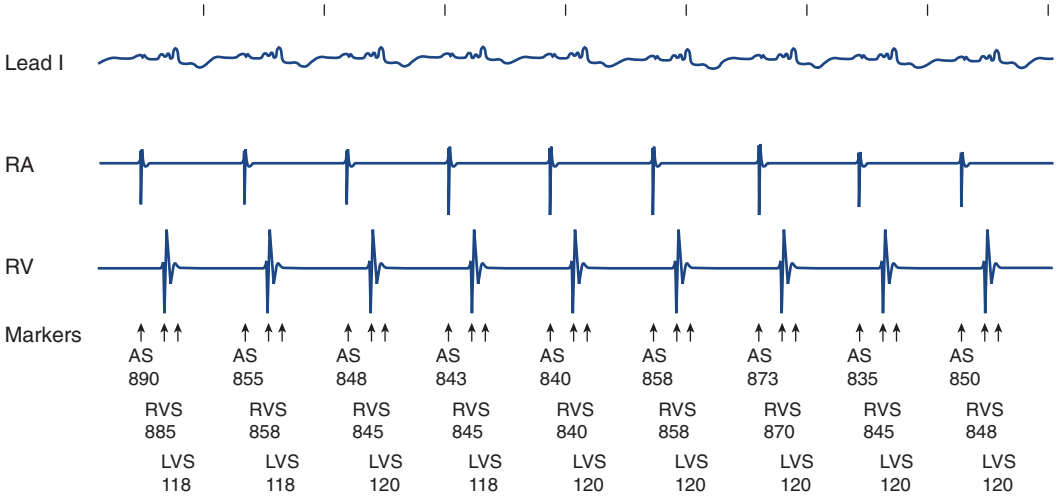

FIGURE 86-12 Printout of an early implantable cardioverter-defibrillator cardiac resynchronization therapy device (Renewal II, Guidant Corporation). Simultaneous intracardiac recording of the atrium and of both ventricles. Annotation markers help in correct classification of the device sensing. *RA*, Right atrium; *RV*, right ventricle.

(every 15 days) was more effective than longer periods (30- or 90-day intervals).

Future Developments

Evidence of long-term pacing for bradycardia at the right ventricular apex being associated with structural changes of the heart, and in some patients probably with the induction of heart failure, is growing. Interest in the hemodynamic effect of the "abnormal" sequence of activation induced by ventricular pacing is increasing as well.[98] Animal studies have shown that long-term changes during continuous right ventricular pacing include asymmetric ventricular hypertrophy and dilation, myocardial fiber disarray, increased myocardial catecholamine concentration, and impaired perfusion.[99] The long-term effect of such a heterogeneous distribution of stretch and workload may be responsible for triggering maladaptation mechanisms that might lead to decreases in pump function, pump failure, or progression of pre-existing heart failure.[100] CRT can potentially reduce, or perhaps normalize, the spatio-temporal distribution of activation and restore the mechanical synchrony of contraction. Recent animal studies have shown that bi-ventricular stimulation, compared with right ventricular pacing, reduced the temporal asynchrony and the spatio-temporal asynchrony of the left ventricular midwall contraction.[99,101] Ventricular function is restored to baseline levels after induction of LBBB by radiofrequency ablation of the left bundle.[102] These data, however, have been generated in healthy canine hearts, which may differ from a diseased human heart. Whether patients in need of standard pacemaker therapy should undergo conventional, biventricular, or left ventricular pacing is an issue that remains to be resolved and deserves further research. Early clinical trials have been suggestive but not conclusive.[103,104]

Important and challenging questions concerning optimizing CRT therapy remain. One of the most important issues is whether electrocardiographic evidence of LBBB is an ideal selection criterion for patients with heart failure who are candidates for CRT.[105] Indeed, increasing evidence points to the presence of mechanical evidence of dyssynchrony as the major basis for CRT intervention, although current indexes may not be ideal.[106] This will need serious study in the future. The optimal site of CRT electrodes will then become open to examination. CRT could therefore be applied in two or more sites in either ventricle. In fact, newer techniques with minimally invasive and robotic lead epicardial placement can make this a reality and are important avenues of future research.[107] Future studies are likely to address the impact of disease progression, optimal timing of intervention, new approaches to CRT, and widening patient populations. CRT has become an important modality in the treatment of heart failure syndromes and its application will continue to increase in the foreseeable future.

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CHAPTER 87

Prevention of Sudden Cardiac Death with Implantable Cardiac Defibrillators and Cardiac Resynchronization Therapy

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Introduction

Sudden cardiac death (SCD) can be defined as cessation of myocardial function within 1 hour of the onset of symptoms. Cardiac arrest leading to SCD is usually assumed to be caused by ventricular tachycardia (VT) or ventricular fibrillation (VF). However, SCD occurs from other causes, including bradycardia, pulmonary embolus, aortic dissection, and other noncardiac conditions. In the United States, SCD is the leading single cause of death and the second leading cause of death after all cancers combined.[1] It claims nearly 325,000 lives annually, accounting for one death every 97 seconds. Globally, it accounts for more than 3 million deaths each year. Only 5% of the victims of SCD survive; for every minute in SCD without defibrillation, the mortality rate rises by as much as 10%.[2,3] The average arrival time for the typical first responder after collapse is 7 to 8 minutes or even longer.[4] Of those who survive to hospital admission, only 3% to 28% are ultimately discharged.[5] In 1947, thoracic surgeon Claude Beck was credited as being the first individual to use a cardiac defibrillator successfully when he saved a 14-year-old boy who developed intraoperative VF during thoracic surgery.[6] Before the advent of implantable devices, the mainstay of therapy to reduce the incidence of ventricular arrhythmias was primarily with Vaughan Williams class I and III antiarrhythmic drugs (AADs). However, these drugs have consistently failed to show a benefit in reducing SCD. More than 30 years later, in 1980, Mirowski and Mower were instrumental in developing the first implantable cardioverter-defibrillator (ICD) for humans.[7] Today, rapid defibrillation is the sine qua non of therapy aimed at restoration of a stable rhythm in those in VT or VF. Additional reductions in the incidence of SCD among high-risk patients are observed with the appropriate use of β-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), aldosterone antagonists, aspirin, and statins. Initially, multiple randomized clinical trials proved that ICDs were superior to standard medical therapy, including AADs, in the secondary prevention of SCD.[8-12] For primary prevention of SCD in several high-risk patient groups, ICDs have also been shown to be superior to optimal medical therapy (OMT) (Table 87-1).[13-18] In high-risk patients with prolonged intraventricular conduction and progressive heart failure, biventricular pacing with or without ICD backup has been proven to offer additional benefit. Several well-designed clinical trials have shown reduction in SCD and all-cause mortality with cardiac resynchronization therapy (CRT) with or without the addition of cardioverter defibrillator capability.[18-21] As with all clinical trials, interpretation of results must be viewed in the context of the patient population studied and the study design in each particular trial. Therefore, this review provides an in-depth summary of the role of ICDs and CRT with or without ICD in the primary and secondary prevention of SCD. Box 87-1 outlines current guidelines for ICD therapy.

Implantable Cardioverter-Defibrillators and Secondary Prevention of Sudden Cardiac Death

Secondary prevention of SCD can be defined as that achieved in those patients who had a previous episode of resuscitated ventricular tachyarrhythmia. The Antiarrhythmics Versus Implantable Defibrillators (AVID) trial, which was published in 1997, was the first of its kind to show that in survivors of VF or sustained ventricular tachycardia causing severe symptoms, an ICD was superior to AADs in increasing overall survival.[8] AVID was a multi-center, randomized comparison of single-lead ICD versus amiodarone or, in a few instances, sotolol. The devices used in the trial were single-lead transvenous devices with tiered therapy, defibrillation, cardioversion, bradycardia pacing, and antitachycardia pacing (ATP) capabilities. A device without ATP was permitted only if a thoracotomy was otherwise required for device implantation.[22] Patients were required to be clinically acceptable for amiodarone therapy to be included in the study. Key inclusion criteria were a history of ventricular arrhythmia as described above and, if VT was the index arrhythmia, an ejection fraction (EF) of 40% or greater. Exclusion criteria were designed to limit the study to patients at high risk for SCD but with life expectancy of greater than 1 year. Key exclusions were New York Heart Association (NYHA) class IV heart failure, inotropic or mechanical support, less than 5 days from revascularization or acute myocardial infarction (AMI), atrial fibrillation (AF), and SCD with a transient or correctable cause. Patients who had transient or reversible causes of SCD and otherwise would have met inclusion criteria were enrolled in a separate AVID registry.

In the AVID trial, 1885 patients were eligible, and of those, 1016 were randomized. The index arrhythmia was VT in 55% of patients. Patients included in AVID had a mean (± standard deviation) EF of 0.32 ± 0.13. More than 90% of patients had NYHA

Table 87-1 Major Implantable Cardioverter-Defibrillator Trials for Prevention of Sudden Cardiac Death

TRIAL	YEAR	NO. PATIENTS	INCLUSION CRITERION: LVEF VALUE	OTHER INCLUSION CRITERIA	HAZARD RATIO*	95% CI	*P* VALUE
MADIT[13]	1996	196	≤35	NSVT and positive EPS	0.46	0.26–0.82	.009
MADIT-II[14]	2002	1232	≤30	Prior MI	0.69	0.5–0.93	.016
MUSTT[15]¶	1999	704	≤40	Asymptomatic NSVT and positive EPS	0.24	0.13–0.45	<.001
DEFINITE[16]	2004	485	≤35	NICM, PVCs, or NSVT	0.65	0.40–1.06	.08
DINAMIT[52]	2004	674	≤35	6 to 40 days after MI and impaired HRV	1.08	0.76–1.55	.66
SCD-HeFT[17]	2005	1676	≤35	Prior MI or NICM	0.77	0.62–0.96	.007
AVID[8]	1997	1016	≤40	Prior cardiac arrest	0.62	0.43–0.82	<.02
CASH[10]†	2000	191	mean, 45 ± 18 at baseline	Prior cardiac arrest	0.77	1.112‡	.081§
CIDS[9]	2000	659	≤35	Prior cardiac arrest, syncope	0.82	0.60–1.10	NS

EPS, *Electrophysiological study;* HRV, *heart rate variability;* LVD, *left ventricular dysfunction;* LVEF, *left ventricular ejection fraction;* MI, *myocardial infarction;* NA, *not applicable;* NICM, *nonischemic cardiomyopathy;* NS, *not statistically significant;* NSVT, *nonsustained ventricular tachycardia;* PVCs, *premature ventricular complexes;* SAECG, *signal-averaged electrocardiogram.*

**Hazard ratios for death from any cause in the implantable cardioverter-defibrillator (ICD) group compared with the non-ICD group.*

†Includes only ICD and amiodarone patients from CASH.

‡Upper bound of 97.5% confidence interval.

§One-tailed.

¶Designed to test electrophysiology study as means of risk stratification for sudden cardiac death.

class II heart failure or less. The ICD arm contained patients with a slightly higher EF (0.32 ± 0.13 vs. 0.31 ± 0.13). This difference was primarily attributable to differences in EF in the subgroup with VF (0.36 ± 0.15 vs. 0.33 ± 0.15). Two thirds of the patients were taking ACE inhibitors, and patients in the ICD arm were four times more likely to be taking a β-blocker. The complication rate of implantation was 5.6%, which was lower than in previous studies. At 18 months, the trial was stopped prematurely after a 31% relative reduction in mortality rate was seen in the ICD arm. After a 3-year follow-up, 39%, 17%, and 31% reductions in mortality rate was seen at 1, 2, and 3 years, respectively. This translated into an average improvement of life expectancy of 2.7 months. However, the increase in life expectancy is likely underestimated because follow-up was only done over 18 months.

Stratified regression analysis of the results from the AVID registry suggested that the differences in outcomes in the two arms attributable to differences in baseline patient characteristics only accounted for 8% of the relative reduction in the primary endpoint. The imbalance in β-blocker use in the ICD arm was examined by Cox regression analysis, and it was found that this imbalance reduced the beneficial effect of ICD only minimally (unadjusted hazard ratio [HR] for the ICD group of 0.62 compared with adjusted HR of 0.67). The benefit of β-blocker use in congestive heart failure (CHF) has been shown to reduce mortality rate in similar patients in other studies.[5] However, an additional benefit may have been observed in patients with paroxysmal AF or sustained VT by reducing inappropriate shocks. Patients in AVID with an index event of VT were more likely to receive shocks or ATP during follow-up. Further retrospective subgroup analysis showed several interesting findings. When the outcomes of those with a left ventricular EF (LVEF) of 35% or less were compared, ICD conferred a 40% relative mortality rate reduction. Of the patients, 39% had an EF less than 35% to 40%. In this subgroup, no statistical benefit in reducing overall mortality rate was observed in the ICD arm.[23] The lack of significant mortality benefit may have been caused by a protective effect of amiodarone in this specific population. Previous observational studies have suggested that amiodarone may have a weak protective effect in preventing arrhythmic death and that this benefit may be more significant in patients with higher LVEF.[24-26] Spielman et al found that in patients with recurrent sustained VT, higher LVEF and the absence of left ventricular aneurysm or hypokinesis were associated with VT suppressibility.[27] In the amiodarone group, survival was strongly correlated with left ventricular systolic function.[28] A retrospective analysis of the data from AVID attempted to identify subgroups that had secondary prevention the lowest rates of recurrent ventricular arrhythmias.[29] The criteria were VF as the index event, no history of cerebrovascular disease, greater EF, no tachyarrhythmia history, and need for revascularization. Taken together, these findings suggested that important electrophysiological differences exist between these two patient populations.

As previously mentioned, patients screened for AVID but excluded for various reasons were enrolled in a registry. In the AVID registry, after adjusting for multiple variables, patients with transient reversible causes of SCD such as electrolyte abnormalities, new ischemia or infarction, and proarrhythmic drug adverse events actually had poorer outcomes compared with those with primary VT or VF. Patients who were excluded because they had VT that was hemodynamically stable had an overall prognosis similar to that of the patients included in the trial with unstable or pulseless VT.[30] These findings argue against the commonly held belief that those with reversible causes of SCD or stable VT have a better prognosis and may not benefit from ICD implantation. Perhaps other clinical characteristics such as the presence of heart failure, stroke, ischemia, or left ventricular dysfunction may be more important discriminators of risk stratification of SCD.

Box 87-1 ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy for Prevention of Ventricular Arrhythmias

CLASS I

- ICD therapy is indicated in patients who are survivors of cardiac arrest caused by VF or hemodynamically unstable sustained VT after evaluation to define the cause of the event and to exclude any completely reversible causes. *(Level of Evidence: A)*
- ICD therapy is indicated in patients with structural heart disease and spontaneous sustained VT, whether hemodynamically stable or unstable. *(Level of Evidence: B)*
- ICD therapy is indicated in patients with syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced at electrophysiological study. *(Level of Evidence: B)*
- ICD therapy is indicated in patients with LVEF less than 35% caused by prior MI at least 40 days after MI and are in NYHA functional class II or III. *(Level of Evidence: A)*
- ICD therapy is indicated in patients with NIDCM who have an LVEF of 35% or less and who are in NYHA functional class II or III. *(Level of Evidence: B)*
- ICD therapy is indicated in patients with left ventricular dysfunction caused by prior MI at least 40 days after MI, have an LVEF less than 30%, and are in NYHA functional class I. *(Level of Evidence: A)*
- ICD therapy is indicated in patients with NSVT caused by prior MI, LVEF less than 40%, and inducible VF or sustained VT at EPS. *(Level of Evidence: B)*

CLASS IIA

- ICD implantation is reasonable for patients with unexplained syncope, significant left ventricular dysfunction, and NIDCM. *(Level of Evidence: C)*
- ICD implantation is reasonable for patients with sustained VT and normal or near-normal ventricular function. *(Level of Evidence: C)*
- ICD implantation is reasonable for patients with HCM who have one or more major risk factors for SCD. *(Level of Evidence: C)*
- ICD implantation is reasonable for the prevention of SCD in patients with ARVD/ARVC who have one or more risk factors for SCD. *(Level of Evidence: C)*
- ICD implantation is reasonable to reduce SCD in patients with long QT syndrome with syncope, VT, or both while taking β-blockers. *(Level of Evidence: B)*
- ICD implantation is reasonable for nonhospitalized patients awaiting transplantation. *(Level of Evidence: C)*
- ICD implantation is reasonable for patients with Brugada syndrome who have had syncope. *(Level of Evidence: C)*
- ICD implantation is reasonable for patients with Brugada syndrome who have documented VT that has not resulted in cardiac arrest. *(Level of Evidence: C)*
- ICD implantation is reasonable for patients with catecholaminergic polymorphic VT who have syncope, documented sustained VT, or both while taking β-blockers. *(Level of Evidence: C)*
- ICD implantation is reasonable for patients with cardiac sarcoidosis, giant cell myocarditis, or Chagas disease. *(Level of Evidence: C)*

CLASS IIB

- ICD therapy may be considered in patients with nonischemic heart disease who have an LVEF of 35% or less and who are in NYHA functional class I. *(Level of Evidence: C)*
- ICD therapy may be considered for patients with long QT syndrome and risk factors for SCD. *(Level of Evidence: B)*
- ICD therapy may be considered in patients with syncope and advanced structural heart disease, in whom thorough invasive and noninvasive investigations have failed to define a cause. *(Level of Evidence: C)*
- ICD therapy may be considered in patients with a familial cardiomyopathy associated with SCD. *(Level of Evidence: C)*
- ICD therapy may be considered in patients with left ventricular noncompaction. *(Level of Evidence: C)*

CLASS III

- ICD therapy is not indicated for patients who do not have a reasonable expectation of survival with an acceptable functional status for at least 1 year, even if they meet ICD implantation criteria specified in the class I, IIa, and IIb recommendations above. *(Level of Evidence: C)*
- ICD therapy is not indicated for patients with incessant VT or VF. *(Level of Evidence: C)*
- ICD therapy is not indicated in patients with significant psychiatric illnesses that may be aggravated by device implantation or that may preclude systematic follow-up. *(Level of Evidence: C)*
- ICD therapy is not indicated for NYHA class IV patients with drug-refractory congestive heart failure who are not candidates for cardiac transplantation or CRT-D. *(Level of Evidence: C)*
- ICD therapy is not indicated for syncope of undetermined cause in a patient without inducible ventricular tachyarrhythmias and without structural heart disease. *(Level of Evidence: C)*
- ICD therapy is not indicated when VF or VT is amenable to surgical or catheter ablation (e.g., atrial arrhythmias associated with the Wolff-Parkinson-White syndrome, right or left ventricular outflow tract VT, idiopathic VT, or fascicular VT in the absence of structural heart disease). *(Level of Evidence: C)*
- ICD therapy is not indicated for patients with ventricular tachyarrhythmias caused by a completely reversible disorder in the absence of structural heart disease (e.g., electrolyte imbalance, drugs, or trauma). *(Level of Evidence: B)*

ACC/AHA/HRS, American College of Cardiology/American Heart Association/Heart Rhythm Society; ICD, implantable cardioverter-defibrillator; VF, ventricular fibrillation; VT, ventricular tachycardia; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; NIDCM, nonischemic dilated cardiomyopathy; NSVT, nonsustained ventricular tachycardia; EPS, electrophysiology study; SCD, sudden cardiac death; HCM, hypertrophic cardiomyopathy; ARVD/ARVC, arrhythmogenic right ventricular dysplasia or cardiomyopathy; CRT-D, cardiac resynchronization therapy with defibrillation.

Modified from 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, J Am Coll Cardiol *51(21):e1–e62, 2008.*

The Canadian Implantable Defibrillator Study (CIDS), which published results in 2000, included a similar study population as AVID. A total of 659 patients were eligible for the study if, in the absence of recent AMI (≤72 hours) or electrolyte abnormalities, they had the following: (1) a history of cardiac arrest, (2) documented sustained VT or VF, (3) sustained VT of at least 150 beats/min, or (4) unmonitored syncope, with depressed LVEF and inducible sustained monomorphic ventricular arrhythmia by programmed ventricular stimulation. Key exclusion criteria were (1) likely survival for less than 1 year, (2) physician discretion against amiodarone or ICD, (3) excessive perioperative ICD implantation risk, (4) previous amiodarone therapy for 6 weeks or more, and (5) long QT syndrome. Patients were randomized to ICD or amiodarone with prespecified stratification by LVEF of 35% or less or greater than 35%. Patients randomized to ICD received a device capable of bradycardia pacing, ATP, cardioversion, and defibrillation. Approxmately 90% of leads were implanted via the transvenous approach, with only 33 undergoing thoracotomy. The primary endpoint was all-cause mortality, and the secondary endpoint was arrhythmic death. Nearly half the patients had VF or

cardiac arrest. Similar to AVID, 89% of patients had NYHA class II or less heart failure but, unlike AVID, the population included a small cohort with NYHA class IV heart failure. Ischemic cardiomyopathy was present in 83%. At hospital discharge, β-blockers other than sotolol were prescribed for only 21.4% of patients in the amiodarone arm and 33.5% in the ICD arm, with these differences remaining through follow-up. Less than 10% of the patients were taking class I AADs. However, class I AADs were four times as likely to be used in the ICD arm and have since been shown to increase mortality rate in this patient population.[31] Mean duration of follow-up was 2.9 years and 3 years in the amiodarone and ICD cohorts, respectively.

At the conclusion of CIDS, the ICD arm had a nonsignificant reduction in the primary endpoint of all-cause mortality from 10.2% to 8.3% ($P = .142$). The reduction in all-cause mortality was primarily attributed to a trend toward reduction in arrhythmic death from 4.5% per year to 3% per year, which translated into a 32.8% relative risk (RR) reduction ($P = .094$). This increases the likelihood that this trend may have been caused by a real benefit from the ICD. Retrospective analysis of the data from CIDS also revealed that differences in patient characteristics might explain the lack of statistically significant differences in outcomes. When examined on the basis of prespecified stratification by LVEF, those with an LVEF less than 35% had a small, nonsignificant trend toward worse outcomes compared with those with lower LVEF. The highest risk patients, defined as those with EF less than 35%, NYHA class III or IV, and age older than 70 years, together had a 50% relative reduction in mortality rate. Patients without one or more of these high-risk features received no benefit from ICD implantation.

The observed risk reduction in CIDS was less than that of AVID, although both trials were similarly designed. However, substantial overlap exists in the confidence intervals (CIs) of the two studies, suggesting that the results are likely similar. At 1 year, 23.7% of those in CIDS in the AAD arm were taking a β-blocker (including sotolol), which was greater than the 16.8% in AVID. The actual benefit of ICD may have been underestimated in CIDS because of a 20% crossover to ICD in the amiodarone arm as well as the greater use of β-blockers in the ICD arm. As previously noted, data suggest that the combined use of amiodarone and β-blockers may potentiate their antiarrhythmic effects.[24,25] The former findings would lessen the impact of ICD benefit in the ICD arm. After the results of CIDS were published, patients were followed up for an average of 5.6 years. The CIDS long-term substudy found progressive increase in benefit of ICD over time.[32]

The results of CIDS were closely followed by the Cardiac Arrest Study of Hamburg (CASH).[10] The study design was more complex than those of previous secondary prevention trials. Enrollment of 407 patients began 4 years before the increased mortality rate associated with class I AADs in patients with structural heart disease was well known.[31] Patients were randomized in a 1:3 fashion to ICD or medical therapy with one of three drugs intended to reduce ventricular arrhythmias. ICD programming was limited to a shock-only device, with rate as the only criterion for the detection of a sustained ventricular arrhythmia. Within the medical therapy arm, patients were randomized to amiodarone, metoprolol, or propafenone. Inclusion criteria were documented sustained ventricular arrhythmias and aborted cardiac arrest. Exclusion criteria were similar to earlier secondary prevention trials. Patients were excluded if the arrest occurred within 72 hours of AMI, cardiac surgery, electrolyte abnormalities, or proarrhythmic drug effect, or if they had NYHA class IV CHF. More than half the participants had mild heart failure (NYHA class II). In the ICD cohort, 55% of the patients underwent epicardial lead placement via thoracotomy. The index arrhythmia was VF in 84% of patients. The mean LVEF was 46%, with 10% of patients having structurally normal hearts. Another 19% in the ICD arm and 21% in the drug arm underwent revascularization during the index hospitalization for SCD. The propafenone arm was discontinued after 119 patients were enrolled and interim analysis revealed a 61% increase in all-cause mortality in the drug group. This difference was noted at a mean of 11.3 months of follow-up and was clustered in the propafenone arm. The remaining 288 patients enrolled after 1992 were randomized in a 1:2 fashion to ICD, amiodarone, or metoprolol. Unlike CIDS and AVID, crossover rates in both groups in this study were relatively low and equal in each arm. In the ICD arm, 5.1% of patients died in the perioperative period versus 1.1% in the drug arm during the same period ($P = .029$). In addition, the overall complication rate in the ICD arm was 23% through the completed follow-up period. Over a mean follow-up of 57 ± 34 months, the crude death rates were 36.4% in the ICD arm and 44.4% in the drug arm, excluding patients who had been on propafenone. This resulted in a nonsignificant 23% reduction in all-cause mortality ($P = .081$), with the majority of the benefit in the ICD arm seen in the first 5 years. The ICD group had a significant improvement in survival free of SCD (HR, 0.423, $P = .005$). The results in the β-blocker arm from CASH helped shed light on previous suggested interaction caused by β-blocker use in the two arms of AVID and CIDS. No significant difference was observed in the crude death rates between the amiodarone and metoprolol groups (29.5% and 35.1%, respectively). As in CIDS, baseline characteristics of patients, lower risk of SCD than predicted, and study design may have limited a demonstrable difference between the ICD and drug arms. Previous studies had suggested those with LVEF greater than 35% may not receive as much benefit from ICD as those with lower LVEF.[23] The mean LVEF in CASH was 46% and one tenth of these patients had no organic heart disease. In addition, the observed 2-year overall mortality rate was 19.6%, which was approximately half as high as projected in the original study design. Thus the study was underpowered to detect any significant differences between the two groups. The significant increase in perioperative death in the ICD arm was much higher than current estimates and likely negated any benefit of ICDs on mortality rate.[33,34] A nonsignificant trend toward greater benefit with ICD was seen in those with lower LVEF and higher NYHA functional class.

The Midlands Trial of Empiric Amiodarone Versus Electrophysiology-Guided Interventions and Implantable Cardioverter-Defibrillators (MAVERIC) study sought to evaluate the efficacy of electrophysiology study (EPS) in predicting outcomes in patients implanted with ICDs or managed with AADs alone.[12] It is important to note that the primary aim of this trial was not to compare ICD versus drug therapy but to determine the role of EPS in this patient population. Patients were randomized to one of two treatment strategies. One group was started on empiric amiodarone therapy. The other underwent a complex EPS-guided algorithm in which implantation of ICD was determined by inducibility of VT or VF as well as the origin of the VT. Those with right ventricular outflow tract VT, bundle branch re-entrant VT, and fascicular tachycardia were referred for ablation and did not undergo ICD implantation. If VT or VF was not inducible by programmed electrical stimulation (PES), a Holter monitor was used to further guide treatment. If the Holter monitor did not reveal more than 30 premature ventricular

complexes per hour, an ICD was then implanted. As part of the protocol, all patients were evaluated and treated for ischemia, if present. Survivors of SCD in the absence of AMI in the past 48 hours met the inclusion criteria. Premenopausal women with life expectancy of less than 1 year were excluded. The primary endpoint was all-cause mortality with secondary endpoints of VT or VF recurrence and crossover in treatment. In total, 214 patients were enrolled in the trial. Two important differences existed between this study and AVID, CASH, and CIDS. First, more than half the patients included in this study had hemodynamically stable VT. Second, amiodarone was compared with EPS-guided therapy and not directly with ICD implantation. This study was limited by the small number of patients receiving ICDs (24% in the EPS arm and 5% in the amiodarone arm). More than half the patients had LVEF greater than 35%. The patients in the Massachusetts Veterans Epidemiology Research and Information Center (another MAVERIC) trial were in a high-risk group, and many of those who were not implanted would meet the current class I recommendations for ICD placement. The net outcome of the trial was neutral with no demonstrable difference between empiric amiodarone versus EPS-guided treatment. Despite the limitations of this study, several points were gleaned from this trial. ICD recipients did consistently better than non-ICD recipients with a greater benefit shown by those with hemodynamically unstable ventricular arrhythmias as their index arrhythmia. This contradicts the subgroup analysis from AVID, which showed no difference in ICD benefit based on hemodynamic stability. As in the previous trials, the authors concluded that advanced age, CHF, and LVEF less than 35% were independently associated with death. In addition, diabetes was an independent predictor of poorer outcomes. Nonrandomized comparison of ICD and non-ICD cohorts revealed an HR of 0.54 for percent alive at the end of follow-up. On the basis of study design, these can be only considered hypothesis-generating results. More important, in the setting of secondary prevention, EPS added no additional benefit to conventional treatment strategies. Therefore EPS has no role in determining whether a survivor of sudden cardiac arrest (SCA) will benefit from ICD implantation.

Another secondary prevention trial performed in a more select group of participants was the Defibrillator Versus Beta Blockers for Unexplained Death in Thailand (DEBUT) trial.[11] In this two-phase study, survivors of sudden unexplained death syndrome (SUDS) were randomized to ICD or the β-blocker propranolol. As a cohort largely with Brugada syndrome, patients in SUDS tended to have ST elevation in the right precordial leads (V1 to V3) and incomplete right bundle branch block.[35] The primary endpoint was all-cause mortality and the secondary endpoints were VT, VF, or cardiac arrest. No differences were observed in baseline characteristics between the two groups, and all patients had structurally normal hearts, with a mean EF of 67%. The results of this trial have somewhat limited applicability because of the significant variability of the underlying pathophysiology of arrhythmia. In this study, 86 patients were randomized to either treatment strategy. The trial was stopped early after 3 years because of an 18% mortality rate in the drug arm and no deaths in the ICD arm. The patients in DEBUT had no contributing factors to death other than VF, which therefore suggests that the ICD fully prevented death.

The results of the aforementioned key secondary prevention trials have been examined further. A meta-analysis published by Connolly et al analyzed the results from AVID, CASH, and CIDS compared with ICD with amiodarone.[36] They found significant relative reductions in total mortality rate of 28% and a significant 50% reduction in arrhythmic death. Over a period of 6 years, implantation of an ICD yielded a 4.4-month survival benefit over AAD therapy. The mortality rate reduction with ICD was realized regardless of the presence of structural heart disease, type of presenting arrhythmia (VT or VF), β-blocker use, or prior surgical revascularization. Although benefit occurred in all groups regardless of LVEF, the benefit was greater in those with lower EF. A second similarly designed meta-analysis by Lee et al in 2003 confirmed the findings of Connolly, thus adding to the statistically nonsignificant benefit of ICD implantation in CIDS and CASH.[37] A subgroup analysis of the three main secondary prevention trials performed by Oseroff, Retyk, and Bochoeyer found that ICDs confer a 28% RR reduction in all-cause mortality. This benefit was greatest in those with LVEF 20% to 34%. Similar to the findings of MAVERIC, those with inducible VT or VF had no worse mortality rates than those who were noninducible with PES at EPS.[38]

Primary Prevention of Sudden Cardiac Death

The results of previous secondary prevention trials showed a benefit of ICDs in reducing the incidence of SCD. However, most patients do not survive SCD, so it was logical to explore the use of ICDs for primary prevention in high-risk patients with no history of sustained ventricular arrhythmias (Figure 87-1). The first major published study of primary prevention of SCD was the Multicenter Automatic Defibrillator Implantation Trial (MADIT), published in 1996.[13] In this trial, patients with ischemic cardiomyopathy with an EF of 35% or less and NYHA class I to III heart failure, a history of nonsustained VT (NSVT), and inducible nonsupressible sustained VT by PES were randomized to ICD or OMT. The primary endpoint was all-cause mortality. Notable exclusion criteria were surgical revascularization in the past 2 months, angioplasty in the preceding 3 months, recent MI (≤3 weeks), criteria for ICD by secondary prevention standards, and life expectancy of less than 1 year. Of the patients, 253 patients had inducible VT that could not be suppressed by intravenous procainamide, and ultimately 196 were then randomized. Mostly, monophasic pulse generators were used, and roughly half the devices were transthoracic implants (before the advent of transvenous systems). Baseline characteristics of the patients were similar, with a mean EF of 26%. Two thirds of patients in each group had a history of bypass surgery. One month after enrollment, amiodarone was the primary AAD in the OMT arm. The use of ACE inhibitors was similar between groups (60% and 55%). In addition, the overall use of β-blockers was low (25%) but more common in the ICD arm. Sixteen crossovers to ICD occurred. Eleven patients in the OMT arm underwent ICD implantation, and five patients in the ICD arm never had an ICD placed. Two patients had their devices inactivated during the trial. Perioperative mortality rate was 0%, and follow-up was completed in 92% of the ICD group and 86% in the OMT group. Over a mean follow-up of 27 months, an overall mortality rate of 39% occurred in the medical therapy arm and 16% in the ICD arm (HR, 0.46; 95% CI, 0.26 to 0.82; $P = .009$). This difference translated into a number needed to treat (NNT) of 3 over 36 months to save one life. Sixty percent of those in the defibrillator group received shocks at 2 years, although the appropriateness of these shocks was not well established given the absence of stored electrograms in many devices. This rate is significantly higher than contemporary estimates of appropriate shocks, and it is now known that

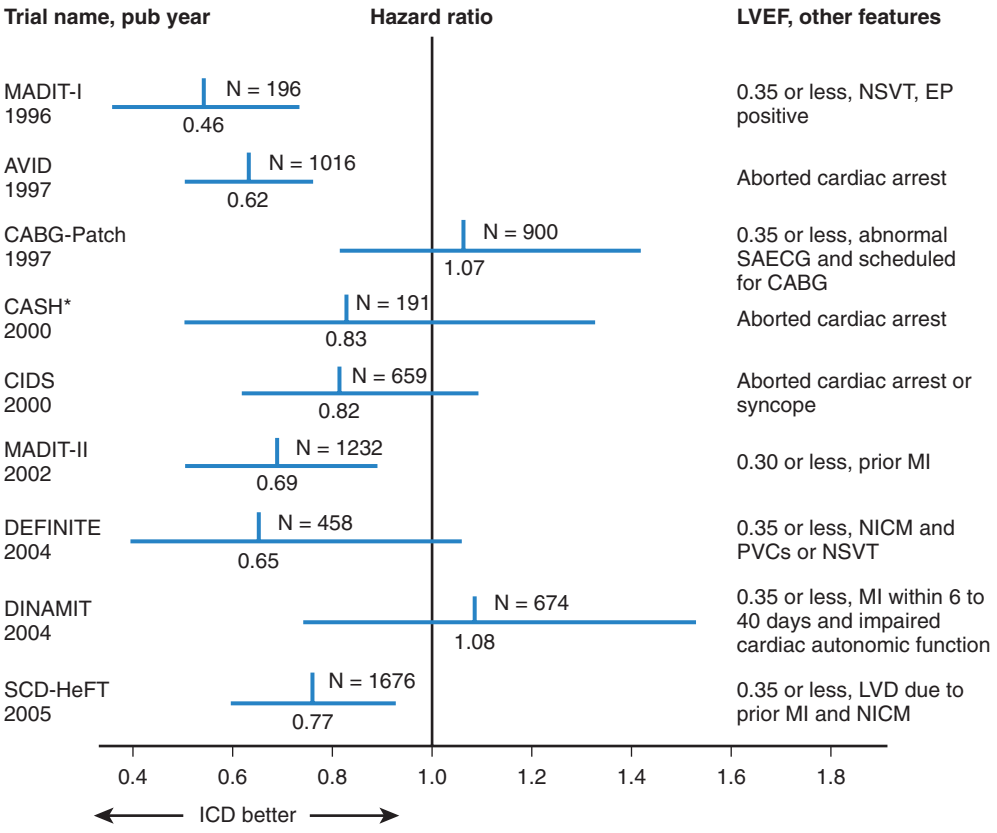

FIGURE 87-1 Major implantable cardioverter-defibrillator (*ICD*) trials. *LVEF*, Left ventricular ejection fraction; *NSVT*, nonsustained ventricular tachycardia; *EP*, electrophysiology; *SAECG*, signal-averaged electrocardiogram; *CABG*, coronary artery bypass grafting; *MI*, myocardial infraction; *NICM*, nonischemic cardiomyopathy; *PVCs*, premature ventricular complexes; *LVD*, left ventricular dysfunction. *(From Epstein AE: Benefits of implantable cardioverter defibrillator,* J Am Coll Cardiol *52:1122–1127, 2008.)*

ICD shocks predict an increase in mortality rate regardless of cause.[39] The majority of the differences in death rates were seen in reduction in primary arrhythmia of unknown cause (occurred outside the monitored setting in the OMT arm). It is unclear if the differences in nonarrhythmic deaths were caused by a misclassification of cause of death or the possible adverse effects of AADs. A nonsignificantly greater overall mortality rate at 1 month was observed in the amiodarone group compared with the defibrillator group (36% and 26%, respectively). However, amiodarone was the most used AAD, and other data suggest that it can be used without excess mortality from heart failure.[40] A Cox regression analysis failed to attribute the difference in the two groups to differences in medical therapy. In addition, the observed crossover would have only diluted observed differences in outcome between the two groups.

High-risk patients who were undergoing bypass surgery were prospectively examined in the Coronary Artery Bypass Graft (CABG)-Patch trial. Patients with an LVEF of 35% or less undergoing elective bypass surgery were eligible if they had an abnormal signal-averaged electrocardiogram (SAECG). Key exclusion criteria were previous or concomitant aortic or mitral valve surgery, history of sustained VT or VF, higher risk of infection, active significant carotid disease, and creatinine level greater than 3 mg/dL. Patients were stratified by EF, and the implanting surgeon had the option not to randomize the patient if the patient was considered to be too high of a risk for implantation or defibrillation threshold (DFT) testing. However, patients were assessed by intention-to-treat analysis. Older generation committed devices (shock was delivered at the end of charging regardless of whether the arrhythmia self-terminated) were used, and they were not capable of storing electrograms. In this study, 1055 patients were enrolled, and 900 were randomized. The mean LVEF in both groups was 27%. Only half the patients had symptomatic heart failure and were taking heart failure medications. More than 90% of the patients had at least two-vessel coronary artery disease. No significant baseline differences were observed between the two groups. In addition, β-blocker use was similar in both arms. During an average follow-up of 32 ± 16 months, 101 deaths occurred in the defibrillator group (71 from cardiac causes) and 95 deaths in the control group (72 from cardiac causes). No significant difference in outcome was observed between the two arms; moreover, no significant effect of ICD was seen on any of the 10 preselected baseline covariates.

Numerous theories have been proposed with regard to why these outcomes were significantly different from those of other previous ICD trials. The 2-year all-cause mortality rate in CABG-Patch was 18% versus 24% in AVID and 32% in MADIT. In MADIT, higher risk patients were selected on the basis of the presence of nonsupressible inducible ventricular arrhythmias, whereas CABG-Patch used the presence of abnormal SAECG. This suggests that the presence of sustained spontaneous or induced ventricular arrhythmias may be a better predictor of SCD

than abnormal SAECG. The ICD firing rate was similar to that in MADIT, but it is unclear if the patients in MADIT had more arrhythmias (neither ICD arm had stored electrograms). It is unclear what proportion of patients who underwent bypass surgery had underlying acute coronary syndrome (ACS) or angina. Nearly half these patients had diabetes. In those with reduced EF, diabetes, and multi-vessel or proximal left anterior descending (LAD) artery disease, a definite mortality benefit is associated with surgical revascularization. This may explain outcomes in total mortality in each arm. Other proposed explanations for the outcomes were possible changes in autonomic tone caused by CABG or a reduction in ischemia as a trigger for VT or VF after surgical revascularization. The benefit of ICD may also have been offset by increased infection rates in the ICD arm, which did occur in this trial.

The Multicenter Unsustained Tachycardia Trial (MUSTT) investigators sought to determine if EPS with PES could identify high-risk patients who would benefit from empiric ICD implantation. Patients with an LVEF of 40% or less and asymptomatic NSVT were randomized to AAD therapy guided by EPS or no AAD therapy. Patients with inducible ventricular arrhythmias were then randomized to various AADs and after four to five repeated doses of PES. The exception was amiodarone, which could be used at the discretion of the investigator. If fewer than 15 ventricular complexes were induced, long-term therapy with that drug was initiated. If ventricular arrhythmia could not be suppressed, the patient could be discharged on an AAD, which resulted in induced hemodynamically stable ventricular arrhythmia. No empiric AAD therapy was used. Early in the trial, ICDs were implanted only if the patients failed three or more AADs. As practices changed during enrollment, patients could undergo ICD implantation after just one AAD failure as determined by PES. Patients were evaluated for obstructive coronary artery disease within 6 months of enrollment. NSVT had to occur within 6 months of enrollment and more than 96 hours after an AMI or a revascularization procedure. Key exclusion criteria included reversible causes of NSVT and VT or syncope more than 2 days after AMI. Of the study patients, 704 were randomized and 353 placed in the ICD arm. The mean EF was 30% in the EPS arm and 29% in the no-AAD arm. Fewer patients in the EPS arm were taking β-blockers (29% vs. 51%, $P = .001$). Distribution of patients across NYHA classes I to III was roughly even, with no class IV patients. Among the 351 patients randomized to EPS, 158 (45%) were discharged on AADs, more than half of which were class I AADs. Another 161 (46%) underwent ICD implantation. Twelve percent of patients initially discharged on AADs eventually underwent ICD implantation. At a mean follow-up of 5 years, a 7% absolute reduction and a 27% relative reduction in mortality were observed in the EPS arm versus the no-AAD arm (25% vs. 32%; 95% CI, 0.53 to 0.99). This difference was caused solely by the ICD in approximately half the patients in the EPS arm. The RR of cardiac arrest or death from arrhythmia in patients who received ICDs was significantly lower (9% vs. 37%) compared with that in patients discharged without ICDs despite more nonsuppressible ventricular arrhythmias in the ICD cohort (RR, 0.24; 95% CI, 0.13 to 0.45; $P < .001$). Neither the rate of cardiac arrest nor death from arrhythmia was lower in the EPS arm assigned to AADs or in those assigned to no AADs (33% vs. 28%; P = not significant). Although this trial was meant to assess the efficacy of EPS in risk stratifying those at high risk for SCD, the impact of ICD was substantial. The requirement that patients undergoing implantation of an ICD failed at least one AAD suggests that those receiving ICDs had a worse overall prognosis. Despite this, patients receiving ICDs had better survival than those who did not receive defibrillators. Furthermore, half the patients on AAD therapy were taking class I drugs, which have since been shown to increase mortality in patients with structural heart disease.[31] β-Blocker use was nearly twice as likely in the cohort not receiving AADs and ICDs (51%) compared with those who did ($P = .001$). All these differences in treatment would tend to offset the suggested benefit of ICDs in reducing mortality. The authors of this study concluded that AAD therapy guided by EPS does not improve survival. They suggested ICD should be implanted in those meeting the high-risk inclusion criteria of this trial in whom PES induces sustained ventricular arrhythmias. A follow-up study compared the outcomes of 1397 patients in the MUSTT database registry with the 353 with inducible tachyarrhythmias.[41] They found that the negative predictive value of SCD of a negative EPS was 88% to 90% over 2 years. Overall mortality rate at 5 years was significantly higher in those with positive EPS (48% vs. 44%, $P = .005$). Although the risk is greater in inducible tachyarrhythmias, the difference between the groups was smaller than expected and indicated a surprisingly high risk despite a "negative" EPS. These findings are often incorporated into current practice. In patients at high risk for SCD with an EF of 36% to 40%, a positive EPS provides grounds for prophylactic ICD implantation.

After the publication of MUSTT, additional substudies were performed to determine if certain populations would derive greater benefit from ICDs. Of the patients in MUSTT who were not prescribed AADs or implanted with an ICD, mortality rate was higher in those with an LVEF of 30% or less compared with those with an LVEF of 30% to 40%.[42] In addition to EF, a further analysis of the MUSTT data suggested that other clinical factors, including functional class, history of heart failure, NSVT unrelated to bypass surgery, age, QRS width, and the presence of AADs, were all linked to increased mortality and arrhythmic death.[43] The authors also noted that the risk for arrhythmic events may be greater in patients with an EF greater than 30% but with the aforementioned risk factors compared with those with an EF less than 30% without additional risk factors.

The MADIT-II investigators studied the prophylactic implantation of defibrillators in patients with prior MI and reduced EF.[14] They hypothesized that myocardial scar left by the previous infarction would serve as a substrate for ventricular arrhythmia and that these patients may benefit from empiric ICD implantation without additional risk stratification based on EPS, NSVT, or SAECG. Patients having ischemic cardiomyopathy with an MI more than 1 month in the past and an EF of 30% or less were randomized in a 3:2 fashion to ICD versus conventional medical therapy. Patients were excluded if they were NYHA class IV at enrollment, had been revascularized in the past 3 months, had advanced cerebrovascular disease, or had a coexisting condition that had a high likelihood of causing death during the trial. ICD recipients underwent implantation of a transvenous ICD with DFT testing to ensure 10-J safety margins. Approximately 45% of the patients had dual-chamber units; ATP was allowed; and the rate cutoff for pacing or shock was not mandated, but most investigators programmed the ICD units to a rate cutoff of 170 beats/min for ATP, shock, or both.[44] This was the earliest of the recent ICD trials to closely mimic current guidelines with regard to medical therapy. The majority of patients in both arms were treated with β-blockers, ACE inhibitors, and statins. AAD use was neither mandated nor encouraged in the medical therapy

arm, with only 10% of patients taking amiodarone and less than 3% prescribed class I AADs. Of the randomized patients, 35% were in NYHA class I, and the average EF was 23%. No baseline differences existed between groups. In this trial, 1232 patients were randomized, with 742 in the ICD group and 490 in the conventional medical therapy group. At the conclusion of the study, 4.5% of patients in the medical therapy arm crossed over into the ICD arm, and 4.3% of the patients randomized to ICD either did not have a device implanted or had the device removed.

During an average follow-up period of 20 months, the all-cause mortality rate in the medical therapy arm was 19.8% versus 14.2% in the ICD arm (HR, 0.69; 95% CI, 0.51 to 0.93; $P = .016$). The mortality benefit began to appear 9 months after randomization. Subgroup analyses showed no significant difference in the benefit of defibrillator therapy with respect to LVEF, age, gender, NYHA class, or QRS width. Similarly, no differences existed in the benefit of ICD on survival with respect to diabetes, hypertension, left bundle branch block (LBBB), AF, time elapsed since MI, or use of a dual-chamber device. A post hoc analysis suggested that no benefit was derived from ICD in those with end-stage renal disease but that a significant benefit was experienced by those with mild to moderate renal dysfunction.[45] Complication rates in the ICD arm were low, with 2.5% of patients over the duration of follow-up requiring surgical lead extraction for lead malfunction or infection. Interestingly, more patients in the ICD arm were hospitalized with heart failure (14.9% vs. 19.9%). This resulted in an overall trend of increased hospitalization in the ICD arm (11.3 vs. 9.4 patients hospitalized per 1000 months of active follow-up; $P = .09$). The reasons for the increases in hospitalization for heart failure in the ICD arm, though nonsignificant, are unclear. This may be a surrogate marker for increased survival as an effect of the ICD; that is, those who otherwise would have died from SCD lived longer to go on and develop more decompensated heart failure. However, in light of follow-up studies of these patients, this seems unlikely. Post hoc analysis of the MADIT-II participants revealed one or more inappropriate shocks occurred in 83 (11.5%) of the 719 patients in the ICD group.[47] Inappropriate shock episodes constituted 184 of the 590 total shock episodes (31.2%). Inappropriate shocks were more likely to occur in patients with a history of smoking, prior AF, and diastolic hypertension, and antecedent appropriate shock predicted inappropriate shock occurrence. AF (44%) and sustained VT (36%) were the most common triggers for inappropriate shock, followed by abnormal sensing (20%). The stability detection algorithm was programmed less frequently in patients receiving inappropriate shocks (17% vs. 36%, $P = .030$), whereas other programming parameters did not differ significantly from those without inappropriate shocks. Importantly, patients with inappropriate shocks had a greater likelihood of all-cause mortality in follow-up (HR, 2.29; $P = .025$). By proportionately increasing mortality, inappropriate shocks may have weakened the overall mortality benefit afforded by the ICD, but it is unclear if this would have resulted in more hospitalizations for heart failure. The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), a more recent study of 829 patients with heart failure who were randomly assigned to ICD therapy, assessed the potential effects of both appropriate and inappropriate shocks.[48] Over a median follow-up period of 45.5 months, 269 patients (33.2%) received at least one ICD shock, with 15% of patients receiving only appropriate shocks, 10% receiving only inappropriate shocks, and 7% receiving both types of shock. An appropriate ICD shock, compared with no appropriate shock, was associated with a significant increase in the subsequent risk of death from all causes (adjusted HR, 5.68; 95% CI, 3.97 to 8.12; $P < .001$). An inappropriate ICD shock, compared with no inappropriate shock, was also associated with a significant increase in the risk of death (HR, 1.98; 95% CI, 1.29 to 3.05; $P = .002$). For patients who survived longer than 24 hours after an appropriate ICD shock, the risk of death remained elevated (HR, 2.99; 95% CI, 2.04 to 4.37; $P < .001$). The most common cause of death among patients who received any ICD shock was progressive heart failure. This suggests that regardless of the etiology of a shock, patients who receive shocks have a higher mortality rate that is more likely related to heart failure. Ongoing studies are evaluating whether shocks contribute to heart failure exacerbations or if they simply reflect the treatment of arrhythmias associated with worsening heart failure.

It is also likely that worsening heart failure may have been the result of frequent right ventricular pacing. The Dual Chamber and VVI Implantable Defibrillator (DAVID) trial suggested that in patients without indication for pacing, VVI pacing at a rate of 40 is superior to DDDR pacing at a rate of 70. A nonsignificant increase in mortality rate and hospitalization for heart failure was seen in the latter group (16.5% vs. 26.1%).[46] Programmed device parameters were available for roughly three quarters of those in the ICD arm.[44] The mean lower rate limit for pacing was 53 ± 12 beats/min, and in patients with dual-chamber devices the mean paced AV delay was 190 ± 43 ms. About 35% of the ICD cohort received right ventricular pacing 50% or more of the time, with 25% receiving right ventricular pacing for more than 90% of the time. The group that was paced more than 50% of the time also had an increased risk of VT or VF requiring ICD therapy (HR, 1.50; $P = .02$). A post hoc analysis of the Mode Selection Trial, a trial of pacemaker therapy for sick sinus syndrome, demonstrated that the cumulative percentage of right ventricular apical pacing was a strong predictor of hospitalization for heart failure.[49] These findings suggest that right ventricular pacing was a likely contributor to increased hospitalization for heart failure despite a significant mortality reduction arising from aborted VT or VF.

Other retrospective analyses of the MADIT-II data were examined to determine particularities of ICD benefit in this patient population. Since this trial was performed in patients after MI, it was postulated that a differential benefit from ICD may exist depending on how remote the ICD was placed relative to the MI.[50] The mortality benefit in remote MI was in those with MI occurring 18 months ago, with no benefit observed with more recent MI. In addition, the mortality benefit increased with time and remained substantial for up to at least 15 years. This contradicts older data, which suggested that the risk is greater in the first year after MI. This paradigm shift may be attributed to changes in current medical therapy, including acute revascularization and medical therapy targeting neurohormonal activation. In terms of revascularization, benefit was not appreciated until 6 months after the last coronary revascularization procedure, suggesting a benefit of anti-ischemic therapy on reducing SCD.[51] Another randomized, controlled trial has shown no overall survival benefit from starting ICD therapy in the early weeks after an AMI in patients with clinical features of increased risk for arrhythmic events.[52] In the Immediate Risk Stratification Improves Survival (IRIS) trial, which randomized almost 900 patients with AMI, overall mortality rate was unaffected by ICD therapy started within 1 month of the event in addition to medical therapy compared with medical therapy alone. Over a follow-up period of about 3 years, the ICD group's HR for death compared with that

of the control group was 1.04 ($P = .78$). Patients implanted with ICDs showed a 45% lower risk of SCD ($P = .049$), countered by an almost-doubled risk of non-SCD ($P = .001$), These results confirm the findings of the Defibrillator in Myocardial Infarction Trial (DINAMIT).

MADIT-II evaluated patients with prior MI 1 month or more after enrollment. As previously described, post hoc analysis of MADIT suggested that the benefit of ICD in ischemic cardiomyopathy may be appreciated long after the index infarction. The DINAMIT study investigated the use of ICDs in the primary prevention of SCD in the period 6 to 40 days after MI.[53] This study randomized 332 patients to ICD and 342 to OMT, with recent MI, LVEF of 35% or less, and evidence of impaired autonomic cardiac function (manifested as depressed heart rate variability or elevated average 24-hour heart rate on Holter monitoring). The primary outcome was all-cause mortality, with death from arrhythmia as a prespecified secondary outcome. Key exclusion criteria were VT or VF, NYHA class IV heart failure, acute volume overload, life expectancy less than 1 year, or coronary artery bypass grafting (or three-vessel percutaneous revascularization) since qualifying MI or planned within 4 weeks of enrollment. ICDs were single-lead systems programmed at VVI 40 beats/min, with VT zone with ATP at a rate of 175 beats/min, and a VF shock-only zone at 200 beats/min. All shock discharges were at maximal output. ATP was specified to deliver four bursts of 6 to 10 beats at 81% of the tachycardia cycle length with 10-ms decrements between ATP attempts. Both groups were similar, with a mean EF of 28%, and more than 85% of patients in both arms were taking β-blockers and ACE inhibitors. Two patients in the ICD arm died before device implantation. After a mean follow-up of 30 ± 13 months, no difference in overall mortality was observed between the two groups. Of the study patients, 62 in the ICD group and 58 in the OMT group died (HR for death, 1.08; 95% CI, 0.76 to 1.55; $P = .66$). A significant reduction occurred in death caused by arrhythmia in the ICD arm (12 vs. 29; HR, 0.42; CI, 0.22 to 0.83; $P = .009$). However, more significantly, more deaths occurred from nonarrhythmic causes in the ICD group (50 vs. 29, $P = .02$). Of the deaths from nonarrhythmic causes, 78% were cardiac in nature. No evidence of procedure-related deaths was present. The authors did not believe that the deaths were caused by excessive right ventricular pacing as in DAVID since patients were all programmed VVI 40.[45] As also proposed in retrospective analysis of the MADIT-II data, the authors suggested that the excessive nonarrhythmic deaths were caused by the natural history of heart failure not otherwise ended prematurely by SCD. These data are consistent with MADIT-II, which showed no benefit of ICD early after MI. Other differences that may have contributed to different overall outcomes in these studies did exist. For instance, LVEF was lower in MADIT-II (23% vs. 28%). In addition, the tests of autonomic function may have not accurately selected the patients at highest risk for SCD, although these tests have previously been shown to predict patients at high risk of pump failure.[54]

The most recent and large scale clinical trial of ICDs and prevention of SCD was the SCD-HeFT.[17] In this study, 2521 patient with an LVEF of 35% or less and NYHA class II to III were randomized to one of three arms: (1) OMT, (2) OMT plus amiodarone, or (3) a conservatively programmed single-lead ICD. The primary endpoint was all-cause mortality. The single-ventricular-lead devices with a single zone were programmed with a detection rate of 187 or more with no ATP. Devices were programmed VVI 35, with no rate response to prevent pacing. DFT testing was performed in all patients with a maximum of two inductions. Interestingly, the first shock was 20 J; if unsuccessful, the next induction was followed by a 30-J shock. If the DFT was 30 J, the device was nevertheless implanted without additional pharmacologic or mechanical intervention in an attempt to reduce DFTs or guarantee a 10-J safety margin. Recently published data from SCD-HeFT suggested there was no benefit from DFT testing in this particular patient population. In addition, baseline DFT testing did not predict long-term mortality or shock efficacy.[55] Patients in the amiodarone arm were loaded with oral amiodarone and placed on a maintenance dose of 200 mg to 400 mg/day based on weight. The dose could be reduced in the event of symptomatic bradycardia. The use of β-blockers, statins, ACE inhibitors, aldosterone antagonists, and aspirin was required if clinically indicated.

Unlike previous primary prevention trials, in SCD-HeFT, roughly 50% of patients included had nonischemic cardiomyopathy (NICM), and 50% had ischemic cardiomyopathy. The mean LVEF was 25%, and 70% of the patients were NYHA class II. Mean follow-up was 45.5 months. In the ICD arm, 49 patients (5.9%) were either not implanted or had their devices removed during follow-up. From the medical therapy arm, 188 crossed over to ICD implantation. In the ICD arm, 182 deaths (22%) occurred, with 244 deaths (29%) and 240 deaths (28%) in the OMT and amiodarone groups, respectively. ICD therapy was associated with a 23% reduction in all-cause mortality compared with the other two arms (97.5% CI, 0.62 to 0.96; $P = .007$). At 5 years, the absolute reduction of death was 7.2%, with an NNT of 14 to prevent one death. No difference in mortality rate was observed between the OMT and amiodarone arms. In the patients with ICDs, 31% received shocks from their ICDs, with two thirds of the shocks occurring for VT or VF. This resulted in an average annual rate of total ICD shocks of 7.5% and 5.1% in the two groups for appropriate shocks, respectively.

A prespecified subgroup analysis of the SCD-HeFT participants was performed based on multiple characteristics. Interestingly, when stratified on the basis of symptomatology, patients with NYHA class II heart failure derived a marked benefit from ICD, whereas class III patients received no benefit from ICDs. A 46% relative reduction in death occurred in the class II patients, translating into an 11.9% absolute reduction in mortality rate at 5 years. This contradicts the findings in the MADIT-II and Defibrillators in Non-ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trials, which showed no differences on the basis of NYHA class and a greater benefit in NYHA class III patients, respectively.[14,16] In addition, the trend in previous trials has been greater treatment benefit with ICDs in sicker patients. Subgroup analysis suggested a greater benefit in patients with an LVEF of 30% or less compared with those with an EF of 30% to 35% as well as patients with a wider QRS.

Primary Prevention of Sudden Cardiac Death in Nonischemic Cardiomyopathy

The role of ICDs in the primary prevention of SCD is somewhat less defined in NICM. The DEFINITE trial exclusively enrolled patients with NICM if they had an LVEF of 35% or less and either NSVT or 10 or more premature ventricular complexes per hour on a Holter monitor. Patients with NYHA class I to III heart failure were included in the study, of which mor than half were in class II. Of the 458 patients enrolled in this study, 229 patients

were randomized to OMT; 229 patients were randomized to OMT and a single-chamber ICD. The ICD was programmed for one zone with VT or VF detection starting at 180 beats/min and VVI 40. Medical therapy was very effective in this study, with 86% of patients treated with ACE inhibitors and 85% with β-blockers. The mean LVEF was 21%. The mean follow-up period was 29 months (shorter than in other similarly designed studies), and the primary endpoint was all-cause mortality. The crossover to the ICD arm was 10%; 39% of patients implanted with ICDs received shocks, with 49 of 90 patients receiving inappropriate shocks for AF or sinus tachycardia. Although the difference in survival between the two groups was not statistically significant, a strong trend toward improved survival was observed with ICD therapy (HR, 0.65; 95% CI, 0.40 to 1.06; $P = .08$). ICD therapy was associated with an 80% RR reduction in SCD (HR, 0.20; 95% CI, 0.06 to 0.71; $P = .006$). Prespecified subgroup analysis revealed a greater benefit of ICD in men and in those with class III heart failure, in contrast to SCD-HeFT. However, only 21% of patients had class III heart failure, which weakens this retrospective analysis. Nonetheless, this group had a 63% RR reduction in death compared with the OMT group (95% CI, 0.15 to 0.90; $P = .02$).

The overall rate of SCD in DEFINITE was lower than in previous trials. This may have been caused by more patients taking β-blockers and ACE inhibitors than in comparable trials. The incidence of SCD as well as the relatively small sample size may have resulted in the lack of significant reduction in all-cause mortality. Similar findings were published in two other smaller NICM primary prevention trials.[56,57] The Cardiomyopathy Trial (CAT) enrolled 104 patients with NICM of recent onset (<9 months) and an EF of 30% or less and randomized patients to ICD or medical therapy. The trial was terminated prematurely because the observed annual mortality rate was 3.7% instead of 30% as predicted. No SCD occurred during the first and second years of follow-up.[56] The Amiodarone Versus Implantable Cardioverter-Defibrillator (AMIOVIRT) study evaluated 103 patients with NICM, an LVEF of 35% or less, NYHA class I to III heart failure, and asymptomatic NSVT.[57] Patients were randomized to receive either amiodarone or an ICD. The primary endpoint was all-cause mortality. In this study, 52% of the patients were taking β-blockers and 85% were taking ACE inhibitors. The mean EF was 23%, and 64% of patients were NYHA class II. The study was stopped when the prospective stopping rule for futility was reached. The percent of patients surviving at 1 year (90% vs. 96%) and 3 years (88% vs. 87%) in the amiodarone and ICD groups, respectively, was not statistically different ($P = .8$). The authors proposed that the lack of a control group, small sample size, and lower than predicted mortality rate explained the lack of difference between the two arms. In 2004, a meta-analysis of randomized clinical trials of patients with non-ischemic dilated cardiomyopathy (NIDCM) was performed.[58] This study analyzed both primary prevention and secondary prevention trials. The primary prevention trials included in the analysis were CAT, AMIOVIRT, DEFINITE, SCD-HeFT, and Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION). The analysis included 1854 patients with NICM. Pooled analysis suggested a significant reduction in total mortality among patients randomized to ICD or CRT plus defibrillator (CRT-D) versus medical therapy (RR, 0.69; 95% CI, 0.55 to 0.87; $P = .002$) (Table 87-2). Mortality reduction remained significant even after elimination of CRT-D trials. The averaged annual mortality rate from these trials was 7%. Assuming a 31% RR reduction this would result in an absolute risk reduction in all-cause mortality of 2% per year. The NNT to prevent one death at 2 years would be 25. In comparison, on the basis of MADIT-II, the NNT to achieve the same primary prevention benefit in ischemic cardiomyopathy is 18 patients.[14]

Cardiac Resynchronization Therapy

Certain patient populations with heart failure have an overall poorer prognosis. Within this group are patients with prolonged QRS duration and worse functional status. When the QRS is prolonged, delayed mechanical activation of the ventricular free wall and septum often occurs, resulting in dyssynchronous contraction of the left ventricle.[59] Dyssynchronous contraction results in decreased systolic performance and efficiency, functional mitral regurgitation (primarily caused by prolonged delay to left ventricular activation), and increased residual end-systolic ventricular volume.[60] Among patients with electrical dyssynchrony marked by QRS widening, bi-ventricular pacing restores ventricular synchrony by activating the left ventricular free wall and the left ventricular septum via pacing from the left ventricular free wall. The left ventricular lead can be placed transvenously via the coronary sinus or through thoracotomy by direct epicardial implantation. Early trials dating back more than a decade have shown significant improvement in NYHA functional class, exercise time, quality of life, and oxygen consumption during metabolic testing.[18,19,21,61-68] These early trials monitored patients for up to 6 months in a blinded fashion. Noninvasive cardiac imaging in these patients showed reverse remodeling, as evidenced by an increase in EF and reductions in end-diastolic and end-systolic volumes. Because of low enrollment, early trials were underpowered to assess clinical endpoints such as total mortality, cardiovascular mortality, and hospitalization. The data supporting the use of CRT to alleviate heart failure symptoms is not reviewed here because it is outside the focus of this chapter. More recently, two large randomized trials evaluated CRT with defibrillator (CRT-D) or with pacing alone (CRT-P).[18,19]

The first large CRT clinical trial to include all-cause mortality as the primary endpoint was the COMPANION trial published in 2004.[18] This trial was designed to determine if CRT with or without an ICD would reduce the risk of death and hospitalization from any cause. Patients enrolled in the trial had an LVEF of 35% or less, QRS duration of 120 ms or greater, P-R interval greater than 150 ms, sinus rhythm, and NYHA class III or IV heart failure, with a hospital admission for heart failure in the previous year. Notable exclusion criteria were a clinical indication for a pacemaker or defibrillator and AF. The use of β-blockers, ACE inhibitors or ARBs, spironolactone, and statins was required if clinically indicated. In the trial, 1520 patients were randomized in a 1:2:2 fashion to OMT, CRT-P, or CRT-D, respectively. Both devices were programmed VDD, with a lower rate well below the patient's lowest intrinsic heart rate to maintain atrial tracking at rest. No differences in baseline patient characteristics or mandated background medical therapy were noted among the three groups. The population was roughly divided between ischemic and nonischemic cardiomyopathies. The mean LVEF was 21%, with QRS duration of 160 ms. Of the patients receiving devices, 71% had an LBBB pattern, and 86% had NYHA class III heart failure. Device implantation was successful in 91% of patients. Five procedure-related deaths (0.8%) occurred in the CRT-P arm, with three procedure-related deaths (0.5%) in the CRT-D arm. Left ventricular lead dislodgement occurred in 2% and 2.5% of the CRT and CRT-D groups, respectively. Specific crossover to the

Table 87-2 Summary of Evidence for CRT Alone or CRT-D in Patients with LVEF ≤35%

	Other Characteristics					
DEVICE	**SYMPTOM STATUS**	**ELECTROCARDIOGRAM CRITERIA**	**QUANTITY OF EVIDENCE FOR PATIENT SUBGROUP**	**QUALITY OF EVIDENCE**	**MAGNITUDE OF EFFECT**	**CONCLUSION**
CRT alone	NYHA class III or IV	QRS >120 ms and sinus rhythm	13 RCTs, 3481 patients	High (multiple RCTs with homogenous results)	Reduced mortality (RR, 0.78; 95 CI, 0.67-0.91) Reduced heart failure hospitalizations (RR, 0.51; 95% CI, 0.41-0.64)	Definite benefit
	NHYA class II	QRS >120 ms and sinus rhythm	5 RCTs, 344 patients	Moderate (1 small RCT plus post hoc meta-regression of aggregate trial data from 14 RCTs, but few patients in NYHA class II)	No significant effect on mortality (in 1 RCT: RR, 1.19; 95% CI, 0.17-8.26); in meta-regression, patients with class II symptoms not significantly associated with reduction in mortality ($P = .76$)	Inconclusive
				REVERSE, RAFT†	Effect on hospitalization smaller in NYHA class II vs. class III or IV heart failure; in meta-regression, patients with class II symptoms significantly associated with reduction in hospitalization ($P = .003$)	Inconclusive
	NYHA class III or IV	QRS >120 ms and bradyarrhythmia or atrial fibrillation	3 RCTs, 191 patients	Low (post hoc meta-regression of aggregate trial data from 14 RCTs)	No significant association in meta-regression between patients with atrial fibrillation and reduction in mortality or hospitalizations ($P = .73$ and $P = .58$, respectively)	
				Other RCTs‡: Trip HF, RAFT†, APAF, BLOCK HF		
	NYHA class III or IV	QRS <120 ms, any rhythm	5 nonrandomized studies, 120 patients	Low (secondary analyses of small observational studies)	Improvements in symptoms and LV remodeling not significantly different between patients with narrow QRS and patients with wide QRS in any of the studies	Inconclusive
	NYHA class I	Any QRS duration, any rhythm	None	No published evidence	Not applicable	Inconclusive
				REVERSE		
Combined CRT-ICD device (vs. no device)	NYHA class III or IV	QRS >120 ms and sinus rhythm	1 RCT, 903 patients in relevant comparison groups	Moderate (1 large RCT)	Reduced mortality (HR, 0.64; 95% CI, 0.48-0.86)	Definite benefit
				Other RCTs: DECREASE-HF, RAFT†	Reduced mortality or all-cause hospitalization (HR, 0.80; 95% CI, 0.68-0.95)	
	All other patient subgroups		None	No published evidence	Not applicable	Inconclusive
				Other RCTs: MADIT-CRT, RAFT†		
Combined CRT-ICD device (vs. CRT alone)	NYHA class III or IV	QRS >120 ms and sinus rhythm	1 RCT, 1212 patients in relevant comparison groups	Moderate (1 large RCT, but comparison was not a priori specified or adequately powered)	No significant effect on mortality (HR, 0.83; 95% CI, 0.66-1.05) and no significant effect on time to death in NYHA class IV subgroup (RR, 1.27; 95% CI, 0.66-2.37)	Inconclusive
	All other patient subgroups		None	No published evidence	Not applicable	Inconclusive

CI, *Confidence interval;* CRT, *cardiac resynchronization therapy;* CRT-D, *cardiac resynchronization therapy with defibrillation;* ICD, *implantable cardioverter-defibrillator;* HR, *hazard ratio;* LV, *left ventricular;* LVEF, *left ventricular ejection fraction;* NYHA, *New York Heart Association;* RCT, *randomized, controlled trial;* RR, *risk ratio.*

**Note that other considerations may outweigh the trial evidence in some situations (e.g., the patient with a "do not resuscitate" order), and there are no data on the effects of either CRT or ICD in patients with advanced age or severe comorbidities, such as end-stage renal disease.*

†Resynchronization/Defibrillation for Advanced Heart Failure Trial (www.clinicaltrials.gov: NCT00251251), as discussed in Chapter 86.

‡Protocols can be found at www.clinicaltrials.gov (Trip HF: NCT00817265; APAF: NCT00111527; BLOCK HF: NCT00267098).

Modified from McAlister FA, Ezekowitz J, Hooton N, et al: Cardiac resynchronization therapy for patients with left ventricular systolic dysfunction: A systematic review, JAMA *297(22):2502–2514, 2007.*

ICD arm was not reported in COMPANION; rather, the total "withdrawal" from the medical therapy arm was presented. This occurred in 26% of those assigned to OMT. The mean follow-up period was only 16 months in the device arms and 12 months in the OMT arm. When compared with OMT, CRT-P reduced the primary composite endpoint of all-cause mortality and hospitalization by 19% (HR, 0.81; $P = .014$), as did CRT-D (HR, 0.80; $P = .01$). Heart failure–related deaths or hospitalizations were reduced by 34% in the CRT-P group ($P < .002$) and by 40% in the CRT-D group ($P < .001$). The secondary endpoint of death from any cause was reduced by 24% ($P = .059$) in the CRT-P group and by 36% ($P = .003$) in the CRT-D arm.

Several interesting findings were noted in the subgroup analysis of COMPANION. In terms of QRS morphology, the benefit of CRT was progressive as QRS duration was prolonged. In addition, the benefit was limited to those with LBBB morphology. The benefit also seemed greater in NYHA class IV heart failure, LVEF of 20% or less, and those taking β-blockers and spironolactone. In those with NICM, CRT-D was associated with a significantly lower risk of all-cause mortality versus OMT (HR, 0.50; 95% CI, 0.29 to 0.88; $P = .015$). The benefit of CRT-D for this endpoint among patients with ischemic cardiomyopathy was nonsignificant. The effect of CRT-P in ischemic cardiomyopathy reflected quite a different trend. Though nonsignificant, it is intriguing that CRT-P reduced all-cause mortality by 9% in NICM ($P = .70$) compared with 28% in ischemic cardiomyopathy ($P = .058$). The authors concluded that much of the reduction of the primary endpoint was caused by the favorable hemodynamic effects of the device and hence a reduction in hospitalization for heart failure. This is supported by statistically significant increases in systolic blood pressure in both device arms. The addition of defibrillator capability to CRT incrementally increased the survival benefit, resulting in a 36% reduction in the risk of death ($P = .003$). The efficacy of these outcomes is especially compelling in current practice, given the adherence to current guideline-based medical therapy.

One year after COMPANION was published, the Cardiac Resynchronization-Heart Failure (CARE-HF) study was published.[19] In this study, inclusion criteria were NYHA class III to IV heart failure for at least 6 weeks, LVEF of 35% or less, left ventricular end-diastolic dimension of 30 mm indexed to height in meters, QRS duration of at least 120 ms, and treatment with OMT. Those with QRS duration between 120 and 149 ms were required to meet two of three echocardiographic criteria for dyssynchrony: (1) an aortic pre-ejection delay of more than 140 ms, (2) an interventricular mechanical delay of more than 40 ms, or (3) delayed activation of the posterolateral left ventricular wall. Key exclusion criteria were conventional indications for a pacemaker or defibrillator, requirement for continuous inotropic therapy, and chronic atrial arrhythmias. The devices had bi-ventricular pacing capability without defibrillator capacity. The CRT-P devices were programmed with backup atrial pacing at 60 beats/min, an interventricular delay of 0, and a programmed AV delay that was echocardiographically optimized. Every attempt was made to ensure that the left ventricular lead was placed along the posterolateral left ventricular wall during implantation guided by fluoroscopy. The primary endpoint was a composite of all-cause mortality or an unplanned hospitalization for a major cardiovascular event. Heart transplantation was counted as a death. The principal secondary outcome was death from any cause. In the study, 813 patients were randomized to OMT or to OMT plus CRT-P. Of the 409 patients, 390 (95%) assigned to CRT-P had a device implanted and 8 had an ICD lead placed in the right ventricle. Device implantation was attempted in 67 patients in the OMT arm, including 43 with CRT-P and 23 with CRT-D systems. Devices were activated in 50 of 404 patients in the OMT arm. The mean follow-up was 29.4 months, with survival status known in all patients. Baseline characteristics were similar between both groups. The mean LVEF was 25% and mean QRS 160 ms, and more than 60% of patients had NICM. More than 90% of patients in both arms had NYHA class III functional status at baseline. More than half the patients were taking β-blockers and spironolactone, with more than 90% taking ACE inhibitors or ARBs. The primary endpoint of death or hospitalization for heart failure was met in 159 patients in the CRT group versus 224 in the OMT group (39% vs. 55%; HR, 0.63; 95% CI, 0.51 to 0.77; $P < .0001$). In the CRT group, 82 deaths (20%) occurred versus 120 (30%) in the OMT group (HR, 0.64; 95% CI, 0.48 to 0.85; $P < .002$). The principal cause of death was cardiovascular in 83%, noncardiovascular in 17%, and not classifiable in 0.5%. In the medical therapy arm, 47% of deaths were attributed to progressive heart failure and 32% to SCD. In the CRT cohort, death was attributed to worsening heart failure in 40% and SCD in 35%. The 1-year all-cause mortality rate was 12.6% and 9.7%, respectively, in the OMT and CRT arms. The 2-year all-cause mortality rate followed a similar trend, with 25.1% in the OMT arm and 18% in the CRT group. As in previous trials of CRT, patients in the CRT arm had significant improvements in subjective and objective measures of heart failure symptomatology. The benefit seemed to be similar in both ischemic and NICM. Patients in the CRT group had significant and continual improvements in the hemodynamic and echocardiographic parameters. At 18 months, the CRT group had a 6.3 mm Hg increase in systolic blood pressure ($P < .001$), 6.9% improvement in EF ($P < .001$), and significant reductions in mitral regurgitation. The estimates of reduction in mortality rate should be interpreted in the setting of previously published literature. This was the first and only trial, thus far, that demonstrated an improvement in all-cause mortality with a pacing strategy alone compared with OMT. On the basis of these data, for every 9 patients implanted with CRT, one death and three hospitalizations for heart failure are prevented. This reduction in mortality rate is similar to that attributed to β-blocker treatment in heart failure versus placebo.[69] Despite multiple trials showing the benefits of CRT in terms of symptom improvement, hemodynamic benefit, and overall mortality, many questions still remain.

Both COMPANION and CARE-HF showed that these patient populations are at significant risk for SCD. Despite the fact that pacing alone in CARE-HF reduced mortality rate, the incidence of SCD in CARE-HF was greater than 30% and not different in either the pacing arm or the medical therapy arm. A similar mortality rate was noted in the pacing-only arm in COMPANION. These findings indicate that the addition of ICD to CRT is appropriate for most patients with an LVEF of 35% or less, QRS width of 120 ms or greater, and NYHA class III or IV heart failure.

Since the approval of CRT devices, observational reports have suggested that bi-ventricular pacing may increase the risk of ventricular arrhythmias in some patients.[70] However, other studies have suggested that bi-ventricular pacing should reduce the risk of ventricular arrhythmias. Bi-ventricular pacing and left ventricular pacing have been shown to better reduce sympathetic nerve activation compared with right ventricular pacing.[71] A substudy of 50 patients from the MIRACLE trial showed that control patients had 25% less heart rate variability compared with those

randomized to CRT.[72] Additional studies have shown that bi-ventricular pacing reduces QT dispersion and ventricular premature beats.[73,74] Studies of appropriate ICD therapy in trials of CRT-D have been neutral.[75]

Although both bundle branch patterns were included in many of the CRT trials, the primary benefit of CRT has been realized in patients with left bundle branch pattern on ECG. Nonetheless, 20% to 30% of CRT recipients do not receive any benefit from device implantation. Accordingly, identifying clinical responders is an important goal. Echocardiographic measures of dyssynchrony did not prove clinically useful in a large multi-center study of CRT.[76,77] At present, the magnitude of QRS prolongation in LBBB remains the best predictor of hemodynamic and clinical responses. Consistent with these observations, the Cardiac Resynchronization Therapy in Heart Failure and Narrow QRS Complexes (RETHINQ) study showed no benefit of CRT among patients with advanced heart failure and narrow QRS durations (≤130 ms) despite mechanical dyssynchrony.[78] Another important group to evaluate are those with mild heart failure. Investigators sought to determine if early implantation of CRT could prevent progression of heart failure events in this patient population. In this regard, REVERSE showed significant reverse remodeling and a reduction of heart failure hospitalizations or mortality rate among patients with NYHA class I to II CHF, LVEF of 40% or less, and QRS duration of 120 ms or greater.[79] Subsequently, the findings of MADIT-CRT were released.[80] In this study, patients with an LVEF of 30% or less, QRS durations of 130 ms or greater, and NYHA class I or II were randomized in a 3:2 ratio to CRT-D or conventional ICD. The primary endpoint was death from any cause or a nonfatal heart failure event. With a mean follow-up of 28 months, 17.2% in the CRT-D group and 25.3% in the ICD only group reached the primary endpoint. This benefit was driven primarily by a 41% reduction in heart failure–related events. Neither REVERSE nor MADIT-CRT showed a reduction in SCD with ICD therapy. However, the study population in both these trials was at very low risk of SCD; the study was therefore underpowered to show a statistically significant reduction in SCD. It is likely that the findings of recent CRT trials will result in indications for CRT in those with more mild heart failure symptoms who otherwise meet the inclusion criteria for REVERSE and MADIT-CRT, except for possibly the exclusion of patients without LBBB.

Conclusion

For patients with a history of SCA, the benefit of ICD over medical therapy and AAD therapy has been established. The benefit of ICD in reducing the risk of SCD and all-cause mortality in patients with ischemic or NICM with LVEF 35% or less and NYHA class II and III heart failure is also clear. Those who have ischemic cardiomyopathy have the best established benefit 1 month or more after MI and 3 months after revascularization. In both primary prevention and secondary prevention trials, the magnitude of benefit in the reduction of SCD appears to be greatest in the cohorts with the lowest EF. As in any clinical trial, the data must be interpreted in light of what defined OMT at the time of study. It is now known that right ventricular pacing, inappropriate and appropriate shocks, and certain AADs worsen outcomes in CHF. In theory, minimizing bradycardic pacing and programming anti-tachycardia therapies to terminate arrhythmia, rather than immediate delivery of shocks, when possible, may result in better outcomes. CRT should be added to an optimal medical regimen in patients with an LVEF of 35% or less, QRS of 120 ms or greater, especially if an LBBB pattern is demonstrated on ECG, and NYHA class III and IV heart failure. Most of these patients would also benefit from the addition of defibrillator capability to CRT. As health care expenditures in the United States continue to rise, more emphasis will be placed on attempting to identify the patients who will incur the greatest benefit from both ICDs and CRT with or without defibrillator.

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All references cited in this chapter are available online at expertconsult.com.

CHAPTER 88

Management of Lead Systems for Implantable Devices: Techniques and Interventions

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Pacemaker and implantable cardioverter-defibrillator (ICD) systems have undergone enormous changes and innovation since the initial invention of the permanent implanted pacemaker.[1] Leads have had to keep pace with the constant demand for improvement, and novel products and patients are surviving longer. It is hardly surprising that this rapid innovation and expanded usage increases the risk of dysfunction. This chapter describes the normal and abnormal functions of implanted leads. The incidence, mode of presentation, and treatment of the common lead-related complications, including lead fracture, insulation failure, perforation, dislodgment, and lead infection, are discussed. Finally, the indications, methods, and complications associated with lead extraction are reviewed.

Lead Design

Pacemaker and ICD leads are designed to transmit current from the generator to the myocardium as well as from the myocardium to the generator. The connection is made through a terminal pin electrically continuous with one or more conductor coils, which, in turn, are continuous with the electrodes making contact with the myocardium (Figure 88-1). The lead tip is stabilized at the myocardial interface by an active fixation mechanism such as a helix or a passive mechanism with tines to reduce the risk of lead dislodgment. The number of conductor coils within each lead varies with the function and complexity of the lead. For example, simple unipolar and bipolar pacemaker leads have one and two conductor coils, respectively.

To reduce complexity, ICD leads may use a defibrillation coil as the proximal pole for sensing ventricular signals, which is termed *integrated bipolar sensing*. An integrated bipolar sensing system will consist of at least two conductor coils, and a true bipolar system will have at least three. A superior vena cava (SVC) coil electrode will necessitate an additional conductor coil. The conductor coils need to be insulated from each other and from the blood pool. Polyurethane and silicone are commonly used as insulation. The repetitive mechanical stresses and the hostile environment of the body create profound challenges in making long-lasting and trouble-free leads.

Implant and Related Complications

Perforation

The incidence of symptomatic perforation is 0.1% to 0.8% for pacemakers and 0.6% to 5.2% for ICDs.[2,3] However, the incidence of asymptomatic perforation rates found incidentally by computed tomography (CT) scan can be much higher: up to 15% for atrial leads and 6% for ventricular leads.[4] Most perforations occur within the first month after implantation; however, they can occur up to 10 months after implantation.[5] This risk appears to be higher when leads are inserted into the right ventricular apex or atrial free wall and with smaller diameter leads.[2,3,5]

Patients with lead perforation may present with symptoms of pleuritic chest pain, diaphragmatic stimulation, and, less frequently, hypotension caused by cardiac tamponade. Interrogation often reveals poor sensing and a high capture threshold with a variable effect on impedance.[6] Imaging often reveals a change in the lead tip position compared with the initial chest radiograph. Lead perforation requires emergent lead revision. The authors of this chapter prefer to perform lead revision in the operating room, where access to urgent pericardiocentesis or thoracotomy, if necessary, in the event of tamponade is available. This risk is low, however, and many centers perform lead revision in an implant room without on-site surgical backup.

Dislodgment

Lead dislodgment can occur in up to 2% of ventricular permanent pacemaker leads, 5% of atrial leads and 5% of ICD leads.[3,7-9] Dislodgment should be suspected if a significant change in sensed amplitude, lead impedance, or capture threshold occurs, particularly within the first month after lead insertion. Subsequent imaging may show that the lead tip has changed compared with the postprocedure radiograph.[10] Most cases of lead dislodgment require surgical revision. In rare cases, the risk of lead revision is prohibitive, and the risk of the lead causing mechanical injury is low. In these cases, programming may satisfactorily resolve abnormal interrogation parameters.

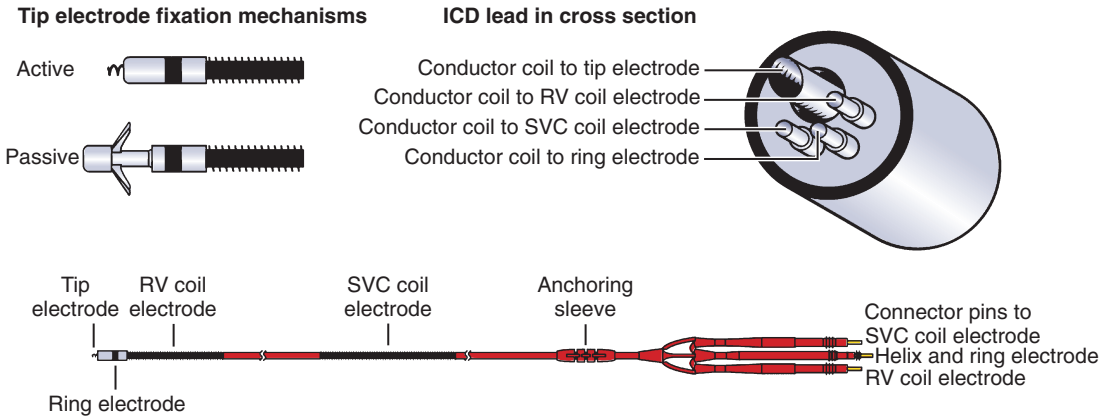

FIGURE 88-1 Implantable cardioverter-defibrillator (*ICD*) lead design. *RV*, Right ventricle; *SVC*, superior vena cava. *(Illustration by D. McClelland.)*

Table 88-1 Causes of High Defibrillation Threshold

LEAD CAUSES
Lead fracture Reversal of the coil terminal pins in a dual-coil system Significantly elevated high-voltage coil impedance
NON-LEAD CAUSES
Large cardiac size Increased body mass Reduction in left ventricle ejection fraction
MEDICATIONS
Antiarrhythmic drugs (dofetilide, lidocaine, procainamide, encainide, amiodarone, and ajmaline) Calcium channel blockers Sildenafil
RECREATIONAL DRUGS (COCAINE)

Table 88-2 Pertinent Implantation Factors

Venous access site (cephalic, axillary, medial/lateral subclavian, or other)
Aberrations in venous anatomy (location and size of veins)
Aberrations in cardiac anatomy (large right atrium, large right ventricle, patent foramen ovale, tricuspid regurgitation, etc.)
Implantation technique (lead prolapsed through the tricuspid valve)
Reason for the final tip location (high capture threshold, poor sensing at previous sites, anatomic variant, etc.)
Final interrogation parameters (lead pacing capture threshold, impedance, and sensing) both through the analyzer and the device
Chest radiograph (to document lead slack, tip position and course, and header/connector pin orientation)
Electrocardiogram (to document paced electrogram morphology)
Lead data (lead manufacturer, model, serial number, fixation mechanism and insulation, polarity, and connector type)

High Defibrillation Threshold

Defibrillation threshold (DFT) testing is performed to assess the minimum energy needed for the device to successfully terminate ventricular fibrillation. The need for DFT testing is still being debated. The authors of this chapter perform DFT testing routinely in patients who have had a cardiac arrest and in cases where circumstances that may impair defibrillation efficacy (e.g., the lead tip is in a nonapical lead position, the generator is on the right side, or the patient is on medications known to increase defibrillation threshold) are present. In the remaining cases, the decision to test is operator dependent and performed in approximately 50% of cases. During the era when DFT testing was routinely performed, DFT was typically less than 10 J.[11] An increase in DFT can be caused by lead factors (Table 88-1) or other factors such as patient factors, medications, and recreational drugs.[12-24] Lead factors that may increase DFT are lead fracture, reversal of the coil terminal pins in a dual-coil system, and all causes that increase the high-voltage lead impedance.

Lead Performance Monitoring

Lead performance monitoring is essential to ensuring appropriate device function and helps be prepared for lead failure. This begins at device implantation by the documentation of specific lead, patient, and implantation factors (Table 88-2). These factors provide a baseline to compare subsequent interrogations.

Clinical Follow-up

Long-term monitoring of lead performance occurs simultaneously with ICD and permanent pacemaker generator follow-up. The recommended frequency of follow-up varies between ICDs and permanent pacemakers (Table 88-3).[25-27] At the authors' center, patients are seen in the clinic 1 week and 3 months after implantation, regardless of device type, and then every year for pacemakers and every 6 months for ICDs. In addition to in-clinic visits, trans-telephonic monitoring and remote monitoring

systems facilitate lead follow-up by transmitting interrogation parameters to the device clinic at scheduled times. This allows the clinician to review the trends in lead performance and to be notified should lead performance deviate from predetermined normal values. Furthermore, should the interrogation parameters deviate from their expected values, the remote monitoring system can automatically transmit this information to the device follow-up team. The authors use remote monitoring systems for patients with leads or generators on advisory, in patients living remote from ready access to a follow-up clinic, and increasingly for all patients as capacity permits.

Many manufacturers have warning systems that alert the patient to system malfunction in the form of an auditory or vibratory stimulus emitted from the device. These warning systems alert the patient to aberrations in the system function of the device. The primary lead parameter that these alerts monitor is lead impedance. If lead impedance deviates outside the programmable range, the alert is triggered, prompting the patient to seek medical attention.[28] At each in-person visit, the pacing or ICD system (generator and lead) is reviewed to ensure normal function. This includes a focused patient history, physical examination, and device interrogation.

Table 88-3 Recommended Device Follow-up Timing

PERMANENT PACEMAKER FOLLOW-UP	ICD FOLLOW-UP
At implantation	At implantation
Within 72 hours of implantation	Within 72 hours of implantation
2–12 weeks following implantation	2–12 weeks following implantation
Every 3–12 months	Every 3–6 months

ICD, Implantable cardioverter-defibrillator.

History

Although the majority of the history and physical examination performed at each clinic visit pertains to ensuring appropriate generator function, certain other factors are also relevant in ensuring appropriate lead function and the elimination of lead-related complications. Focused history in the clinic includes a review of symptoms and risk factors for lead-related complications. For example, pertinent questions include inquiry regarding symptoms of diaphragmatic or phrenic nerve stimulation, myopectoral stimulation, infection, erosion, subclavian vein occlusion, lead dislodgment, or perforation; the clinician also inquires about symptoms of lead malfunction, such as lightheadedness, syncope, or other factors that can affect lead performance, for example, the progression of underlying cardiac disease (hemochromatosis, sarcoidosis, or ischemic heart disease), recent systemic infection, and current medications. Routine physical examination related to lead-related complications or malfunction includes examination for signs of infection, perforation, erosion, or venous thrombosis or obstruction. Subsequent history taking, physical examination, and further tests (including electrocardiogram [ECG] and chest radiograph) are dictated by the findings of device interrogation.

Measured Data

In their current iterations, many devices routinely assess lead performance by performing impedance, sensing, and capture threshold tests (Figures 88-2 through 88-4). These tests are typically performed daily and allow interrogation parameters to be tracked over time. At each clinic follow-up, lead performance is confirmed manually to ensure that the values measured daily by the device are valid and not discrepant from those measured automatically. Specifically, evaluation of lead function includes a pacing capture threshold test, impedance measurement, and P-wave and R-wave sensing.

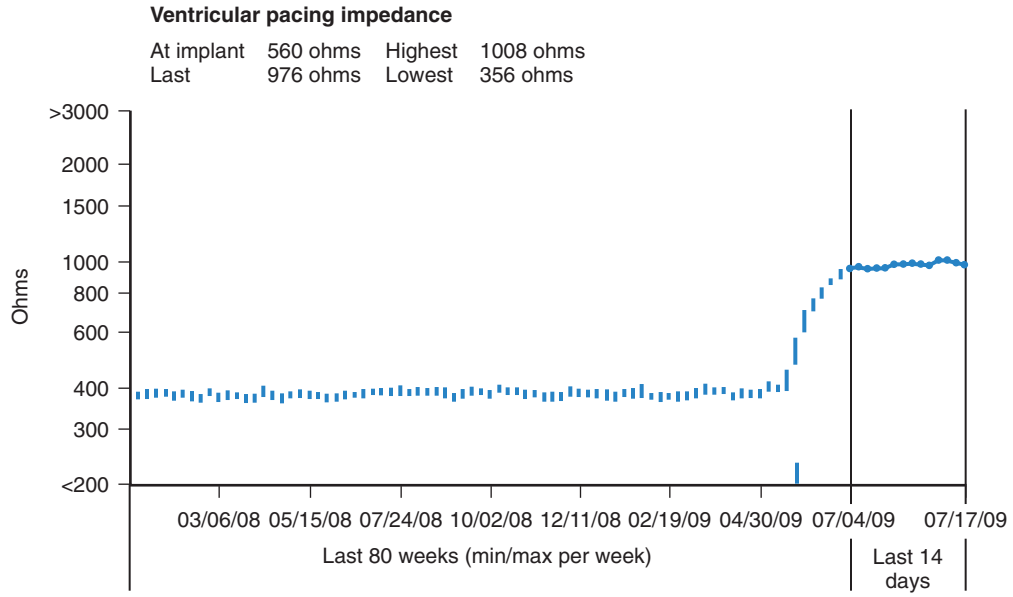

FIGURE 88-2 Impedance trend on the pace/sense portion of an Implantable cardioverter-defibrillator lead over time. Note the abrupt rise in impedance that was associated with a lead fracture.

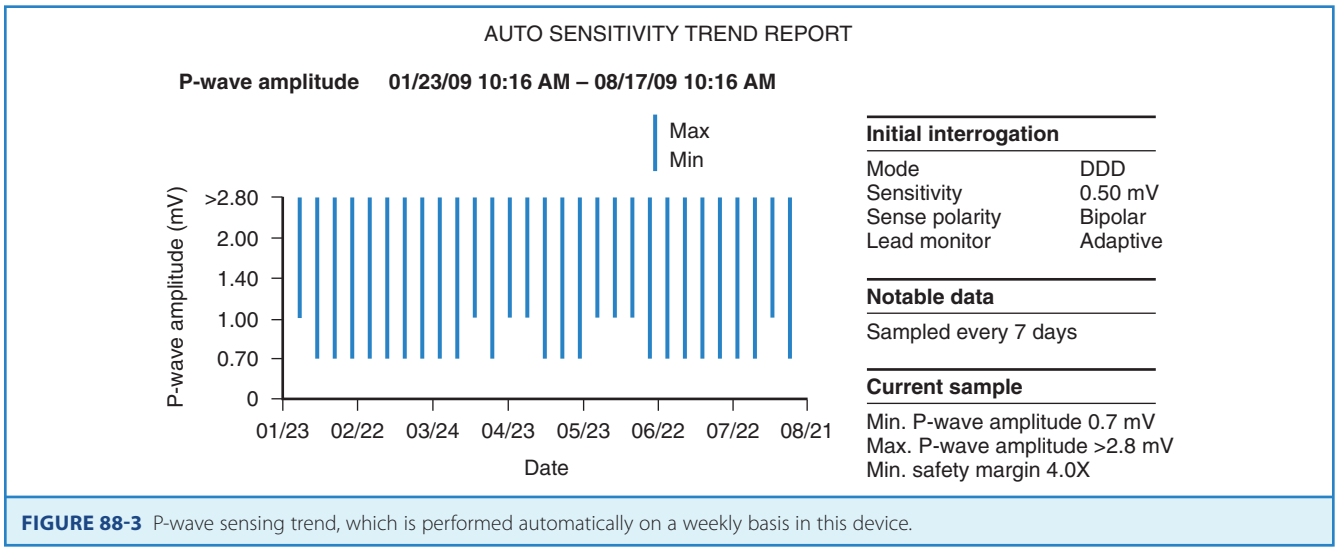

FIGURE 88-3 P-wave sensing trend, which is performed automatically on a weekly basis in this device.

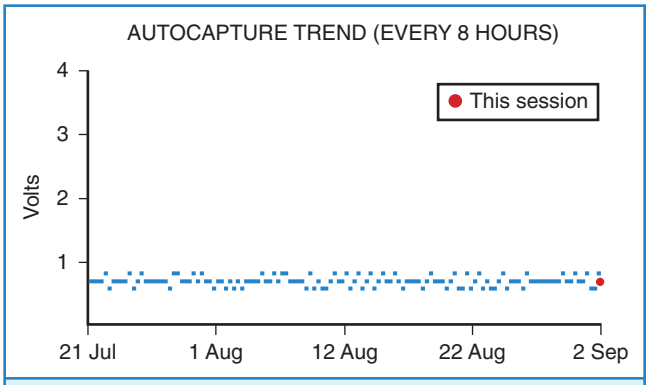

FIGURE 88-4 Capture threshold trend.

Cardiac Resynchronization Therapy–Specific Follow-up

Cardiac resynchronization therapy (CRT) follow-up is similar to pacemaker and ICD follow-ups. In addition, left ventricular lead threshold should be assessed, anodal stimulation should be excluded, and right/left ventricular timing optimization should be evaluated. In newer devices, one can perform a capture threshold on both right and left ventricular leads individually. The authors find that it is helpful, and often necessary, to perform the capture threshold test with simultaneous 12-lead rhythm strips to determine when each lead fails to capture. Unipolar left ventricular leads use the lead electrode tip as the cathode and the right ventricular proximal ring or right ventricular coil electrode as the anode, depending on whether the lead is a true bipolar lead or an integrated bipolar lead. Occasionally, the anode will also capture the myocardium, as is more frequently seen at higher pacing outputs or with right ventricular leads that are true bipolar or pace/sense leads. This can result in unwanted right ventricular capture in the case of programmed left ventricular only capture or triple-site capture (left ventricular cathodal and right ventricular cathodal and anodal captures) with biventricular pacing. Performing a left ventricular lead capture threshold test with a 12-lead rhythm strip will aid in distinguishing anodal stimulation, pure left ventricular capture, and loss of capture.[29]

Improvements in heart failure symptoms and mortality associated with left ventricular stimulation is thought to be attributable to an improvement in left ventricular, interventricular, and atrioventricular synchronization. It is currently unclear if attempts should be made to optimize synchronization with the use of imaging such as echocardiography. In the authors' institution, the nominal programmed left ventricular to right ventricular timing is not adjusted following implantation of the left ventricular lead. If the patient's heart failure symptoms persist, timing is optimized with echocardiographic guidance.

Lead Failure and Related Lead Problems

The incidence of pacemaker lead failure is highly variable. At one end of the spectrum, optimally performing leads fail at a rate of 0.2% to 1.0% per year after 5 to 10 years. In contrast, some leads fail at an unexpectedly high rate of 15% to 35% at 5 years, as high as 5.7% per year.[30-32] However, it is reasonable to expect the annual failure rate of modern pacing leads to be less than 0.5%.[30,33-35] ICD leads are much more complex, are larger, and thus have an attendant higher "expected" failure rate. In the current generation of ICD leads, the reported average annual failure rate ranges from 0.58% to 3.75%.[36-38] The failure rate increases as leads age and can be as high as 20% per year in leads more than 10 years old.[38] The estimated overall survival of ICD leads at 2, 5, and 8 years is approximately 91% to 99%, 81% to 95%, and 60% to 95%, respectively (Table 88-4).[36-43] Lead design directly affects lead performance. For example, the type of insulation material correlates well with the risk of insulation failure. Although the median time to insulation failure is 7.2 years, this is significantly shorter with polyurethane insulation than with silicone insulation (5.7 years vs. 9.4 years).[44]

In addition, certain alterations in lead design have adversely affected lead safety and performance. The Accufix (Telectronics Pacing Systems, Engelwood, CO) atrial lead incorporated a preformed J-curved wire into the distal portion of the lead to allow for ease of positioning of the lead tip within the right atrial appendage. Over time, this wire protruded from the insulation resulting in laceration of the right atrium and, rarely, fatalities. In other cases, the J-wire fractured and embolized into the pulmonary

Table 88-4 Estimated ICD Lead Survival

	LEAD AGE (YEARS)					
	1	2	3	4	5	8
Lead survival[36-43]	99%	91%–99%	88%–99%	82%–98%	81%–98%	60%–95%

ICD, Implantable cardioverter-defibrillator.

circulation.[45] Ironically, more patients died during interventions to remove the leads than from consequences of lead malfunction.[45]

More recently, an apparent improvement in reducing the size of an ICD lead resulted in suboptimal performance with the Sprint Fidelis ICD lead. This lead is a 6.6-F bipolar high-voltage lead, whose distribution was suspended in 2007 because of a higher-than-normal fracture rate.[46] Although implantation technique and patient factors (age and ejection fraction) may contribute to lead fracture, the lead's reduced diameter and construction are presumed to be the primary reasons for the increased risk of fracture.[46]

The rates and causes of lead failure are estimated on the basis of clinical variables and interrogation parameters. For example, lead fracture is often diagnosed with significant increases in lead impedance in the absence of other causes. Confirmation of the precise cause of lead failure is often not possible, as many leads that fail are either abandoned or damaged during extraction. These inferential observations, however, are often inaccurate in predicting the cause of lead failure and likely overestimate the incidence. When the leads with suspected failure are returned to the manufacturer for analysis, a substantial portion are found not to have the proposed malfunction.[36]

Mode of Presentation

Most (68%) of the pacemaker lead malfunctions are detected at routine follow-up or during scheduled remote follow-up monitoring. The remaining lead malfunctions are detected at unscheduled clinic visits (21%) or at the time of pulse generator replacement (9.1%).[44] The indicators of lead failure include failure to capture on ECG (33%), high pacing threshold (14% to 30%), undersensing (13%), oversensing (12%), high impedance (5%), low impedance (12%), and a combination of capture and sensing abnormalities (13% to 15%).[31,44]

Patients with ICD lead malfunction most commonly present with inappropriate shocks (33% to 76%) caused by oversensing of intracardiac signals, particularly T-wave oversensing or sensing of artifact.[38] The remainder of the patients are found to have an abnormally high-voltage lead impedance (56%), an increased capture threshold (22%), or noise on the lead (11%). These findings are typically discovered at routine testing (24% to 61% of lead problems) or at the time of elective generator replacement (2%).[36,38,40,42]

Lead Impedance Abnormalities

Lead impedance is an estimate of the combined effects of capacitance, resistance, and inductance in opposition to current flow. In simpler terms, it is a measure of stimulation resistance. Lead impedance is affected by lead electrode design (size, configuration, and materials). For example, smaller-diameter leads and bipolar leads tend to have higher impedance. The normal trend in pacemaker or pace/sense lead impedance is to slowly decrease over lead lifespan.[47,48] However, lead impedance should not change significantly from visit to visit. A marked change from the previous measurement (i.e., over 200 ohms) is abnormal and warrants careful assessment.

Up until recently, high-voltage ICD lead impedance could only be tested following a shock or at device replacement or implantation. Presently, the high-voltage lead impedance can be measured during routine follow-up interrogation in all ICDs at regular intervals and through remote monitoring systems. This has provided insight into the normal trend and fluctuation in lead impedance of high-voltage leads. Normal high-voltage lead impedance falls slightly in the first few months after lead implantation, after which it can be expected to rise to baseline values within a year of implantation. From visit to visit, fluctuations in ICD lead impedance up to 6 ohms are often seen. However, a change in impedance of over 12 ohms should prompt an investigation, as this is unusual in normally functioning leads.[49] Large fluctuations in impedance or aberrations in lead impedance, which are induced by provocative maneuvers at the time of device interrogation, may be caused by problems that manifest intermittently, such as conductor fracture, insulation break, or a loose set screw.

A marked increase in lead impedance in the short term after lead implantation is most likely caused by lead dislodgment, perforation, or an incomplete circuit caused by a header-connector problem, such as a loose connection between the lead and the pulse generator or when the lead is not fully inserted into the header. A rise in lead impedance beyond the early postimplant period may be caused by lead conductor fracture. A marked reduction in lead impedance after the early implant phase is most often caused by an insulation break (see below).[41]

Output Failure

Failed output occurs when an expected current is not generated at the conductor tip. This can be the result of generator or lead malfunction or more often erroneously suspected in normally functioning devices (Table 88-5). Lead-associated problems that result in failure to output include conductor fracture or a header connector problem, such as incomplete insertion of the lead pin into the connector block, incompatible lead and pulse generator, or a loose set screw.[7]

Abnormalities in Capture Threshold

Capture threshold is the minimum amount of current necessary to elicit an evoked potential. The long-term trend in capture threshold varies from lead to lead. Historically, capture threshold would often rise after implantation because of the inflammatory response at the distal electrode. Current leads elute steroid from the distal electrode, typically eliminating this problem. As such,

Table 88-5 Causes of Failure to Output

NORMAL DEVICE FUNCTION (PSEUDOFAILURE)
Hysteresis Sleep or rest mode PVARP extension after a PVC Fast ECG recording speeds
GENERATOR CAUSE
Generator component failure Total battery depletion
LEAD CAUSE
Conductor fracture Lead disconnection (lead pin is not fully inserted into the connector block, lead, and pulse generator are not compatible Loose set screw Air in pocket or device out of pocket (unipolar leads)
ABSENCE OF ECG PACING ARTIFACT DUE TO SIGNAL PROCESSING IN CASES OF FAILURE TO CAPTURE

PVARP, Postventricular atrial refractory period; PVC, premature ventricular contraction; ECG, electrocardiogram.

Table 88-6 Causes of Failure to Capture

Inappropriately low energy output settings
Isoelectric R wave or P wave
Functional noncapture (attempts to pace in the myocardial refractory period)
Intrinsic cardiac disease Myocardial ischemia/infarction Infiltrative cardiomyopathy
Medications Antiarrhythmic drugs: sotalol, propafenone, lidocaine, bretylium, amiodarone, moricizine, flecainide, quinidine, procainamide Antihypertensives: verapamil, β-blockers
Metabolic/electrolyte Hypercarbia Hyperkalemia Severe hyperglycemia Acidosis Alkalosis Hypoxemia Myxedema

capture threshold should not deviate significantly from baseline over the lead's lifetime.[47,48]

Failure to capture may or may not be lead related (Table 88-6). Unrelated causes include intrinsic cardiac disease, metabolic or electrolyte derangement, or medications.[7,21,50,51] The most common causes of early lead-related failure to capture are lead dislodgment and lead perforation.[52,53] Lead insulation break and conductor fracture are the most common causes of failure to capture later in the follow-up period.[7] Local exit block is an uncommon cause of failure to capture and can occur at any time after lead insertion. In the acute setting, this is caused by inflammation at the lead-electrode interface. In the long term, fibrosis develops at the lead tip–myocardium interface, resulting in an associated increase in capture threshold.

The appropriate treatment of failure to capture depends on the suspected mechanism, the impact of the elevated capture threshold on pacing and generator longevity, and ease of revision or replacement. Factors that favor lead revision or replacement include a right ventricular lead, a narrow pacing safety margin, lead fracture, insulation failure, lead perforation, or lead dislodgment suspected to be the mechanism of failure. Furthermore, lead repositioning is more easily performed in the first few months after lead implantation. In other cases, reprogramming by increasing the programmed output or pulse width may be sufficient. In cases of dual-chamber devices in which the atrial lead is not capturing, switching from the dual-chamber mode to the ventricular mode may be sufficient, particularly if the atrial lead is used predominantly for sensing.

Abnormalities in Sensing

Sensing is the ability of the device to detect intrinsic myocardial depolarization. The long-term R-wave amplitude is predicted by the R wave at first follow-up.[47,48,54] Sensing abnormalities can be in the form of undersensing when intrinsic myocardial depolarization is not detected or oversensing when signals that do not represent myocardial depolarization are sensed.

Undersensing can result in inappropriate pacing in both pacemakers and ICDs and in the inappropriate withholding of therapy in ICDs (anti-tachycardia [ATP] and shocks). Undersensing can be caused by patient factors, generator factors, or lead factors or can be erroneously suspected in a normally functioning device (Table 88-7).[7,51] Lead causes of undersensing include lead dislodgment, fibrosis at the tip electrode, poor initial lead position, lead insulation defect, and lead conductor coil fracture.[7]

Oversensing can result in inhibition of pacing in both pacemakers and ICDs and in inappropriate therapy in ICDs (ATP and shocks).[10,55] Oversensing can be caused by the inappropriate sensing of physiological signals or artifacts; both can be associated with lead malfunctions (Table 88-8).[7,56,57] For example, atrial depolarizations can be sensed on a ventricular lead in cases of insulation failure in the segment of the lead that is within the atrium. Often, the sensing of physiological signals such as P waves, R waves, T waves, or diaphragmatic myopotentials occurs because of lead electrode position and necessitates lead repositioning or replacement. However, certain processes such as hyperkalemia, hyperglycemia, Brugada syndrome, ischemia, and exercise can result in T-wave oversensing that improves with resolution of the underlying cause. Artifact can often be the result of lead malfunction.[58-61] For example, a loose set screw, conductor coil fracture, failed insulation between anode and cathode conductors in a bipolar system, interaction between active and abandoned pacing electrodes, and a loose distal fixation helix or screw can all result in sensed make-break signals.[62-66]

It is difficult to differentiate oversensing from failure to output on a surface ECG. Oversensing is considerably more common. However, if the event occurs at the time of device interrogation, device annotation will differentiate the causes. Annotation of a sensed event in the absence of an intrinsic depolarization will indicate oversensing and not failure to output.

The clinical scenario determines the appropriate course of action. After correcting any non–device-related causes of abnormal sensing, such as metabolic abnormalities, and avoiding external sources of artifacts, one can consider lead repositioning or

Table 88-7 Causes of Undersensing

LOW-AMPLITUDE ELECTROGRAM
New bundle branch block
Ischemia/infarction
Cardiomyopathy
Hypothyroidism
Body position/respiratory motion
Medications
Electrolytes
Tissue fibrosis
Following cardioversion or defibrillation
ERRONEOUSLY SUSPECTED IN A NORMALLY FUNCTIONING DEVICE
Magnet mode
Change to a nonsensing mode caused by environmental noise
Functional undersensing
Safety pacing
Triggered mode
Monitor artifact (false pacemaker spikes on the recording system)
Algorithms that increase ventricular pacing, as with cardiac resynchronization therapy
GENERATOR MALFUNCTION
Impending battery depletion
Component malfunction (sensing circuit abnormality or stuck reed switch)
LEAD ABNORMALITIES
Lead dislodgment
Lead maturation
Poor initial lead position
Lead insulation defect
Lead conductor coil fracture

Table 88-8 Causes of Oversensing

PHYSIOLOGICAL SIGNALS
P waves, T waves, R waves
After-potentials or myopotentials
Electromagnetic interference
MAKE-BREAK SIGNALS
Loose set screw
Conductor coil fracture
Insulation break in inner insulation between anodal and cathodal conductor coils
Interaction between the active lead and abandoned leads
Loose distal fixation helix

replacement or programming changes. Adjustment of the sensitivity will resolve the sensing issue in many cases. In addition, altering the RV-LV timing may resolve T-wave oversensing in biventricular devices.[61,67] In ICD leads, oversensing is particularly troublesome, as decreasing the sensitivity may result in underdetection of ventricular arrhythmias. However, performing defibrillator threshold testing after decreasing the sensitivity will test the detection ability of ventricular arrhythmias and provide a surrogate for the detection ability of clinical arrhythmias. If adjustment of the sensitivity does not provide a sufficient safety margin to ensure appropriate sensing, lead repositioning or replacement may be necessary. Furthermore, lead replacement or revision is necessary if a lead fracture, insulation failure, lead perforation, or lead dislodgment is suspected. Occasionally, the risk of lead repositioning or replacement is prohibitive, and programming does not resolve the sensing problem. Satisfactory noninvasive alternatives may include changing the mode to a triggered or asynchronous mode, particularly if the ventricular lead is affected. Changing to a ventricular-based mode may be a satisfactory solution when atrial leads have abnormal sensing.

Nonphysiological Interval Detection

Modern ICDs have a measure that documents the presence and frequency of nonphysiologically short V-V intervals (typically sensed cycle lengths shorter than 130 ms). This is designed to provide early warning of lead failure and should prompt an investigation or more frequent follow-up. Alerts are typically triggered if frequent short intervals are detected over a brief period.[68,69] The cause of nonphysiologically short V-V intervals includes lead fracture, header-connector problem, T wave oversensing followed by a premature beat, and lead dislodgment.[26]

Lead Fracture

The term *lead fracture* refers to a fracture in the lead's conductor coil. Lead fracture rates are typically less than 2% per year, although the incidence with certain leads can be as high as 4%.[7,70] Although lead fractures can occur at any time following implantation, the risk increases with age, with the median time to conductor fracture being 5.2 years.[44] Lead fractures often occur at stress points such as near the pulse generator, at the venous access site, or at the lead tip, where repetitive motion places stress on the conductor coil.[7,44] Certain patient and anatomic factors increase the risk of lead fracture. For example, the risk of lead fracture at the proximal portion of the lead appears to be higher if the angle of the lead is acute, either at the entry point to the header or at the point of venous access.[44] A medial venipuncture may trap the lead between the first rib and clavicle, costoclavicular ligament, or subclavius muscle, resulting in subclavian crush.[71] Other risk factors for lead fracture include stress on the distal tip at the time of implantation when maneuvering the lead tip to its final position, younger patient age, and lead trauma.[7,44,70]

Lead fracture may result in undersensing, oversensing, failure to output, or all.[7] In ICD leads, lead fractures may also result in inappropriate shocks from sensed artifacts from the fractured lead, often with nonphysiologically short sensed intervals.[70,72] If a fracture occurs within the high-voltage conductor coil, the ability to deliver therapy may be compromised.[44] In most cases of lead fracture, lead interrogation will show an increase in lead impedance, which may rise transiently or abruptly.[72-75] In cases of lead fracture, a new lead must be inserted, unless the lead can be abandoned. Whether the fractured lead should be removed in addition to the insertion of a new lead is still being debated. Replacing a lead carries the risk of lead extraction but may decrease the risk of worsening tricuspid valve regurgitation, oversensing caused by lead-lead interaction, lead infection, and venous thrombosis.[76,77] Although cases of inappropriate shocks from oversensing noise caused by lead-lead interaction when the ICD lead is abandoned have been reported, the rate of inappropriate

shocks does not appear to be higher than baseline.[78] Furthermore, the theoretical increase in DFT caused by shunting of energy to the abandoned ICD lead does not appear to be a common occurrence in clinical practice.[78]

In ICD leads, the pace or sense conductor coil, the high-voltage conductor coil, or both coils can fail. Opinions regarding the appropriate response to the failure of one component of an ICD lead vary widely. The concern is that other components of the lead may also be at higher risk of failure over time. At present, data to support or refute this concern are insufficient. However, it appears that the risk of high-voltage conductor coil fracture is low in leads with pace or sense conductor coil fracture when only a pace or sense lead was inserted.[79]

Insulation Failure

Insulation failure accounts for up to 56% of PPM and ICD lead failures.[9,36,38,40,42,44] The incidence of insulation failure increases with lead age, with a median time to failure of 9.4 years for polyurethane leads and 5.7 years for silicone leads.[44] Breakdown of insulation can occur because of friction that may occur between the generator and the lead within the device pocket or between two leads.[13,80] In addition, polyurethane insulation is subject to deterioration caused by metal ion oxidation (MIO), which typically occurs at areas of high mechanical stress, such as the costoclavicular space.[7,41]

The clinical manifestations of insulation failure depend on the location of the insulation failure and lead design. In unipolar leads, where insulation surrounds the only conductor coil, insulation failure can manifest as complete or intermittent failure of myocardial capture caused by reduced myocardial current delivery as a result of dissipation of current from the conductor coil into the surrounding tissues at the site of failure.[7] In addition, insulation break can result in a reduction in the sensed amplitude of myocardial depolarization and, as a result, undersensing. Oversensing of both physiological and nonphysiological events can occur at the site of the insulation failure.[7] Lead diagnostics may also show a reduction in lead impedance. The clinical manifestations of insulation failure, however, may be exacerbated or ameliorated by lead orientation. As such, all of these clinical manifestations, including impedance reduction, may be transient and not manifest at the time of the device interrogation.

Unipolar leads, whose insulation is failing, are not reliable. As such, a new lead should be inserted, unless a lead is no longer clinically necessary.

In bipolar leads, an inner layer of insulation separates the inner and outer conductor coils, and an outer layer of insulation surrounds both coils. If the inner insulation fails, current may pass from the inner conductor coil to the outer conductor coil via the insulation failure without reaching the electrode tip, which will result in loss of capture. In addition, if the inner and outer conductors make contact, voltage transients occur, which will result in oversensing. An inner insulation breach may result in a higher unipolar impedance than bipolar impedance. This is opposite to what is expected in a normally functioning lead.

Outer insulation failure is more common than is inner insulation failure. An outer insulation defect proximal to the proximal conductor may result in a large-amplitude pacing artifact on the surface ECG, as is usually seen with unipolar leads. Furthermore, the lack of insulation may result in stimulation or sensing of extracardiac tissues such as the pectoral muscle or diaphragm. Both inner and outer insulation failures may result in undersensing because of a reduction in the sensed amplitude of myocardial depolarization.

Inner insulation failure results in unreliable lead performance and typically a nonfunctional lead. As such, it is necessary to replace or add a new lead. With outer insulation failure, programming the pacing configuration to unipolar (if possible) usually results in normalization of the capture threshold and resolves undersensing. However, voltage transients continue to occur as a result of intermittent contact between the proximal and distal conductor coils, resulting in oversensing, which makes this only a temporary solution prior to definitive lead replacement or the insertion of a new lead.

Lead Infection

Lead infection is difficult to differentiate from generator infection or pocket infection, as the specificity of infectious signs and symptoms for localizing the site of infection is poor. Leads may become infected as a result of extension from pocket infection or when intravascular seeding results in lead colonization. The risk of device infection is 0.68% in the first year and can occur in up to 12.6% of all patients.[81,82] Although the majority of device infections occur within 1 year of device implantation or reimplantation (median 52 days), a substantial portion of cases can occur later.[81-84] The clinical presentation of device infection manifests as either localized symptoms (69%), systemic symptoms (11%), or both (20%).[83] These include fever (29% to 78%), local symptoms including pocket erythema (55%), pocket pain (55%), pocket warmth (23%), draining pocket sinus (42%), pocket swelling (36%), chills (22%), sepsis (fever and tachycardia; 11.5%), malaise (21%), anorexia (11.5%), and nausea (8%).[82-84]

Positive blood cultures are detected in 81% to 93% of patients with device infection, with the highest yield with tissue biopsy found in pocket infection, or lead cultures with lead infection (63% to 93%), in contrast to blood cultures (51% to 68%).[82,83,85-87] The most common organisms cultured are the *Staphylococcus* species (mostly *S. epidermidis* and *S. aureus*).[82,85,87,88] Other implicated pathogens include *Streptococcus bovis*, *S. viridens*, *S. mitis*, *Enterobacter cloacae*, and *Klebsiella oxytoca*, with a small number of infections being polymicrobial (13%).[82,83]

Several factors appear to increase the risk of device-related infections. These include immunosuppression (cancer, glucocorticoid therapy, or diabetes mellitus), fever within the 24 hours preceding implantation, temporary pacing before implantation, early reintervention (e.g., for hematoma or lead repositioning), repeated pocket procedures (i.e., replacement or revision), pocket hematoma, and absence of prophylactic antibiotics.[81,82] The impact of the number of leads on risk infection is being debated.[81,89]

Complications associated with lead infection include lead vegetation, pulmonary embolism, and death. Lead vegetations are a rare complication of device-related infection and are often only detected by trans-esophageal echocardiography.[82] It is essential to distinguish a vegetation, a sterile thrombus, stranding, and a fibrous mass when there is a mass on a lead, as their treatments vary markedly. However, this is often difficult, and the etiology is presumed according to clinical factors. In the authors' group, it is presumed that a mass is a vegetation in a patient who has clinically suspected pacemaker infection (septicemia, noncardiac manifestations of endocarditis, pocket infection). In contrast, a

mass is presumed to be a sterile thrombus, stranding, or a fibrous mass in the absence of infectious symptoms, particularly in patients with a reduced ejection fraction or atrial fibrillation.[90] If the etiology of the mass is unclear, typically periodic clinical evaluation and serially imaging with either transthoracic or transesophageal echocardiography are conducted and treatment is determined on a case-by-case basis.

Although the risk of pulmonary embolism with lead-related endocarditis is low, it appears higher in patients with vegetations greater than 10 mm in diameter.[82] Device-related mortality rates are variable but can be as high as 18% at 6 months.[85] Risk factors for mortality in patients with device-related infection are renal insufficiency, positive blood cultures, significant atrioventricular valve regurgitation, right ventricular dysfunction, pulmonary hypertension, and pulmonary or systemic emboli.[85]

Treatment of Infection

The initial treatment of cellulitis over the device pocket as well as pocket infection is with antibiotics. However, a substantial portion of patients with only local symptoms will have bacteremia or will eventually be found to have intravascular lead infection.[83,87] As such, most cases will require complete extraction of the generator and all leads. In clear cases of device infection, attempts to avoid lead extraction by removing the device and débriding the pocket with lead abandonment, cutting leads, and allowing them to retract into the vein or long-term antibiotics have a substantially increased risk of recurrent infection (50%) compared with complete device removal (1%).[84,87] An incomplete extraction should only be considered when the risk of lead extraction is higher than that of recurrent infection.

The total duration of therapy and the type of antibiotics will depend on the etiology and severity of infection and usually requires the expertise of an infectious disease specialist. Ideally, device reimplantation can be postponed until no further signs or symptoms of local or systemic infection are present. Following this, the new device should be implanted at a site remote from the original infected pocket to decrease the risk of recurrent infection.[84] At the authors' institution, a semi-permanent pacing system with an externalized active fixation permanent pacing lead attached to a pacemaker is used in dependent patients as a bridge to reimplantation (Figure 88-5).[91] This allows the patient freedom of movement and reduces the risk of dislodgment.

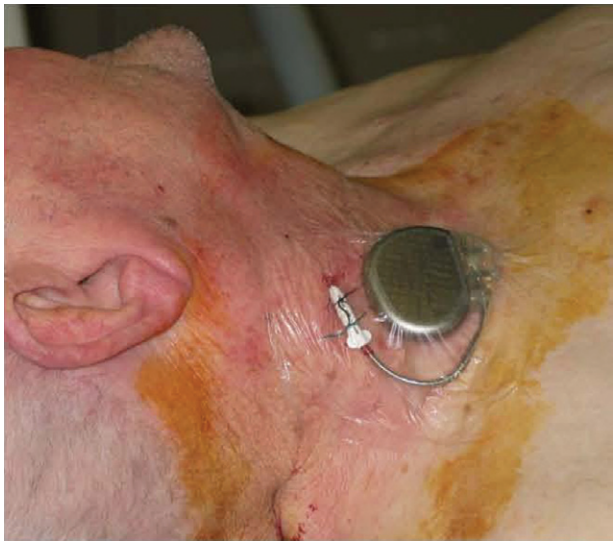

FIGURE 88-5 Semi-permanent pacing as a means of temporary pacing in a patient who underwent lead extraction for systemic infection. An active-fixation, permanent pacing lead is inserted into the right internal jugular vein and connected to an external permanent pacemaker. This provides longer-term, more stable fixation and allows patients to be ambulatory while undergoing antibiotic therapy prior to reimplantation.

Lead Extraction

The number of lead extractions is increasing in parallel with the increased number of device implants and, to some degree, because of expanding indications in patients at increased risks of lead malfunction and infection associated with increased lead age and multiple device replacements.[71] The reader is directed to a recent comprehensive review and extraction guideline by the Heart Rhythm Society.[92,93] *Lead extraction* is defined as the removal of a lead more than 1 year after implantation, where the lead removal requires specialized extraction tools or where the lead is removed by a route other than the implanting access site.[92] The indications for lead extraction are described in Table 88-9.[92] The most common reasons for extraction are infection (54% to 60%), removal of a nonfunctioning or incompatible leads (29% to 40%), and to facilitate device upgrade (8.8%).[89,94]

The risk of major complications associated with lead extraction is 0.6% to 5.6%.[44,95] These include death, superior vena cava (SVC) laceration, tamponade, septic shock, pulmonary or air embolism, tricuspid valve injury, pneumothorax, hemothorax, and hematoma at the pocket type.[96] The risk factors for complications are described in Table 88-10.[96-99] The presence of intracardiac vegetations increases the risk of pulmonary embolism associated with lead extraction. Most operators will perform transvenous lead extraction when vegetations are <2 cm in diameter.[71] Transvenous extraction of vegetations <4 cm in diameter has been performed.[98,100]

Lead extractions are most often performed in the operating room or in the procedure room, where access to emergency cardiovascular surgical backup, extracorporeal membrane oxygenation perfusion, and adequate fluoroscopy are readily available.[71] A pre-extraction checklist is provided in Table 88-11. In the operating room or the procedure room, the patient is connected to pads capable of defibrillation and pacing. The authors' group routinely performs lead extractions with general anesthesia and with arterial line access for continuous blood pressure monitoring, although some operators perform extraction with neuroleptic sedation and local anesthesia. Intravenous access is obtained with a large-bore catheter for urgent fluid resuscitation, as necessary, and the chest is prepared with sterile solution to prepare for urgent thoracotomy, if needed.[98,101] The authors obtain femoral vein access and place a long wire into the internal jugular vein contralateral to the extraction site to permit deployment of a 22-Fr SVC dilating balloon to tamponade bleeding in case of major vessel laceration.[102] This also allows for an access site for urgent circulatory support.[71] Continuous monitoring with transesophageal echocardiography is often performed to monitor for complications such as tricuspid valve regurgitation, pericardial effusion or tamponade, and embolization of vegetations.

Table 88-9 Indications for Lead Extraction

CLASS I INDICATIONS
Sepsis caused by infection of any intravascular pacing system component
Where the intravascular portion of the pacing system cannot be aseptically removed from the infected pocket
Life-threatening arrhythmias secondary to retained lead fragments
Where the lead or lead fragment poses an immediate or imminent physical threat
Thromboembolic events caused by retained lead or lead fragment
Obliteration or occlusion of all usable veins with the need to implant a new device
Retention of a lead that interferes with the operation of another implanted device
CLASS II INDICATIONS
Localized pocket infection
Erosion of chronic draining pocket that does not involve the transvenous portion of the lead system when the lead can be cut through a clean incision that is totally separate from the infected area
Occult infection where the pacing system is presumed to be the source of infection
Chronic pain at the pocket or lead insertion site that is refractory to medical or surgical alternatives
Where a lead which, because of its design, may pose a risk to the patient but where the threat is not imminent or immediate
Where a lead interferes with the treatment of a malignancy
Where a lead interferes with reconstruction of a traumatic injury
Where a lead prevents access to the venous circulation for newly required implantable devices
Nonfunctional leads in a young patient
CLASS III INDICATIONS
Any situation where the risk posed by removal of the lead is higher than the benefit of removing the lead
A single nonfunctional transvenous lead in an older patient
Any normally functioning lead that may be reused at the time of pulse generator replacement, provided the lead has a reliable performance history

Table 88-10 Factors that Increase the Risk of Complications with Lead Extraction

PATIENT FACTORS
Increased age
Female gender
Low body mass
Poor overall health and comorbid diseases
Inability to receive blood products for religious or antigenic reasons
Pacemaker dependency
LEAD FACTORS
Lead vegetations
Increased number of leads
Lead calcification
Increased lead age
Certain lead physical characteristics (fragile lead, extruding J with Accufix [Telectronics Pacing Systems] J lead)

Table 88-11 Pre-extraction Checklist

Discussion with patient about risks and benefits of extraction and alternatives
Anesthesia consultation
Discontinuation of anticoagulants
Investigations Cross-match for blood type Coagulation screen Imaging to document the intravascular course of all leads Echocardiogram to document the presence or absence of intracardiac vegetations
Documentation of device system Pacemaker dependency/amount of pacing Lead model(s) and design(s) (passive versus active fix; unipolar versus bipolar) Implantation date(s) Review of initial operative report (implantation technique, venous access, anatomic variants, any difficulty in lead position, etc.) Generator model

Extraction can be performed transvenously; with a parasternal, subxiphoid, or intercostal transthoracic approach; or with an open thoracotomy.[98] The latter two approaches are used only when a transvenous approach is not feasible, such as with very large vegetations. Transvenous extraction initially begins with incising and débriding of the pocket and freeing the leads from fibrosis through their extrathoracic course.[98] Electrocautery is advised for pocket dissection to reduce lead damage. The suture on the suture sleeve is dissected and removed, and the lead's retractable helix is retracted, if applicable. If the helix does not retract fully, counterclockwise rotation of the lead may free the tip from the endocardial surface. In potentially minimally fibrosed leads, the lead may be removed at this stage with constant, gentle traction. Caution should be exercised, as excessive force may damage the lead, thus limiting the ability to deploy a proper locking stylet, and may also result in chest pain, myocardial or SVC perforation, right ventricular collapse, and ventricular arrhythmias.[71] Extracting the most recently implanted lead first will often increase the success of the extraction of subsequent leads.[98,100]

Manual traction is more likely to be successful in leads that have been inserted for a short duration, but success has been reported even in cases where the lead had been in place up to 4 years. Manual extraction with traction alone is facilitated by leads with more tensile strength, such as those with silicone insulation or coaxially aligned conductor coils.[71,89]

If traction alone is unsuccessful, then a locking stylet should be inserted. Typically, lead preparation includes cutting the lead to remove the proximal connector component and cutting the insulation to expose the proximal inner conductor coil lumen. The lumen's inner diameter is sized with a sizing stylet to direct and lock the appropriately sized locking stylet. Recent universal locking stylets make sizing the lumen unnecessary. A suture is then tied from the insulation to the locking stylet such that manual traction can be applied to both the insulation and conductor coil via the locking stylet.[71,98] Manual traction with the use of a locking stylet results in successful lead removal in up to 46% of cases.[86,96] This appears to be more likely in leads that have been

in place for a short duration, those extracted because of systemic infection, and pacemaker leads as opposed to ICD leads.[89,96,98,103]

The inability to remove a lead with manual traction with or without a locking stylet is primarily caused by fibrosis around the lead. Fibrosis is more likely to occur in young people and at the venous entry site, at curves within the veins, and in the region from the anodal ring to the lead tip or ICD coils.[71] Patients at the extremes of age appear to have an increase in the degree of fibrotic calcification, a finding that also makes manual traction less successful.[71]

Sheaths can increase the likelihood of success of lead extraction as they disrupt, dilate, and cut through fibrous tissue when they track the lead within the vessel wall.[71] Sheaths are either nonpowered sheaths such as those made of steel, Teflon, and polypropylene or powered sheaths such as laser or electrosurgical dissection sheaths. The laser sheath cuts an oblique ring to a depth of 100 μm, whereas the electrosurgical dissection sheath uses radiofrequency energy at its tip to dissect through fibrous tissue.[71] Neither of the powered sheaths can cut through bone, though they may pass through calcified fibrotic tissue. Powered sheaths are more successful at disrupting fibrous tissue than are nonpowered sheaths.[71] Steel sheaths are used primarily for fibrosis at the venous access site, as they cannot follow the venous curves. Both Teflon and polypropylene sheaths are flexible and can track the lead as it courses within the venous system. Traction is placed on the lead and locking stylet as the sheath is advanced to allow it to track the lead within the vessel lumen. When advancing a powered sheath, the leading edge of the bevel should be kept toward the inside of the curve so that the vessel is not lacerated. Furthermore, when crossing the tricuspid valve, the leading edge of the bevel should be kept on the nonvalvular side (most often on the medial-superior portion of the tricuspid valve) to decrease the risk of valvular injury.

As the sheath is advanced, it may create a "snow plowing" effect by pushing fibrous tissue or the components of the lead forward. If this occurs, upsizing the sheath or withdrawing and redirecting the sheath with the bevel rotated in a different direction may allow the sheath to advance. Powered sheaths should not be used at the interface between the lead and the endocardium because of the expected effect of perforation. The blunt end of a nonpowered sheath should be used in a countertraction maneuver to advance the endocardium away from the lead while providing traction on the lead.[71,100]

Leads may be extracted to create a conduit for the insertion of a new lead.[71,95,104] If the lead dislodges from the endocardial surface prior to sheath insertion, the distal lead can be snared with a snare system inserted via the femoral vein. This allows countertraction to be placed on the distal portion of the lead while the sheath is inserted.[105]

Leads inserted into the thin-walled coronary sinus also appear to develop significant fibrosis.[71] These leads can also be extracted both by manual traction and the use of laser and other sheaths.[71] The technique is similar in that used for noncoronary sinus leads. However, powered sheaths should not be used within the coronary sinus because of the excessively high risk of tamponade. Additional care is necessary when using nonpowered sheaths within the coronary sinus, as it can be easily lacerated.[106]

At times, it is necessary to snare the lead from a catheter inserted into a remote vein, typically the right femoral vein. This may be the case if the lead is torn or cut and inaccessible from the initial extraction site, it cannot be extracted at its entrance site, or if a risk of tearing or puncturing the vein with the lead is present, as is the case with the Accufix J-wire if the wire is protruding.

Complete transvenous lead extraction is successful in 90% of cases.[96] Predictors of unsuccessful lead extraction include advanced lead age, multiple leads, ventricular and tined leads, and younger age of the patient.[71,96] Following transvenous lead extraction, it is recommended that the patient be observed in the hospital for 24 hours and have a chest radiograph and transthoracic echocardiogram performed to ensure no late complications are present.[102] In the authors' experience, local venous thrombosis is sufficiently common, anticoagulation is routinely started within 24 hours and continued for 4 weeks following extraction to prevent subclavian vein thrombosis, particularly if there has been significant endovascular manipulation.[92,98,100,107]

Approach to a Lead Advisory

The reader is directed to the recently published comprehensive *Heart Rhythm Society Guidelines* on lead monitoring and advisories.[43] A description of the function and response system of the Canadian Heart Rhythm Society's Device Advisory Committee is also summarized in two recent papers.[108,109] The course of action in the event of a lead advisory is determined by balancing the risk of death or serious harm with close follow-up alone with the risk of operative treatment such as the placement of a new lead with or without extraction of the advisory lead. These risks depend on patient factors such as pacemaker dependence, comorbid illnesses, risk of surgical revision or replacement, anxiety about lead failure, and the risk of future ventricular arrhythmia in patients with ICDs. Lead factors that alter these risks include the rate and predictability of lead failure, clinical consequences of lead failure, and the availability of systems that warn or mitigate this risk.[110] Recent device advisories have resulted in early device replacement, arguably a procedure with less risk than lead extraction. This operative intervention has resulted in unexpectedly high complication rates, which emphasizes the importance of careful risk assessment.[111-113] Currently, it is recommended that a noninvasive approach be used in patients with pacemakers who are not pacemaker dependent, in patients with ICDs who have never had a ventricular arrhythmia (both before and after ICD insertion), and in patients whose operative risk is high.[30,43]

Conclusion

Leads for implanted devices have become increasingly capable and complex. Although lead malfunction is not common, leads are clearly the "weak link" of the device system. Lead design must not only facilitate insertion but also focus on withstanding significant daily mechanical stress. To minimize the complications associated with lead malfunction, the causes of lead failure must be recognized and the means to detect problems and their appropriate management must be well understood.

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CHAPTER 89

Diagnostic Aspects of Implantable Devices

Paul Ziegler, Douglas Hettrick, Luigi Padeletti, and Sanjeev Saksena

Implantable devices were originally introduced for the treatment of cardiac rhythm disorders. Monitoring of cardiac rhythm was intrinsic to the function and intervention of these devices. Since the introduction of cardiac pacing in the 1960s, the monitoring function has gradually expanded, but a marked acceleration in this capability has been seen only in the past 2 decades. Concomitantly, the role of implantable device therapy to prevent bradycardia has expanded to include delivery of anti-tachycardia pacing and defibrillation, cardiac resynchronization therapy, and atrial fibrillation (AF) reversion with electrical techniques. Recent developments in monitoring now include qualitative and quantitative measurements of AF, ventricular tachyarrhythmias, bradycardias, hemodynamic status, and intracardiac pressures or electrograms on a continuous time-stamped basis. This chapter will discuss the salient diagnostic information currently available from implantable rhythm management devices.

Monitoring of Atrial Fibrillation

Atrial tachycardias and atrial fibrillation (AT/AF) are significant components of the global burden of cardiovascular disease and their incidence is increasing rapidly because of the aging of the population; projections indicate that the prevalence of AF could exceed 12 million in the United States by 2050.[1] These conditions occur concomitantly with bradycardias, supraventricular tachycardias, and ventricular tachyarrhythmias and are frequently observed in populations with these conditions when an implantable device is prescribed therapeutically.

Atrial tachyarrhythmias result in poor quality of life for patients, as they may cause symptoms of tiredness, palpitations, and dizziness. However, in many patients, AT/AF episodes can be completely asymptomatic.[2,3] Whether it is symptomatic or asymptomatic, AT/AF also increases the risk of stroke in the presence of clinical risk factors, and it is estimated that 1 out of every 6 strokes occurs in patients with AT/AF.[4] It leads to more hospital admissions than any other arrhythmia and increases mortality rates.[5,6] Management of this arrhythmia with pharmacologic agents, ablation, and implantable devices requires accurate assessment of the arrhythmia at baseline and after treatment. Regardless of the AF treatment strategy chosen, diagnostics from implantable devices can provide valuable information to help evaluate treatment efficacy and guide clinical decisions. Other important clinical imperatives for monitoring include the following:

1. Physicians need to evaluate if a patient's symptoms are caused by AT/AF. When confirmed, symptoms may be related to rapid ventricular response to AT/AF, loss of atrial contribution to cardiac output, or rapid atrial rates. In all instances, rhythm monitoring is valuable in assessing symptoms.

2. If a rhythm control strategy is selected, the objective is to reduce the total duration (burden) of AT/AF that a patient has had over a given period.

3. In contrast, rate control requires maintenance of physiologically appropriate ventricular rates during AT/AF. Maintaining ventricular rate control within prespecified target limits during AT/AF is associated with improvement of these symptoms.[7]

4. If the patient's symptoms are not the result of AT/AF, other potential causes for either of these complaints can be explored.

5. Measurement of symptomatic or asymptomatic AT/AF episodes can be used to assess need for anticoagulation therapy and its maintenance.

6. Monitoring allows physicians to quantify and objectively assess the efficacy of their rhythm and rate control therapies. Optimization of treatment strategies based on AT/AF diagnostics may lead to improved patient outcomes.

Monitoring Methods

Monitoring of AT/AF has traditionally relied on patient-reported symptoms or the intermittent use of external devices to capture asymptomatic episodes. However, both approaches have significant limitations in the diagnosis and management of atrial arrhythmias.

Symptoms Versus External Recorders

Monitoring AT/AF on the basis of patient symptoms is appealing because it is relatively inexpensive and has clinical relevance. However, studies have shown that the vast majority of AT/AF episodes are asymptomatic and that most symptoms attributed to AT/AF are not actually associated with arrhythmia.[2,3,8,9] Therefore, even if supplemental event recorders are used to verify the presence of an arrhythmia during symptoms, most atrial arrhythmias

will escape detection because of lack of symptoms. Since the risk of stroke is similar among patients with symptomatic and asymptomatic AT/AF, current anticoagulation guidelines do not differentiate on the basis of symptoms,[10] which emphasizes the importance of identifying asymptomatic AT/AF.[10-12]

Because of the highly insensitive and nonspecific nature of patient symptoms, external devices were developed to monitor asymptomatic episodes of AT/AF. External devices such as Holter monitors are commonly used to continuously record cardiac data for 24 or 48 hours. Newer systems, such as mobile cardiac outpatient telemetry, are capable of monitoring patients continuously for up to 30 days and have been shown to increase the yield for arrhythmia detection compared with a single 24-hour Holter monitor.[13,14] These systems have the benefits of moderate cost and being a noninvasive procedure. However, these external devices often are bulky and interfere with daily activities such as showering. In addition, the patch electrodes can cause skin irritation with prolonged use. Consequently, patient compliance with such systems often is quite low.[8,13] Furthermore, since external monitoring can only be performed intermittently over time and for relatively brief durations, the likelihood of missing paroxysmal episodes of asymptomatic AT/AF episodes is quite high.

Implantable Monitors

Therapy Devices

Devices such as implantable pulse generators, implantable cardioverter-defibrillators (ICDs), and cardiac resynchronization therapy (CRT) devices are capable of monitoring arrhythmias continuously over the lifetime of the device with a high sensitivity as well as a high specificity for AT/AF detection.[15,16] Although these devices require an invasive implantation procedure, patient compliance is generally not an issue, and these devices rarely interfere with normal daily activities. Patients can communicate with many modern implantable devices via an external activator to record the occurrence of symptoms in the memory of the device. This symptom information can be retrieved later by the clinician when the device is interrogated via telemetry. However, the monitoring capabilities afforded by these sophisticated devices are available only to those AF patients with comorbid conditions requiring device therapy.

Subcutaneous Monitors

One strategy to address the need for continuous monitoring in a broader population of patients with AF is to use small implantable devices that are capable of monitoring atrial arrhythmias continuously over the lifetime of the device with a high sensitivity and a high specificity for AT/AF detection.[17] These devices, about the size of a cigarette lighter, do not have intracardiac leads, as the bipolar recording electrodes are generally located on the surface of the device itself. These monitoring devices are placed subcutaneously, are relatively small in size (3 to 5 cm), and are typically implanted in the left pectoral region in the precordial area, though axillary implants have been described (Figure 89-1, *A*). Implantation parallel to and in an intercostal space is most desirable for avoidance of local erosion and aesthetics. A local anesthetic agent is infiltrated at the site of entry and in the adjoining subcutaneous tissue where the device pocket will be made. Typically, a small (1 to 2 cm) vertical or horizontal incision is made at one end of the pocket, and the pocket created by blunt dissection (Figure 89-1, *B*). The device is placed and the electrogram quality assessed using a hand-held wand or wireless connection by the device programmer. If clear electrogram quality and satisfactory amplitude are obtained, the pocket can be closed. If not, device repositioning is needed so that the surface electrodes have an appropriate vector to obtain quality recordings. Although a small skin incision is required to implant these devices, patient compliance is not an issue, as these devices rarely interfere with normal

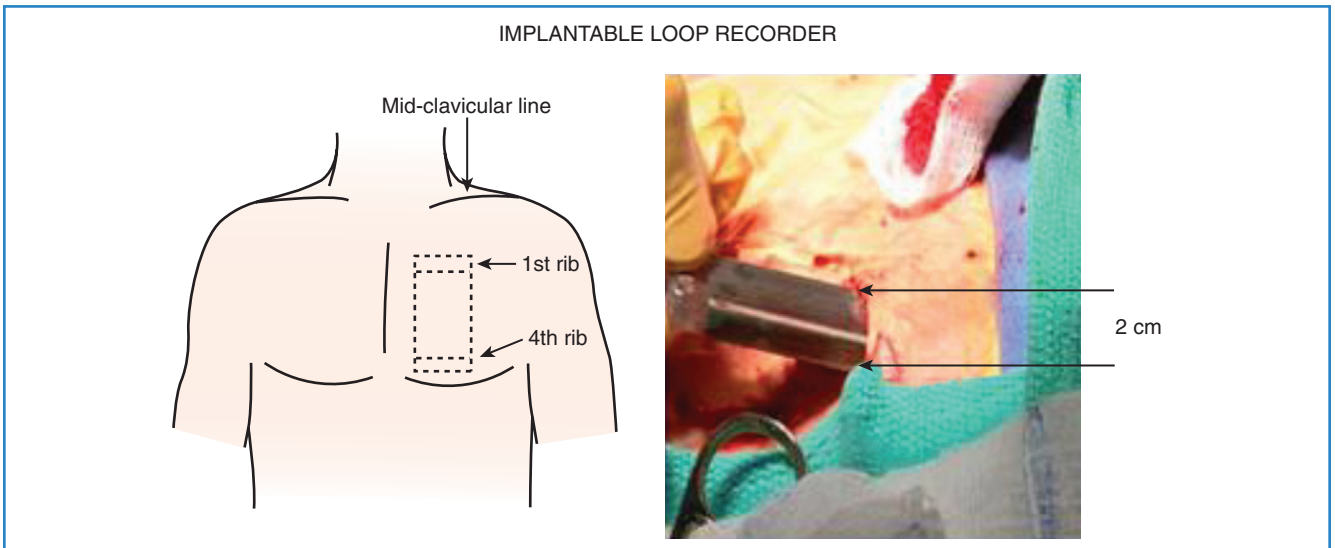


FIGURE 89-1 Surgical placement of an implantable loop recorder device. **A,** Schematic of potential locations in the left-sided intercostal spaces of the recorder. **B,** The recorder being inserted subcutaneously through a 2-cm incision with local anesthesia. Longevity of the recorder is 3 years. Event storage with electrocardiogram is 49.5 minutes: 22.5 minutes for patient-activated episodes and 27 minutes for automatic activated episodes (ventricular tachycardia, fast ventricular tachycardia, asystole, bradycardia [1-minute episodes], atrial tachycardia, and atrial fibrillation [2-minute episodes]). Total event logs include 180 automatic and 10 patient activated.

daily activities. Until recently, subcutaneous monitoring devices had only been available for the diagnosis of syncope, but they have now become available for the monitoring of atrial arrhythmias as well. Patients are able to record the occurrence of symptoms in the memory of the device with an external activator, and these data can be retrieved later by the clinician.

Comparison of Monitoring Methods

Methods of identifying patients with AT/AF through their symptoms, intermittent external monitoring, and continuous monitoring with implantable devices have been compared in a recent study.[18] Symptom-based and intermittent external monitoring methods were shown to have significantly lower sensitivity (range, 31% to 71%) and negative predictive value (range, 21% to 39%) for identification of patients with AT/AF (Figure 89-2) and underestimated AT/AF burden, compared with continuous monitoring. The reported efficacy of clinical procedures such as pulmonary vein ablation for the treatment of AT/AF can vary greatly, depending on how the arrhythmia is monitored. One study reported a success rate of 70% on the basis of symptoms alone and only 50% when intermittent external monitoring was also considered.[8] These results were achieved despite the fact that 47% of the patients did not complete the external monitoring protocol and compliance with the monitoring schedule was only 42%. Such results highlight the clinical need for continuous monitoring that does not rely on patient symptoms or patient compliance.

Data Collection and Organization

While implantable devices are capable of continuously monitoring cardiac rhythms over the life of the device, two important reasons why this information must be condensed and summarized must be considered. First, memory limitations of the device would not permit continuous storage of electrogram and other data for each cardiac cycle. A patient experiences approximately 100,000 heartbeats per day and 6 months may elapse between follow-up visits, at which time the data can be extracted from the device via telemetry. This means that the device might monitor more than 18 million heartbeats between clinic visits. Second, this amount of data would be far too much for the physician to process and interpret for each patient. The challenge for device manufacturers is to convert this vast amount of *detection* information into *diagnostic* information that is manageable for both the device and the clinician.

To accomplish this, the device stores information on atrial arrhythmias in a hierarchical fashion. Extremely detailed information is stored for only a small subset of the episodes, while very general information is tabulated across all episodes. For example, one of the most memory-intensive pieces of information is the electrogram waveform. These data can be crucial for the clinician to verify that the device is detecting correctly and aid in troubleshooting when it is not. Because this information requires extensive amounts of memory (as well as additional battery resources), only small portions of electrograms from a select number of episodes are stored by the device. On the other end of the spectrum, a continuous running tally of the duration of all AT/AF episodes is important so that the physician can assess the AT/AF burden experienced by the patient. Between these two extremes are a variety of other parameters that may be tabulated per episode, per day, or per follow-up period. The goal is to strike a balance between not providing enough information to be clinically useful in managing the patient and providing too much data that would overwhelm the clinician. Specific examples of device diagnostics for rhythm control, rate control, and anticoagulation management of patients with AT/AF will be presented in the remainder of this section.

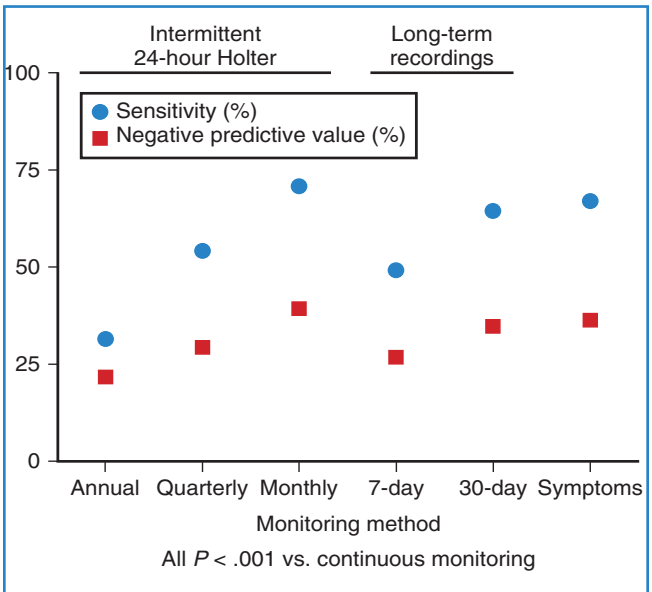


FIGURE 89-2 Sensitivity and negative predictive value for identification of patients with any atrial tachycardia/atrial fibrillation episodes identified by various intermittent external monitoring methods or patient symptoms. *Annual, quarterly,* and *monthly* refer to 24-hour Holter recordings.

Rhythm Control

One of the most important diagnostics for rhythm control is to know what percentage of time was spent in an atrial arrhythmia (i.e., AT/AF burden). Accurate monitoring is crucial whether or not the patient is being treated by ablation, drugs, device therapies.

Figure 89-3 shows diagnostic information that can be used to evaluate the efficacy of rhythm control. The total hours of AT/AF per day (AT/AF burden) can be continuously monitored over a period of 14 months before the data get overwritten. Other diagnostics that can provide additional rhythm control clarity are an AT/AF episode duration histogram, episode start time histogram (Figure 89-4), and the duration of the longest episode.

Pulmonary Vein Ablation

Figure 89-5 shows a series of patients who were treated for AT/AF by undergoing a pulmonary vein ablation procedure anywhere from 6 to 36 months after device implantation. These patients had a pacemaker implanted for their bradycardia, and the device was subsequently used to monitor the effectiveness of the ablation procedure. Patient data are aligned such that the date of ablation corresponds with month 0. The amount of AT/AF experienced each day is plotted over the follow-up period and shown in blue. Despite an improvement in symptoms and quality of life in all patients after the ablation, many still experienced significant amounts of AT/AF.[19] This example also illustrates that after an

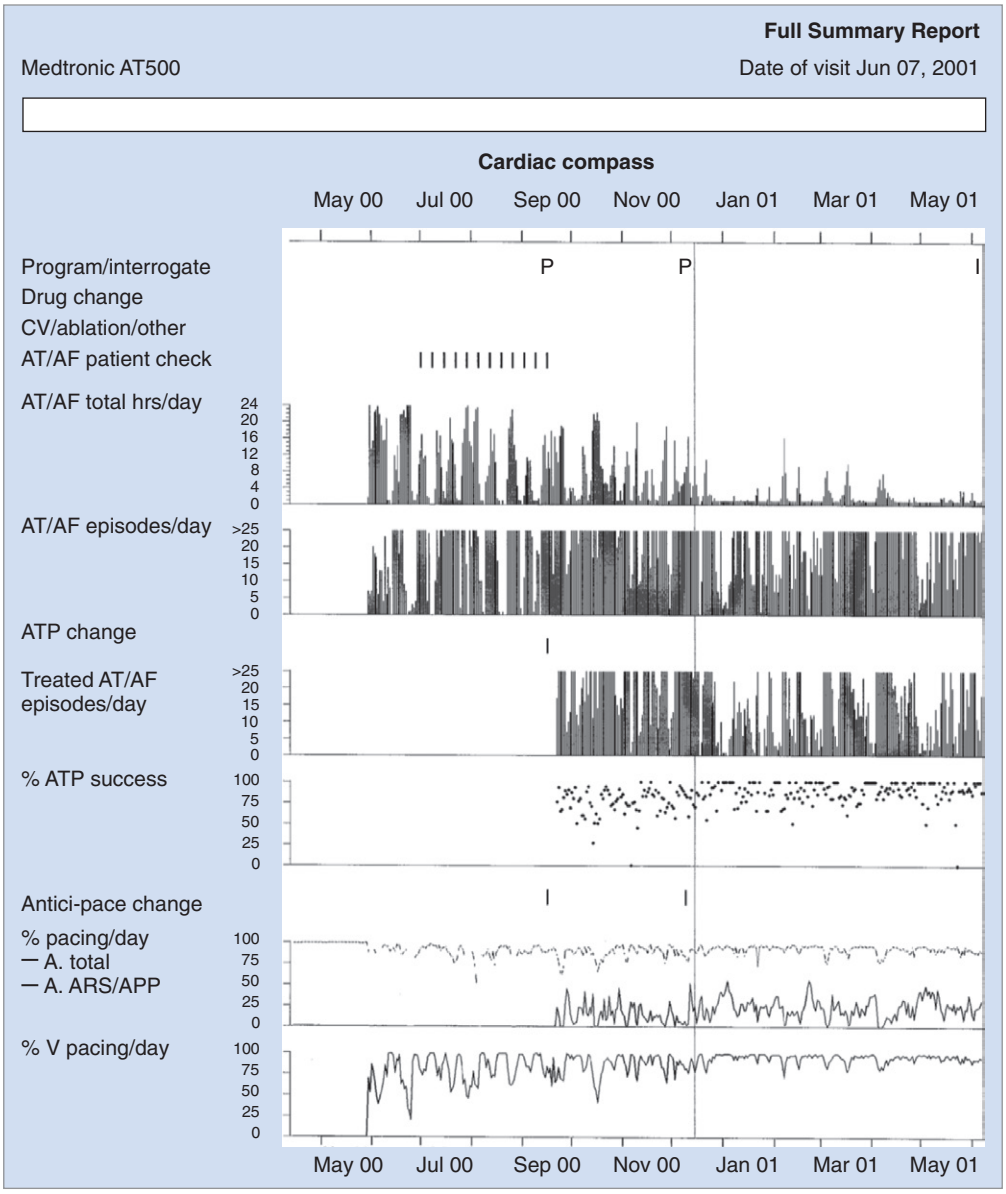


FIGURE 89-3 Diagnostic data from a patient with an implanted pacemaker. Various physiological parameters are plotted daily for up to 14 months. Marks made by the patient with atrial tachycardia/atrial fibrillation (*AT/AF*) indicate when the patient marked an AT/AF episode as being symptomatic. Daily burden (AT/AF total hours per day) and frequency (AT/AF episodes per day) of AT/AF are plotted along with treated episodes per day, percent anti-tachycardial pacing (*ATP*) efficacy, and percent atrial and ventricular pacing per day.

ablation procedure, patients can go for many months without an AT/AF episode and subsequently experience recurrences that would be difficult to record with intermittent monitoring methods. This long-term trending information enabled the physicians conducting the study to perform additional ablation procedures (indicated by the red arrows) in select patients who did not respond completely to the initial procedure.

Antiarrhythmic Drugs and Cardiac Pacing

Response to antiarrhythmic drug therapy can be assessed by device-based diagnostic data. Figure 89-6 shows an example of change in AT/AF burden, with conversion of persistent AF to paroxysmal AF, after the initiation of sotalol. The patient continued to have symptomatic paroxysmal AF and was then transitioned to dronedarone, which resulted in the resolution of symptomatic paroxysmal AF.

Recurrence Patterns

While there is clinical value in knowing whether or not a patient has experienced AT/AF and the percentage of time that has been spent in AT/AF, understanding the pattern of these AT/AF recurrences may be of additional value. The patient data in Figure 89-7 show a very consistent recurrence pattern that persists for the entire 14-month period covered by device diagnostics. On closer

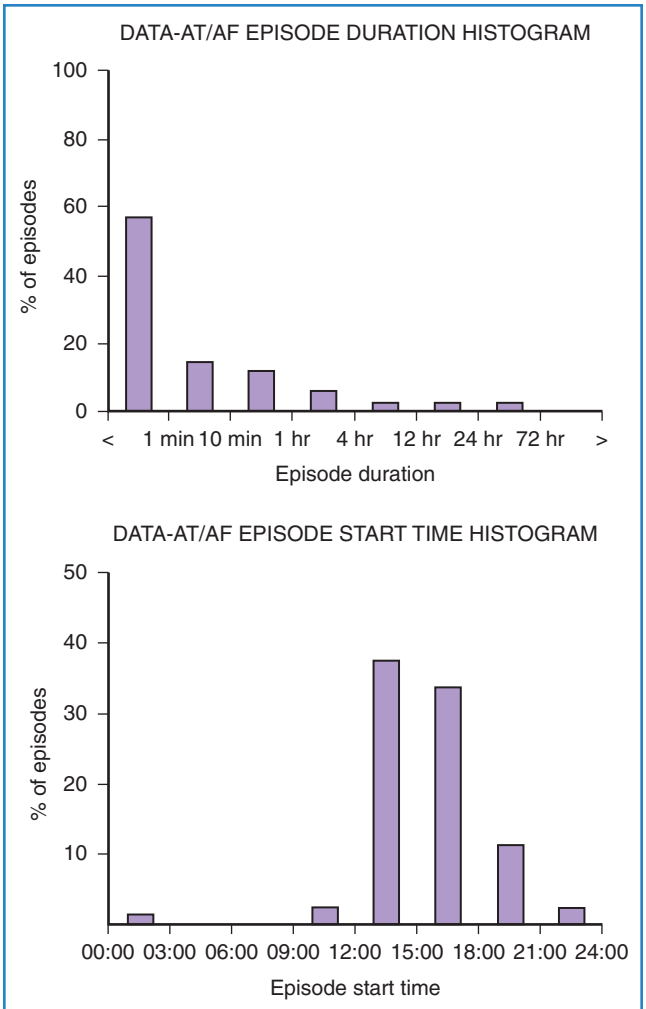


FIGURE 89-4 Atrial tachycardia/atrial fibrillation (*AT/AF*) duration (*top*) and AT/AF episode start time (*bottom*) histograms, which are device diagnostics used in assessing the efficacy of rhythm control.

examination, it was found that this patient experienced AT/AF predominantly on weekends, with episodes generally initiating on Fridays or Saturdays and typically terminating on Sundays or Mondays. With intermittent arrhythmia monitoring, it might have been erroneously concluded that this patient was either always in AT/AF or always in sinus rhythm, depending on the day(s) selected for monitoring. With continuous monitoring, a more complete picture of the patient's arrhythmia can be obtained, which may provide additional insight into the patient's disease and lead to different treatment strategies. In addition to providing more complete information on individual patients, device diagnostics can inform us on the nature of atrial arrhythmias across entire populations. Figure 89-8 shows the percentage of patients with implantable devices (pulse generator, ICD, and CRT) who experienced at least 5 minutes of AT/AF over each day of the year.[20] A clear pattern is seen, with a peak incidence in the month of May and a minimum incidence 6 months later in November. While the underlying cause of this cyclic variation is not fully understood, it is interesting to note that the occurrence of stroke has been shown to exhibit a similar recurrence pattern.[21]

Transition from Paroxysmal Atrial Fibrillation to Persistent Atrial Fibrillation

AT/AF recurrence patterns are not static and may change over time as the disease progresses or as new treatments are applied. Device diagnostics have shown that the transition from paroxysmal AT/AF to more persistent forms of AT/AF can occur relatively abruptly (Figure 89-9).[22,23] This finding is consistent with changes in the substrate as opposed to an increase in atrial premature beat triggers or paroxysmal AT/AF episodes. This monitoring approach shows the progression of persistent AF events as well as promotes understanding of the disease state.[23] Device diagnostics can heighten the awareness of this sudden change in the arrhythmic state so that a change in treatment strategy can be implemented in a timely manner.

Rate Control

For several reasons, it is important to control the ventricular rate in patients with implantable devices, as listed below:

1. Rapid and irregular ventricular rates can cause symptoms of palpitations, dyspnea, and angina or precipitate heart failure in many patients.

2. The likelihood of inappropriate shocks being delivered to patients with ICDs is increased by poor rate control during AT/AF. Although it occurs infrequently, rapid and irregular ventricular conduction can occasionally mislead the device into sensing that a life-threatening ventricular arrhythmia is present, which would result in painful unnecessary shock delivery to the patient.[23]

3. Control of the ventricular rate is necessary to ensure that patients with CRT devices receive continuous therapy. With CRT, pacing leads in the right and left ventricles are used to synchronize ventricular contraction and mitigate the effects of heart failure. Rapid intrinsic ventricular rates during AT/AF inhibit the delivery of CRT therapy.[24]

Rate Control Diagnostics

Some implantable devices have the capability to continuously monitor the ventricular rate during AT/AF and to report this information as a daily tabulation of the average and maximum ventricular rates over the past 14 months (Figure 89-10, *A*) or as a histogram of rates since the previous follow-up visit (Figure 89-10, *B*). The average ventricular rate during sinus rhythm can also be reported separately for day and night periods. Timely notification of poor rate control may help clinicians prevent the occurrence of symptoms, reduce inappropriate shocks, and ensure continuous CRT therapy in patients with AT/AF. Some newer devices have a wireless alert feature that can notify the clinician if the average ventricular rate exceeds a specified threshold for a programmable period (Figure 89-11).

Anticoagulation

Continuous monitoring of rhythm control is critically important for managing a patient's anticoagulation regimen. Key questions

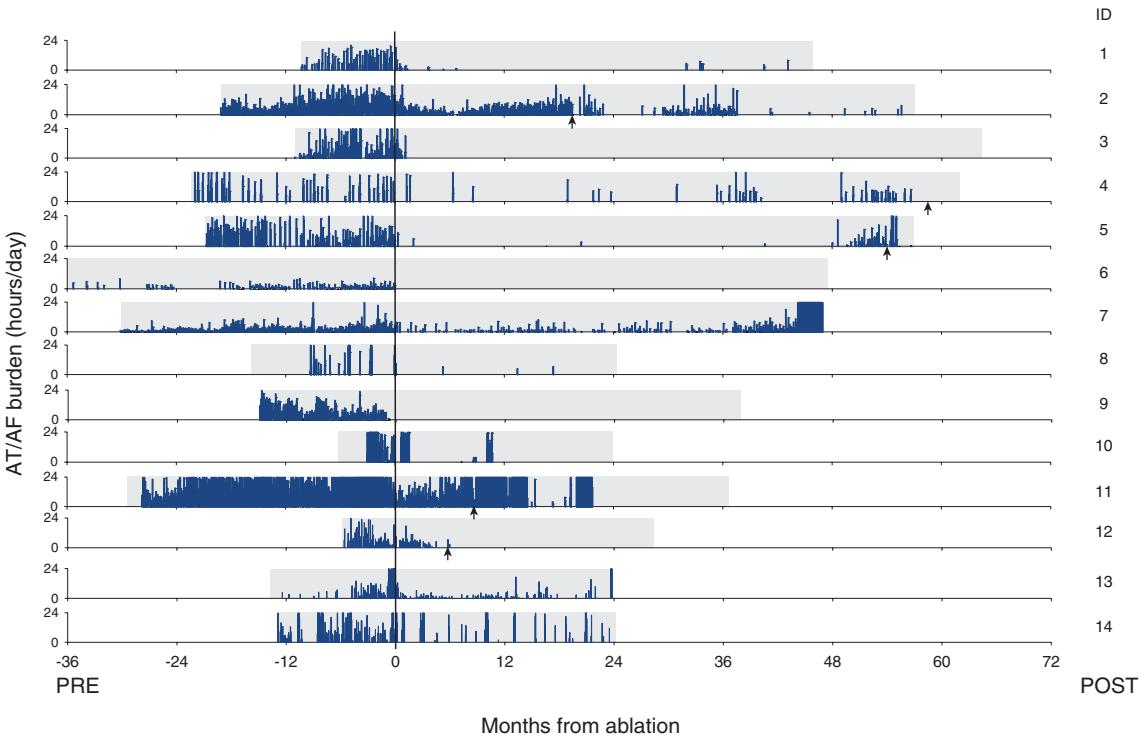


FIGURE 89-5 Daily atrial tachycardia/atrial fibrillation (*AT/AF*) burden both before (*PRE*) and after (*POST*) pulmonary vein ablation in 14 patients. *Gray shading* indicates the follow-up experience for each patient, and the *blue lines* indicate the AT/AF burden experienced each day. Repeat ablation procedures are indicated by the *arrows*.

involve timing of initiation of anticoagulation therapy and timing of safe discontinuation. Current guidelines recommend anticoagulation for patients with risk factors and AT/AF, regardless of the amount of AT/AF or associated symptoms.[10] Therefore, it is important to identify patients who experience even relatively brief episodes of AT/AF. Studies have shown that continuous monitoring via implantable devices is particularly well suited to this purpose.[18] The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study demonstrated a high risk of stroke in patients who discontinued anticoagulation because it was thought that rhythm control was adequate on the basis of symptoms and infrequent monitoring.[7] Studies are in progress to assess the risk of manifest stroke or cryogenic stroke in populations with AF using these devices. The example in Figure 89-5 also shows that patients can go for many months without an AT/AF episode only to experience recurrences that would be difficult to capture with intermittent monitoring methods. Key to timely anticoagulation management may be the early notification of "new-onset" AT/AF (i.e., a patient's first episode of AT/AF). With most implantable devices, the clinician does not become aware of the presence of new-onset AT/AF until the patient's device is interrogated in the clinic setting. This could cause a delay of up to 6 months from the time of the first AT/AF occurrence to the first opportunity to treat it. Some newer devices with wireless alert capabilities can automatically send a notification to clinicians when a programmable AT/AF burden threshold is exceeded on a given day (see Figure 89-11). This early notification could enable physicians to intervene sooner and initiate an anticoagulation regimen, thus reducing the risk of stroke in patients who were unaware of their atrial arrhythmias. Figure 89-12 shows data from a patient without a history of AF and no device-recorded AF in the first 8 months following implantation. However, the patient then abruptly went into an episode of persistent AF and suffered an ischemic stroke 8 days after the onset of AF. While this device did not have the capability to notify the physician or the patient as to the presence of AF, the time (8 days) would have been sufficient to implement a treatment strategy to prevent this event had there been awareness of AF. As mentioned before, some modern implantable devices have the capability to generate wireless notifications when prolonged AF episodes occur. Another study showed that approximately 30% of patients with a prior history of thromboembolism and no history of AF were identified as having newly detected AF (NDAF) via continuous monitoring with implantable devices.[25] While AF occurred on fewer than 10% of follow-up days in 72% of patients with NDAF, it also persisted for at least 6 hours on at least a day in the majority of patients with NDAF. This highlights not only the difficulty of detecting AF with traditional methods but also the importance of identifying AF in this population. In fact, 62% of patients with NDAF were identified beyond the initial 21 days of the study, which suggests the value of long-term arrhythmia monitoring in this population.

Burden Thresholds for Stroke

While the exact relationship between AT/AF burden and stroke risk is not fully understood, data from implantable devices can be used to gain a better understanding. Several earlier studies have

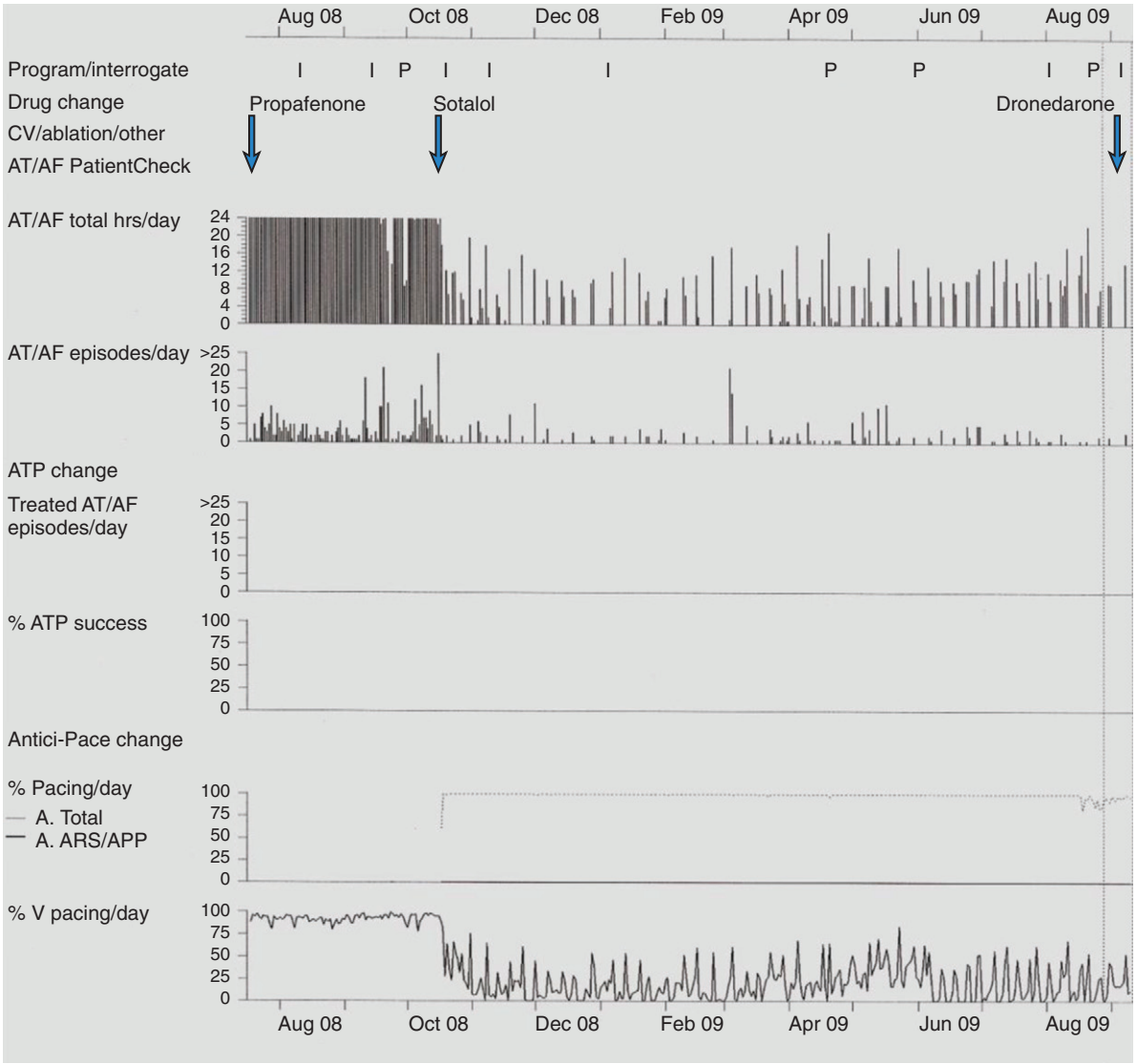


FIGURE 89-6 Example of an implantable pacemaker report showing monitoring of atrial fibrillation (*AF*) burden, episodes, and pacing interventions over a 1-year period. The relationship to drug therapy is shown. The patient was in persistent AF during propafenone therapy, and introduction of sotalol converted this to paroxysmal AF. The patient remained symptomatic and was switched to dronedarone, which resulted in improvement in symptoms and reduction in events. *AT,* Atrial tachycardia; *CV,* cardiovascular.

examined the relationship between AF burden and outcome in patients with devices. A substudy of the Mode Selection Trial (MOST) reported that the composite endpoint of non-fatal stroke and death was significantly higher in patients having at least 5-minute episodes of high-rate atrial arrhythmias.[26] A study by Italian investigators showed that atrial arrhythmias lasting longer than 24 hours increased the risk of thromboembolic events threefold compared with those having shorter duration or no episodes.[27] The TRENDS study reported that an arrhythmia burden of 5.5 hours or more on any of the past 30 days appeared to double the risk of thromboembolic events compared with no burden.[28] Taken together, these studies suggest that quantitative AT/AF burden detected by implanted devices is a risk factor for thromboembolism and that the burden threshold for increased risk may be relatively low.

Potential Role of Device Monitoring in Heart Failure Therapy

Long-term management of patients with congestive heart failure is a growing burden on health care systems. In addition, signs and symptoms within this population are often poorly correlated with actual disease status.[29,30] Swan-Ganz catheterization and echocardiography are costly and not well suited for repeated serial measurement. Recently, considerable investigation has focused on the development of alternative methods of assessing the disease status in heart failure. Implantable hemodynamic sensors offer a potential surrogate for serial invasive catheterizations in tailoring and titrating medical therapy. Furthermore, continuous monitoring of hemodynamic measurements might

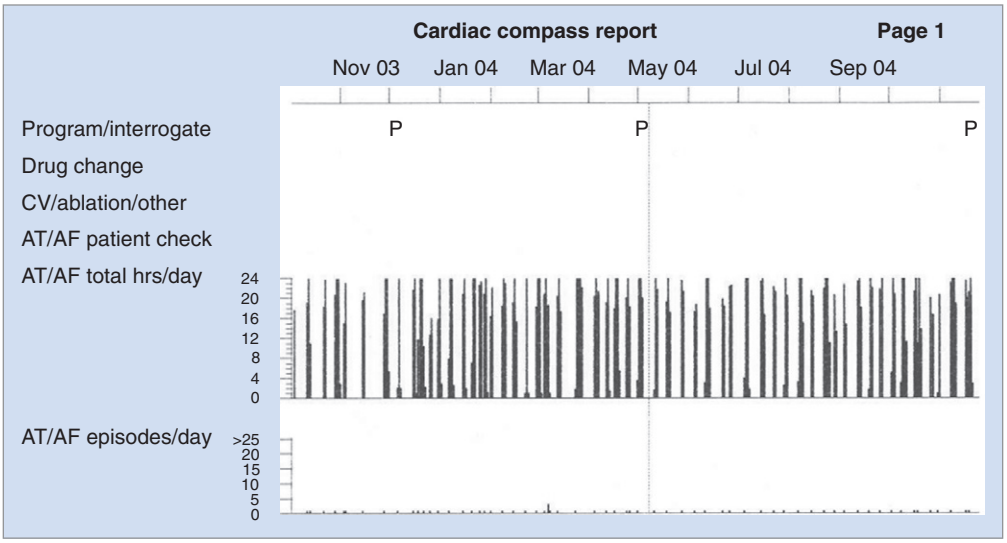


FIGURE 89-7 Unique and repetitious atrial tachycardia/atrial fibrillation *(AT/AF)* burden pattern from a patient who predominately experienced AT/AF on Saturdays and Sundays. *CV,* cardiovascular.

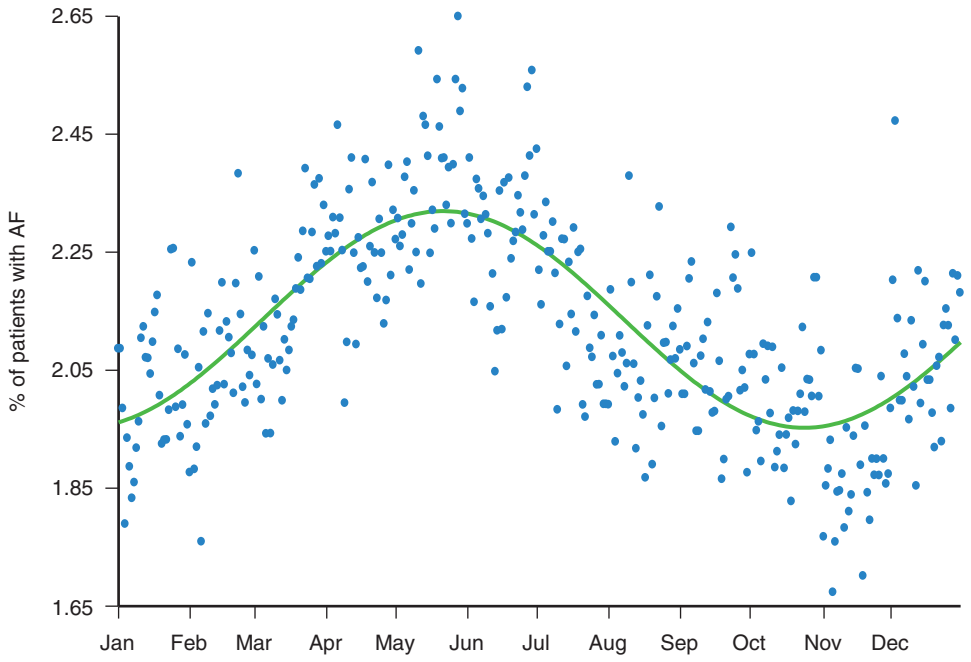


FIGURE 89-8 The percentage of northern hemisphere patients who experience at least 5 minutes of atrial tachycardia/atrial fibrillation (*AF*) on any given day, with a peak in May and a valley in November.

provide unique insights into pathophysiological mechanisms and chronic responses to therapeutic regimens.

Pressure Monitoring System

Right-Sided Pressure Monitoring

A totally implantable hemodynamic monitor (IHM) system consists of a pacemaker-like device that processes and stores information and a transvenous lead incorporating a high-fidelity pressure sensor near its tip.[31] The implantation procedure is similar to that of a single-chamber pacemaker system. The pressure sensing lead is positioned in the right ventricular outflow tract or in the high right ventricular septum in an area of high blood flow. In addition to right ventricular systolic and diastolic pressures and estimated pulmonary arterial diastolic pressure, the IHM also measures and stores peak positive and negative dP/dt, heart rate, patient activity, right ventricular pre-ejection and systolic time intervals, and body temperature. A strong correlation (r = 0.84) has been demonstrated between actual pulmonary artery pressures and the

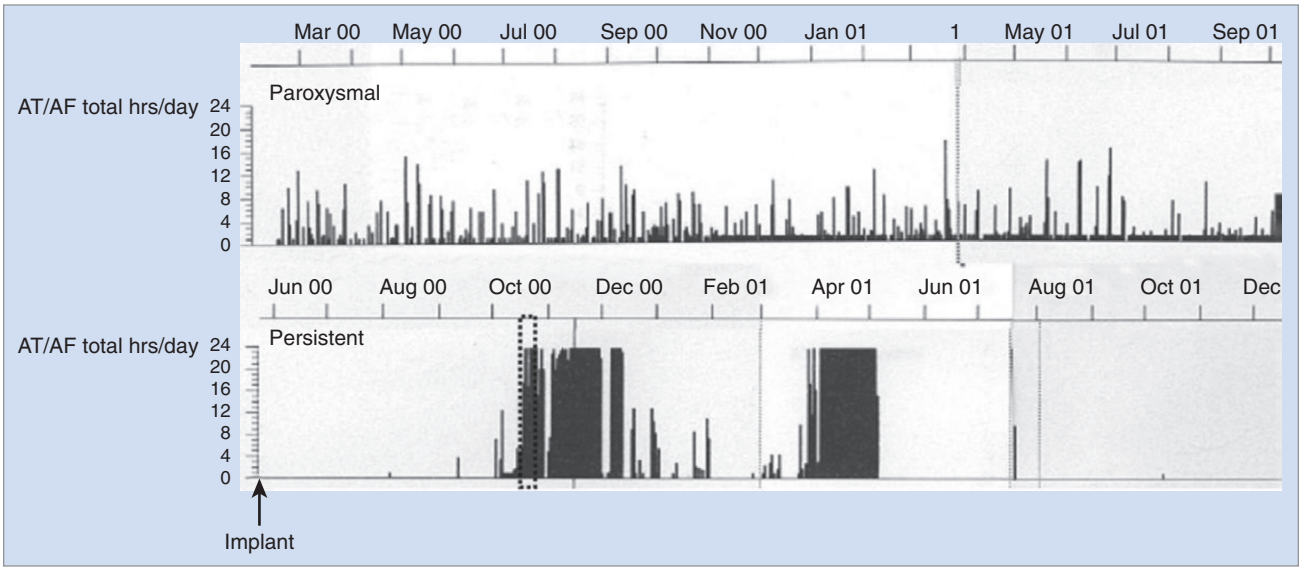
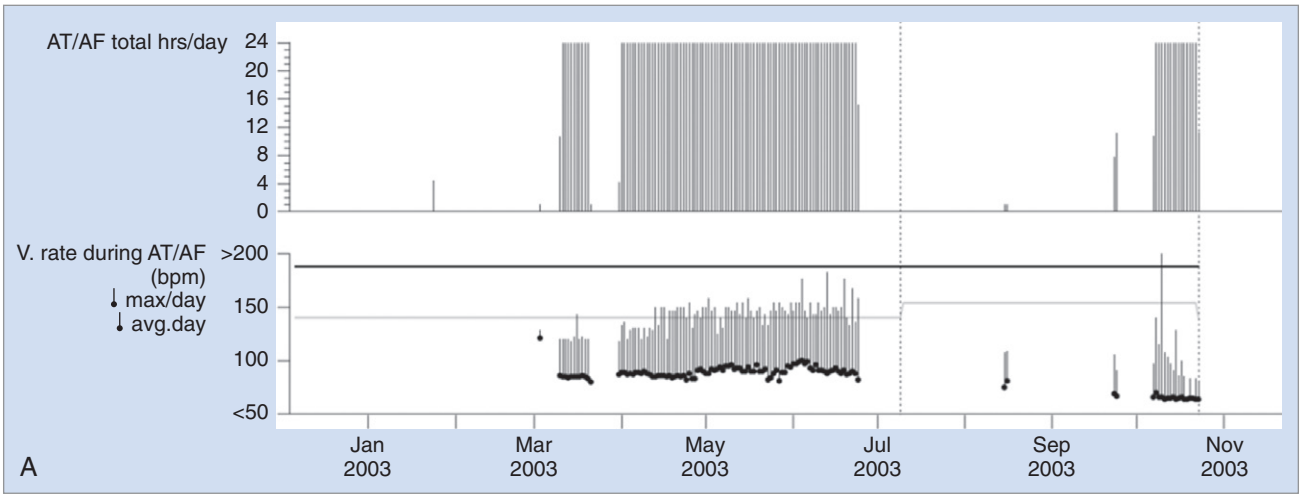


FIGURE 89-9 Device-recorded daily atrial tachycardia/atrial fibrillation (*AT/AF*) burden for two patients. Data from the first patient (*top*) show typical patterns of paroxysmal AT/AF recurrence beginning at the day of implant (*arrow*). The data from the second patient (*bottom*) demonstrate the abrupt transition from paroxysmal AT/AF to persistent (sustained) AT/AF around mid-October of 2000 (*dotted line*). Complete datasets for each patient were concatenated from multiple follow-ups. AT burden over time is quite stable in the patient with paroxysmal AF (*top*), whereas the burden transitions abruptly from paroxysmal to persistent in the second patient (*bottom*).



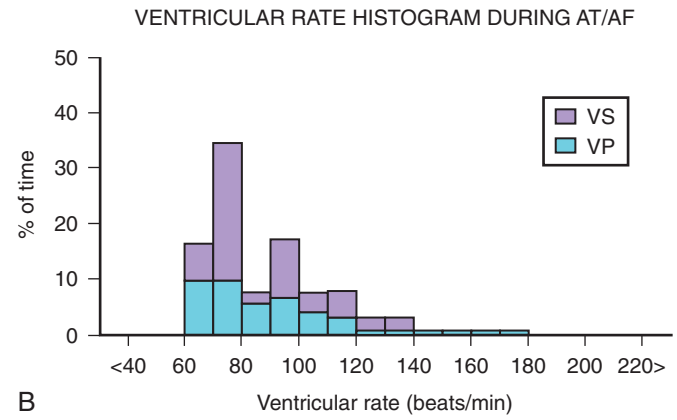


FIGURE 89-10 A, Implantable devices can track measures of rhythm control (atrial tachycardia/atrial fibrillation [*AT/AF*] total hours/day) and rate control (*V*, rate during AT/AF) over extended periods. The average and maximum ventricular rates during AT/AF are tabulated on a daily basis to show trends in these parameters. **B,** A histogram of ventricular rates (*VS*, ventricular sense, *VP*, ventricular pace) during AT/AF can be used to assess rate control efficacy between follow-up visits.

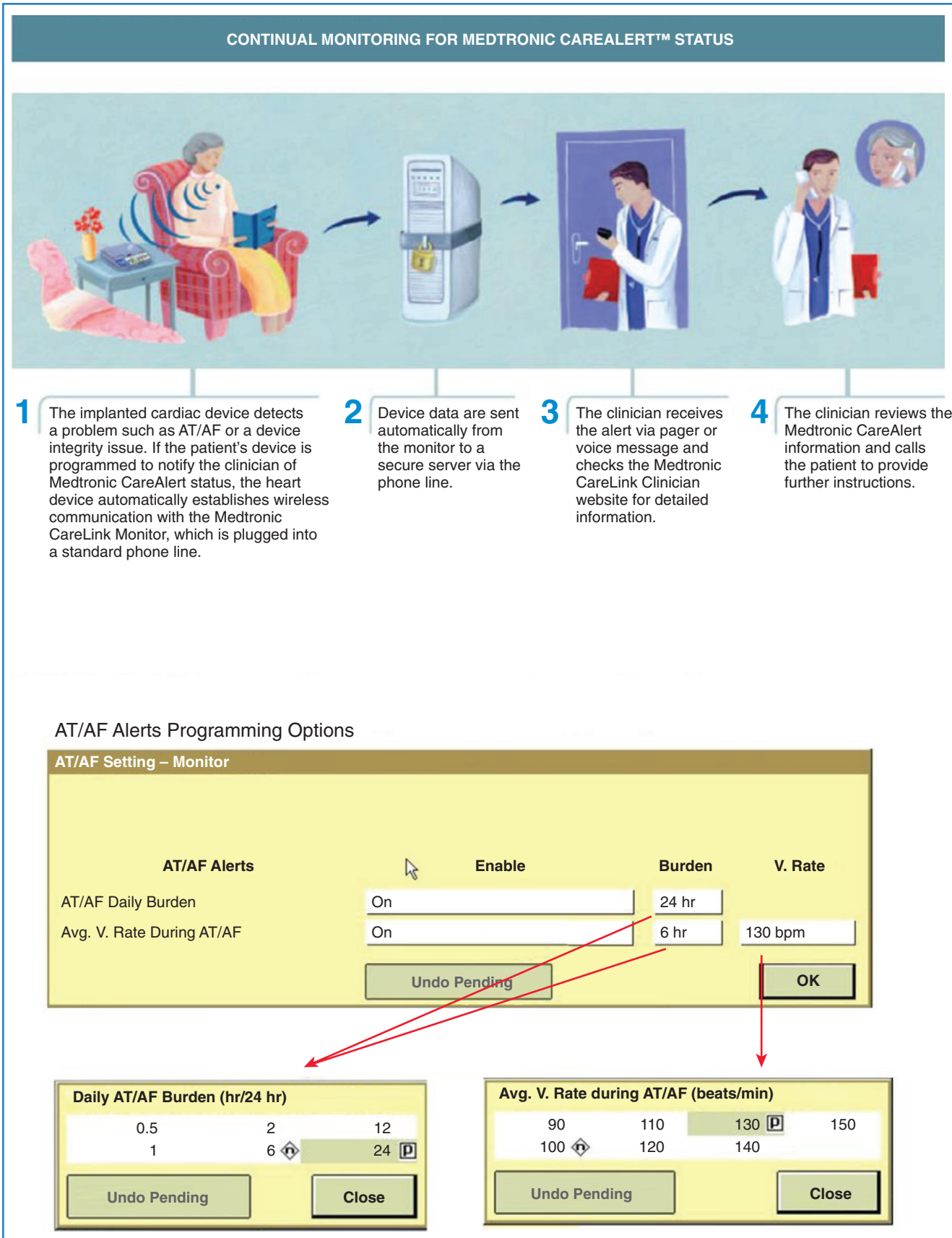


FIGURE 89-11 Wireless notifications can alert a physician to changes in a patient's atrial tachycardia/atrial fibrillation (*AT/AF*) status (*top*). Alert thresholds for AT/AF burden and the average ventricular rate during AT/AF can be programmed in some newer implantable devices (*bottom*).

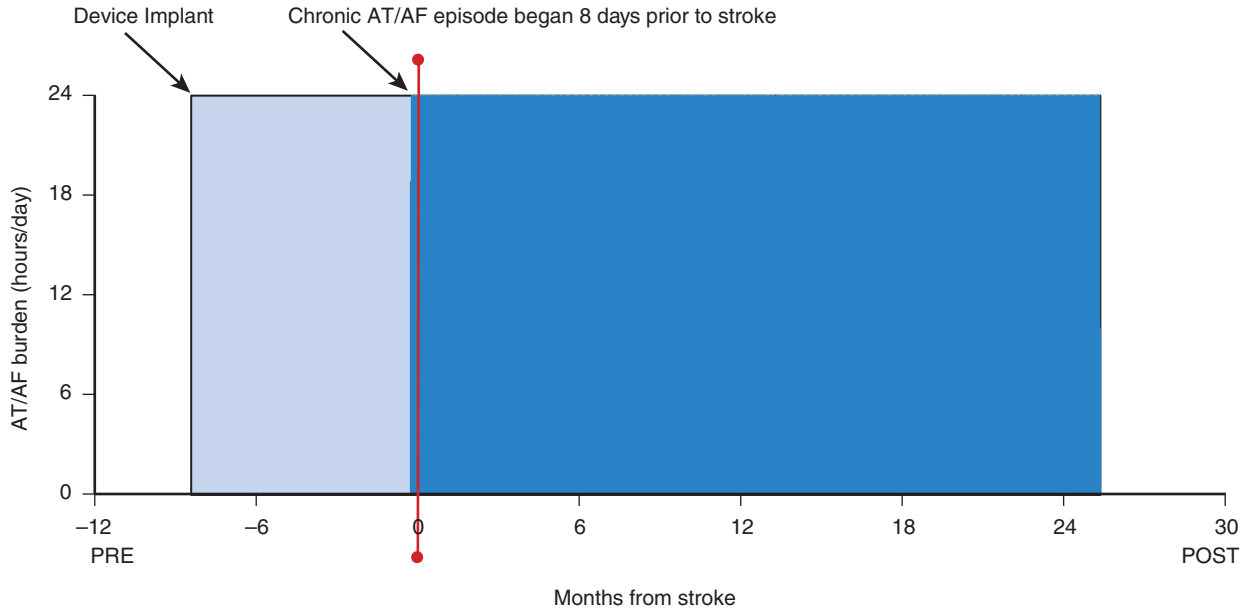


FIGURE 89-12 Continuous atrial tachycardia/atrial fibrillation (*AT/AF*) monitoring data from a patient who had an ischemic stroke 8 days after the onset of persistent AT/AF.

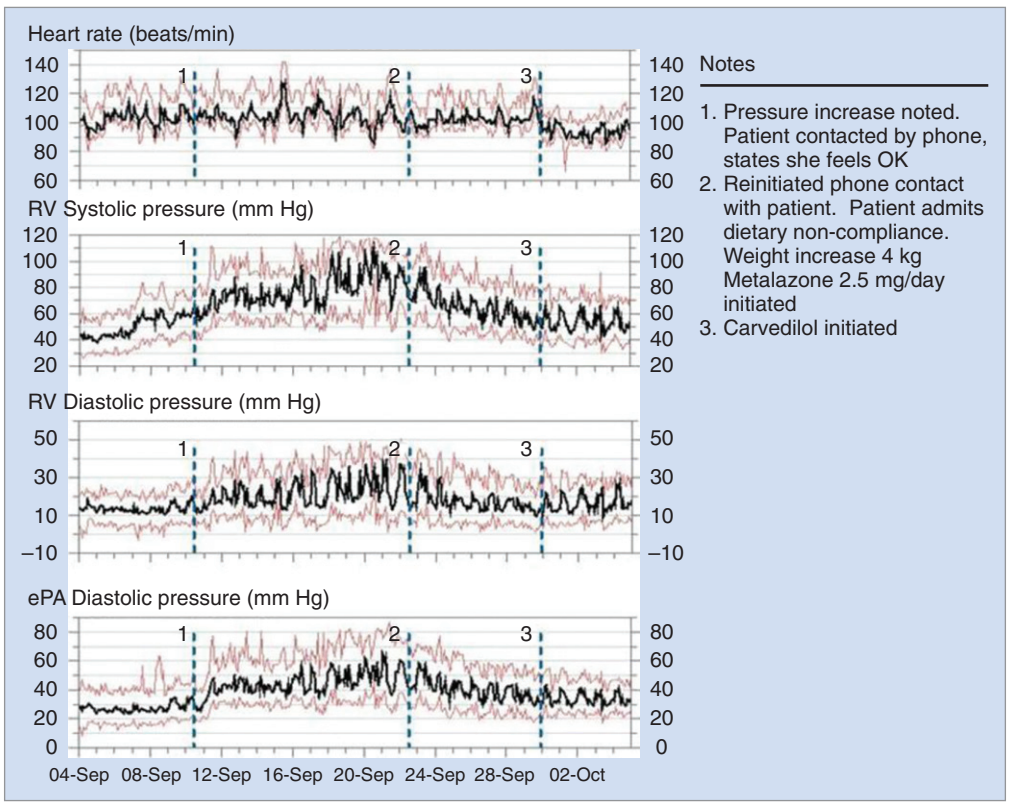


FIGURE 89-13 The trends show the daily median (*black line*) and the daily ranges (*pink lines*) of various pressure-derived parameters over 1 month when the patient admitted to nonadherence to dietary restrictions. Clinical notes corroborate the associated pressure changes.

pulmonary arterial diastolic pressure estimates under a variety of physiological conditions.[32-35] The implantable system continuously monitors and stores hemodynamic information that can be accessed remotely via the Internet. The Web interface automatically processes and concatenates new data received from the device and displays visual trends over time (Figure 89-13).

Numerous clinical studies have demonstrated the safety as well as the accuracy of the implantable hemodynamic monitoring system. The Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure (COMPASS-HF) trial randomized 274 NYHA class III to IV patients to a Chronicle-guided management group (n = 134) or to a control group (n = 140) and monitored them for 6 months.[36,37] The study demonstrated that the IHM was safe and had the ability to reduce the rate of heart failure-related events. However, the observed 21% reduction in heart failure events was not statistically significant. Retrospective analyses from the COMPASS-HF study provided new insights into the pathophysiology of the transition from stable, compensated HF to the decompensated state in subjects with left ventricular ejection fraction less than 35% and among HF patients with preserved left ventricular ejection fraction. The currently ongoing Reducing Events in Patients with Chronic Heart Failure (REDUCEhf) trial will prospectively test the hypothesis that the ambulatory hemodynamic monitoring can, indeed, reduce the rate of heart failure–related hospitalization.[38]

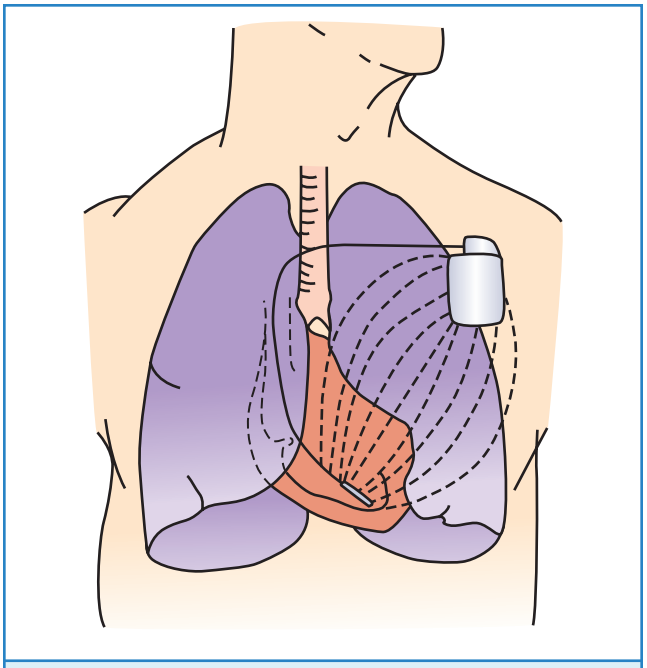


FIGURE 89-14 Intrathoracic impedance measurement. A low amplitude constant current pulse is transmitted from the right ventricular therapy lead to the device case, and the resultant voltage and impedance are determined.

Left-Sided Pressure Monitoring

In addition to right-sided cardiac pressure monitoring, an implantable device that measures left atrial pressure directly is currently being tested in clinical trials.[39] The implanted system consists of a hand-held patient-activated monitor that stimulates a passive subcutaneous antenna coil. A lead connects the coil to the sensor module that is anchored in the left atrium from the right side via the fossa ovalis through a femoral venous approach. An initial clinical trial of eight patients determined that "monitoring of direct left atrial pressure with a new implantable device was well tolerated, feasible, and accurate at a short-term follow-up."[40] A larger randomized clinical trial is under way at the time of this writing.

Intrathoracic Impedance Monitoring

The correlation between changes in biologic impedance and physiological parameters, such as respiration rate and cardiac hemodynamics, has been the subject of scientific investigation for decades.[41-43] Recently, the theories behind impedance monitoring of hemodynamic events have been applied to implantable devices. The recent MidHeft trial provided the first clinical evidence that daily monitoring of intrathoracic impedance measured between the right ventricular defibrillation coil and the devise case (Figure 89-14) could provide a clinically useful tool for monitoring the onset of decompensation in acute heart failure.[44] Device-recorded daily impedance data from this nonrandomized, double-blind prospective trial (n = 33) were used to develop and validate an algorithm to detect acute pulmonary fluid accumulation based on day-to-day changes in the actual recorded daily intrathoracic impedance. The algorithm automatically calculates a dynamic reference impedance on the basis of trends in the measured daily intrathoracic impedance. Differences between the measured daily impedance and the calculated reference impedance are used to increase or reset a "fluid index" (Figure 89-15). Results from the trial validation set indicated that the fluid index crossed a predetermined fluid index threshold (60 ohm-days) prior to hospitalization in over 77% of the events. The changes in the calculated fluid index occurred, on average, 15 days prior to symptom onset. The rate of fluid index threshold crossings that were not immediately associated with hospitalization was 1.5 events per patient per year.[44]

Several recent investigations have further validated the clinical usefulness of chronic heart failure monitoring via intrathoracic impedance. Vollmann and colleagues performed a nonrandomized, multiple-center investigation of 372 patients with CRT-D with intrathoracic impedance monitoring.[45] Most subjects were also alerted to fluid index threshold crossings by an audible alert tone transmitted by the device. The results indicated an adjusted sensitivity of 60% and positive predictive value of 60% for various clinically relevant events associated with heart failure. In another study, Ypenburg and colleagues monitored 115 subjects with CRT-D with intrathoracic impedance monitoring over 9 months.[46] The sensitivity and specificity of the fluid index reportedly depended strongly on the programmed detection threshold. The authors concluded that optimal algorithm performance may require individualized optimization of the threshold value for the particular patient. Small and colleagues also recently investigated intrathoracic impedance monitoring in 326 patients with CRT-D with no audible alert, since the alert is currently unavailable within the United States.[47] The analysis included univariate and multivariate linear regressions of changes in the fluid index as well as other device-recorded diagnostic parameters. The results indicated that each intrathoracic impedance fluid index threshold crossing was associated with a 35% increased probability of hospitalization for heart failure within the same year as the crossing

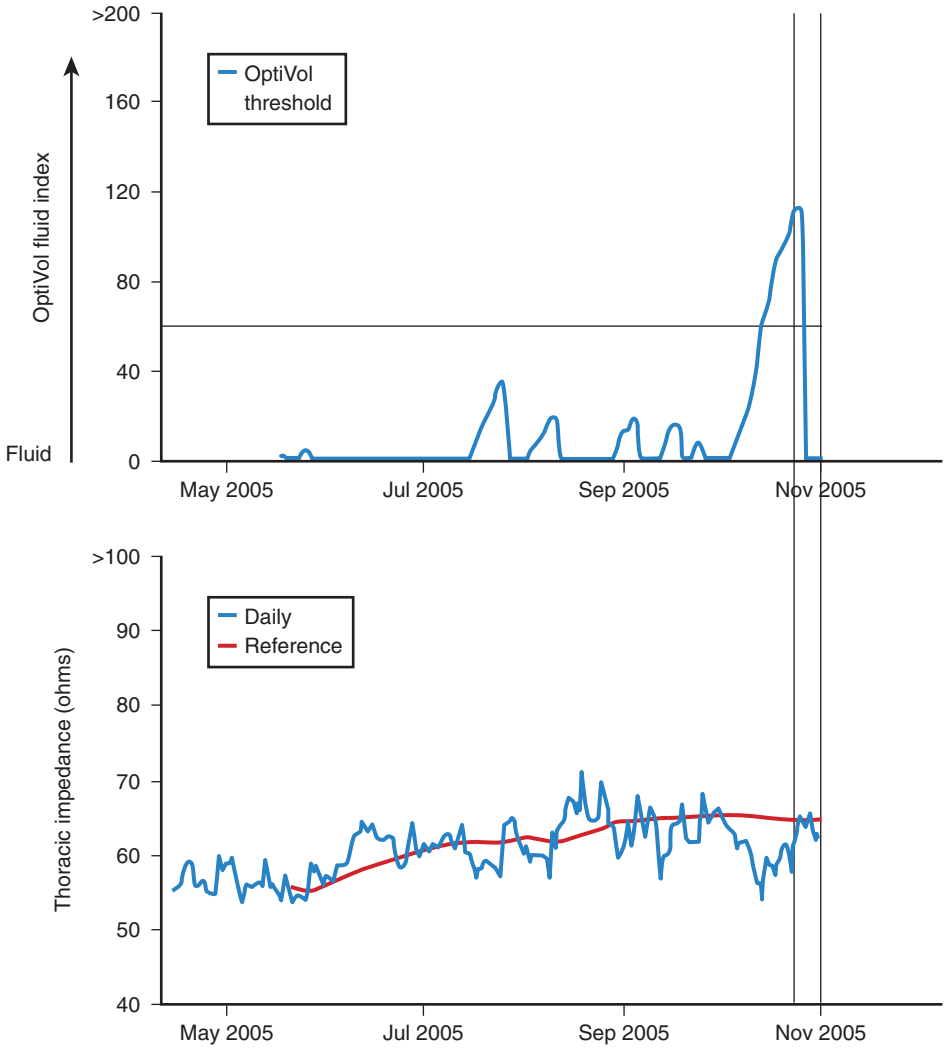


FIGURE 89-15 Sample diagnostic report for patient with implantable device, which includes intrathoracic impedance fluid index and programmable threshold, as well as the raw recorded daily and calculated reference impedance. Decreases in the trend of the measured daily impedance are reflected by consistent increases in the calculated fluid index. Fluid index values greater than the pre-programmed threshold indicate potentially worsening heart failure caused by thoracic fluid accumulation.

(Figure 89-16). Additional trials have also shown that acute changes in intrathoracic impedance are correlated with both weight and brain natriuretic peptide levels.[48-50] All the data from these trials have confirmed that intrathoracic impedance monitoring can provide a useful clinical tool to help manage patients with congestive heart failure.

Peak Endocardial Acceleration

The relative motion of the right ventricular wall, including the septum, can be detected by measuring the peak endocardial acceleration (PEA) by using a sensor integrated into a ventricular pacing lead.[51-53] Bordachar et al have correlated this index with LV dP/dT.[51] A recent multiple-center observational trial of 15 patients concluded that increases in PEA amplitude were associated with pharmacologic inotropic stimulation and were paralleled by changes in RV dP/dt_{max}, suggesting that PEA is an index of myocardial contractility.[53] Indeed, algorithms to use closed-loop feedback from a lead-based accelerometer to control device therapies, including pacing rate and CRT therapy, have been developed. However, some debate whether the PEA signal is independent of heart sounds still continues, since these two signals are strongly temporally correlated.[54] Likewise, the inclusion of additional sensors on ventricular pacing leads may have an uncertain impact on long-term pacing lead reliability.

Heart Rate Variability and Day/Night Heart Rate

Most implantable devices are able to monitor both paced and intrinsic ventricular cycle lengths and hence changes in both day and night heart rates as well as heart rate variability. Such diagnostic data may provide insight into the function of the autonomic nervous system. Recently, Adamson and colleagues reported reductions in device-measured indices of heart rate variability prior to episodes of acute heart failure decompensation.[55] Similarly, the OptiVol Fluid InSynch Sentry Registry (OFISSER)

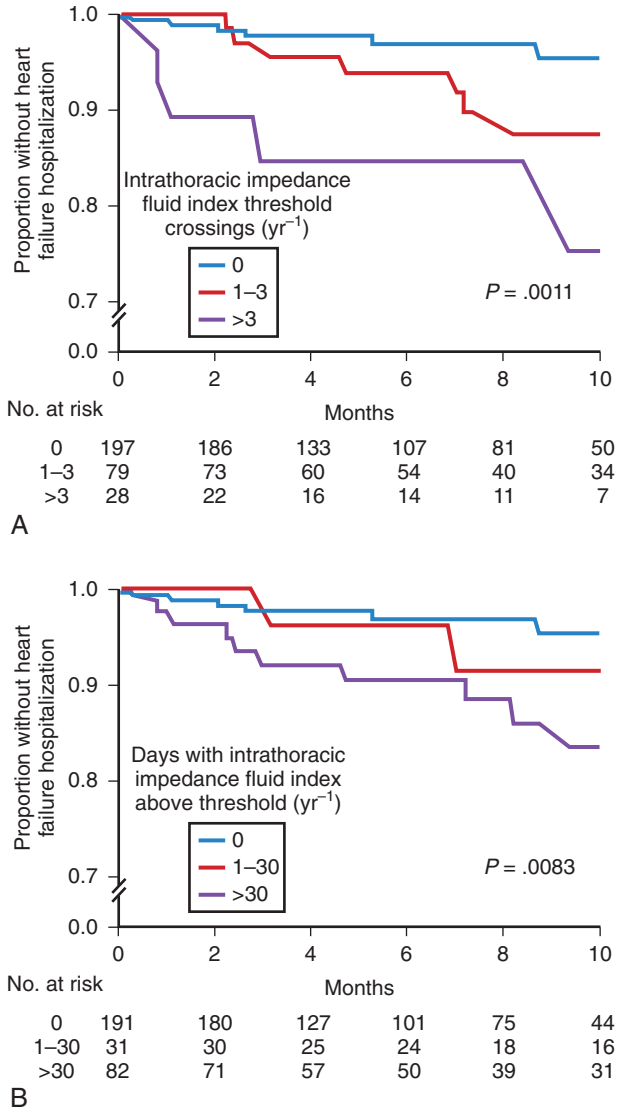


FIGURE 89-16 Kaplan-Meier survival analysis of time to first hospitalization for heart failure for groups of patients with similar frequency of thoracic impedance fluid index threshold crossings. Patients with more frequent crossings and patients with longer duration crossings over the previous 4 months were significantly more likely to be hospitalized for heart failure over the subsequent months. *(From Ypenburg C, Bax JJ, van der Wall EE, et al: Intrathoracic impedance monitoring to predict decompensated heart failure,* Am J Cardiol *99[4]:554–557, 2007.)*

clinical trial results demonstrated that increased night heart rates were associated with decompensation in acute heart failure in patients receiving CRT-D therapy.[47] However, diagnostic parameters based on heart rate have important limitations. Heart rate variability parameters assume that the rate is controlled by the sinus node. Thus, if the subject is in AF, or if the device is controlling the atrial rate by frequent atrial pacing, then the diagnostic information will not be available. This scenario may represent a significant proportion of time for some patients with implantable devices, especially those who are pacemaker dependent.

Clinical Adoption and Remote Monitoring

Many devices may automatically transmit all sensor-derived parameter trends from the patient's home directly to the clinic via a bedside monitoring/telemetry device. This device may be programmed by the clinic to transmit automatically on a preset schedule. Alternatively, diagnostic data transmission can also be triggered on the basis of detected clinical events. For example, some devices can be programmed to alert the clinic directly if the patient experiences new-onset atrial tachyarrhythmias or if the ventricular rate during a sustained atrial tachyarrhythmia exceeds a pre-programmed threshold. Such remote monitoring "care alerts" may be quite useful to monitor rate and rhythm control strategies. Also, remote monitoring of heart failure parameters was recommended in at least one published guideline.[56] Such remote monitoring capabilities also offer the potential to transmit non–device-recorded information automatically, such as weight, blood pressure, and associated symptoms to the managing clinic.

Integrated Diagnostics

The availability of useful physiological clinical parameters derived from implantable device–based sensors is likely to increase. Future devices may include additional sensors to track respiration rate, minute ventilation, sleep apnea, tissue perfusion, cardiac output, acute ischemia, electrical alternans, and heart rate turbulence. Indeed, some recently released devices already contain some of these fascinating capabilities. The development of practical chemical sensors is also feasible. For example, some external glucose pumps for the chronic management of diabetes also contain chronic glucose monitoring sensors.[57] The ability of such chemical sensors to augment other device monitoring capabilities for heart failure or other risks will require additional investigation.

Conclusion

In summary, implantable devices are capable of continuously monitoring cardiac rhythm, hemodynamics, and other cardiac indices. They use complex detection algorithms to identify the occurrence of AT/AF, heart failure, and heart rate changes. They can consolidate this vast amount of information into a manageable amount of clinically relevant diagnostics and enable clinicians to effectively manage their patients with AT/AF, heart failure, and bradycardias. Further advances can be expected to increase the ability of these devices to provide clinically relevant information for more efficient management of patients with AF and heart failure.

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CHAPTER 90

Devices for the Management of Atrial Fibrillation

Werner Jung and Sanjeev Saksena

Atrial fibrillation (AF) is the most common sustained arrhythmia in clinical practice and occurs most often in association with cardiovascular disease. AF incidence increases with age and affects 2% of the population older than 65 years and 4% of the population older than 80 years, with a median age of the AF population being approximately 75 years.[1,2] Patients with AF have a near doubling of cardiovascular mortality rate in men and a 50% increase in women.[3] In addition to symptoms of palpitations, patients with AF have an increased risk of stroke and may also develop decreased exercise tolerance and left ventricular dysfunction. AF is a frequent and costly health care problem representing the most common arrhythmia, accounting for more than one third of all admissions for arrhythmias.

The importance of antithrombotic therapy is now undisputed, but the management of the arrhythmia itself remains controversial. Although prospective studies as Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE),[4] Strategies of Treatment of Atrial Fibrillation (STAF),[5] and Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM)[6] have not shown improved morbidity or mortality rates with rhythm control, effective rhythm control was not often achieved in these studies due to the use of an antiarrhythmic drug–based strategy. The inability to maintain rhythm control is due to the limited efficacy of antiarrhythmic drugs, a finding that has been repeatedly documented in clinical trials. In the STAF study, only 23% of the patients actually achieved freedom from AF on amiodarone therapy.[5]

Recently, an increasing number of nonpharmacologic options have become available and can supplement or even attempt to replace drug therapy in selected patients. Currently, available nonpharmacologic strategies revolve around implantable device therapy and ablative approaches. Implantable devices that have been used to manage AF include cardiac pacemakers as well as atrial or atrioventricular (AV) defibrillators.

Pathophysiologic Basis for Device Therapy in Atrial Fibrillation

Significant new knowledge has emerged regarding potential mechanisms of AF in different patient populations as well as the impact of therapies on these mechanisms. AF in humans depends on the interaction between triggers and a vulnerable substrate for facilitating the process of functional, anatomic, or spiral wave re-entry. These triggers consist of automatic or autonomically triggered atrial premature depolarizations (APDs) or organized automatic or re-entrant atrial tachycardia (AT). Triggers may emanate from the right atrium (RA) or left atrium (LA), particularly in the presence of structural heart disease.[7] Enhanced sympathetic tone increases the frequency of triggers, and conditions of vagotonic bradycardia can shorten atrial effective refractory periods and increase dispersion of atrial refractoriness. Perpetuation of AF is associated with structural and electrical remodeling of the substrate.[8] These changes include areas of intra-atrial or interatrial conduction delay, shortening and dispersion of the atrial refractoriness, and a loss of rate adaptation. Atrial fibrosis is common, increases with age, and progresses to heart failure. This substrate provides the milieu for conduction delay, re-entry, and/or vortex shedding of daughter wavelets. Consequently, organized monomorphic AT (Figure 90-1) have been demonstrated during the onset and maintenance of AF.[9,10] Further knowledge has emerged regarding the determinants of endocardial septal activation and conduction over interatrial connections. It has been shown that electrical coupling of the right and LA in humans is predominantly provided by muscular connections at the level of Bachmann's bundle and the coronary sinus. The true septum (the fossa ovalis and its limbus) of the RA and LA is asynchronous and discordant, usually without contralateral conduction during sinus rhythm or atrial pacing.[11]

The rationale for pacing therapy can now be refined on the basis of this new knowledge. Atrial-based pacing can prevent AF by several mechanisms. Thus its effect on triggers, initiating or onset arrhythmias, mechanisms that maintain AF, and their contributions can be examined in different patient populations. Trigger density is a critical element in the high event rate for asymptomatic and symptomatic AF events seen in patients with refractory AF. Although antiarrhythmic drugs have been commonly used to suppress atrial ectopic beats, overdrive atrial pacing and novel atrial pacing algorithms can reduce ectopy (Figure 90-2). Overdrive pacing can also suppress triggers, such as automatic AT or atrial premature depolarizations.[12,13] Alternate-site pacing can reduce atrial conduction delay and shorten the activation time. Atrial-based pacing can also affect the electrophysiological properties of the substrate by pre-exciting regions critical to re-entry, such as sites of conduction delay.[14,15] Reduced interatrial and intra-atrial conduction delay and dispersion of refractoriness have been shown with septal and multi-site atrial pacing (Figure 90-3). With dual-site right atrial or biatrial pacing, regional atrial activation is resynchronized. Hesselson and Wharton demonstrated acute suppression of pulmonary vein foci with overdrive right atrial pacing, but suppression of AF occurred only when dual-site atrial pacing was used.[15] Dual-site right atrial

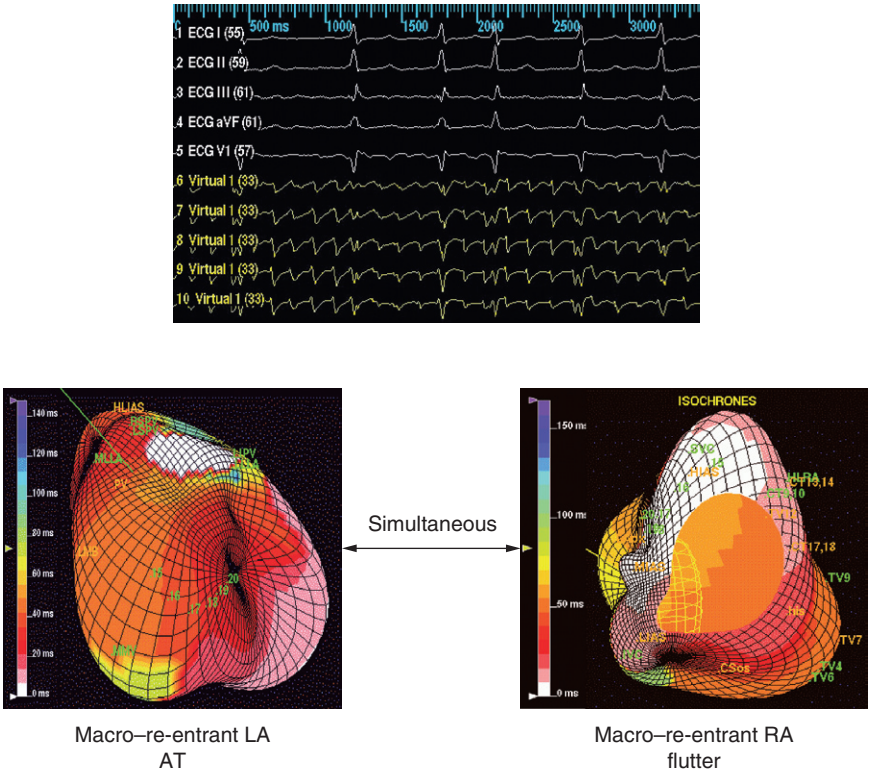


FIGURE 90-1 Three-dimensional map showing focal left atrial tachycardia *(AT)* and macro–re-entrant right atrial *(RA)* flutter coexisting simultaneously in a patient with permanent atrial fibrillation. The *top panel* shows surface electrocardiogram leads and virtual electrograms at numbered sites in the atrial maps. The color coding shows activation times at different right and left atrial regions during the cycle. *LA,* Left atrium.

pacing and Bachmann's bundle pacing reduce or markedly truncate the window of AF induction by APDs.[14,16] Dual-site right atrial pacing has also been shown to improve atrial mechanics by increasing atrial filling velocities and preventing the left ventricle (LV) and LA dilation seen with right ventricle (RV) apical pacing (see Figure 90-3).[17] Furthermore, dual-site right atrial pacing has been shown to increase left atrial appendage flow and to shift the transmitral flow pattern toward a lower passive component in patients with sick sinus syndrome and paroxysmal AF.[18] Multi-site pacing resulted in in earlier left atrial contraction and reversal of the typical right-left atrial contraction sequence as well as providing greater left atrial contraction synchrony.[19,20]

Recent data from the Atrial Fibrillation Therapy (AFT) trial show that sinus bradycardia preceded onset of AF in 22% of study patients.[21] This deviation in sinus rate can be modest, greater than 5 beats/min or more and transient (5 minutes or more) but can create the opportunity for triggering AF. Demand atrial pacing can prevent this event. Finally, common right atrial isthmus-dependent atrial flutter is an important and hitherto underrecognized trigger for AF. Treatment of this rhythm with anti-tachycardia pacing (ATP) can be effective in its termination and AF prevention.

The second part of the arrhythmogenic chain is the onset or transitional tachycardia in AF. This tachycardia can be transient or prolonged in duration and can simulate AF on the electrocardiogram (ECG). Mapping has demonstrated such rhythms in both spontaneous and induced AF.[7,22] Three-dimensional mapping of individual atria has characterized these rhythms as macro–re-entrant AT (see Figure 90-1), common atrial flutter, and atypical atrial flutter.[22,23] Multi-site pacing can reduce or eliminate the initiation of these arrhythmias by altering substrate properties (Fig. 90-4). ATP can be used for termination of these rhythms and prevent progression to sustained AF (Figure 90-5).[24]

Evolution to sustained AF requires electrophysiological mechanisms that result in perpetuation of the arrhythmia. More than one re-entrant tachycardia may coexist in this phase, or a single tachycardia may persist; both models can demonstrate fibrillatory conduction.[25] Critical requirements for such persistence include structural and/or electrophysiological remodeling of the AF substrate. Atrial conduction delays manifest as prolonged or abnormal P waves or prolonged atrial conduction intervals and are a prime predictor of AF recurrence. Resynchronization therapy with multi-site atrial pacing can reduce this delay in multiple atrial regions. Dual-site right atrial pacing therapy may have novel effects that lead to reverse remodeling of the atrial substrate by improving atrial transport and reducing atrial stretch. Recently, Avitall and coworkers demonstrated a significant benefit in the prevention of AF by simultaneous high-density biatrial pacing directly targeted to the pulmonary vein antra and other LA locations known to be AF triggers, compared with single-site pacing. By using a multi-site simultaneous pacing protocol, they showed favorable changes in one of the key electrophysiological parameters that contribute to AF, slowed atrial conduction, specifically in response to single premature atrial contractions.[26]

Termination therapies, such as ATP, can terminate common and non-isthmus-dependent atrial flutter by burst, ramp, or a combination of rapid pacing sequences. This can interrupt the chain of AF development or its maintenance. In our laboratory, 50-Hz pacing (Figure 90-6) has been shown to terminate atypical non-isthmus-dependent atrial flutter but not sustained AF.[27] Atrial defibrillation shocks produce conduction delay and block (Figure 90-7).

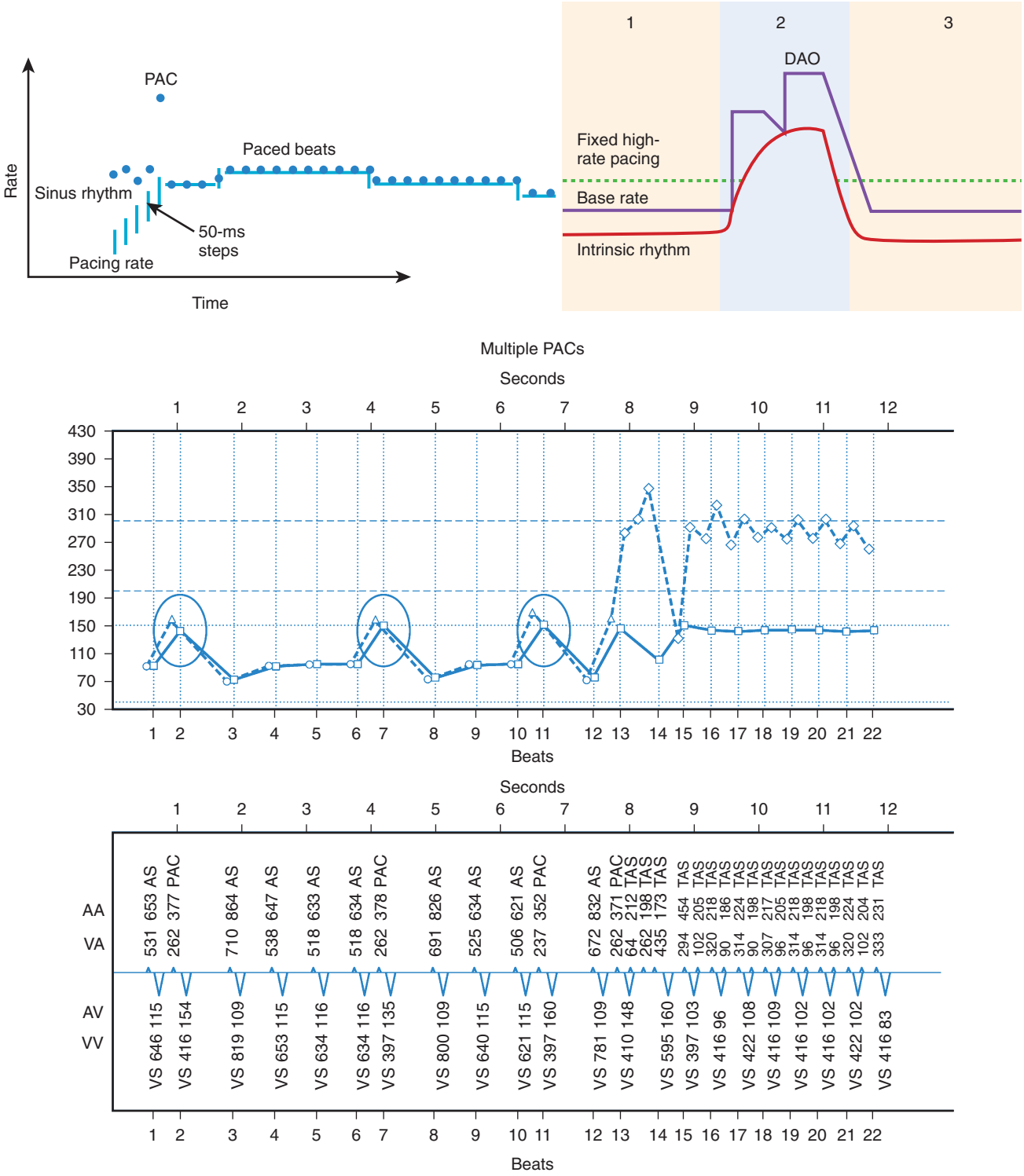


FIGURE 90-2 Two trigger suppression pacing algorithms available in pacemakers with atrial fibrillation therapies. *Top left*, Function of the atrial rate stabilization algorithm (Medtronic, Inc.) demonstrating an increase in atrial pacing rate in 50-ms increments after a premature atrial complex (*PAC*) to overdrive suppress subsequent premature beats. *Top right,* Dynamic atrial overdrive algorithm (St Jude Medical), which demonstrates the dynamic increase in overdrive rate as related to underlying changes in sinus cycle length. The algorithm periodically steps down until the sinus rate is encountered and can step up again as needed. The two pacing panels below show the response to multiple premature beats with a Vitatron Selection pacemaker (Vitraron Medical BV) algorithm.

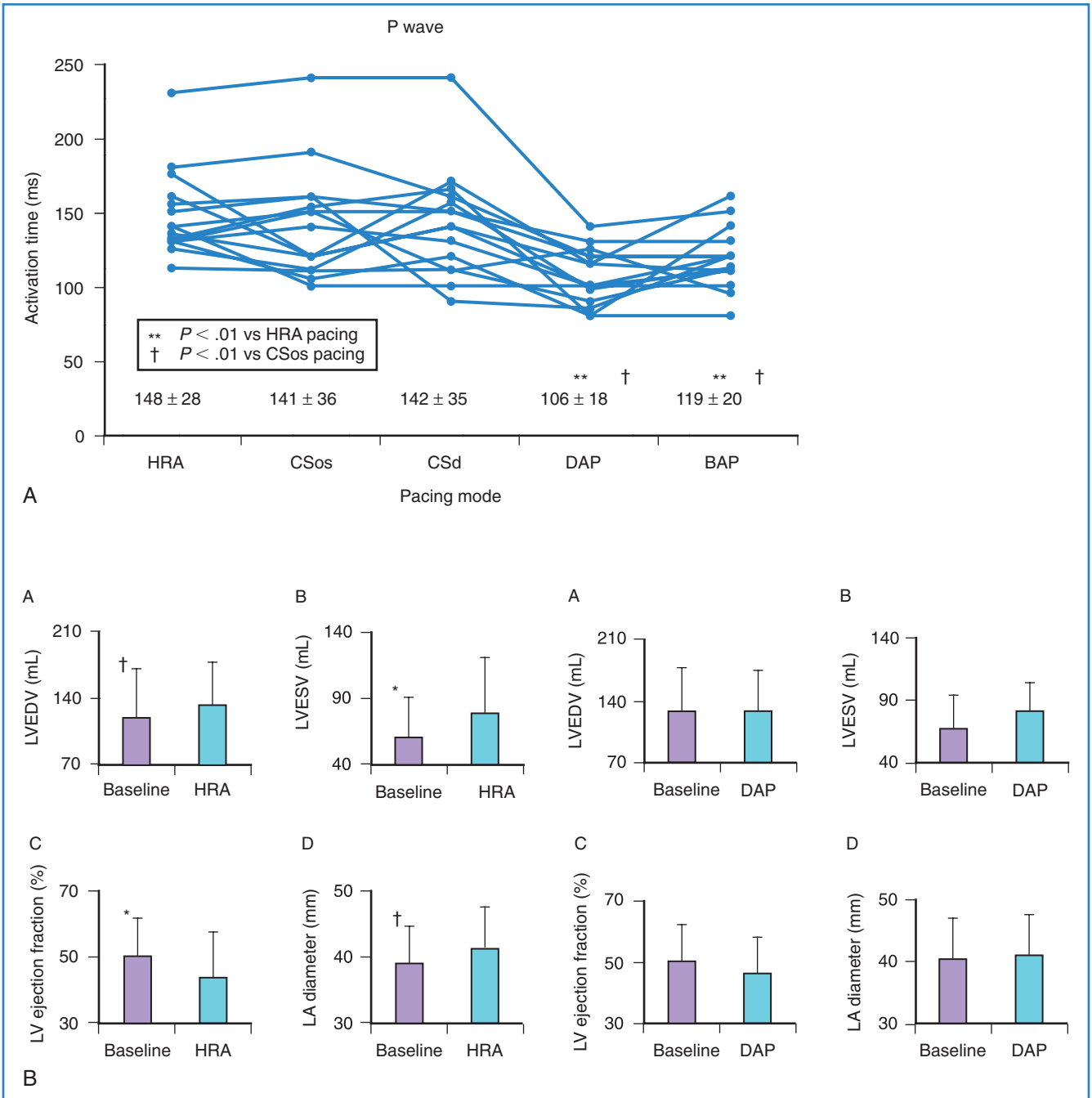


FIGURE 90-3 A, P-wave duration during different atrial pacing modes in patients with atrial fibrillation. Total P-wave duration is shown on the *y*-axis. **B,** *Left,* Changes in atrial and ventricular function during single-site high right atrial (*HRA*) pacing compared with unpaced baseline data. Data are mean ± SD; **P* < .05 vs. baseline, †*P* < .10 vs. baseline. *Right,* Changes in atrial and ventricular function during support pacing compared with unpaced baseline data. *P,* nonsignificant for all comparisons. *CSos,* Coronary sinus ostium; *CSd,* distal coronary sinus; *DAP,* dual-site right atrial pacing; *BAP,* bi-atrial pacing; *LVEDV,* left ventricular end-diastolic volume; *LVESV,* left ventricular end-systolic volume; *LV,* left ventricular; *LA,* left atrial. (A, *From Prakash A, Delfaut P, Krol RB, Saksena S: Regional right and left atrial activation patterns during single and dual site atrial pacing in patients with atrial fibrillation,* Am J Cardiol *82:1197–1204, 1998.)*

Although extensive mapping data are unavailable for internal atrial defibrillation, mapping of external shocks demonstrates that even ineffective shocks modify the underlying atrial activation patterns in AF, resulting in transient or persistent slowing.[28] Successive shocks may be effective when the first one modifies the sustained AF mechanisms, resulting in vulnerability to the next shock or even spontaneous termination mediated by an unstable circuit or concealed penetration by an atrial premature beat (Figure 90-8).

Initial studies on catheter atrial defibrillation used two small surface area defibrillation electrodes and monophasic shocks. Defibrillation could be accomplished with shock energies of

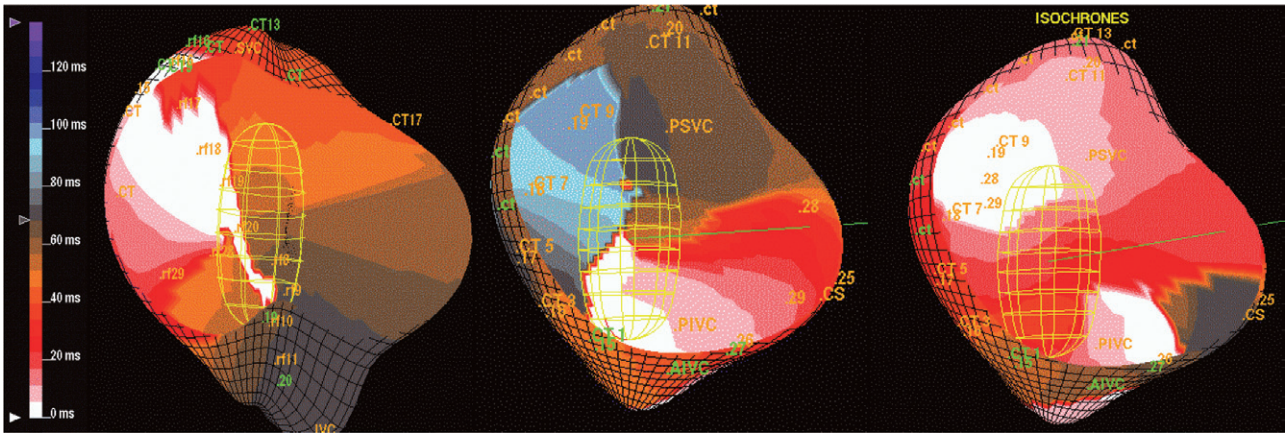


FIGURE 90-4 Right atrial (*RA*) three-dimensional activation maps during high right atrial (*HRA*), septal, and dual-site RA pacing. Note the shorter activation times and two simultaneous activation wavefronts in the dual-site pacing mode that abbreviate and synchronize atrial activation.

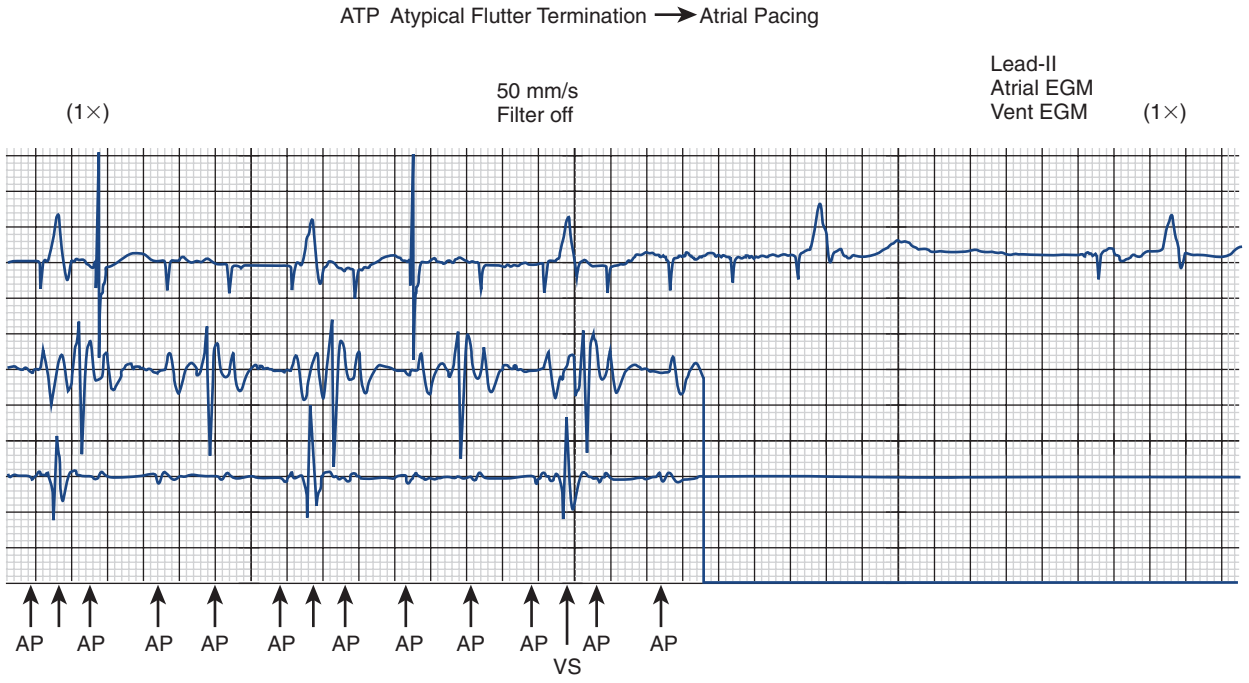


FIGURE 90-5 Rapid atrial anti-tachycardia pacing (*ATP*) terminates atypical atrial flutter in this patient with permanent atrial fibrillation (see Figure 90-1) implanted with a Guidant pacemaker (Boston Scientific, Inc.) and later with a Guidant Vitality AVT dual defibrillator with dual-site atrial pacing. The patient reverts to an atrial paced (*AP*) rhythm. *EGM,* Electrogram; *VS,* ventricular sensed event.

less than 1 J but was poorly reproducible.[29] Ventricular fibrillation was occasionally induced (2.4%) when shocks were delivered more than 115 ms after QRS onset. Kumagai and coworkers reported efficacy rates of 47% at energies less than 0.5% and 74% at 1 J.[30] Biphasic shocks are associated with lower thresholds than are monophasic shocks.[31] Experimental studies have demonstrated that the right atrium to coronary sinus defibrillation vector is associated with the lowest defibrillation thresholds.[32] This optimized waveform with individual phase durations of 3 ms and the optimal shock vector (E50) has been estimated at 1.3 J. In the sheep model, bi-phasic shocks with an RA-left thoracic patch vector had a 47% efficacy at 1 J.[33] Epicardial atrial defibrillation thresholds have been studied and have shown extremely low energy needs with an efficacy of 42% in the 0.3 J range.[34] In contrast to clinical data, these experimental studies suggested that atrial defibrillation could be achieved at values below the pain perception threshold for shock therapy.

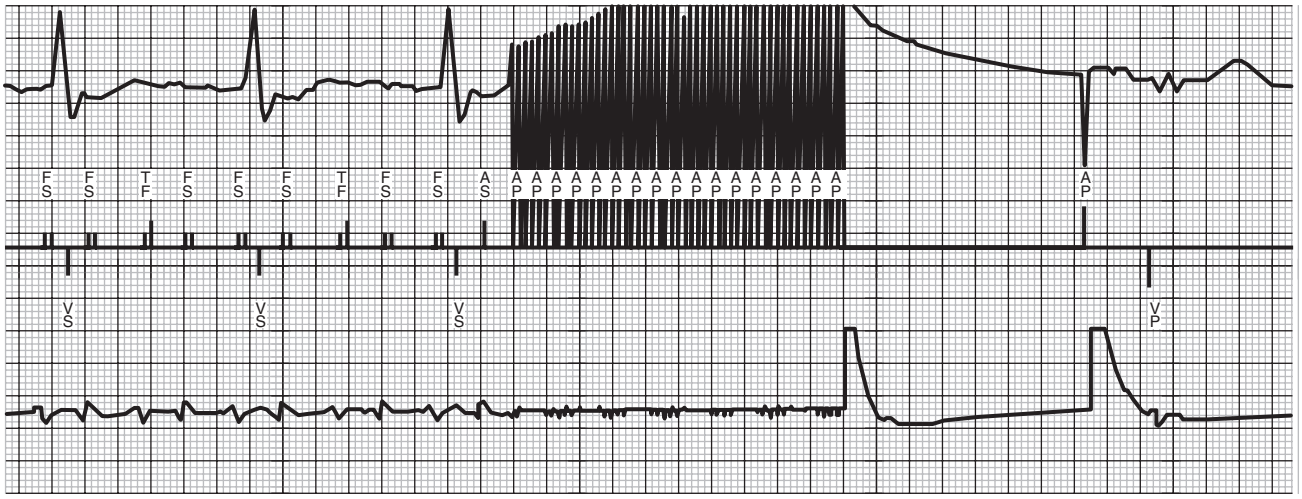


FIGURE 90-6 Termination of atypical atrial flutter in the auto-discrimination zone of a Medtronic Jewel AF dual defibrillator using a 50-Hz high-frequency pacing burst. Note the regularity of the rhythm despite the surface electrocardiogram suggesting atrial fibrillation. *FS,* Fibrillation zone marker; *TF,* tachycardia zone marker.

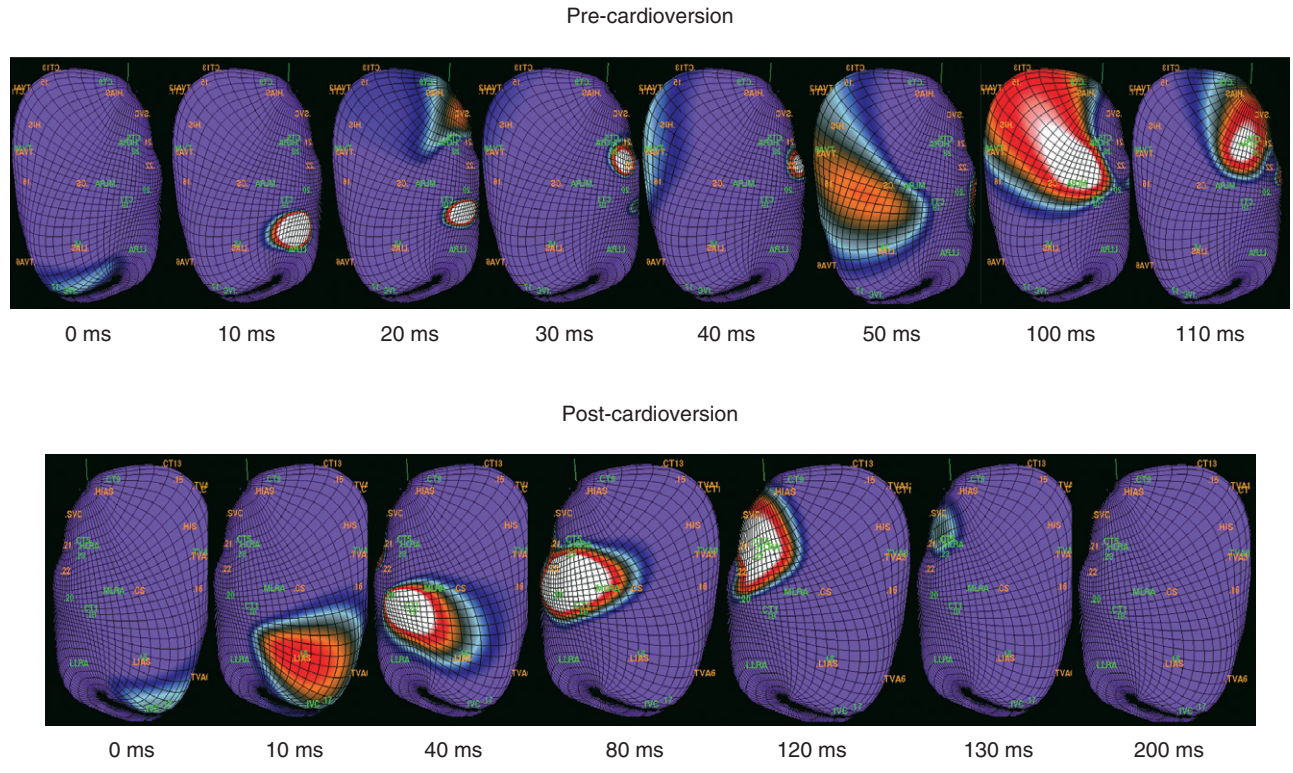


FIGURE 90-7 Three-dimensional noncontact right atrial maps of atrial activation patterns before and after delivery of a cardioversion shock. Before cardioversion, more than one wavefront is present; after the shock delivery, only a single macro–re-entrant wavefront is left. Although classified as a failed cardioversion, delivery of the shock fundamentally altered the tachyarrhythmias. Individual frames of the activation wavefront and their timing in milliseconds relative to shock delivery are shown.

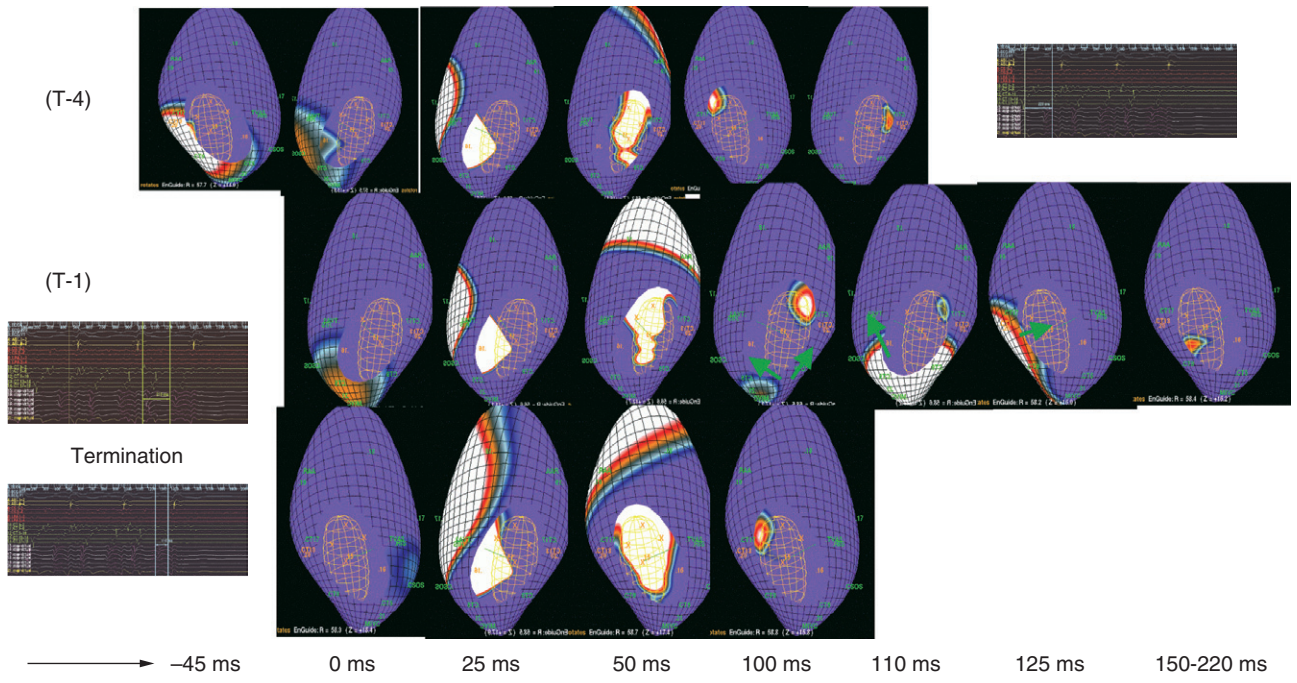


FIGURE 90-8 Three-dimensional noncontact right atrial maps of atrial activation patterns before spontaneous termination of an atrial fibrillation event. Select individual frames from the last four cycles before termination are shown, with their timing relative to each other in milliseconds. Before termination, only a single wavefront is present in the fourth cycle before cessation. In the cycle immediately before termination, a concealed atrial premature beat invades the excitable gap in the single circuit and gives rise to antidromic and orthodromic wavefronts. The former collides and terminates the original tachycardia, and the latter circulates for one cycle and spontaneously stops propagating, resulting in atrial fibrillation episode termination.

Atrial Pacing for the Primary Prevention of Atrial Fibrillation

Pacing to Prevent Atrial Fibrillation After Cardiac Surgery

Postoperative AF is a frequent complication, occurring in 30% to 50% of patients after cardiac surgery.[35] The utility of prophylactic atrial pacing to prevent AF after cardiac surgery has been investigated in a number of trials, but clinical guidelines for its use are lacking.[36,37] Nine randomized, controlled trials addressed prophylactic atrial pacing after cardiac surgery to prevent AF.[38] Prophylactic right atrial pacing and prophylactic left atrial pacing have yielded inconclusive results. Prophylactic bi-atrial pacing reduced the incidence of AF significantly in four studies,[39,40] reduced it nonsignificantly in one study, and had no effect in one study.[41,42] Newer pacing techniques such as high-frequency stimulation of the right inferior fat pad have yielded a significant decrease in ventricular rate during postoperative AF.[43] On the basis of the literature, it can be concluded that prophylactic atrial pacing to prevent AF after cardiac surgery is safe. We recommend that bi-atrial pacing be considered, particularly in patients who are at high risk for the development of postoperative AF. Several mechanisms have been advocated to explain the high incidence of postoperative AF.[44] Besides mechanical effects, systemic inflammatory responses have been considered of greatest importance. Analysis of several electrocardiographic parameters has shown that premature atrial contraction activity, frequency-domain heart rate variability, and heart rate turbulence parameters were the best discriminators for postoperative AF occurrence.[45] These data suggest that dual-site pacing may be effective in primary prevention in certain populations and could enhance efficacy. The Pacing of the Atria in Sinus Node Disease (PASTA) trial has been designed to re-examine this issue by comparing the impact of different atrial pacing lead positions on the incidence of AF in patients with sinus node disease. The evaluation of an AF burden greater than 1% and the total AF burden after 24 months did not show differences in the incidence of AF in patients with dual-chamber pacemaker therapy for sinus node disease. In addition, a significant influence of RA lead position on the incidence of AF recurrence could not be demonstrated.[46]

Pacing Mode and Atrial Fibrillation

The role of permanent pacing to prevent AF has been highlighted in several reviews.[47-51] Many retrospective and several prospective, randomized, controlled clinical trials have reported that atrial or dual-chamber pacing prevents paroxysmal and permanent AF in patients with symptomatic bradycardia as an indication for cardiac pacing.[52-54] The Danish Trial of Physiologic Pacing (DTPP) in sick sinus syndrome was the first prospective trial comparing atrial-based pacing in the AAI mode with an active control arm using ventricular demand (i.e., VVI pacing). Despite initial equivalence, long-term follow-up (mean, 5.5 years) demonstrated a 46% relative risk reduction in the incidence of AF with atrial pacing.[52] These findings suggest a slow reverse atrial remodeling effect with atrial pacing. The Pacemaker Selection in the Elderly (PASE) study[53] was conducted to assess specifically the

effect of pacing on health-related quality of life. No difference in the development of AF was observed in the PASE study between the two pacing modes, but those with sinus node dysfunction as the primary indication for pacing who were randomized to the dual-chamber pacing mode tended to be less likely to have AF (19%) compared with those randomized to the ventricular pacing mode (28%, $P = .06$).[53]

The three largest parallel-design trials randomizing patients to VVI(R) or DDD(R) pacing, the Canadian Trial of Physiologic Pacing (CTOPP),[54] the Mode Selection Trial (MOST),[55] and the United Kingdom Pacing and Cardiovascular Events (UKPACE)[56] trial have demonstrated no mortality rate benefit from physiological mode selection. CTOPP[54] reported an 18% risk reduction in the development of AF over 3.1 years ($P = .05$) in patients randomized to physiological pacing compared with ventricular pacing, which was sustained over longer term follow-up (20% risk reduction; $P = .009$ at 6 years).[57] MOST[55] showed a 21% relative risk reduction for developing AF over 3 years in patients randomized to physiological pacing compared with ventricular pacing ($P = .008$) (Figure 90-9). It is worth noting that during the trial, 31% of the ventricular pacing group crossed over to physiological pacing, potentially diluting any benefit relating to this therapy. A similarly high crossover rate (26%) to dual-chamber pacing among patients assigned to ventricular pacing was observed in PASE.[53] UKPACE randomized 2021 patients aged 70 years or older with high-grade AV block to implantation with dual-chamber or single-chamber ventricular pacemakers, and further subdivided the single-chamber population into two groups: fixed-rate ventricular pacing (n = 504), and rate-modulated single-chamber pacing (n = 505).[56] After a median follow-up period of 4.6 years for the primary endpoint, all-cause mortality, and 3 years for cardiovascular events and AF (2.8% DDD vs 3.0% VVI; $P = .74$), no significant differences were found between physiological and ventricular-based pacing.[58]

A meta-analysis of these trials,[59] which included 35,000 patient-years of follow-up, showed that atrial pacing is superior to ventricular pacing and resulted in a significant reduction in AF (hazard ratio [HR], 0.80; 95% confidence interval [CI], 0.72 to 0.89; $P = .00003$) and conferred a modest reduction in stroke risk (HR, 0.81; $P = .038$). Furthermore, subgroup analysis suggested a greater benefit of atrial pacing in patients with sinus node dysfunction in terms of stroke and cardiovascular death, but these results must be interpreted cautiously. An important consideration that may have limited the benefit of atrial pacing in the prevention of AF is the observation that most patients in these trials received DDD pacemakers, and the resultant increase in right ventricular pacing may have counterbalanced the reduction in the incidence of AF. Mode selection, however, did not affect all-cause mortality and stroke or heart failure hospitalization in the overall group.[59]

Primary prevention trials of atrial-based pacing are summarized in Table 90-1. They uniformly demonstrate a relative risk reduction in the propensity to develop AF in patients with sinus node dysfunction during long-term follow-up. Interestingly, a greater risk reduction was seen with single-site atrial pacing than with dual-chamber pacing modes, with the exception of the

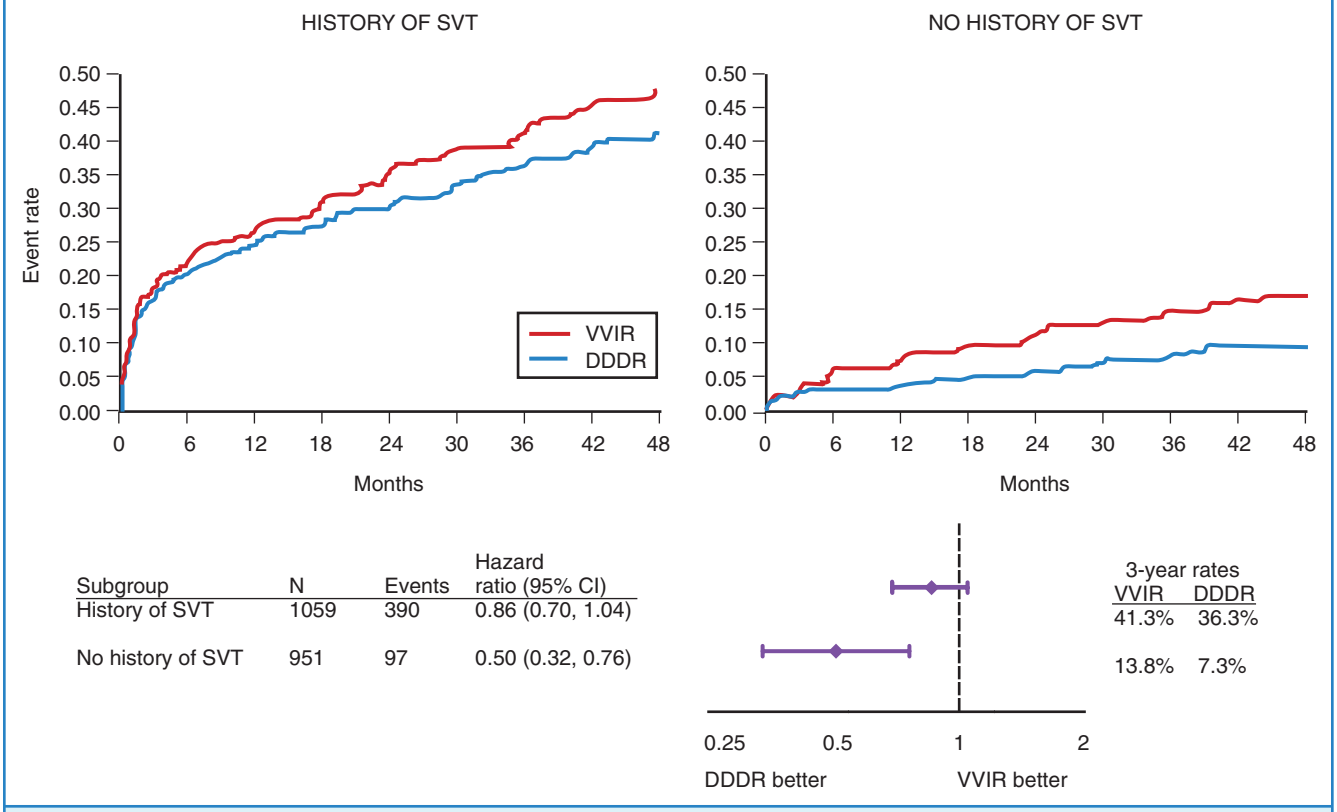


FIGURE 90-9 Primary prevention of permanent atrial fibrillation by atrial-based pacing in the DDDR mode in the MOST trial. Note that the relative risk of progression to permanent atrial fibrillation is reduced by 50% in patients with sick sinus syndrome who do not have a prior history of supraventricular tachyarrhythmia (*SVT*). *CI,* Confidence interval.

Table 90-1 Trials of Physiological Pacing

TRIAL	NO. PATIENTS	TRIAL DESIGN AND PATIENT POPULATION	OUTCOME
PRIMARY PREVENTION TRIALS			
Danish Trial of Physiological Pacing (1988–1996)	225	AAI vs. VVI in SND patients	34% relative risk reduction in all-cause mortality and 46% relative risk reduction for the development of AF in 5.5 years
Canadian Trial of Physiological Pacing (CTOPP 1997–2000)	2568	DDDR vs. VVIR in SND and AVB patients	18% reduction in annual rate of AF and 27% reduction in chronic AF
MODE Selection Trial (MOST 1998–2002)	2010	DDDR vs. VVIR in SND and AVB patients	21% relative risk reduction for development of AF in 3 years
United Kingdom Pacing and Cardiovascular Events (UK PACE 1998–2003)	2021	Single vs. dual-chamber pacing in elderly patients with AVB	No differences in mortality and AF incidence at 3 years
STOP-AF	350	DDD(R)/AAI(R) vs. VVI(R) or VDD(R) with AVD = 300 ms	No difference in survival
DANPACE (2010)	1415	DDD(R) vs. AAI(R)	24% relative risk reduction in risk for paroxysmal AF development, 50% reduced risk of reoperation with DDDR mode
SECONDARY PREVENTION TRIALS			
Atrial Pacing Periablation for Paroxysmal AF(PA[3] 1999–2000)	77	DDDR vs. VDD in patients with AV nodal ablation	43% developed AF in 1 year with no difference from control arm
Prevention by Overdrive Study (PROVE 2000)	78	Overdrive pacing resulted in 84% prevalence of pacing	No decrease in total arrhythmic episodes; 34% decrease in mode switches; 48% reduction in duration of arrhythmia episodes

AF, *Atrial fibrillation;* AVB, *atrioventricular conduction block;* AVD, *atrioventricular delay;* DANPACE, *Danish Multicenter Randomized Study on AAI versus DDD Pacing in Sick Sinus Syndrome;* PAF, *paroxysmal atrial fibrillation;* SND, *sinus node dysfunction.*

Danish Multicenter Randomized Study on AAI Versus DDD Pacing in Sick Sinus Syndrome (DANPACE). In this study, AAIR and DDDR did not differ with respect to survival, stroke risk, or development of chronic AF. Paroxysmal AF was reported more frequently with the AAIR mode, but surveillance did not include full-disclosure device data logs. In contrast, patients with AV block do not show this reduction in AF incidence with dual-chamber pacing. This could potentially be due to less use of atrial pacing in this population or disease localized to the AV junction. Perhaps the higher levels of ventricular pacing inherent with DDD devices and conventional programming, including ventricular dyssynchrony, were negating the potential benefits of maintaining AV synchrony, explaining the modest benefits observed in the individual dual-chamber pacing trials.

Atrial Pacing for the Secondary Prevention of Atrial Fibrillation

Clinical investigation of atrial pacing techniques for management of AF in symptomatic AF populations has been performed in several high-profile prospective clinical trials.[60-65] Analysis of the clinical benefit of atrial pacing is complicated by limited knowledge of the natural history of AF in different AF populations and by a lack of standardized endpoints for quantifying clinical benefit. Many studies lack a control group without atrial pacing therapy to judge efficacy. Approaches to date have included standard high right atrial or dual-chamber pacing alone or with rate response (see Table 90-1), right atrial pacing with novel pacing algorithms (Table 90-2), or alternate-site (high or low septal pacing) and dual-site atrial pacing (Table 90-3) and newer pacing algorithms minimizing ventricular pacing.

Site-Specific Atrial Pacing for Prevention of Atrial Fibrillation

Standard Right Atrial Pacing

The efficacy of standard high right atrial pacing alone for prevention of symptomatic paroxysmal AF has been evaluated in clinical studies and currently remains unproven. High right atrial pacing alone for prevention of symptomatic drug-refractory paroxysmal AF patients without bradycardia who are awaiting AV junctional ablation was evaluated in a prospective, randomized, crossover study by Gillis and coworkers, the Atrial Pacing Peri-Ablation for the Prevention of AF (PA[3]) trial.[60] They observed no prolongation in the time to recurrent AF compared with placebo. In patients with refractory AF as the sole arrhythmia, only the Jewel AF device (Medtronic, Inc., Minneapolis, MN) trial showed that high right atrial pacing appeared to reduce frequency but not AF burden initially, but more detailed analysis failed to confirm long-term benefit.[61] The Prevention by Overdrive study (PROVE), a randomized crossover trial, evaluated a similar device, the Talent DR 213 pacemaker (ELA Medical, Paris, France), combining atrial overdrive pacing with an automatic rest rate function.[62] Overdrive

Table 90-2 Secondary Prevention Trials with Novel Atrial Pacing Algorithms

TRIAL	NO. PATIENTS	PACING ALGORITHMS AND PATIENT POPULATION	OUTCOME
Atrial Therapy Efficacy and Safety Trial (ATTEST 2003)	368	DDDR pacing with atrial preventive and ATP algorithms ON vs. OFF	No decrease in AT/AF episodes (1.3 vs. 1.2/mo)
Adopt A (2001)	400	DDDR vs. DDDR with DAO; resulted in 92.9% pacing	Initial 26% reduction in AF burden and 65% reduction in organized atrial arrhythmias
Italian study (2001)	61	Use of CAP algorithm to increase pacing percentage from 77% to 96%	No decrease in AF (78% vs. 75%)
Atrial Fibrillation Trial (AFT 2001)	372	Preventive atrial pacing algorithm with DDDR	30% reduction in mean AF burden; 68% reduction in AF episodes with pacing algorithm
AT500 Verification Study Investigators (2001)	325	Preventive pacing and atrial ATP algorithms in AT500 Device	Atrial pacing increased from 62% to 97%, terminating 53% of AT episodes; AF episodes and time in AF not different

AT/AF, *Atrial tachycardia/atrial fibrillation;* AT, *atrial tachycardia;* ATP, *atrial tachycardia pacing;* CAP, *continuous atrial pacing;* DAO, *dynamic atrial overdrive pacing.*

Table 90-3 Trials with Alternate and Multi-site Pacing

TRIAL	NO. PATIENTS	PACING SITE AND PATIENT POPULATION	OUTCOME
SECONDARY PREVENTION TRIALS			
Dutch Trial (2000)	26	Single site vs. dual site with antiarrhythmic drugs	Less need for cardioversion for AF >24 h with dual-site pacing
Bailin (2001)	120	Bachmann's bundle vs. RAA pacing; 67.5% SND	Survival free from permanent AF increased to 75% from 47% with septal pacing
New Indication for Preventive Pacing in AF (NIPPAF 2001)	22	DAP with CAP. Algorithm vs. HRA pacing or no pacing	25% progressed to permanent AF in 1 yr
Pacing in Prevention of AF (PIPAF 2002)	91	DAP vs. DAP and DAO algorithm vs. HRA pacing	Reduction of AF events by 1.5 times
Dual Site Atrial Pacing for Prevention of AF (DAPPAF 2002)	120	DAP vs. HRA vs. support pacing as a part of hybrid therapy	Trend toward less AF in dual-site group with significant reduction in AAD group or infrequent AF group
Atrial Septal Pacing Efficacy Clinical Trial (ASPECT 2002)	298	Septal vs. nonseptal pacing	Improved mode adherence (5.8 vs. 4.7 vs. 3.3 mo) Improved AF-free survival (HR, 0.715 vs. 0.835 vs. 0.835) Longer time to recurrence (1.77 vs. 0.62 vs. 0.44 mo) No decrease in overall AF episodes and no effect on AF burden
PRIMARY PREVENTION TRIAL			
Pacing of Atria in Sick Sinus Syndrome Trial (PASTA 2008)	142	High right atrial vs. septal vs. CSO vs. dual-site right atrial pacing	No significant difference in patients with sinus node dysfunction and no AAD

ADD, *Antiarrhythmic drug;* AF, *atrial fibrillation;* CSO, *coronary sinus ostium;* DAO, *dynamic atrial overdrive pacing;* DAP, *dual-site atrial pacing;* HR, *hazard ratio;* HRA, *high right atrium;* RAA, *right atrial appendage;* SND, *sinus node dysfunction.*

pacing resulted in an improved atrial pacing percentage (84%) but did not reduce the total number of episodes, although there appeared to be a reduction in AF episode duration.

Another approach using high right atrial pacing in combination with other antiarrhythmic therapies, such as drugs, can also be considered but has not been formally studied in prospective studies. In an early experience from our group, antiarrhythmic drug therapy combined with high right atrial or septal pacing prolonged arrhythmia-free intervals, but no long-term data were available on rhythm control.[63]

Alternate-Site Atrial Pacing

Alternative single-site pacing involves placement of a septal RA lead. This can be further subdivided into high (Bachmann's bundle), mid (fossa ovalis), or low septal pacing (triangle of Koch).

Alternate-site and multi-site atrial pacing methods, such as dual-site right atrial pacing and bi-atrial synchronous pacing, have been evaluated for AF and atrial flutter prevention (see Table 90-3). Several studies of atrial septal pacing have shown a decrease in AF frequency and burden compared with right atrial appendage pacing, whereas other studies have not observed any difference in short-term follow-up.[64-67] Bailin and colleagues[64] randomized 120 patients with paroxysmal AF and bradycardias to high septal pacing or right atrial appendage pacing. Patients with high septal pacing had improved freedom from permanent AF at 1 year compared with standard right atrial pacing (75% vs. 47%), but there was no observed decrease in symptomatic AF event frequency. Despite improvement, a significant proportion (25%) of patients progressed to permanent AF. A control arm without pacing therapy was absent in this trial. With a similar study design, Hermida et al reported their findings in patients without AF as an inclusion criterion.[65]

The Atrial Septal Pacing Efficacy Clinical Trial (ASPECT)[66] randomized patients to low septal or standard right atrial pacing and used preventive pacing algorithms with the Medtronic AT500 pacemaker. In this study, low septal pacing was not associated with a reduction in AF frequency or burden. De Voogt et al performed the Overdrive Atrial Septum Stimulation (OASES) study[67] and examined the effect of atrial overdrive in patients with right atrial appendage and low interatrial septal pacing in 177 patients. With a 3-month crossover design, they found no significant effect of atrial overdrive on AF burden or mode switch number in either the right atrial appendage or septal paced groups.

Compared with multi-site atrial pacing, these alternative pacing sites require less hardware. The relative efficacy of right atrium high versus low atrial septal pacing for AF prevention remains unknown; however, the use of high septal pacing is associated with a lower risk of ventricular far-field sensing. Despite these findings, it is important to note that no large multicenter clinical trial of alternative-site pacing to prevent AF has been performed. Until these types of data are available, the use of alternative-site pacing should be considered unproven.[49]

Multi-Site Atrial Pacing

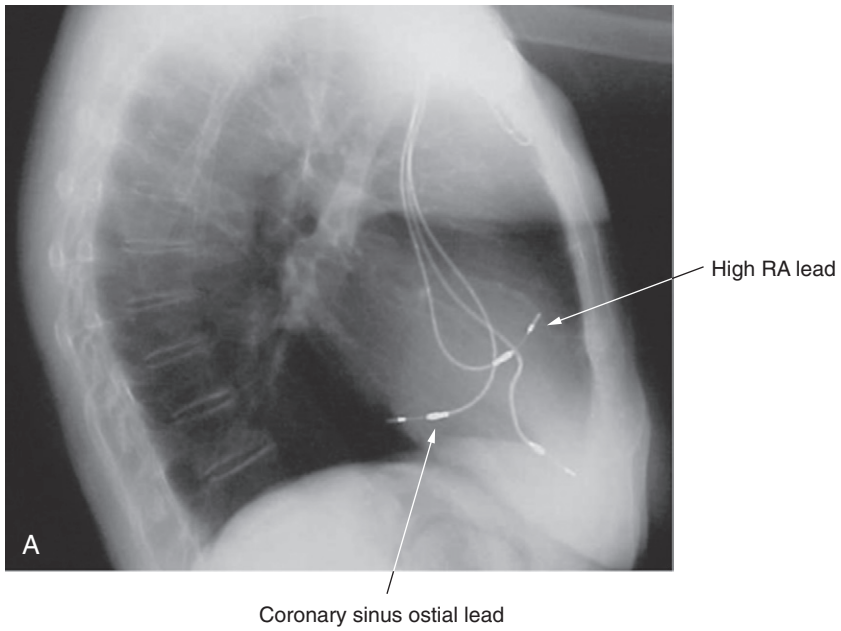
Biatrial Pacing

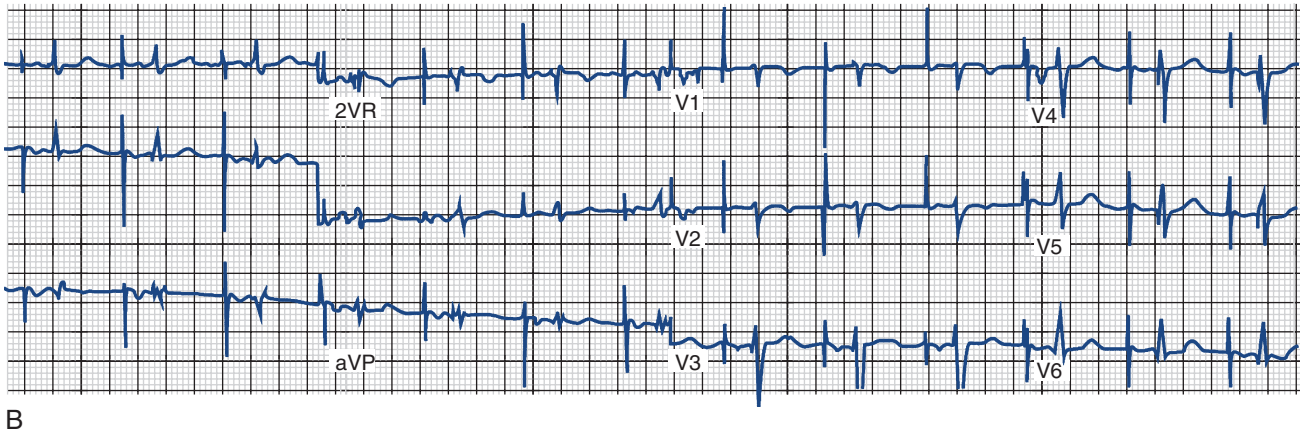
Synchronous bi-atrial pacing appears to be an interesting therapeutic modality for the management of refractory atrial arrhythmias to correct the deleterious electrophysiological consequences of high-grade intra-atrial or interatrial conduction disorders. In the majority of patients, the device implanted featured three pacing leads: two atrial leads linked by a bifurcated Y-connector to the atrial port of a dual-chamber pacemaker, the RA lead in cathodic configuration and the left atrial lead in anodic configuration, and a third lead placed in the right ventricular apex and linked to the ventricular port of the pacemaker. This configuration allowed standard DDD pacing with simultaneous bi-atrial pacing, forming a "triple chamber" pacemaker. The pacemakers were programmed in either triggered mode AAT(R) or DDD(R) mode. Synchronous Biatrial Pacing for Atrial Arrhythmia Prevention (SYNBIAPACE), a randomized crossover study, compared synchronous bi-atrial, high right atrial, and demand pacing during 3-month treatment arms. Patients were included if they had a standard indication for pacing, two or more episodes of AF in 3 months, and a P-wave duration of at least 120 ms. There was a nonsignificant increase in AF-free interval with bi-atrial pacing alone compared with high right atrial pacing.[68] Long-term effects of biatrial synchronous pacing in patients with intra-atrial conduction delay and recurrent atrial flutter and fibrillation to prevent recurrent AT/AF have been encouraging but variable.[69] In this 9-year follow-up study, at a mean follow-up of 33 months, 64% of the patients remained in sinus rhythm, whereas the others had repeated episodes of paroxysmal AF or developed persistent AF. A majority of these patients were receiving antiarrhythmic drug therapy.

Dual-Site Right Atrial Pacing

For dual-site right atrial pacing, an additional atrial pacing lead is inserted just outside the coronary sinus ostium for stability and left atrial stimulation (Figure 90-10, *A*). During simultaneous pacing of the high right atrium and coronary sinus ostium, the ECG shows a biphasic P wave in the inferior leads with abbreviation of P-wave duration (Figure 90-10, *B*). Several small, randomized trials were initially reported in addition to single-center pilot experiences. In our pilot experience, patients with drug-refractory symptomatic AF and bradycardias showed trends suggesting benefit with dual-site right atrial pacing in 3-month crossover interim analyses, but significant benefit of dual-site over high right atrial or septal pacing was obvious only after 1 year.[63] In a short-term randomized, 12-week comparative study of symptomatic AF patients without bradycardia, New Indication for Preventive Pacing in AF (NIPPAF), Lau and coworkers reported an increase in mean time to first AF recurrence from 15 to 50 days in patients during dual-site pacing compared with no pacing.[70] These single-center experiences have been followed by short-term randomized, multicenter studies.

The Dual Site Atrial Pacing for Prevention of Atrial Fibrillation Trial (DAPPAF) was a medium-term multicenter crossover study with 6-month treatment arms comparing dual-site right atrial, high right atrial, and support pacing.[71] It enrolled patients with frequent, symptomatic, and drug-refractory AF with bradyarrhythmias requiring cardiac pacemaker insertion. After dual-site right atrial pacing system implant, optimization of drug and pacing therapies was performed. The three modes of pacing were then randomly selected for 6-month periods. Patient tolerance and adherence to the pacing mode were superior in dual right atrial pacing compared with support ($P < .001$) and high right atrial pacing ($P = .006$) (Figure 90-10, *C*). Freedom from any symptomatic AF recurrence tended to be greater with dual right atrial (HR, 0.72; $P = .07$) but not with high right atrial pacing ($P = .19$) compared with support pacing. Combined symptomatic and asymptomatic AF frequency in patients was significantly reduced during dual right atrial pacing compared with high right atrial pacing ($P < .01$). However, in antiarrhythmic drug–treated patients, dual right atrial pacing increased symptomatic AF-free survival compared with support pacing ($P = .011$) and high right atrial pacing (HR, 0.67; $P = .06$). In drug-treated patients with less than one AF event per week, dual right atrial pacing significantly improved AF suppression compared with support pacing (HR, 0.46; $P = .004$) and high right atrial pacing (HR, 0.62; $P = .006$). Lead dislodgment was uncommon (1.7%), with coronary sinus and high right atrial lead stability being comparable. Thus DAPPAF showed improved adherence to pacing and rhythm control in the dual-site mode, especially when combined with antiarrhythmic drugs. This study supports the use of a hybrid or "add-on" therapy use of dual atrial pacing for rhythm management. In another prospective crossover trial with 6-month treatment periods performed in patients with recurrent symptomatic AF without





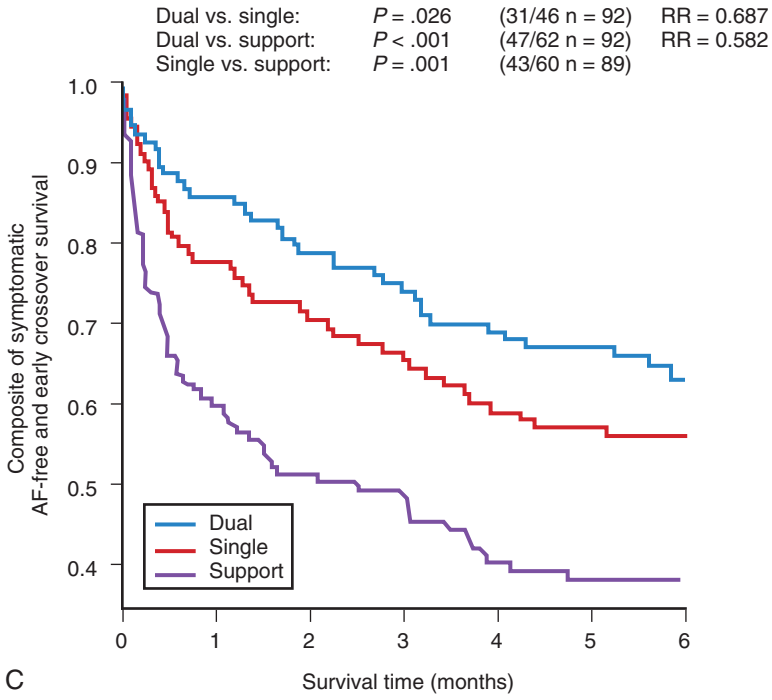


FIGURE 90-10 A, Radiograph of the chest in a patient with an implanted dual-site right atrial (*RA*) pacing system. Note the dual atrial leads in the high right atrial appendage and outside the ostium of the coronary sinus for atrial resynchronization therapy. **B,** Electrocardiogram showing the typical inversion and biphasic nature of the atrial paced P wave in the inferior leads in a patient with dual-site right atrial pacing leads. **C,** Composite endpoint of tolerance for atrial pacing therapy and freedom from recurrent atrial fibrillation in the Dual-Site Pacing for Prevention of Atrial Fibrillation (DAPPAF) trial. Note the superiority of dual-site RA pacing over single-site high right atrial pacing and support pacing. *AF,* Atrial fibrillation.

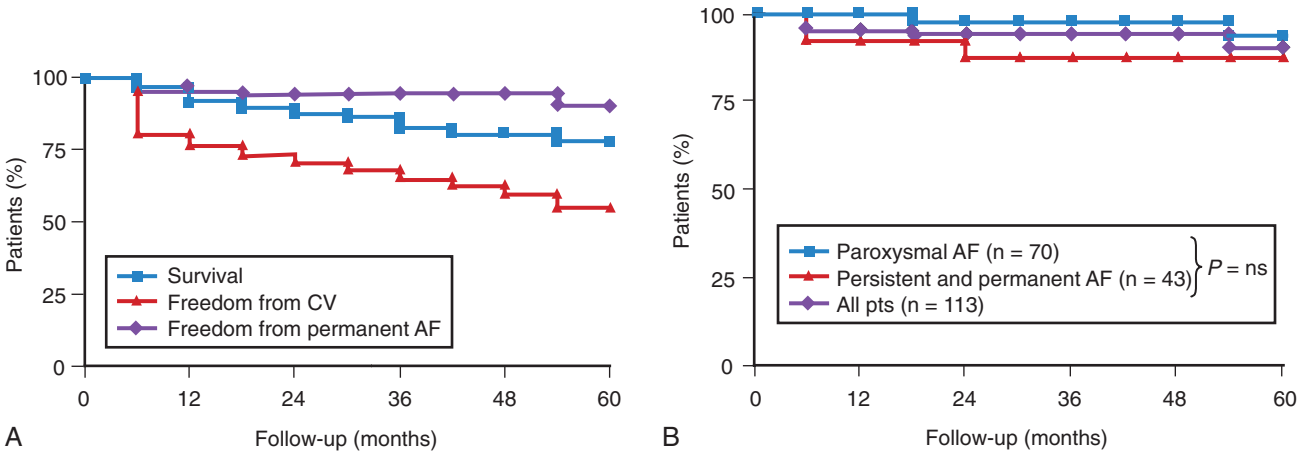


FIGURE 90-11 A, Long-term rhythm control, survival from all-cause mortality, and need for cardioversion (*CV*) therapy in study population by actuarial analysis. **B,** Comparison of long-term rhythm control in atrial fibrillation (*AF*) subpopulations with paroxysmal AF and persistent or permanent AF. Total population data are shown as a reference. *(From Madan N, Saksena S: Long-term rhythm control of drug refractory atrial fibrillation with "hybrid therapy" incorporating dual site right atrial pacing, antiarrhythmic drugs and right atrial ablation,* Am J Cardiol *100:569–575, 2004.)*

structural heart disease, Ramdat Misier and coworkers have shown a significant increase in time to recurrent AF and interventions for symptomatic AF recurrence.[72]

Longer term experience in secondary prevention of drug-refractory AF with dual-site right atrial pacing is now available (Figure 90-11). This experience has been acquired in patients with recurrent, symptomatic, and frequent drug-refractory AF, with or without concomitant bradycardias. In our long-term experience initially involving more than 125 patients with follow-up ranging to 10 years, the overall patient survival rate is 80% at 5 years. Rhythm control, as documented by device data logs, was achieved in more than 90% of patients at 3 years or more of follow-up. The overall stroke incidence was 1.0% per year.[73] Similar efficacy rates can be achieved in paroxysmal, persistent, and permanent AF (see Figure 90-11, *B*). However, occasional cardioversion and linear right atrial ablation was needed in approximately half of the patients with persistent and permanent AF for rhythm control. A nonrandomized, parallel-cohort experience from Europe in patients with bradycardias who required pacing and had paroxysmal AF supports long-term efficacy with dual-site right atrial pacing.[74] Of 83 patients, 30 had dual-site right atrial pacing systems and 53 had single-site high right pacemakers implanted. Patients with dual-site systems had a longer duration of AF (8.1 vs. 3.8 years for high right atrial systems; $P < .001$) and more did not show a positive response to drug trials (2.4 vs. 1.6 for high right atrial systems; $P < .05$). During a mean follow-up of 18 months, symptomatic paroxysmal AF recurred in nine patients after dual right atrial pacing compared with 24 patients after high right atrial pacing ($P = .03$). Permanent AF supervened in only one patient after dual right atrial pacing and in 12 patients after high right atrial pacing ($P < .05$).

The safety of dual-site right atrial pacing has been established by these studies. Lead dislodgment rates are well within estimates for any type of atrial pacing, and long-term dislodgment concerns have been obviated by the dual right atrial lead technique. The remaining complications have been largely similar to those in any pacemaker implant procedure. In contrast, bi-atrial pacing is associated with higher lead dislodgment rates (up to 15%) and greater potential for ventricular oversensing. The requirement for two atrial leads and a Y-connector has been an issue for both bi-atrial and dual-site right atrial pacing because two atrial ports are not available in current devices. Furthermore, only dual-site atrial pacing has been preferable when compared with low septal atrial pacing in a short-term study. More comparative studies are needed between alternative atrial pacing sites.

Novel Pacing Algorithms

A number of dedicated pacing algorithms have been developed for AF. The potential mechanism(s) of these algorithms are summarized in Table 90-2. These algorithms have been added to the armamentarium of device-based approaches for preventing AF and have been shown to increase the frequency of atrial pacing compared with conventional rate-response pacing. Prevention algorithms can be divided into two groups; continuous or triggered.

Continuous prevention algorithms act by pacing the atrium above the intrinsic atrial rate. Programmable features may include setting the number of beats above the intrinsic rate desired, an upper therapy rate after which the algorithm is disabled and the decay rate, which is the deceleration rate at which the atrial overdrive pacing rate reduces until the underlying intrinsic sinus rate, is re-identified. Triggered algorithms activate in response to a stimulus. The four examples of triggered algorithms include premature atrial contraction (PAC) suppression, "short-long" prevention, post-exercise response, and early re-initiation of atrial fibrillation suppression.

The dynamic atrial overdrive algorithm (St Jude Medical, Inc., St Paul, MN), is a continuous prevention algorithm that increases the atrial pacing rate when two P waves (consecutive or nonconsecutive) are sensed in a window. The atrial preference pacing (Boston Scientific, Natick, MA) algorithm increases the atrial pacing rate when sensed atrial events occur. Other pacing algorithms include atrial rate stabilization (Medtronic, Inc.), which paces after a PAC to avoid short-long cycles, and post–mode switch overdrive pacing, which paces at an elevated rate for a

defined period after a mode-switch event, and atrial pacing preference, which increases the pacing rate when an atrial event is sensed.

Single Algorithm Trials

Atrial Fibrillation in Bradycardia Tachycardia Syndrome

Trials using the novel algorithms for AF suppression in patients with concomitant bradycardia are summarized in Table 90-2. The AT500 pacemaker was a DDDRP device with two preventive atrial pacing leads. Atrial preference pacing changed the base pacing rate in response to atrial premature beats, with a programmable increment. Atrial rate stabilization intercedes after premature beats, altering the post-ectopic escape interval by markedly reducing it and then slowly easing down to the base pacing rate. ATP, as illustrated in Figure 90-5, can terminate common and non-isthmus-dependent atrial flutter by burst, ramp, or combination rapid pacing sequences. These algorithms are now present in the Medtronic EnRhythm pacemaker.

The Atrial Overdrive Pacing (AOP) trial prospectively evaluated overdrive single-site pacing in the right atrium for AF prevention in 145 patients in a randomized study design. This study did not reduce the frequency of AF events as indirectly as assessed by mode switch episodes. No symptomatic improvement was noted, but the pacing mode was well tolerated.[75] The Stimolazione Atrial Dinamica Multisito (STADIM) study from Italy compared the efficacy of single- and dual-site atrial pacing, with or without a dynamic atrial overdrive pacing algorithm, in AF prevention.[76] The algorithm significantly increased the percentage of atrial pacing, regardless of the atrial pulse configuration and pacing site, while maintaining a slower ventricular heart rate. There was no impact on AF frequency assessed by mode switch events in either unipolar and bipolar modes in patients with sick sinus syndrome. Similar results were reported in other studies using continuous atrial pacing algorithms, with an increased (84%) prevalence of atrial pacing and significant reduction in atrial premature beats (by 79%) with no effect on symptomatic AF event frequency. However, a moderate reduction (48%) in AF episode duration was observed with a modest improvement in quality of life.[77] The Biotronik (Lake Oswego, OR) closed loop system (CLS) uses a feedback mechanism to modulate its overdrive pacing algorithm. Results of a three-arm parallel comparative study of DDD(R), DDD plus atrial overdrive, and DDD plus physiological rate response algorithms showed that AT/AF burden was significantly lower with the new algorithm (20.3 ± 63.1 min/day; $P < .01$) versus DDD plus overdrive (56.0 ± 184.0 min/day) or DDD(R) (63.1± 113.8 min/day) modes.[78]

The Atrial Dynamic Overdrive Pacing Trial (ADOPT-A) randomized 399 patients with sinus node dysfunction and paroxysmal AF to DDD(R) pacing versus DDD(R) pacing plus dynamic overdrive pacing.[79] Patients were monitored 1, 3, and 6 months after pacemaker insertion. The primary study outcome was symptomatic AF burden, defined for this trial as percentage of days with symptomatic AF events. The investigators reported a very modest but statistically significant reduction in symptomatic AF during follow-up. However, the absolute benefit diminished over time: 1.25% at 1 month compared with 0.36% at 6 months.[80] In contrast, Menezes et al reported marked reduction in AF event rates when this algorithm was combined with atenolol and dual-site right atrial pacing. The Prevention of Immediate Reinitiation of Atrial Tachyarrhythmias (PIRAT) investigators assessed the efficacy of an early recurrence of AF suppression algorithm, with a high intervention rate of 120 beats/min. The control arm and active arm of this crossover study included the full suite of AT500 algorithms.[81] No significant difference in median number of AT episodes (0.34 vs 0.37), AT/AF burden (both 1%), percentage of early recurrence of AF (28 vs 30) symptoms, or quality of life was found. In summary, the impact of novel pacing algorithms when used alone is variable, ranging from modest improvement to little or no effect. Antiarrhythmic drug therapy was not strictly controlled in many of these studies, and its impact is unknown.

Atrial Fibrillation without Concomitant Bradycardia

The PAF-PACE study enrolled 42 patients without a bradycardia pacing indication and involved a three-way crossover design comparing no pacing (OAO mode) with two atrial overdrive algorithms of different intensity.[82] Medium (median, 0.88, $P = .01$) and high atrial overdrive (median, 0.75; $P = .002$) pacing reduced symptomatic AF episodes as documented by ECG versus no atrial overdrive (median, 2.03). Subgroup analysis showed that patients with a high resting heart rate also derived benefit from atrial overdrive. In a randomized crossover pilot study, 38 patients with symptomatic paroxysmal AF "without bradyarrhythmias" were randomized to atrial pacing lower rate 70 beats/min and prevention and ATP therapies ON or to atrial pacing lower rate 34 ppm and prevention and ATP therapies OFF.[83] This hybrid therapy of preventive and ATP pacing and antiarrhythmic drugs may significantly reduce but not abolish AF burden if septal pacing is realized.

Multiple Algorithms Trials

Atrial Fibrillation in Bradycardia-Tachycardia Syndrome

The Atrial Septal Pacing Clinical Efficacy Trial (ASPECT) randomized 298 patients with symptomatic bradycardia and AF to septal or right atrial appendage pacing.[84] After a 1-month stabilization period, patients were randomized to three atrial pacing algorithms for prevention of AF, ON or OFF, and followed for 3 months. Patients were then crossed over to the alternate pacing strategy and monitored for an additional 3 months. The primary outcome measure was AT/AF burden determined from the diagnostic counters in the Medtronic AT500 and measured as percentage of time in AF. The combined three pacing algorithms, Atrial Pacing Preference, Atrial Rate Stabilization, and Post Mode Switch Overdrive Pacing, did not result in a significant reduction in AF burden despite the demonstration of a significant reduction in supraventricular premature beat frequency.

The VIP Registry was a prospective, nonrandomized, multicenter, three-phase study conducted in 84 centers in 11 European countries that investigated the efficacy of preventive pacing algorithm selection in reducing AF burden in 126 patients with a conventional antibradycardia pacemaker indication.[85] A 3-month diagnostic phase with conventional pacing identified a substrate group (>70% of AF episodes with more than two PACs before AF onset) and a trigger group (≤70% of AF episodes with fewer than two PACs before AF onset). This was followed by a 3-month therapeutic phase in which the trigger group algorithms were enabled with the aim to avoid or prevent a PAC. Continuous atrial overdrive pacing was enabled in the substrate group. A subgroup of patients was identified for whom the selection of appropriate pacing algorithms, based on individual diagnostic data, translated

into a reduced AF burden. Trigger AF patients were more likely to respond to preventive pacing algorithms as a result of PAC suppression.

The aim of one Vitatron Selection 9000 pacemaker (Vitatron Medical BV, Arnhem, The Netherlands) study was to compare the effects of different pacing strategies to prevent AF in 117 patients with a standard pacing indication: triggered atrial overdrive pacing versus the combination of triggered and continuous overdrive pacing.[86] The three triggered algorithms assessed were PAC suppression, "short-long" prevention, and post-exercise response. Triggered atrial pacing functions alone resulted in a low AF burden. The additional activation of continuous atrial overdrive pacing increased the percentage of atrial pacing but had no beneficial effects on the prevention of paroxysmal AF. Based on the available data it seems more likely that triggered algorithms had a beneficial effect rather than overdrive had a detrimental effect.

The Study of Atrial Fibrillation Reduction (SAFARI) was designed to determine the impact of preventive pacing algorithms on AF among patients with paroxysmal AF.[87] In the largest preventive pacing trial to date, a unique combination of six triggered and continuous overdrive prevention pacing therapies was applied to target multiple triggers of AF. The primary study objective was to determine whether prevention pacing therapies were safe and effective in reducing AF burden, without increasing the incidence of permanent AF. Patients who met standard pacemaker indications and documented symptomatic AF were implanted with a Selection 9000 pacemaker. The primary efficacy endpoint was AT/AF burden, defined as the average number of hours per day spent in AT/AF during follow-up with satisfactory atrial sensing having been previously documented. A significant burden decrease of 0.87 hours/day occurred during follow-up with algorithms on compared with a decrease of 0.38 hours/day with algorithms off (P = .01). No significant change in AF frequency, average sinus rhythm duration, hospital admissions, or cardioversions was seen. The results from SAFARI provide robust evidence that modest benefits relative to arrhythmia burden are conferred by the use of multiple pacing algorithms in paroxysmal AF patients with preexisting bradycardia but clinical benefits remain to be demonstrated. Their use should be considered in this population to complement other therapies rather than as a stand-alone therapy.

Atrial Fibrillation without Concomitant Bradycardia

The Pacing in Prevention of AF (PIPAF) study randomized 190 patients with bradycardia and AF to a trial of three atrial pacing prevention algorithms for prevention of AF.[88] Patients were followed up for a total of 6 months in this crossover study. No differences in the primary outcome or total mode switch duration were observed when the pacing prevention algorithms were programmed on (11.9 ± 27.7 days) compared with when they were programmed off (11.6 ± 26.5, P = not significant). In a subanalysis of the PIPAF trial, the greatest benefit to atrial overdrive pacing was noted in the group of patients who had the least amount of concomitant ventricular pacing. The Atrial Fibrillation Therapy (AFT) study recruited 372 patients, with only one third having coexisting bradycardia. Phase 1 was a monitoring phase.[89] Phase 2 randomized 154 patients to DDD 40, DDD(R) 70 or DDD(R) 85 in a parallel design. Phase 3 randomized 153 patients to either DDD 70 or DDD70 + multiple trigger suppression algorithms. Phase 4 further randomized 95 patients into four groups, and each evaluated one of the studied algorithms in a crossover design. A substantial amount of data was excluded from the analysis because of atrial sensing artifacts. Further limitations included a significant proportion of patients with no AF, and the small sample limited power to assess subgroup differences in phase 4. In the conventional pacing phase, no significant differences were found between various lower rates and the control group receiving single-rate pacing at 40/min or between single-rate and rate-responsive pacing. Patients receiving preventive pacing with all four therapies enabled had a similar AF burden compared with patients treated with conventional pacing at 70/min (P = .47). No significant effect on device-derived AF burden was found in any phase.[90]

The Pacemaker Atrial Fibrillation Suppression (PAFS) study was designed to evaluate continuous atrial overdrive, post-AF response, and ventricular rate regularization pacing algorithms both separately and in combination, with monitoring of these effects by sophisticated Holter functions incorporated into the pacemaker.[91] Patients with and without a conventional bradycardia indication for pacing were assessed. The ventricular rate stabilization algorithm was designed for symptom control, whereas atrial overdrive and post-AF response were designed to prevent AF occurrence. Forty-two percent of paroxysmal AF patients did not show any AF after enrollment, suggesting that bradycardia pacing alone eliminates AF.[91] The rate-soothing algorithm by atrial overdrive pacing reduced PAC-initiated paroxysmal AF. However, there was no overall change in AF burden, paroxysmal AF episodes, patient symptoms, or quality of life. There was a consistent finding in both AFT and PAFS that bradycardia pacing alone prevented AF in approximately 40% of patients. Based on these data, it is evident that the use of pacemakers with multiple algorithms is not indicated in patients without coexisting bradycardia.

Pacing Algorithms to Enhance Intrinsic Ventricular Conduction

Right ventricular apical pacing has been shown to increase the risk of the development of persistent AF. It can elevate ventricular filling pressures, increase AV valve regurgitation, and induce changes in ventricular relaxation and geometry that may adversely affect atrial function. The risk of AF increases linearly with the cumulative percentage of ventricular pacing from 0% to 85% in both the DDD(R) (HR, 1.36; 95% CI, 1.09 to 1.69) and VVIR (HR, 1.21; 95% CI, 1.02 to 1.43) groups.[92] Ventricular dyssynchrony introduced by ventricular pacing can increase the risk of AF in sinus node dysfunction even when AV synchrony is preserved. When compared with AAIR pacing or DDD(R) pacing with a long AV delay, DDD(R) pacing with a short AV delay increased left atrial diameter (P < .05) and decreased fractional shortening of the LV (P < .01).[93] Subsequently, these investigators demonstrated a significant reduction in AF in the AAIR group (7.4%) versus the DDD(R) short (23.3%) and DDD(R) long (17.5%) groups (P = .03).[94]

Benefits for patients with paroxysmal AF with minimizing right ventricular pacing are less uniform. In a subanalysis of the PIPAF trial, only patients with minimal right ventricular pacing had a significant reduction in AT burden and frequency with the use of preventive pacing algorithms.[88] Other studies have not found similar relationships between paroxysmal AF burden and percentage of right ventricular pacing.[85,89,91] New algorithms to enhance intrinsic ventricular conduction have been developed by many manufacturers (MVP algorithm in Medtronic devices,

AAISafe2 algorithm integrated in Sorin (Sorin Group, Milan, Italy) pacemakers, Intrinsic AV conduction detection in St Jude Medical pacemakers, and AVSH implemented in Boston Scientific devices), but efficacy studies are still sparse.[95,96] All these algorithms allow a functional AAIR pacing mode to be achieved with a mode switch back to DDD(R) in the case of dropped ventricular beats. Recently, the Search AV Extension and Managed Ventricular Pacing for Promoting AV Conduction (SAVE PACe) trial has provided an prospective assessment of benefits of such an approach. A total of 1065 patients with sinus node disease, intact AV conduction, and a normal QRS interval were randomly assigned to receive conventional dual-chamber pacing or dual-chamber minimal ventricular pacing.[97] A marked reduction in right ventricular pacing was confirmed (9.1% in the minimal ventricular pacing algorithm compared with 99% in the conventional DDD(R) pacing group). The likelihood of developing persistent AF during a mean follow-up of 1.7 years was reduced (HR, 0.60, $P = .009$) with dual-chamber minimal ventricular pacing. Total mortality rate (a secondary endpoint) was similar in the two groups. These benefits may evolve over time.

The short-term study on minimal ventricular pacing (MinVPace) demonstrated effective reduction in right ventricular pacing without improvement in AF burden in 110 patients with symptomatic paroxysmal AF.[98] No additional benefit or adverse outcome was found with preventative anti-AF algorithms in combination with MinVP algorithms. Whether AAAIR pacing or MVP algorithms achieve these aims was being addressed by DANPACE II,[99] which showed comparable outcomes of these two modes, suggesting that patients unsuitable for long-term AAIR pacing may use DDDR pacing for long-term therapy. AAIR pacing may use DDDR pacing with such algorithms to achieve similar benefit. Based on these data, attempts should be made to enhance intrinsic conduction in patients with sinus node disease by extension of the AV delay, use of AAIR pacing, or by minimal ventricular pacing algorithms. Future studies such as the Minimize Right Ventricular Pacing to Prevent Atrial Fibrillation and Heart Failure (MINERVA) study,[100] the Mode Evaluation in Sick Sinus Syndrome Trial (MODEST),[101] the Prefer Managed Ventricular Pacing (PreFER MVP) study,[102] and the EnPulse on Search AV+ Influence (EnTRINSIC) trial[103] will examine other endpoints. These algorithms have not been evaluated in patients without bradycardias.

Pacemaker Monitoring of Atrial Fibrillation

Diagnostic information retrieved from a pacemaker offers the ability to improve patient care. Pacemaker diagnostic data provide information regarding pacemaker function and activity, lead function, arrhythmia occurrence, and data to aid in optimal pacemaker programming. Current pacemakers incorporate greater storage capabilities, more efficient means of storing and presenting data between follow-up visits, and more options for programming diagnostic functions and algorithms.[104] These have been discussed in detail in several other chapters in this text. Analysis of pacemaker sensing of atrial tachyarrhythmias has highlighted various important issues relevant to the interpretation of AF pacing trial endpoint data and AF management based on device diagnostics. Aberrant sensing in the atrial channel due to far-field R-wave oversensing or undersensing of atrial tachyarrhythmia signals can compromise this data and should be evaluated at implant and early follow-up. Oversensing and undersensing also cause adverse device behavior such as inappropriate induction of atrial pacing therapies and ventricular tracking, respectively.[105]

The accuracy of device measurement of AF episode frequency and duration has been validated by a number of studies comparing the accuracy of atrial arrhythmia detection between device and Holter monitoring. Intermittent or infrequent AF undersensing remains common but has little effect on AF burden. AF episode number and individual AF episode duration, however, are significantly affected by undersensing and should always be validated by using stored intracardiac electrograms. The devices must be programmed appropriately to avoid far-field R-wave oversensing and atrial undersensing to ensure a high sensitivity and specificity for AF detection. Analysis of pacemaker-derived data has made it apparent that the majority of atrial tachyarrhythmias are asymptomatic. Furthermore, AF episode recurrences are not randomly distributed, making interpretation of individual patient data and trial-based, device-derived data difficult.

AF onset mechanisms were studied in the Atrial Fibrillation Therapy (AFT) study.[89] The most common onset scenario involved PACs before AF (48% of all episodes per patient), followed by bradycardia (33%), sudden cycle length changes (17%), and tachycardia (0%) before AF. Combinations of onset scenarios were frequent (median of three different scenarios per patient). A main study finding was the significance of repetitive AF, with 33% of onsets per patient being initiated within 5 minutes of a previous AF episode. Sudden onsets were more frequent among patients with than without repetitive AF (24% vs. 0% onsets per patient, $P = .011$), whereas the proportion of PACs before AF was not statistically different (50% vs. 37%, $P = .52$); however, patients with repetitive AF had more PACs per hour (72 vs. 29, $P = .023$) and a higher number of AF episodes per day (17 vs. 0, $P = .001$) and were more likely to have at least one PAC-related onset (90% vs. 53%, $P < .0001$).[89]

A retrospective analysis from MOST emphasized the clinical impact of device measurement of atrial arrhythmia episodes. In this study, the presence of any atrial high-rate episodes was an independent predictor of total mortality (HR for atrial episodes compared with no episodes over a median follow-up of 27 months, 2.48; 95% CI, 1.25 to 4.91; $P = .0092$) and for death or nonfatal stroke (HR, 2.79; 95% CI, 1.51 to 5.15; $P = .0011$).[106] These observations have been extended to the increased risk of arterial embolism for AF episodes lasting longer than 1 day.[107] The Prospective Study of the Clinical Significance of Atrial Arrhythmias Detected by Implanted Device Diagnostics (TRENDS) examined the potential of pacemaker data logs to assess stroke risk. This was a prospective, observational study enrolling 3045 patients with one or more stroke risk factors according to the $CHADS_2$ score receiving pacemakers or defibrillators that monitor AT/AF burden.[108] The thromboembolic rate in this study was low and did not meet its primary endpoint. The data were analyzed post hoc to stratify thromboembolic risk as a quantitative function of AT/AF burden or episode duration. AT/AF burden of 5.5 hours or longer on any of 30 prior days appeared to double thromboembolic risk.[109] In a subanalysis of TRENDS, newly detected episodes of AT/AF were found via continuous monitoring in 28% of patients with previous thromboembolic events.[110] Additional studies are needed to investigate more precisely the relationship between stroke risk and AT/AF burden. A large ongoing clinical trial of elderly hypertensive patients (Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial [ASSERT]) undergoing pacemaker implantation for standard bradycardia indications is

assessing the value of asymptomatic atrial high-rate events for the prediction of stroke and other vascular events.[111]

Atrial Fibrillation Termination Therapies

Anti-tachycardia Pacing

One rationale for incorporating atrial ATP into AF devices has been that atrial flutter and AT frequently coexist in the patient with AF, and AF not uncommonly organizes to atrial flutter. Atrial tachyarrhythmias are detected when the median atrial cycle length over 12 beats is less than the programmed atrial tachyarrhythmia rate and the ratio between atrial and ventricular activity is greater than 1:1 for at least 24 ventricular beats. The device further classifies the rhythm based on cycle length and cycle length regularity. Several pacing algorithms have been designed to terminate AF. These algorithms include 50-Hz pacing as well as burst and ramp sequences. In one of the most well-studied devices, the AT500 (see Table 90-2) ATP for AF termination has been evaluated in randomized and nonrandomized studies. Several observational studies, including prospective multicenter studies, demonstrated the successful termination of atrial tachyarrhythmias in the atrial flutter zone with ATP and modest success with high-frequency burst pacing in the AF zone. However, prospective observational or randomized trials have not shown that pacing termination strategies reduce or eliminate symptomatic AF or total AF burden.

The AT500 Verification Study evaluated 325 patients for the efficacy of atrial preventive and ATP, device safety, and reliability of atrial tachyarrhythmia detection.[112] Patients served as their own controls. Although preventive pacing algorithms were found to increase the median percentage of atrial pacing from 62% to 97%, the frequency and duration of AF episodes were unchanged. Fifty-three percent of AT episodes were terminated with ATP; there was an 88% complication-free survival rate at 3 months and 97% reliable detection of atrial tachyarrhythmia episodes. This study supports a role for ATP in AF device therapy.

The Atrial Therapy Efficacy and Safety Trial (ATTEST)[113] prospectively randomized bradycardia patients with the AT500 pacemaker after implantation to preventive pacing plus ATP activation or standard high right atrial pacing in the DDDR mode. ATP in this study also terminated 54% of episodes, and the positive predictive value for AT detection was 99%. Although quality of life improved in both groups, there were no significant differences in frequency or burden of atrial tachyarrhythmia episodes. Gillis et al assessed the effects of ATP therapies in 151 patients with dual-chamber cardioverter-defibrillators.[114] Fifty-two percent of patients were known to have atrial arrhythmias, and 623 episodes were treated by device. Device-reported success rates were 40% for AT and 26% for AF episodes but were not validated by external recordings.[114] The Italian AT500 registry prospectively evaluated the efficacy of ATP therapy in 346 patients with paroxysmal AF and sinus node disease. During a median follow-up of 19 months, AF-related hospitalizations decreased significantly and mean AT cycle length increased significantly. These data suggest that pacing termination therapies can modify AT/AF progression.[115] Device diagnostics can be fallible in assessment of pacing termination of AT/AF. In a crossover study, 50-Hz pacing did not terminate AF despite device interpretation suggesting successful termination.[116] Forty-two percent of AT terminations were judged to be correctly diagnosed by device logic as successful ATP termination by active ATP.

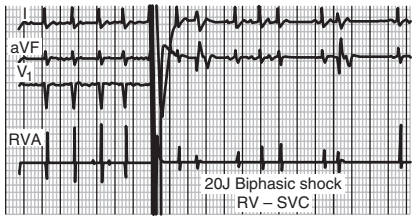
The Worldwide Jewel AF Investigators described their observations from 537 patients implanted with a dual-chamber cardioverter-defibrillator for ventricular arrhythmias. ATP successfully treated 48% of AT/AF episodes (device classified). They noted that the efficacy was greater for AT than AF and was significantly affected by AT/AF cycle length, which is in line with other investigators.[117] These findings have been confirmed in other trials.[118] More recently, the Reduced Incidence and Duration of Atrial Fibrillation (RID-AF) investigators studied the impact of atrial prevention and termination therapies on overall AT/AF burden in patients receiving a dual-chamber defibrillator for ventricular arrhythmias.[119] No significant change in overall AT/AF burden was observed, perhaps because of the low AT/AF burden in this population. In a subgroup of patients with history of AT/AF, there was a trend toward a reduction in mean burden. The Worldwide Jewel AF-only Investigators implanted 144 Jewel AF devices in patients with drug-refractory AF.[120] ATP successfully treated 49% of AT episodes and 23% of AF episodes, but there was no effect on AF episodes frequency. In the randomized, parallel ATP Natural History study, combined prevention and termination algorithms were evaluated in 48 patients.[121] Patients were strongly encouraged to use a manual activator to document their symptoms throughout the 12-month follow-up period. Among patients with symptomatic bradycardia and a history of AF, symptoms of AF often were not associated with documented atrial tachyarrhythmias, and more than 90% of atrial tachyarrhythmias were clinically silent. In a retrospective meta-analysis,[122] AT/AF burden was compared in 261 patients who received a Medtronic AT500 pacemaker for treatment of AT/AF in the setting of symptomatic bradycardia based on device-classified atrial ATP efficacy of less than 60% and 60% or more. The high-efficacy group showed a significant reduction in AT/AF burden when ATP therapies were activated (median of 2.46 hours/day vs. 0.68 hours/day; $P < .001$). In contrast, the low-efficacy group showed an increase in AT/AF burden over time (median of 2.77 hours/day vs. 2.92 hours/day; $P = .01$). Up to 30% of patients with frequent episodes of paroxysmal AF and symptomatic bradycardia have a reduction in AT/AF burden from atrial ATP therapy over time. ATP was more efficacious in regular rhythms with longer cycle lengths. The high-efficacy group tended to have a clinical history of atrial flutter. Recently, longer term evaluation of these combined ATP plus Prevention algorithms did not show long-term benefit compared with conventional DDD(R) pacing.[123] This underlines the progressive nature of AT/AF burden and the limited role of trigger suppression and termination therapies. It would be reasonable to conclude that atrial ATP is effective in select patients and often in a subgroup of atrial tachyarrhythmia events. This therapy is a valuable adjunctive component in devices when used in a hybrid therapy algorithm.

Atrial Defibrillation

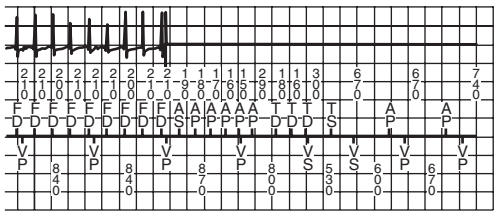
Clinical Efficacy

Catheter-based internal cardioversion of AF was first reported by Jain and coworkers in 1969, and early studies were performed by Mirowski and colleagues.[124] High-energy shocks delivered by a right atrial catheter electrode and a thoracic patch electrode were reported by Levy, who noted a 90% success rate for atrial defibrillation with 200 to 300 J damped sinusoidal waveform shocks.[125] Epicardial and wholly endocardial electrodes greatly reduced energy requirements for atrial cardioversion (Figure 90-12). For RA to coronary sinus shock vectors, the mean defibrillation

Prototype AF pacemaker



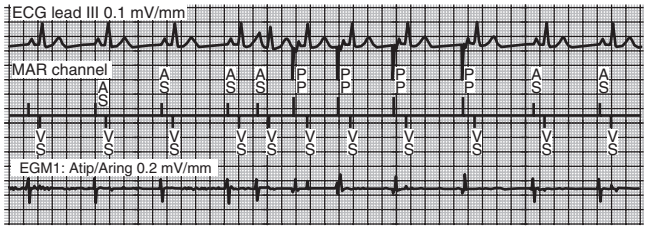
Atrial defibrillation



Atrial pace termination

Prototype dual AV ICD

Patient activator



Preventative atrial pacing algorithm

FIGURE 90-12 First-generation technology for cardiac pacemakers and dual-chamber atrioventricular (*AV*) defibrillators with atrial fibrillation (*AF*) detection and therapy features. *Left,* Illustrations of the implantable pulse generator (*top,* Medtronic AT500 series pacemaker; *bottom,* Medtronic Jewel AF defibrillator). The *top center panel* shows the preventive pacing algorithm present in both devices (atrial rate stabilization) operating in a patient with premature atrial complexes. The *bottom center panel* shows a prototype patient activator for the defibrillator device that can be used for AF detection and treatment under patient or physician guidance. The *top right panel* shows burst atrial anti-tachycardia pacing for atrial tachyarrhythmia termination present in both devices. The bottom right panel shows delivery of an atrial defibrillation shock in a patient with spontaneous AF with successful AF termination and sinus rhythm (*SR*), but frequent atrial premature beats after shock delivery lead to early recurrence of AF. *ICD,* Implantable cardioverter-defibrillator.

threshold was 4.7 J for monophasic shocks and 2.5 J for biphasic shocks in acute feasibility studies of induced AF.[126] Initial prospective, randomized, controlled studies of different shock vectors in AF patients, however, showed that defibrillation thresholds routinely exceeded 10 J for right-sided vectors, and right atrium to pulmonary artery configurations averaged 8.6 J.[127] This was well above the pain threshold, and patients required sedation for shock tolerance. Lower atrial defibrillation thresholds were seen in the absence of heart disease, higher left ventricular ejection fraction, and lower left ventricular dimensions.

The safety and tolerance of atrial defibrillation shocks were extensively debated in the early years. Early studies performed in patients without structural heart disease and right atrium to coronary sinus shock vectors showed virtually no proarrhythmic risk. Subsequently, low and intermediate energy shocks delivered in an R-wave synchronous mode with a RV to RA or RA to thoracic cutaneous electrode induced nonsustained ventricular tachycardia. A rare episode of sustained ventricular tachycardia has been reported. In AF populations with structural heart disease, ventricular tachyarrhythmias have been observed for the first time after AF device therapy had been instituted. This has been used as an argument to have ventricular defibrillation capability available when atrial defibrillation is performed. This has also led to the use of dual-chamber AV defibrillators in preference to atrial defibrillators in this population. Bradyarrhythmias are more common after atrial defibrillation shocks. We have observed a 28% incidence of sinus node or AV conduction delays.[128] Thus demand ventricular pacing should be available when atrial defibrillation shocks are used.

Shock Tolerance

Tolerance for intracardiac shocks was initially examined when cardioversion for ventricular tachyarrhythmias was evaluated.[129,130] In 1985, our studies showed that shocks of more than 1 J were poorly tolerated by 88% of patients.[131] Nathan reported that intra-atrial shocks of even less than 1 J were often poorly tolerated by awake patients.[132] In our prospective study, 20% of patients reported pain at 1 J, 40% at 2 J, and the majority reported pain by 3 J.[130] Subsequently, a variety of efforts have been made to improve tolerance to these shocks. Although shock waveform changes have had modest beneficial effects, it has been demonstrated that repeated shock delivery enhances pain perception and shock intolerance. Thus a single, high-energy successful shock is better tolerated than several low-energy shocks of lesser efficacy. Current therapeutic strategies are therefore designed for successful first shock or nocturnal shock delivery strategies to improve patient acceptance of this therapy and, more importantly, to consider patient-activated shocks for outpatient management of recurrent AF.

Implantable Atrial Defibrillator

Device Technology

The development of implantable device technology was achieved in the late 1990s and a prototype device was used in pilot studies. The prototype devices, Metrix models 3000 and its successor 3020, differed principally in their maximum energy outputs, 3 J for the Metrix 3000 and 6 J for the Metrix 3020.[133-135] Both delivered a biphasic truncated exponential waveform of 3/3 ms and 6/6 ms duration, respectively, which accounts for the increased energy output of the model 3020. The device, with a weight of 79 g and a volume of 53 mL, was implanted in the pectoral region, as with a conventional pacemaker. Graded shock therapy of up to eight shocks (two at each level) for each episode of AF programmable in 20-V increments up to 300 V were permitted. Atrial defibrillation was accomplished by a shock delivered between electrodes in the right atrium and the coronary sinus. One defibrillation lead was fixed in the right atrium. The second defibrillation lead was placed in the coronary sinus and had a spiral configuration for retention in the coronary sinus. A separate bipolar right ventricular lead is used for R-wave synchronization and demand pacing. The Metrix defibrillator induced AF by using R-wave synchronous shocks and atrial defibrillation threshold testing. Defibrillation therapy could be programmed into one of the following five operating modes: fully automatic, patient activated, monitor mode, bradycardia pacing only, and off. The device could also store intracardiac electrograms for up to 2 minutes from the most recent six AF episodes (Figure 90-13). The device used extensive signal processing for AF detection and R-wave synchronization.[136] Two detection algorithms are run in series. The first, the "quiet interval analysis algorithm," discriminates between a sinus beat and another atrial rhythm in the 8-second electrogram segment. The second algorithm, the "baseline crossing test," is invoked to detect AF (see Figure 90-13). This latter algorithm examined electrical activity during parts of the cardiac cycle that are quiescent during sinus rhythm and most organized atrial arrhythmias, but not during AF where atrial activity is random and unrelated to the cardiac cycle. The first algorithm, the quiet interval algorithm, is highly sensitive for detection of AF and highly specific for sinus rhythm. The second algorithm, the baseline crossing algorithm, is highly specific for AF. The result was a highly sensitive and extremely specific detection algorithm for AF. The Metrix device used a dual-channel synchronization algorithm to achieve high specificity at the expense of sensitivity. Thus the algorithm was designed to ensure that all shocks will be delivered only to correctly synchronized R waves to avoid risk of proarrhythmia. Before synchronization was attempted, the two electrograms are evaluated simultaneously in real time for integrity and data quality.

Patient Selection, Follow-up, and Outcomes

In the pilot clinical study, 51 patients from 19 centers in nine different countries were enrolled. Patients had to meet specific inclusion criteria: (1) prior episodes of symptomatic AF that had spontaneously terminated or been converted to normal sinus rhythm with intervals of recurrence between 1 week and 3 months and (2) previous treatment with at least one class I or class III antiarrhythmic agent that proved ineffective or was not tolerated because of side effects. Postoperative evaluation, including AF detection and R-wave synchronization tests, was performed at predischarge, 1, 3, and 6 months and thereafter at 6-month intervals until completion of the study. Atrial shock energy was programmed either at the maximal output of the device or at least well above the atrial defibrillation threshold obtained at the time of implant.

During this initial study, 3719 shocks were delivered for AF induction, atrial defibrillation, and testing or termination of spontaneous AF episodes.[137] Of these 3719 shocks, 3049 were delivered during testing and 670 were delivered for treatment of spontaneous episodes of AF. All shocks for spontaneous episodes were given during physician observation. There were no reported cases of induction of ventricular arrhythmias or inaccurately synchronized shocks during the study. A larger and longer term experience confirmed these initial observations. Correct synchronization was observed for all the marked R waves, and the accuracy of synchronization was 100% during both sinus rhythm and AF or atrial flutter. Analysis of the AF detection algorithm performance revealed 100% specificity for the recognition of sinus

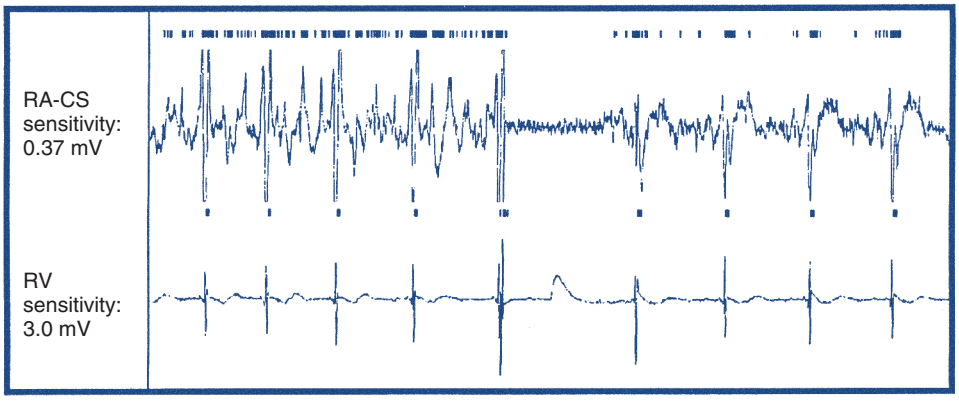


FIGURE 90-13 Stored electrogram of a successful conversion of atrial fibrillation with the automatic implantable atrial defibrillator. Sinus rhythm is restored by application of an internal automatic shock. *Upper trace,* Recordings of the intracardiac electrograms with their corresponding markers between a right atrial (*RA*) and a coronary sinus (*CS*) electrode using a sensitivity of 0.37 mV. *Lower trace,* Recordings of the right ventricular (*RV*) bipolar lead and marker signals with a sensitivity of 3.0 mV.

rhythm and 92.3% sensitivity for the detection of AF. From the same data, the positive predictive value of the AF detection algorithm was 100% and the negative predictive value was 92.6%. One important aspect of the device was its ability to permit prolonged AF monitoring. In the early experience, one or more valid monitoring periods were available from 46 of 51 patients. A total of 1161 valid episodes of AF was obtained during a mean follow-up period of 260 ± 144 days (average recurrence rate of 3.9 ± 5.0 episodes per patient-month). The median duration of the 190 treated episodes falling within a valid monitoring period was 17.6 hours, and 3 hours for the 971 nontreated episodes. Of the 190 treated episodes, 28% were equal to 8 hours in length compared with 78% of the nontreated episodes. Five patients with a total of 29 episodes documented in the device memory did not seek therapy treatment for any episodes. These findings demonstrated for the first time the pattern and density of symptomatic and asymptomatic AF events in the symptomatic AF population.[138] These patterns have now been confirmed in larger experiences and with other devices.

Forty-one of the 51 patients had spontaneous episodes of AF that were treated with device therapy (average of 5.6 episode per patient with a range of 1 to 26 episodes). A total of 670 shocks was delivered for the treatment of 227 episodes, with an average of three shocks per episode. After shock delivery, 95.6% of the episodes were terminated. Recurrence of AF within 4 minutes of successful defibrillation was observed in 27% of AF events and occurred in 51% of patients (Figure 90-14). Considering only those episodes in which sustained sinus rhythm was restored, the clinical efficacy of the defibrillation therapy for these spontaneous episodes was 86.3%. By October 1998, more than 200 Metrix systems had been implanted worldwide. Safety and efficacy data for the first 186 implants confirmed the initial experience. Most Metrix patients had highly symptomatic, drug-refractory AF, usually without cardiovascular disease. The conversion to sinus rhythm and the clinical success rate were similar during a long-term experience, with an electrical success rate of 93% and a clinical efficacy rate of 84%.

The atrial defibrillator also provided a programmable, patient-controlled mode. As of August 1998, 57 patients had their Metrix devices programmed to this mode. This option enabled these patients to deliver therapy when and where it was appropriate and convenient. A total of 276 spontaneous episodes of AF were treated in this manner. Most patients chose to deliver shocks with no analgesia or sedation. Most AF episodes treated outside the hospital terminated with a single shock, with a mean number of 1.7 shocks per episode. No inappropriate therapy was delivered in this mode. Patients administering therapy outside the hospital successfully terminated 81% of spontaneous AF episodes versus 84% in the hospital.

Although the initial atrial cardioverter permitted shocks of up to 6 J and ventricular pacing, higher energy requirements in many patients or when other lead systems were used, coupled with the risk of ventricular proarrhythmia without ventricular defibrillation and pain with atrial defibrillation, limited wider adoption. Although ventricular proarrhythmia resulting from atrial defibrillation shocks was rare in animal and human studies, it had been documented in both experimental and clinical studies in diseased hearts. Thus the initial clinical experience with atrial defibrillators was encouraging and suggested that effective and safe atrial defibrillation was feasible.

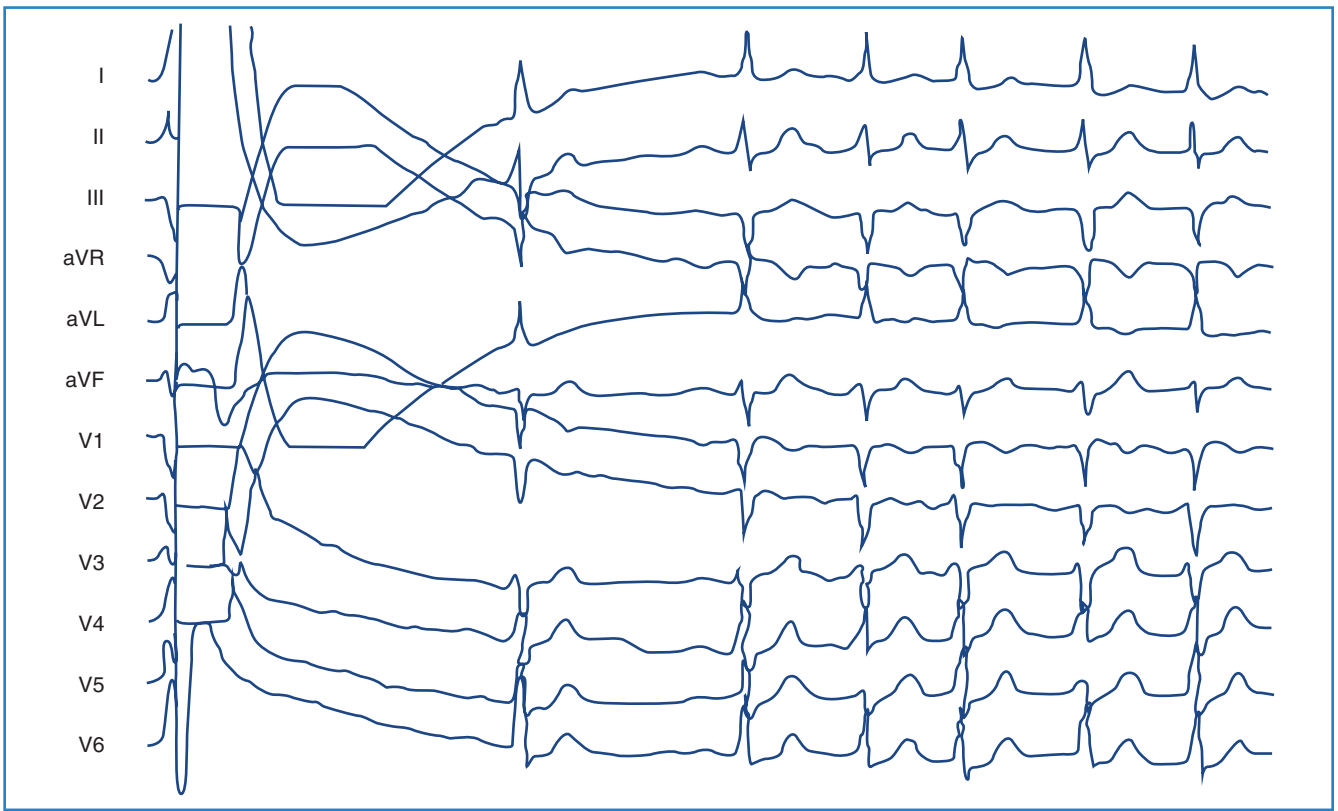
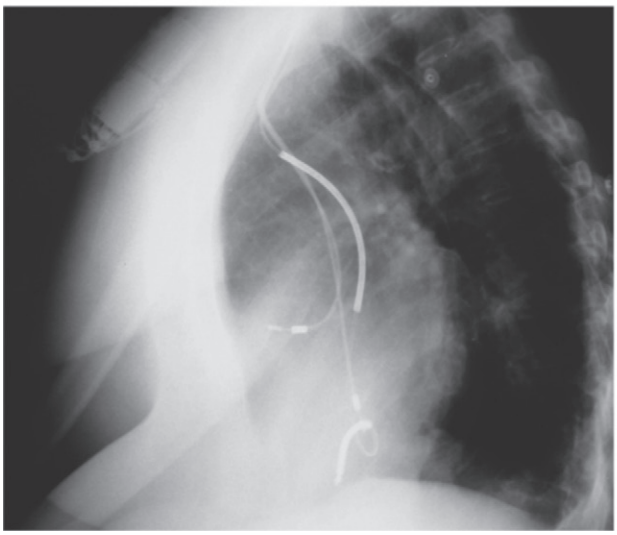


FIGURE 90-14 Early recurrence of atrial fibrillation after shock.

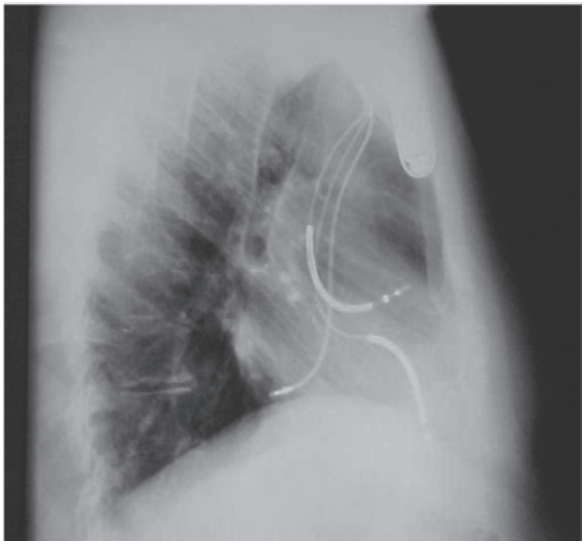
Dual-Chamber Atrioventricular Defibrillator

Device Technology

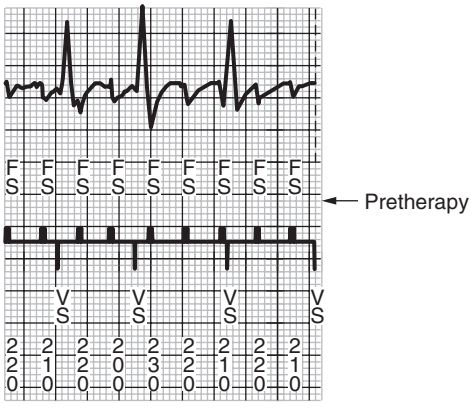
The first generation atrial defibrillation device was succeeded by a commercially available dual-chamber AV defibrillator.[139] The prototype device was the Jewel AF, with a weight of 93 g and a volume of 55 mL (Figure 90-15; also see Figure 90-12). This device requires a two- or three- pacing/defibrillation lead system, including atrial pacing/sensing electrodes, ventricular pacing/sensing electrodes, atrial or superior venacaval high-voltage electrode(s), and a ventricular high-voltage electrode. An additional lead may be placed in the coronary sinus, if needed, to lower atrial defibrillation thresholds. As opposed to the Metrix device, the can of the Jewel AF device is an active electrode. This device, shown in Figure 90-12, permits atrial and ventricular ATP, cardioversion, and defibrillation. The most important new features of the Jewel AF system and its successor, the GEM 3 AT device (Medtronic, Inc.) or the Guidant Vitality AVT device (Boston Scientific, Inc.), include dual-chamber pacing, a new dual-chamber detection algorithm for rejection of supraventricular tachycardias, detection and painless treatment modalities of atrial arrhythmias, prevention strategies for atrial arrhythmias, and automatic or patient-activated atrial defibrillation with complete ventricular backup defibrillation. The detection algorithm uses P:R pattern recognition and timing rules for rhythm classification and has been shown to provide improved dual-chamber detection.[140-142] Figure



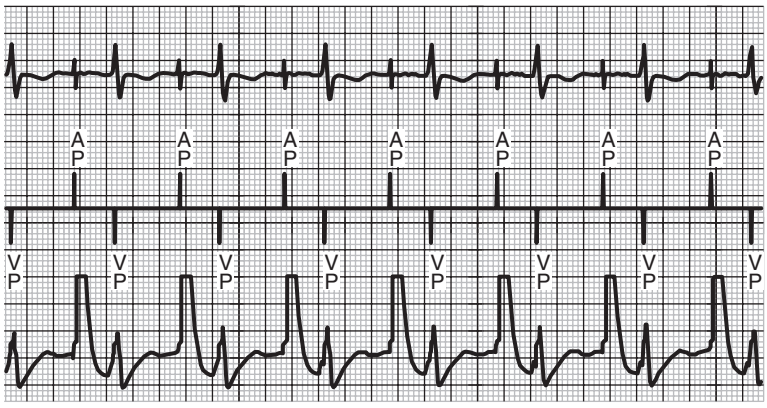
Dual-chamber AV defibrillator



Dual-site dual-chamber AV defibrillator



Stored electrograms and marker channel for detection



Dual-site RA pacing in dual-chamber AV ICD

FIGURE 90-15 *Top,* Lateral radiographs of atrioventricular (*AV*) defibrillator in situ. *Left,* Atrial and ventricular pacing and defibrillation leads are seen in situ. *Right,* A third coronary sinus ostial lead is present to achieve dual-site pacing with an AV implantable cardioverter-defibrillator (*ICD*). *Bottom,* Stored electrograms and marker channel in the atrioventricular ICD *(left).* The *top trace* shows atrial flutter with variable AV conduction as seen by device-detected intracardiac electrograms. The *middle trace* is a marker channel with upward deflections marking atrial potential detections and downward deflections marking ventricular potential detections. The *bottom trace* is a numeric record of atrial electrogram cycle lengths. *Right,* Telemetered electrograms (bottom channel) marker channel (as in *left tracing*) and surface electrocardiogram (top channel) in dual-site, dual-chamber AV defibrillator. Dual-site atrial pacing is in progress in the overdrive mode. *RA,* Right atrium.

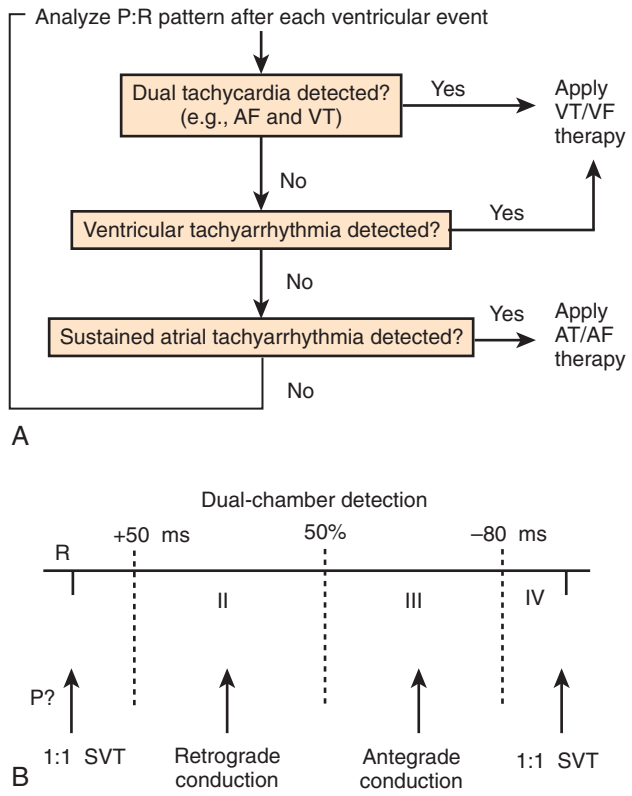


FIGURE 90-16 A, Hierarchy of dual-chamber detection in the Jewel AF (Medtronic, Inc.). The device is constantly monitoring the rhythm in the atrium as well as the ventricle. When a dual tachycardia or a ventricular tachyarrhythmia is detected, the device delivers ventricular therapy. If not, the device looks for possible atrial arrhythmia and may deliver atrial therapy. **B,** Definition of time intervals for interval codes. The detection algorithm looks for the position of the P wave relative to the R wave. The R-R interval is divided into four time intervals, I to IV. Atrial senses are expected to occur in intervals I and IV for junctional rhythms. Interval II (normal sinus rhythm, sinus tachycardia) is the normal antegrade conduction interval that extends from the midpoint of the R-R interval to the beginning of interval IV. Atrial events resulting from retrograde conduction of a ventricular event are expected to be sensed in interval II. So-called *couple codes* based on the interval codes of the current and previous R-R intervals are used to describe rhythm syntaxes. Sequences of those couple codes are used to classify the rhythm. *AT,* Atrial tachycardia; *AF,* atrial fibrillation; *VT,* ventricular tachycardia; *VF,* ventricular fibrillation; *SVT,* supraventricular tachycardia.

90-16 presents the hierarchical structure of one of the dual-chamber detection algorithms. Atrial and ventricular or AV activation pattern analysis and cycle lengths are analyzed. The ventricular tachyarrhythmia detection conditions are examined first. Specificity-enhancing rules make use of AV pattern recognition to determine if a high ventricular rate is due to AF, AT, sinus tachycardia, or other 1:1 supraventricular tachycardia. If the criteria for either ventricular tachycardia or ventricular fibrillation are satisfied and no specificity-enhancing rule is satisfied, ventricular tachyarrhythmia therapy is initiated. This therapy is also initiated if rules for dual tachycardia detection are satisfied (e.g., ventricular tachyarrhythmia arising during the presence of a supraventricular tachyarrhythmia). If ventricular tachyarrhythmia or dual tachycardia is not detected, the supraventricular tachyarrhythmia detection conditions are then evaluated. These rules are designed to detect and discriminate between AF and other ATs without 1:1 conditions by using atrial cycle length thresholds and P:R pattern information. The median atrial cycle length is used to define three detection zones: the AF detection zone, the AT zone, and the auto-discrimination zone formed by the overlap of the two zones. When the cycle length for a detected rhythm is in the auto-discrimination zone, the rhythm is classified as AF if the atrial cycle lengths are irregular and AT if the cycle lengths are regular. The criterion for atrial cycle length regularity is evaluated on each ventricular event. P:R pattern information is incorporated into the algorithm by an evidence counter that uses a pattern recognition algorithm specific for supraventricular tachycardia without 1:1 AV conduction. This counter has up-down counting properties and is incremented on each ventricular event in which the AV pattern shows evidence of a supraventricular tachyarrhythmia. If there is no evidence, the evidence counter is decremented. The counter has two stages of operation. The first stage is preliminary detection, which defines the start of an AT/AF episode, when the evidence counter reaches a predefined threshold. Once the start of an episode is defined, the episode duration timer begins incrementing and the evidence counter switches to the sustained detection stage. During this stage, the evidence counter uses criteria that are less strict, allowing some atrial undersensing.

Patient Selection and Clinical Outcomes

Initial clinical studies were conducted in patients with lethal ventricular tachyarrhythmias who may or may not have coexisting AF. In the initial studies, 211 patients with a history of ventricular tachyarrhythmias only (n = 53) or both a history of ventricular tachyarrhythmias and AF (n = 158) were enrolled in a worldwide study from 37 centers.[142] For inclusion in the latter group, patients had to have ECG-documented spontaneous atrial tachyarrhythmias occurring within the year before implant and a history of such arrhythmias.

Overall, 90% of the patients enrolled in the study received a two-lead defibrillation system, and fewer than 8% received a three-lead defibrillation system. The mean atrial defibrillation threshold in a representative subgroup of 42 patients was 6.1 ± 4.3 J. The positive predictive value of the detection algorithm was 93% for AF and AT and 88% for ventricular tachyarrhythmias. During the course of the study, 21 patients had 165 spontaneous, appropriately treated AT episodes in which the last therapy to treat the episode was either ATP (99 episodes) or high-frequency burst (i.e., 50-Hz pacing; 66 episodes). The success rate for spontaneous AT episodes as defined by the device was 86% with ATP. An additional 35% of episodes were terminated by 50-Hz pacing. Only 11 patients had 22 episodes of AF as classified by the device, 20 of which were successfully terminated by an atrial shock therapy, approaching an efficacy rate of 91%. During 410 R-wave synchronized atrial shocks delivered for both spontaneous and induced AF episodes, no ventricular proarrhythmia was seen.[143,144]

Multicenter trials have evaluated the use of the dual-chamber AV defibrillator in patients with recurrent atrial tachyarrhythmias who had other indications for ventricular ICD insertion. Device therapy resulted in a significant reduction in atrial tachyarrhythmia burden.[117,118] One of these other trials also recently demonstrated an improvement in quality of life scores.[118] Moreover, these improvements were not attenuated by shock therapy.

Table 90-4 Studies on Dual Atrioventricular Defibrillators

TRIAL	NO. PATIENTS	FOLLOW-UP (MO)	PATIENT POPULATION	LVEF (%)	EFFICACY OF PACING FOR AT/AF (%)	EFFICACY OF DEFIBRILLATION FOR AT/AF (%)	LEAD DISLODGMENT (%)	SURVIVAL (%)
Atrioverter-Metrix Investigators (1999)	179	9	Recurrent drug-refractory AF	58 ± 11	—	86.3	4	—
JEWEL VT/VF/AF Trial World Wide Investigators (2001)	293	7.9 ± 4.7	Qualifying ventricular arrhythmia with two documented AT episodes in the last year	38 ± 17	4534 AT = 59 AF = 30	74	2.4	91
JEWEL AF only Trial (2001)	144	12	Drug-refractory AF with no VT/VF	51 ± 18	58.4 AT = 49 AF = 23	86.7	6.8	97.6
Italian study (2002)	112	11 ± 9	68% with IHD and 55% with prior AT	40 ± 11	37.9 AT = 70.9 AF = 24.3	76	1.8	95.5
GEM III AT World Wide Investigators (2002)	151	2.6 ± 1.3	—	38 ± 16	35 AT = 40 AF = 26	Used only for two induced episodes	Not reported	—

AT/AF, *Atrial tachycardia/atrial fibrillation;* LVEF, *left ventricular ejection fraction;* IHD, *ischemic heart disease.*

However, no control arm existed in this trial. More recent data suggest a reduction in AF hospitalizations with these devices.[145] Thus the future of this technology in a hybrid therapy format remains cautiously promising. Dual-chamber AV defibrillators are currently approved for use in patients with drug-refractory, symptomatic AF and coexisting ventricular tachyarrhythmias, or in patients with refractory atrial fibrillation. The outcomes in various trials eith AV defibrillators are summarized in Table 90-4.

Specific Device Features

Device Monitoring of Atrial Fibrillation

An important feature of new devices for AF therapy is their ability to provide extensive monitoring capabilities for AF and atrial tachyarrhythmia detection. Figure 90-17 shows data logs from implantable pacemakers or dual-chamber AV defibrillators that can provide the clinical practitioner with extensive time-stamped and quantitative information on AF events. The practitioner can program the arrhythmia detection criteria. Duration, frequency, and total time elapsed in the arrhythmia (referred to as the *arrhythmia burden*) can be monitored between clinic visits or after interventions. This feature allows quantitation of asymptomatic and symptomatic AF events and permits accurate assessment of rhythm control after therapy.

Patient Activator

This handheld device has evolved from a simple activator that could initiate therapies (Figure 90-10) to a device that allows patients to know their cardiac rhythm status and activate therapies at home or proceed to a medical facility for further therapy. This allows increased patient control of arrhythmia management and permits outpatient therapy in long-term management. This feature is expected to reduce hospitalizations and emergency department visits that now frequently punctuate the long-term management of AF patients.

Hybrid Therapy

Devices have been increasingly used in the "hybrid therapy" strategy for the management of atrial fibrillation (Table 90-5). Although the most frequent combination therapy has been with antiarrhythmic drugs, atrial ablation techniques have also been combined with device and drug therapy.[146,147] The former strategy has been detailed in the clinical evaluation trials for these devices as well as the observational studies for dual-site right atrial pacing. Catheter-based linear ablation with drug therapy and dual-site/high right atrial pacing has also been examined in several reports. There is a decrease in progression to permanent AF, restoration of rhythm control, and resolution of persistent and permanent AF in patients who underwent right atrial Maze and atrial flutter ablation procedures in conjunction with device therapy (see Table 90-5). These studies suggest that a hybrid approach may be effective for rhythm management. For a more detailed treatment of this subject, the reader is referred elsewhere.[23,29]

Role of Implantable Device Therapy in Atrial Fibrillation

The selection of device therapy and the preferred technology should depend on the type of AF, clinical characteristics of atrial or ventricular systolic function, the presence of structural heart disease, age, and the presence of coexisting bradycardias. Devices

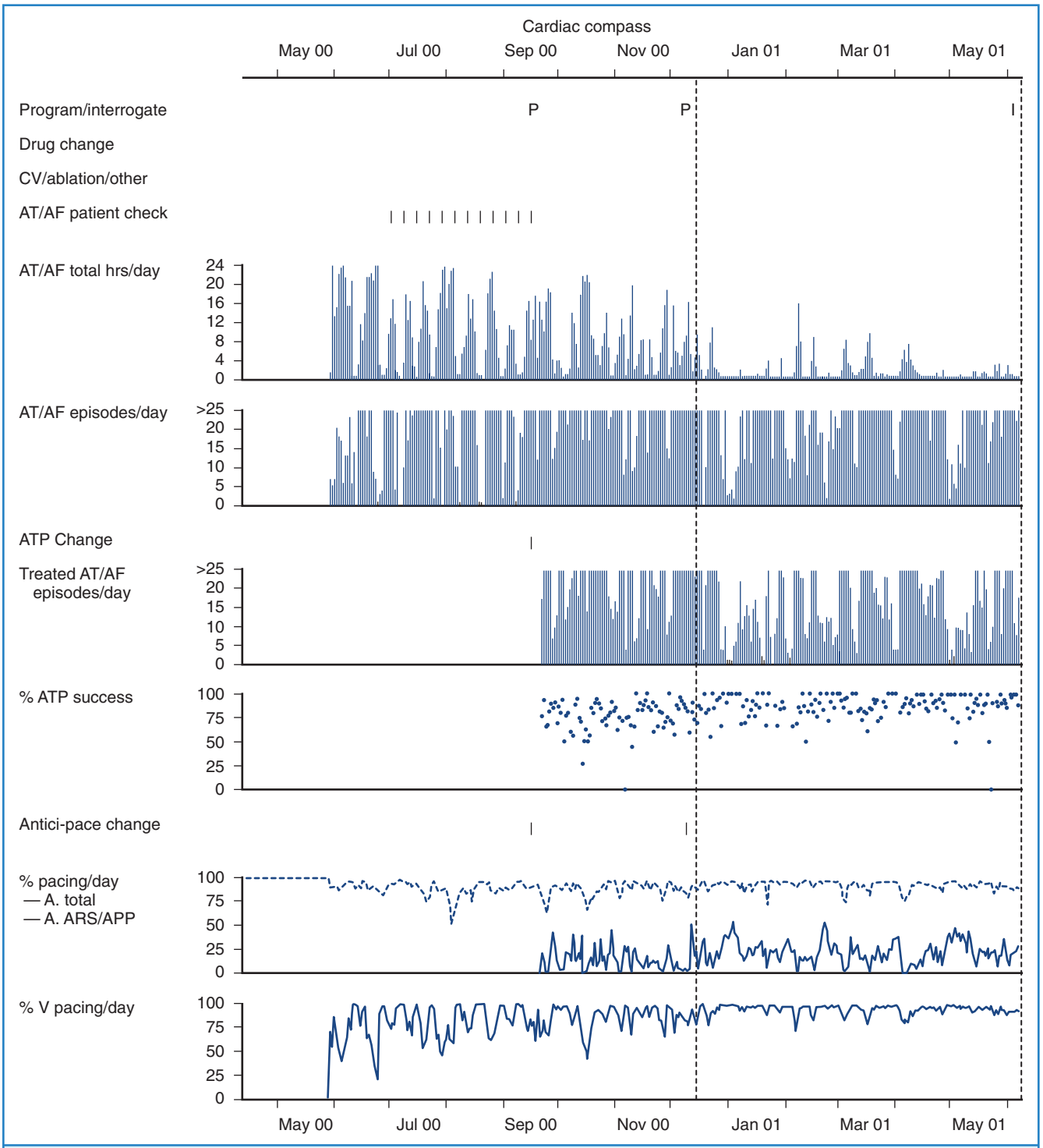


FIGURE 90-17 Implantable device data log report stored in device memory for quantitation of atrial fibrillation (*AF*) burden, frequency, antitachycardia pacing (*ATP*) outcomes, percent success, and percent pacing in the atrium and the ventricle. These reports make management of asymptomatic AF possible and provide important insights into AF event behavior in an individual patient. *CV,* Cardioversion; *ARS,* atrial rate stabilization; *APP,* atrial preference pacing.

may be implanted empirically in patients with bradycardias. Based on current data, dual-site pacing systems are preferable for secondary prevention of AF. Electrophysiological studies in individual patients with refractory AF can characterize the triggers and substrate and identify monomorphic tachycardias responsible for AF initiation and maintenance. Mapping guided ablation or anatomically based linear ablation for atrial compartmentalization or isolation of triggers or substrate can be performed before device implant. AF populations can now be divided into specific categories for purposes of device therapy.

Table 90-5 Hybrid Therapy Strategy Trials Incorporating Device Therapy

SERIES	DEVICE TECHNIQUE	PATIENT POPULATION	MEAN	FOLLOW-UP (MO)	RHYTHM CONTROL	COMPLICATIONS (%)
Metrix	Atrial ICD	186	Persist AF	9	84%	6 (device related)
Jewel AF	AV ICD	537	VT/VT + AF	11 ± 8	9	?
Madan	Dual right atrial pacing	113	PAF, persistent/permanent AF	30 ± 23	90% at 5 yr	Early, 3.5%; late, 2.7%
D'Allones	Biatrial pacing	64	PAF	33	64%	?
Prakash	DAP + Isth ABL	40	PAF/AFL	26 ± 14	75% at 3 yr	
Filipecki	AP/ICD + RA	25	Persistent/permanent AF	17 ± 10	75% at 18 mo	Maze

AF, *Atrial fibrillation;* ABL, *ablation;* AFL, *atrial flutter;* AP, *atrial pacing;* DAP, *dual-site atrial pacing;* ICD, *implantable cardioverter-defibrillator;* Isth, *isthmus;* PAF, *paroxysmal atrial fibrillation;* RA, *right atrium,* VT, *ventricular tachycardia.*

Primary Prevention of Atrial Fibrillation

In patients with symptomatic bradyarrhythmias from sinus node dysfunction, the relative merits of high right atrial pacing have been demonstrated. In addition, bi-atrial pacing can be beneficial in AF prevention after coronary bypass surgery.

Secondary Prevention of Atrial Fibrillation

In patients with refractory symptomatic paroxysmal AF, single-site atrial pacing from the high right atrial or septum has not provided clinically relevant benefit. Hybrid device therapy using dual-site right atrial pacing in combination with antiarrhythmic drug therapy has shown more efficacy in maintenance of sinus rhythm in this population.

In patients with drug-refractory persistent and permanent AF, another hybrid approach using a combination of antiarrhythmic medications, catheter-based right or left atrial linear ablation, and dual-site right atrial pacing using pacemakers or AV defibrillators can restore or improve rhythm control. In patients with symptomatic drug-refractory AF and coexisting ventricular arrhythmias, dual-chamber AV defibrillators with the ability to manage both arrhythmias have been used—usually with adjunctive antiarrhythmic pharmacologic therapy.

In summary, device therapy now offers new opportunities for restoration of rhythm control in patients with drug-refractory AF. This therapy often requires a combination of devices with preexisting drug therapy or catheter ablation methods.

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All references cited in this chapter are available online at expertconsult.com.

CHAPTER 91

Electrical Therapy for Tachyarrhythmias: Future Directions

David Steinhaus and Paul J. DeGroot

In their 25 years of existence, implantable cardioverter-defibrillators (ICDs) have moved to the forefront as the best therapy for the prevention of sudden cardiac death (Figure 91-1). Since their inception, they have transitioned from a cumbersome, last-ditch therapy to the standard of care for patients at risk of ventricular tachyarrhythmias. Despite this record of tremendous innovation during this relatively short history, in the minds of some, ICDs have become "good enough" and are on their way to becoming a commodity, with only simplification and reduction of inappropriate shocks being the remaining challenges to differentiate existing products from future products. In contrast to that perspective, this chapter serves to describe the multiple opportunities and challenges that portray an exciting future for devices providing electrical therapy for tachyarrhythmias.

Therapies for Ventricular Tachyarrhythmia Termination

Defibrillation

The most essential therapy an ICD is intended to provide is termination of ventricular fibrillation (VF). The loss of coordinated cardiac contraction associated with fibrillation causes patients to lose blood pressure and consciousness immediately, which, if not quickly reversed, results in death. Electric countershock has long been known to interrupt fibrillation. The re-entrant wavefronts that are the hallmark of fibrillation can only be halted by nearly simultaneous depolarization of the ventricular myocardium. To achieve this, a sufficient amount of energy must be provided such that a voltage gradient of approximately 5 V/cm traverses most of the heart.[1] Traditionally, such shocks have been delivered by discharging a capacitor between two electrodes on, in, or near the heart. Early ICDs used monophasic truncated exponential waveforms. Biphasic waveforms proved to have much better defibrillation efficacy and thereby significantly advanced the use of ICDs in the early 1990s.[2-6]

Capacitors

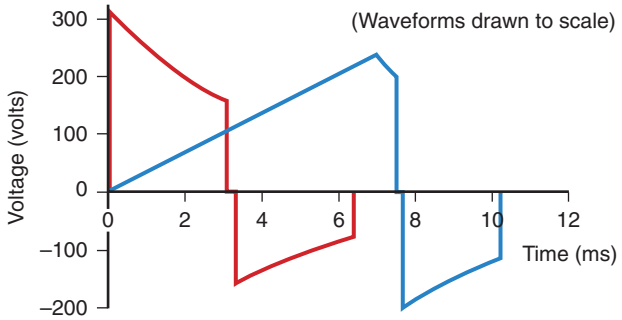
Today's ICDs use capacitors in the range of 100 to 140 μF. Connected with transvenous electrode systems, their discharge time constant is in the order of 4 to 6 ms. Mathematical modeling has predicted that the optimal discharge time constant to minimize the energy required for defibrillation is around 2 to 4 ms.[7] A shorter time constant could be achieved by simply reducing capacitance below 100 μF. In an ICD, the shock is actually discharged from a bank of multiple (typically three) capacitors. Each capacitor can hold a maximum of approximately 250 V (a property determined by their chemistry, which is most commonly aluminum electrolytic). Stacked in series, the total voltage adds up to approximately 750 V. Using the formula $\frac{1}{2}CV^2$, the total stored energy for a 125 μF system is 35 J. If the discharge time constant were to be optimized by reducing the capacitance to 100 μF or less, the stored energy would be reduced to 28 J or less. While the waveform would be more optimal, the reduction in total stored energy would decrease more quickly with decreasing capacitance than would the energy required to defibrillate, thus reducing the energy safety margin. This dilemma can only be resolved by improvements in capacitor technology such that individual components can hold a higher peak voltage and thereby maintain the same maximum energy despite the reduction in capacitance. Research into new metal oxides or entirely different materials may allow the development of the required capacitor improvements. Recent development has focused on tantalum oxide rather than the currently used aluminum for capacitor construction. In addition to the potential for higher peak voltage, tantalum capacitors offer higher energy density and can be shaped more easily to conform to the desired form of the overall device. These factors are likely to yield devices that are smaller with shapes better suited for implantation.

Battery Technology

Another key component affecting ICD performance is the battery. While every implantable device relies on a battery with adequate energy density to maximize longevity, an ICD has the additional requirement of delivering a high-energy defibrillation shock quickly and thus requires significantly higher power and charge flux than do traditional pacemaker batteries. In fact, the energy required for defibrillation with current technology is approximately a million times the requirement than that for pacing. In addition to increasing the likelihood of syncope, clinical studies have demonstrated that longer duration of VF may produce higher defibrillation thresholds. Thus, there is significant incentive to shorten charge times as much as possible. Early ICD batteries were composed of lithium vanadium oxide, whereas lithium iodine was widely used in conventional pacemaker batteries. This combination provided adequate power to charge a capacitor to 30 to 35 J in approximately 15 seconds. A significant disadvantage of

	Medtronic PCD	Medtronic Secura DR
Year	1989	2008
Volume	209 cc	37 cc
Mass	281 g	68 g
Dimensions	118 × 95 × 27 mm	64 × 51 × 15 mm
Implant site	Abdominal	Pectoral
Leads	Epicardial	Transvenous
Therapies	ATP, shock	ATP, shock
Predicted longevity	4.9 years	9.0 years
Distance telemetry	No	Yes
Patient alerts	No	Yes
Clinical trend data	No	Yes

FIGURE 91-1 Comparison of Medtronic Model 7216A PCD and Medtronic Model D224DRG Secura DR implantable cardioverter-defibrillators. PCD entered clinical trials in 1989 and was released by the U.S. Food and Drug Administration in 1993. Secura was released in 2008. Note that earlier ICDs from Cardiac Pacemakers Inc. offered shocks only for tachyarrhythmia therapy. *(Courtesy Medtronic, Inc., Minneapolis, MN.)*



	Ramp	Truncated exponential	*P* value
Threshold voltage	239 ± 62 V	313 ± 85 V	< .01
Threshold energy	5.4 ± 2.6 J	6.5 ± 3.4 J	< .02

FIGURE 91-2 Waveshape and defibrillation thresholds for ramp and truncated exponential waveforms.

this chemistry was the change in voltage and internal resistance over time, which decreased power and increased charge times as the battery aged. The advent of highly organized lithium or silver vanadium oxide batteries made charge times under 10 seconds achievable and allowed more constant charge times throughout the life of the device. It is likely that new hybrid-type batteries will yield even higher energy densities or higher power over the next decade. Many advances have been made in rechargeable batteries as well. However, multiple challenges are faced by this technology, including some limitations on the number of times batteries can be recharged, the time required to recharge, and issues related to device integrity if the battery is allowed to discharge completely. Incorporating a rechargeable battery into a class III medical device intended to prevent sudden cardiac death (SCD) will require significant safety mechanisms. Nonetheless, the allure of reduced device size, the potential for nearly infinite longevity, and the requirement to power other electronic components may make rechargeable batteries an attractive alternative for ICDs in the future.

Defibrillation Waveforms

The truncated exponential waveform used in ICDs has the advantage of being easy to generate from the small components required for an implantable device, but it is not ideally suited for depolarizing excitable membranes. Since cell membranes cannot react completely to a rapid step increase in voltage, slow-rise defibrillation waveforms are theoretically more efficient.[8] Studies on humans have shown that ramp waveforms can defibrillate with approximately 20% lower delivered energy and 24% lower peak voltage (Figure 91-2).[9] However, with currently available components, the technology required to produce ramp waveforms cannot be incorporated into small ICDs. In the future, new or more efficient technology may facilitate inclusion of new waveforms that may have better defibrillation efficacy, result in less tissue damage, or be associated with less discomfort.

Shock Delivery Systems

Shock delivery leads and electrodes are a vital component of the total ICD system. From experimental and modeling data, the ideal electrodes would deliver a uniform electric field of approximately 5 V/cm across the ventricles for an effective defibrillation shock. To accomplish this task, the earliest commercial ICDs used large surface area epicardial patches placed directly around the heart. Thoracotomy, with its attendant risks, was required for patch placement; therefore, transvenous electrode systems were developed and soon supplanted epicardial leads. Transvenous electrode systems with their less uniform electric fields would likely not have been as effective an alternative, were it not for the significantly improved defibrillation efficacy of biphasic shock waveforms; these systems became available around the same time. Today, almost all ICD implants include a combination of a coil electrode in the right ventricle (RV) and the metal housing of the ICD (the "Can" electrode). A majority of implants also include a coil electrode in the superior vena cava (SVC) incorporated into the same lead as the RV coil, a so-called *dual-coil lead*. When the SVC coil is electrically coupled to the Can electrode, a dual-coil lead has been shown to have lower defibrillation thresholds than a single-coil (RV only) system in most paired studies in humans, though the differences are relatively small.[10-13] Accordingly, many physicians choose to use a single-coil system, which, at least in theory, might offer improved reliability because of the simpler design and improved extractability because of less fibrous growth in the region of the SVC coil. If patients do not meet the required implant criteria with standard transvenous systems, other alternatives include placement of another coil lead in the SVC, azygous vein, or left posterior subcutaneous region (Figure 91-3).[14-16]

In order to eliminate some of the disadvantages of transvenous lead systems, recent research has explored the efficacy of totally subcutaneous ICD systems. Defibrillation would be achieved by

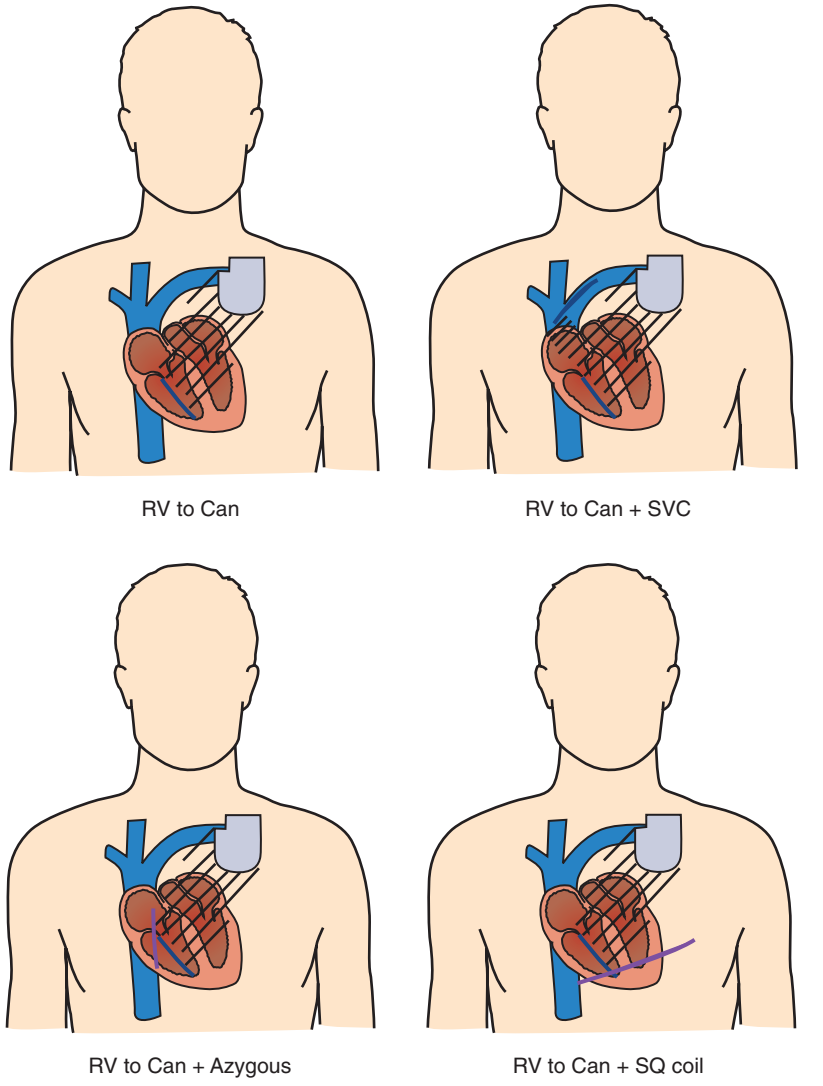


FIGURE 91-3 Electrode configuration and schematic representation of electric field distribution for standard Can-RV system and three alternatives used in patients with a high defibrillation threshold. A superior vena cava (*SVC*) coil adds a vector that steers the current across the right ventricle (*RV*), while a coil in the azygous vein or posterior subcutaneous tissue steers the current across the posterior left ventricle (not shown).

shocking transthoracically between the device and one or more subcutaneous coil electrodes with either an anteroposterior vector or a vector solely on the left anterior quadrant (Figure 91-4).[17-19] The feasibility of defibrillation has been established for at least some patients, albeit with higher energy requirements than for traditional transvenous ICD devices; however, published literature on the sensitivity and specificity for the detection of ventricular arrhythmias using an entirely subcutaneous system is sparse. One study on recorded signals has reported sensitivity and specificity comparable with transvenous ICD systems.[20] Before understanding the future potential of such a system, other trade-offs, such as increased device density, increased charge times, the difficulty to reliably pace for bradycardia following shock discharge, and inability to use painless anti-tachycardia pacing (ATP) instead of full defibrillation shock energy, must be resolved.

Importance of Shock Reduction

While shocks are essential to avert SCD when a patient is in VF, it is equally important that ICDs shock only when necessary to save a life. Significant research has occurred in the past 2 decades to make shock delivery sensitive and specific to treat only life-threatening ventricular arrhythmias. Detection algorithms allow adjustment of thresholds for both rate and duration to aim at treating only hemodynamically compromising arrhythmias. Discrimination algorithms attempt to prevent shocks for supraventricular tachycardia. More recently, anti-tachycardia pacing has been shown to play an increasingly important role in terminating a majority of more rapid ventricular tachycardias (VT), which used to be shocked by earlier generations of ICDs.

The importance of shock reduction has multiple benefits. Improved device longevity by not delivering unnecessary high power shocks is the more straightforward benefit. In the current ICDs, each shock reduces device longevity by approximately 1 month. Another obvious benefit is enhanced quality of life for patients who are spared discomfort. Research has shown that patients with ICDs suffer from psychological distress ranging from general anxiety to post-traumatic stress disorder, with shocks being a primary factor.[21,22] Another potential benefit may be monetary savings, since shocks are a significant reason for hospitalization of patients with ICDs.[23] Perhaps the most

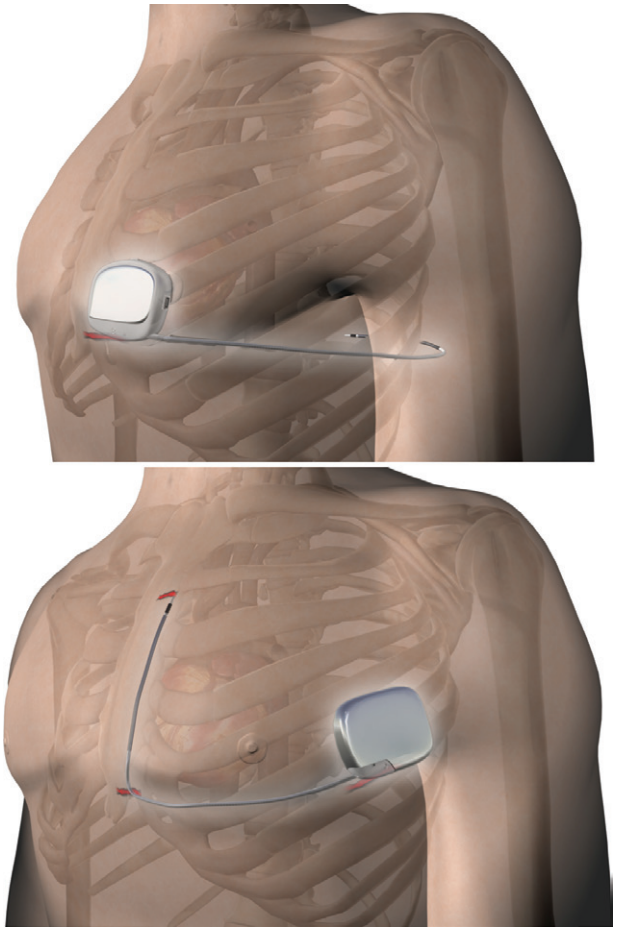
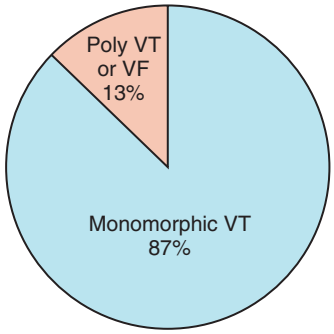


FIGURE 91-4 Two proposed electrode configurations for a subcutaneous-only defibrillation system. The anteroposterior configuration (*top*) should theoretically yield lower defibrillation thresholds because of more uniform current distribution, whereas a configuration with electrodes only on the left anterior quadrant (*bottom*) may be easier to implant because of simplified surgical preparation of the patient.



Number of spontaneous episodes (%)

Trial	Mono VT	Poly VT/VF
PainFREE Rx	1070 (97%)	30 (3%)
PainFREE Rx II	1208 (90%)	134 (10%)
EnTrust	358 (93%)	28 (7%)
EMPIRIC	1363 (83%)	271 (17%)
WAVE	1063 (79%)	286 (21%)
Combined	5062 (87%)	749 (13%)

FIGURE 91-5 Distribution of monomorphic ventricular tachycardia (*VT*) versus polymorphic VT and ventricular fibrillation (*VF*) in five clinical trials sponsored by Medtronic Inc. (Minneapolis, MN) showing a predominance of monomorphic rhythms amenable to anti-tachyarrhythmia pacing.[27-30,48] Numbers shown are for spontaneous episodes adjudicated to be ventricular in origin. The detected rhythms are influenced by trial population, device type, and protocol for implantable cardioverter-defibrillator programming, but all studies demonstrated that polymorphic VT and VF represent only a minority of the episodes.

Table 91-1 Mortality Hazard Ratios

TRIAL	APPROPRIATE SHOCKS ONLY	INAPPROPRIATE SHOCKS ONLY	ANTI-TACHYCARDIA PACING (ATP) ONLY
MADIT II	3.36 ($P < .01$)	2.29 ($P = .02$)	P = NS
SCD-HeFT	5.68 ($P < .001$)	1.98 ($P = .002$)	Not applicable
ATP Trials*	1.15 ($P = .0006$)	P = NS	P = NS

**PainFREE Rx, PainFREE Rx II, EMPIRIC, PREPARE.*

important factor is a recent analysis showing the significant impact of shocks on patient mortality. Analysis of data from the Multicenter Automatic Defibrillator Implantation Trial (MADIT-II) and the Sudden Cardiac Death in Heart Failure (SCD-HeFT) trial revealed a significant increase in mortality risk associated with both appropriate and inappropriate shocks (Table 91-1).[24,25] From the available data, it is unclear whether this association is related to shock therapy itself or only to the episodes that precipitate their occurrence. Analysis of data pooled from multiple trials focused on the use of ATP for shock reduction showed that shocks, but not ATP therapy for appropriately detected VT/VF episodes, were associated with increased mortality; the analysis also concluded that shocks for inappropriately detected VT/VF did not have a significant impact on mortality (see Table 91-1).[26] Given the established benefit of SCD prevention with ICDs in both the MADIT-II and SCD-HeFT trials, despite the trials' reliance on shocks for VT/VF termination, it is possible that the ICD survival benefit was underestimated and, in fact, could have been greater if ATP had been used more aggressively in these trials. Further research into the possible mechanism may allow future ICDs to modify shock therapy to reduce any avoidable consequences associated with shocks.

Anti-tachycardia Pacing

While defibrillation is the most essential therapy for an ICD, ATP for ventricular arrhythmias is actually the most frequently delivered therapy. Even in so-called *primary-prevention patients*—those without a prior history of VT/VF—monomorphic VT represents more than 90% of the ventricular tachyarrhythmias detected by ICDs (Figure 91-5).[27,28] It is interesting to note that the use of ATP and the first implantable anti-tachyarrhythmia

devices were, in fact, pacemakers for the treatment of supraventricular tachycardia. It was known at the time that ATP could also be effective for the termination of VT, but the possibility of acceleration of a relatively well-controlled rate to a more hemodynamically significant arrhythmia prevented its widespread use for the treatment of VT until combined devices with high-voltage defibrillation capability were developed.

While ATP has long been used for the treatment of slow monomorphic tachycardia as a painless alternative to shock therapy, a series of trials in the past decade have demonstrated the success of empirically programmed ATP in treating fast ventricular tachycardia (FVT) as well. The Pacing Fast Ventricular Tachycardia Reduces Shock Therapies (PainFREE Rx), PainFREE Rx II, and EMPIRIC trials all delivered at least one sequence of burst ATP for fast ventricular tachycardia with a rate of 189 to 250 beats/min (320 to 240 ms).[27-29] ATP was effective in terminating 49% to 78% of FVT episodes, providing a significant reduction in the need for shocks. One of the studies, PainFREE Rx II, had a control arm in which patients with similar FVT episodes received shocks. The results demonstrated a significant quality-of-life improvement for patients in the ATP arm compared with patients in the shock arm, which provided solid evidence for the benefit of shock reduction. The EMPIRIC trial had a control arm in which devices received physician-tailored programming as opposed to preset nominal programming. While both arms had similar rates of all-cause shocks, the trial demonstrated that the study's nominal programming could be used empirically, thereby minimizing time spent during the implantation session. The relative paucity of VT acceleration or syncopal episodes was equally important in the trials. As further evidence becomes available, the use of ATP for FVT as a method of limiting shocks is expected to become more common. Some current ICDs, to eliminate any delay in therapy, incorporate a feature that allows ATP while also charging the capacitors.[30] To preserve battery life, these devices can withhold charging once ATP termination has been established successfully.

Enhancements of Anti-tachycardia Pacing

One common belief with regard to the mechanism of ATP failure has been the lack of proximity of the pacing site to the re-entrant circuit responsible for VT. It has been postulated that when pacing from the RV apex, pacing wavefronts are unable to reach the left ventricular site of re-entry. However, recent work has suggested that the number of pulses required to reach the re-entrant circuit via decreasing or peeling back the refractory period may vary depending on the pacing site, but that, under most circumstances, the pacing train will reach the circuit regardless of where the pacing lead is placed. In a paired, randomized comparison of induced VT, ATP applied from both RV and left ventricular (LV) sites were equally effective at termination.[31] In addition, in trials comparing RV ATP with biventricular (RV-LV) ATP for spontaneous VT, no significant difference based on pacing site was found.[32,33]

Given that physically reaching the re-entrant circuit is not dependent on the pacing site, a remaining explanation for ATP failure would be the inability of the pacing train to electrically interact with and terminate the re-entry. Clinical research is under way to exploit available information on the effect of heart rate and return cycle length following entrainment to automatically adjust the pace train, thus improving the results with better conduction into the excitable gap.[34,35]

Therapies for Prevention of Ventricular Arrhythmia

To date, implantable arrhythmia devices have focused on the successful detection and termination of life-threatening arrhythmias. An equally compelling opportunity would exist for the device to entirely prevent an arrhythmia. Several attempts have been made to demonstrate that specific pacing activity may effectively reduce episodes of VT. Some evidence exists that pacing at intervals shorter than the underlying sinus rhythm, the so-called *ventricular overdrive pacing*, may accomplish this task in secondary-prevention patients with VT. One clinical trial tested overdrive suppression in a randomized crossover design in patients presenting with frequent VTs, or *ventricular tachycardia storm*.[36] Though the 17% reduction in the number of sustained VT episodes did not reach statistical significance ($P = .06$), results did establish a 78% reduction in the number of nonsustained VTs ($P = .004$). Although continuous overdrive pacing may have negative effects in some patients with exacerbated heart failure (HF) or ischemia, further research may determine a population that may benefit or may determine the conditions that predict impending episodes and the opportunity for appropriate intermittent application of prevention algorithms.

Another proposed method for VT/VF prevention is to suppress pauses associated with premature beats. It has been shown that approximately 10% to 20% of VTs may be associated with short-interval or long-interval onset following premature ventricular contractions. In one randomized crossover study of a pause suppression ICD feature, no significant decrease was found in VT/VF events.[37] However, a post hoc analysis found a significant reduction in the subset of patients who exhibited at least one short-interval or long-interval onset of VT during the follow-up.[38] Again, even if not universally applicable, the concept that an ICD may be able to detect conditions in some patients when a prevention algorithm would be beneficial should be explored for future ICDs.

Hybrid Therapies

So far, this discussion has focused on electrical cardiac therapies for the management of ventricular tachyarrhythmias. Advances in technology, however, provide exciting opportunities for *hybrid therapy* for VT/VF.

The important influence of the nervous system on cardiac function and arrhythmias has long been recognized. However, the idea of using this heart-brain connection for the chronic management of arrhythmias has only recently been explored. Prospective research in animal models revealed that spinal cord stimulation, which was first applied for the control of pain associated with angina, could reduce the number of animals experiencing reperfusion VT/VF.[39-41] More recently, chronic spinal cord stimulation has been shown to reduce cardiac dimensions and other HF metrics in animal models of chronic HF.[42] The possibility that a spinal cord stimulator, which is still in its infancy, could be used in concert with an ICD to concurrently manage arrhythmias represents an exciting area of research.

A second area for hybrid devices in arrhythmia management is a combination of an ICD and a drug delivery system. While implantable drug pumps are not presently used in the management of cardiac disease, focused research in this area may

eventually yield closed-loop drug pump therapy systems for the control of tachyarrhythmias or HF. For example, research on using ICD electrograms for the detection of acute myocardial ischemia is already being conducted. One can certainly imagine a hybrid device capable of detecting acute myocardial infarction (MI) and providing thrombolytic therapy.

Detection and Discrimination of Ventricular Arrhythmias

Electrical therapy for the treatment of VT and VF by ICDs requires detection and discrimination of the arrhythmias. Even the most effective therapy will not terminate an arrhythmia if it is not applied. Most ICDs rely primarily on a rate-counting algorithm to determine the application of therapy. By sensing R waves from an RV electrogram, the device will apply the proper therapy on the basis of the timing of sensed events. A pacing pulse is delivered when no signal is detected after the lower rate interval is surpassed. ATP or cardioversion is applied if an event is sensed in the VT detection interval window, and high-energy defibrillation shocks are delivered if an R wave is sensed in the VF detection interval window.

With current technology, ICDs achieve greater than 99% sensitivity in detecting ventricular tachyarrhythmias. Maintaining a high specificity for treating only fast rhythms of ventricular origin is far more difficult. Both supraventricular tachycardias (such as sinus tachycardia and atrial flutter/fibrillation) and oversensing (including T waves, myopotentials, and nonphysiological noise) overlap in rate with VT/VF. To be most successful, ICDs incorporate various discrimination algorithms to differentiate true VT from inappropriate sensing. The two primary methods involve either simultaneous analysis of atrial sensed events or a morphology analysis of the ventricular electrogram. The advent of dual-chamber ICDs in the 1990s added not only the ability to provide atrial-based pacing but, more importantly, also an atrial electrogram for incorporation into discrimination algorithms. The use of an atrial signal allows for a comparison of the atrial rate as well as the sequence and relative number of P waves and R waves to differentiate fast rhythms that are ventricular from those of supraventricular origin. Dual-chamber discrimination algorithms have yielded supraventricular tachycardia (SVT) detection specificity of about 55% to 90%, with rapid one-to-one conducted rhythms being the most challenging to discriminate.[43-45] Though the earliest ICDs had crude morphology algorithms, more sophisticated morphology algorithms have been developed to differentiate narrow R waves that are presumably supraventricular in origin from wide R waves that imply VT.[46] These ventricular electrogram morphology algorithms have demonstrated a reduction of inappropriate SVT detection of 55% to 90%.[47-49] Until now, ICD detection and discrimination algorithms have relied solely on processing passively sensed physiological signals. During acute testing in the electrophysiology laboratory, both atrial and ventricular stimuli are often used to discriminate ventricular arrhythmias from supraventricular arrhythmias. Future ICDs may incorporate algorithms to use atrial pacing, ventricular pacing, or both to discriminate fast one-to-one rhythms not easily identified with existing single-chamber or dual-chamber algorithms.[50] In one early investigation on spontaneous rhythms, the "discriminating" stimuli terminated approximately 80% of one-to-one VTs and subsequently correctly classified 649 (99.7%) of 651 ongoing one-to-one SVTs.[51]

While discrimination algorithms have continued and will continue to offer increased specificity of tachyarrhythmia detection, inappropriate shocks remain a significant obstacle for the acceptance of ICDs and will undoubtedly be the focus of significant research in the coming decade.

Sustained Versus Nonsustained Episodes

The time that an ICD should wait to declare that an ongoing VT is sustained and therefore treatable has received increased attention as it has become clear that at nominal detection settings ICDs may over-treat ventricular arrhythmias. This suggestion has been raised by data from randomized controlled ICD survival trials, which indicate that more treated VT events occur in the ICD therapy groups than do deaths in the control groups. Therefore, a treated event—even if it is fast ventricular tachycardia—does not necessarily equate to a truly lifesaving therapy but, rather, might be an event that would have terminated spontaneously. The dilemma for physicians and device manufacturers is how long the ICD should stand by in spite of knowing that added duration of tachycardia may increase the likelihood of syncope or even defibrillation failure.[52,53] A recent clinical trial (Primary Prevention Parameters Evaluation [PREPARE]) programmed ICD detection to a threshold of at least 30 fast intervals before satisfying criteria for sustained treatable VT/VF.[29] The trial results established a marked increase in time to first shock and a reduction in the number of treated events, compared with historical controls using a shorter duration of episodes. This reduction in treated events was partly related to self-terminating episodes of VT and partly to the improved function of the discrimination algorithm related to the longer duration allowed. Importantly, neither syncope nor more serious consequences increased significantly.

Reviewed in the context of previously described ATP trials, PREPARE also sheds light on the true efficacy of ATP versus nonsustained episodes appearing as ATP success. The earlier trials all prescribed FVT detection requiring 12 of 16 intervals (PainFREE Rx) or 18 of 24 (PainFREE Rx II and EMPIRIC) to be 320 ms or less with the last eight intervals greater than 240 ms. In the shock arm of PainFREE Rx II, half the patients were randomized to receive shocks for FVT, and 34% of those episodes self-terminated before shocks, providing evidence that at least some of the ATP successes in the ATP arm were likely spontaneously terminating VT.[28] In the PREPARE study, which required 30 of 40 intervals to be between 240 and 320 ms for detection, the ATP efficacy was 49%.[54] With the earlier trials showing 72% to 78% ATP success, PREPARE confirmed the PainFREE Rx II shock arm results that approximately one third of detected FVT episodes will spontaneously terminate if left untreated for a brief additional period.

Sensor-Driven Detection

Besides processing electrical signals, future ICDs are likely to include sensors that will use other physiological inputs aimed at further refining the sensitivity and specificity of detection algorithms. One signal commonly incorporated into the algorithms for determining pacing rate is an accelerometer-based activity sensor. Because ICDs have rate-responsive pacing, this signal is already available in most of them. By incorporating the activity signal into a detection algorithm, it may be possible to further refine the discrimination of sinus tachycardia from VT. A

three-dimensional accelerometer could add information not only of activity but also of posture that might be relevant in discriminating tachycardias or even determine a preferred sequencing of pacing and shock therapies for true VT. Systemic or intracardiac pressure sensors, such as those currently under investigation for the management of chronic HF, might serve as valuable discrimination tools. As with the activity sensor, knowledge of pressure changes may also aid in sequencing VT therapy. For example, anti-tachycardia pacing might be continued for multiple sequences during a hemodynamically stable episode of VT but advance immediately to high-voltage shock therapy should the pressure diminish. Other possible sensors that may improve the detection and discrimination abilities of ICDs include impedance algorithms, which may indicate changes in cardiac output, or heart sounds that might suggest changes in cardiac function.

Monitoring and Diagnostics

Information management has become an important consideration in implantable medical devices. With significant component miniaturization and improvements in storage capacity of device memory in the past 2 decades, ICDs have transitioned from storing only primitive event counter information to more complex diagnostics. Such features include high-quality stored electrograms for each detected episode, device function diagnostics, and daily trend information for extended periods on multiple cardiac metrics (Figure 91-6). Stored electrograms may be used to interpret events that trigger device detection, to determine the efficacy of programmed therapies, or to diagnose lead malfunction. Automatic monitoring of device function has become a standard feature in ICD devices that feature programmable patient alerts with different levels of urgency. Elective replacement indicators have long been a relatively nonurgent indicator of impending battery depletion. Other more urgent warnings might include failed therapies, potential lead fractures, or inadvertent inappropriate programming of detection suspension.

Monitoring Comorbidities

Patients requiring ICD devices frequently have comorbidities such as hypertension, HF, diabetes, coronary artery disease, renal insufficiency, and sleep apnea. As devices become more sophisticated, other physiological information in addition to cardiac arrhythmias may be monitored. For example, the Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure (COMPASS-HF) trial studied the ability of an RV pressure monitoring device (Chronicle) to improve outcomes in patients with chronic HF. The primary endpoint to reduce all-cause HF-related events was not met, but the Chronicle group did have a nonsignificant 21% reduction compared with the control group.[55] An analysis of the time to first HF hospitalization did show a 36% reduction in the relative risk of an HF-related hospitalization in the Chronicle group. It is possible that such a monitoring device may have had a statistically significant impact if compared with a control group not being monitored as closely as those under the rigor of this trial. As mentioned earlier, a unique investigational ICD records and stores information on RV pressure to assist in the management of HF as well as providing traditional pacing and high-voltage therapy. Another parameter to aid in HF management provided by some ICDs is a metric related to fluid volume in the lungs. For example, transthoracic impedance information that relates to lung wetness may be trended to detect changes in HF status even before significant alterations in symptoms or other classic signs appear. In an early 2-year trial of 33 patients, in which 10 were hospitalized for fluid overload, intrathoracic impedance reduction began approximately 2 weeks before the onset of worsening symptoms.[56] Automated detection of impedance decreases was 77% sensitive in detecting hospitalization for fluid overload, with a low false-positive rate. This ability allows earlier detection of HF decompensation leading to earlier treatment and the prevention of adverse events such as hospitalization. Management of such information may be provided by health care professionals; or in the future, patients will increasingly be empowered to modify their lifestyle or alter therapy themselves.

In addition to monitoring HF status, future devices will aid in the management of comorbidities. Under current implantation guidelines, the majority of ICD recipients have ischemic cardiac disease. Cardiac repolarization changes associated with acute ischemia have been observed on intracardiac electrograms available to ICDs (Figure 91-7).[57-59] Detection algorithms to alert physicians and patients to serious ischemic events are being designed and are under study.[60-62] Such information might allow earlier acute coronary intervention, or in the future, devices may be incorporated with drug delivery systems to provide closed-loop pharmacologic therapy.

Hypertension is a common disease in general and no less common in the population of patients who receive implantable electrical devices. As we learn more about the disease, it is clear that intermittent blood pressure measurements in the clinical setting may not always be adequate for diagnosis or long-term management, leading to at least some interest in external or implantable ambulatory monitoring.[63,64] Small sensors that can easily be implanted are in development. Using device memory and telemetry, accurate recordings can be acquired and stored over time. In addition, there are 5% to 30% of patients with significant hypertension who are refractory to current pharmacologic therapy.[65,66] It is certainly not hard to imagine that implantable devices might help treat hypertension using electrical stimulation for autonomic modulation or even closed-loop systems for drug delivery.

Likewise, diabetes mellitus is a common comorbidity in the population of patients who require ICDs. While external pumps for insulin delivery are common today, little effort has been made to link information between the diabetes clinic and the electrophysiologist. It is not hard to imagine that a strong correlation could exist between glucose levels and complex cardiac metrics, such as heart rate variability or arrhythmia risk. Initiation of studies to gather longitudinal information on the correlation of metrics routinely stored by diabetes and cardiac management devices will yield fruitful observations.

Connectivity and Communications

Only a few years ago, ICDs required a telemetry wand placed directly over the implanted device to establish a communication link, but current devices are capable of communicating with a receiver meters away. The two clear benefits of the availability of distance telemetry are as follows: (1) In the implant suite, the ability to interrogate and program a device from a short distance away means the telemetry wand no longer has to be placed in the sterile field. This decreases procedure time and reduces the risk of infection. (2) In the course of follow-up, the ability of the device

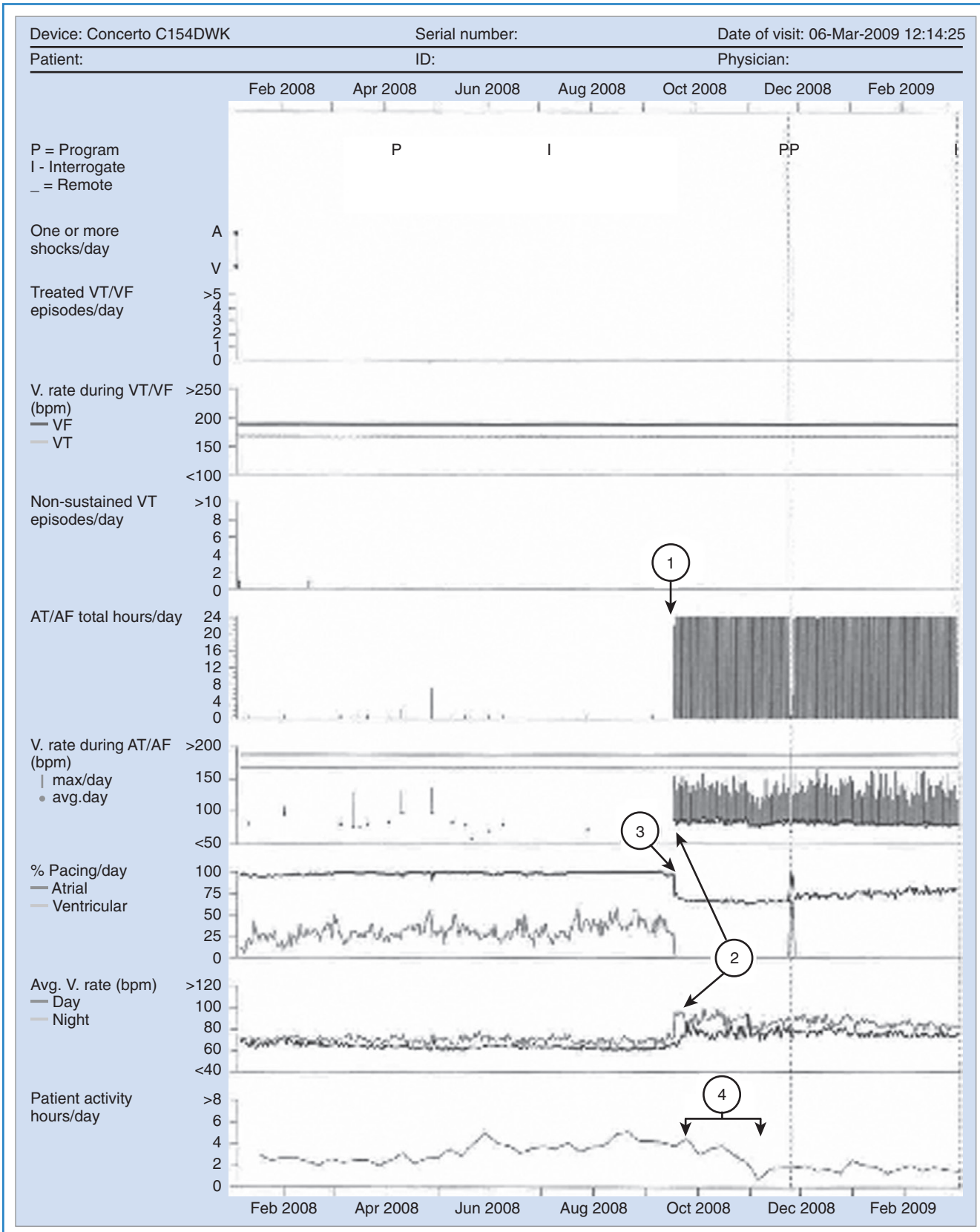


FIGURE 91-6 Trend information available via Cardiac Compass in recent Medtronic (Minneapolis, MN) implantable cardioverter-defibrillators. In the example shown, the patient was relatively stable over the first 8 months. The patient then went into persistent atrial fibrillation (*AF*) (1) resulting in a high ventricular rate (2) and accompanying loss of biventricular pacing (3). The patient also exhibited a steady decrease in activity, which started around the same time and continued for approximately 1 month (4). *VT,* Ventricular tachycardia; *VF,* ventricular fibrillation; *AT,* atrial tachycardia.

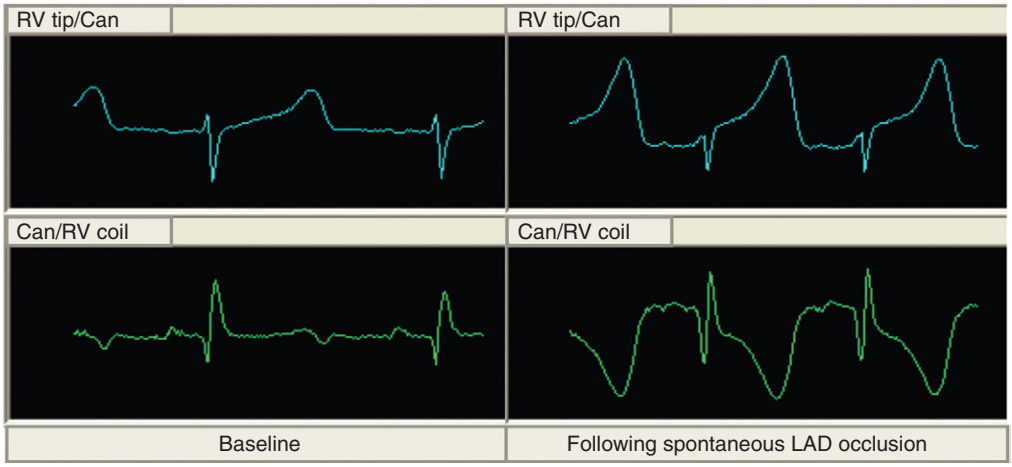


FIGURE 91-7 ST-segment elevation in electrogram recordings from implantable cardioverter-defibrillator (ICD) electrodes implanted long term in a porcine model. The *top panels* show a signal recorded between the right ventricular (*RV*) tip electrode and the ICD Can. The *bottom panels* show a signal between the Can and the RV coil. The *left panels* show a baseline reference, and the *right panels* show signals following a spontaneous coronary artery occlusion occurring days after stenting the left anterior descending coronary artery (*LAD*).

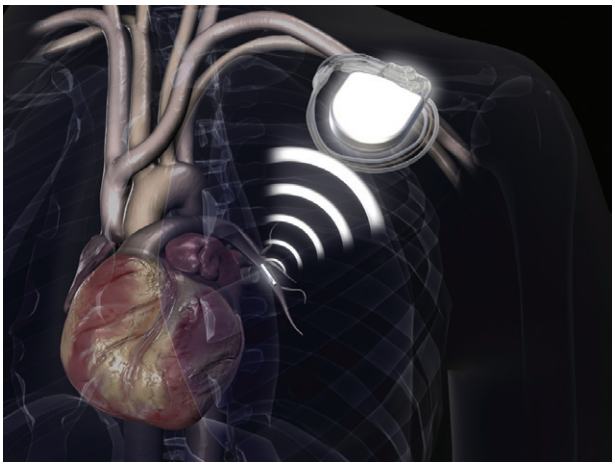


FIGURE 91-8 Conceptual figure of a future system whereby implanted devices will communicate wirelessly in the body.

to download information automatically to a bedside monitor eliminates direct patient action and thereby reduces the need for compliance. The information, which may be physiological or device related, is then transmitted to the clinic, where appropriate action may be taken. The more frequent monitoring generated by this remote contact may increase the safety profile by earlier notification of patient condition or device malfunction. Future devices may rely more on portable technology, which will allow frequent and instant communication. At present, remote telemetry transmits data from implanted devices to a patient management system. Future systems will likely allow actual programming or changing of device parameters using remote connectivity. Clearly improved security and safeguards will be necessary to facilitate this approach, but the added capability will improve efficacy and convenience.

Another new aspect of device communication will likely be intrabody communication (Figure 91-8). With the advance of technology, it is possible, if not likely, that patients may benefit from several devices to treat other chronic diseases. Especially as the information collected by monitoring devices becomes more diverse and devices become smaller, a significant challenge will be the exchange of information among devices, that is, establishing a central point for communication with external systems as well as coordination between systems.[67] In addition to using sensors to monitor chronic disease, it is likely that such technology will also be applied to a system for personal health care.[68]

It is the combination of sophisticated device electronics, physiological sensors, remote connectivity, and closed-loop technologies that will transform the care of patients with cardiac rhythm disorders. These systems will also create comprehensive datasets and facilitate iterative algorithms using multiple physiological measurements, thus establishing the place of implantable devices in the management of chronic diseases.

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CHAPTER 92

Three-Dimensional Cardiac Mapping Techniques in Catheter Ablation

Oliver R. Segal, Nick W.F. Linton, Louisa Malcolm-Lawes, and D. Wyn Davies

Introduction

The development of intracardiac mapping was based on the use of individual contact catheters. Despite the ability to record information from different sites with multi-polar catheters, complex arrhythmias and arrhythmias that occur in complex substrates can be difficult to characterize with these techniques. A system that could provide information from a whole cardiac chamber or chambers was required.

Following the development of epicardial mapping techniques used during surgery, basket catheters were developed for endocardial use. These catheters are no longer in frequent use. Later, electroanatomic mapping systems were developed that could record electrophysiological data and also measure the three-dimensional location of the recording electrode. Chamber geometries could be created from points recorded along the endocardial surface. The latest systems are significantly more accurate and also offer the electrophysiologist many more features to help facilitate the mapping of complex arrhythmias. Voltage mapping, propagation maps, rapid mapping with multi-polar catheters, and mapping of fractionated electrograms are all now possible, and datasets can be merged with preoperative computed tomography (CT) or magnetic resonance imaging (MRI) scans of the heart or rotational angiograms. Different approaches to complex mapping are noncontact mapping and the very new "ripple mapping."

Electroanatomic Mapping Systems

Electroanatomic mapping systems build a three-dimensional image of a cardiac chamber by incorporating sequential electrogram data from an entire cardiac chamber or chambers if necessary. An electrophysiological catheter in contact with the endocardium or the epicardium records voltage (amplitude of the electrical signal) and timing (relation of the recorded electrogram to a fixed-reference electrode electrogram). Low-voltage areas and scar can be easily identified, which makes it possible to elucidate the overall underlying substrate through which an arrhythmia persists. Recording electrogram timings throughout the chamber enables an activation map to be created, which is color coded to differentiate between "early" and "late" signals with respect to the reference electrode (Figure 92-1). These data can also be viewed in the form of a propagation map, in which a representation of the excitatory wavefront of activation advances across the chamber geometry (see Video 92-1 on the Expert Consult site for this text). Maps can be rotated on the monitor or viewed in multiple orientations simultaneously so the wavefront can be followed throughout the cardiac cycle. Electroanatomic mapping systems are not particularly suitable for activation mapping during unstable rhythms, although mapping in discrete areas can be performed during separate tachycardia episodes, thereby building a map over a longer period. Data acquired during sinus rhythm can also be used to target ablation, which is particularly useful when mapping ventricular tachycardia (VT) in abnormal hearts. This method obviates the need for mapping during tachycardia by defining the arrhythmogenic substrate (Figure 92-2).

Once generated, the combination of voltage and activation maps can be very useful in guiding the electrophysiologist in placing focal ablation lesions or creating lines of ablation. This may be between important scar boundaries (e.g., lines of ablation transecting the diastolic pathway in VT circuits) or between inert structures (e.g., linear ablation between the tricuspid valve annulus and the inferior vena cava in isthmus-dependent atrial flutter [AFL]). In addition, these systems facilitate the encirclement of cardiac structures, the best example of which is the encirclement of pulmonary veins as part of the treatment for ablation of atrial fibrillation (AF). Maps do not have to be viewed exclusively from the outside. Sagittal, coronal, or transverse sections, or any other user-defined plane, can be mapped so the operator can view the chamber from the inside (Figure 92-3).

Over the past 10 years, there has been an escalation in the use of three-dimensional mapping systems, particularly for the ablation of AF. The advent of electroanatomic mapping has enabled the deployment of complex linear lesions within the left and right atria—most notably the roof line between left and right superior pulmonary veins and the mitral isthmus line, between the left inferior pulmonary vein and the mitral valve annulus. Although these lines are often performed by using conventional techniques alone, three-dimensional mapping systems truly allowed electrophysiologists to think in three dimensions within the left atrium.

Another particular advantage of these systems is that they are nonfluoroscopic; that is, x-ray radiation is not required to visualize catheters, which can be positioned and moved within a cardiac chamber or chambers solely by using the electroanatomic system. At present, electrodes of each catheter and their positions can be visualized. In the future, however, incorporation of electrodes into the shaft of catheters and long sheaths would offer a more complete view of the equipment within in the heart and would assist electrophysiologists still further in catheter positioning without the use of x-ray radiation.

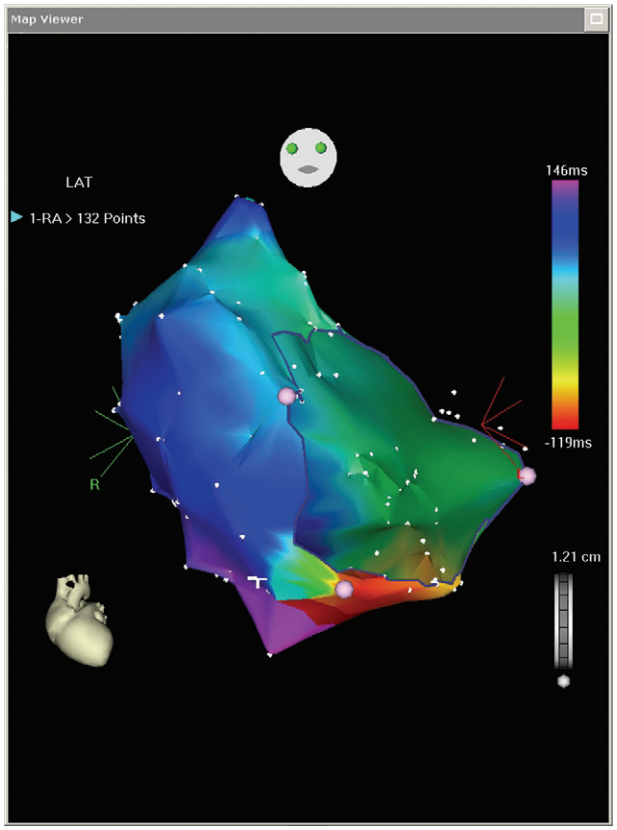

FIGURE 92-1 Right atrial geometry collected on CARTO XP (Biosense Webster), with local activation map displaying color-coded timings of each activation point. This demonstrates a re-entrant tachycardia mechanism because the early and late signals are adjacent to each other. The tachycardia displayed is a clockwise typical right atrial flutter.

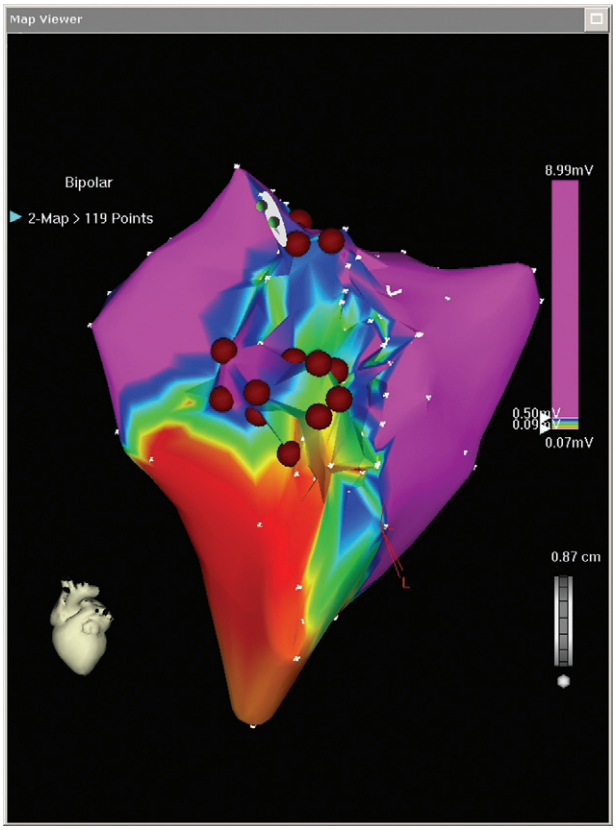

FIGURE 92-2 CARTO XP (Biosense Webster) geometry of the left ventricle displaying a map of ventricular voltage, with areas of healthy myocardium in pink and colored areas depicting areas of scar.

The CARTO System

The CARTO system (Biosense Webster, Diamond Bar, CA) works on the principle that a conducting coil placed in a changing magnetic field will generate an electrical current. In the XP version of this system, an attachment is fixed to the operating table. This generates magnetic fields from three different locations that can be distinguished because they are generated with different frequencies. A purpose-built catheter that has three small coils implanted in the tip at different orientations is used. The magnetic fields induce currents in these sensing coils, which are measured to calculate the distance from the source of each magnetic field. The position of the catheter tip is then calculated by trilateration, and the orientation of the catheter tip is also estimated. The position information from the catheter is gated with the electrocardiogram to reduce the effects of cardiac motion. In addition, a reference patch is attached to the patient's back, which can be used to detect and compensate for horizontal movement of the patient (but not rotation or rolling). Navigation is accurate to a resolution of 1 mm, and maps can be enlarged and reduced to aid catheter placement.

The latest iteration of this technology is the CARTO 3 system. In addition to the use of magnetic location technology, this system also uses six additional patches on the patient's skin. Integration of information from current measurements between the catheters

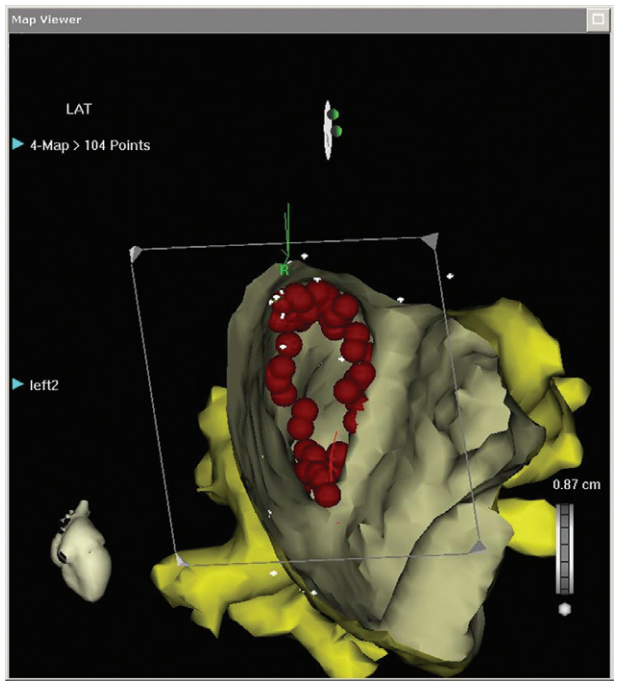

FIGURE 92-3 CARTO Merge (Biosense Webster) image with a sagittal clipping plane to allow visualization of the antrum of left-sided pulmonary veins.

and these patches with information from the magnetic location technology has a number of advantages. Multiple catheters can be tracked, and the system is able to compensate better for patient movement (Figure 92-4). Maps can be generated rapidly by collecting data from all the electrodes of a circular mapping catheter simultaneously. It is also possible to alter the degree of interpolation between points, thereby reducing the potential to create "false space" within geometries and reproduce the true endocardial surface more accurately. Increased mapping technology accuracy reduces the requirement for fluoroscopy and also for contrast angiography, which has been the gold standard for delineation of endocardial shape and is used in many centers prior to geometry creation. From initial experience, CARTO 3 may reach this degree of accuracy and may mitigate the need for x-ray exposure even more than other available systems. In addition, the system produces higher quality recordings of the electrograms, removing the problems from 50 Hz noise that were present on earlier systems.

CARTO Merge

The CARTO system can also integrate digital CT or MRI images of the heart into a mapping study so that a patient's actual anatomy can be superimposed and used, instead of an acquired geometry.

Digital images are imported into the system and segmented manually. They are then integrated into the mapping study at the time of the procedure. With fluoroscopy, fixed anatomic landmarks close to the chamber of interest are identified and acquired as geometric location points, such as the left atrial appendage or the ostia of the pulmonary veins. These points are then registered with their corresponding sites on the CT or MRI image and are then merged so the catheter tip can be navigated within the scanned anatomic image on screen (Figure 92-5).

Electroanatomic mapping with CT or MRI image integration is particularly useful in patients with complex anatomy, such as those with congenital heart disease. Detailed chamber anatomy is also helpful in pulmonary vein isolation procedures by delineating the location, size, and orientation of the pulmonary vein ostia. This system depends on the quality of the digital images available (CT currently has a higher resolution than MRI) and the ease with which the images can be segmented. In addition, chamber size can vary significantly depending on the patient's hydration status. A scan performed weeks before a mapping procedure may identify a chamber significantly larger than on the day of the procedure after a period of fasting. It can also be difficult to merge a scan with the three-dimensional geometry in all three different spatial planes, which can result in the catheters appearing outside of the superimposed geometry.

Cartosound

The CARTOSOUND variant of the CARTO system integrates intracardiac echocardiography (ICE) or transesophageal echocardiography (TEE) data with the CARTO mapping system. One of its principal advantages is the ability to construct a left atrial geometry before obtaining left atrial access with an ICE/TEE probe placed in the right atrium or other right-sided structure, such as the left pulmonary artery. The latest version uses three-dimensional echocardiographic technology, and three-dimensional ICE images can be displayed alongside CARTO mapping geometries. The ICE data can also be used to merge with a CT or MRI scan as above. The other potential advantages of this approach relate to the use of ICE/TEE in general. Echocardiographic imaging can guide trans-septal puncture, confirm catheter-tissue interface or tenting, identify catheter-related thrombus formation, and other potential complications, including cardiac tamponade (Figure 92-6).

Magnetic Navigation and CARTO RMT

CARTO RMT is used as part of Niobe Magnetic Navigation Technology (Stereotaxis, St Louis, MO). This magnetic technology "pulls" specially designed ablation catheters inside the heart

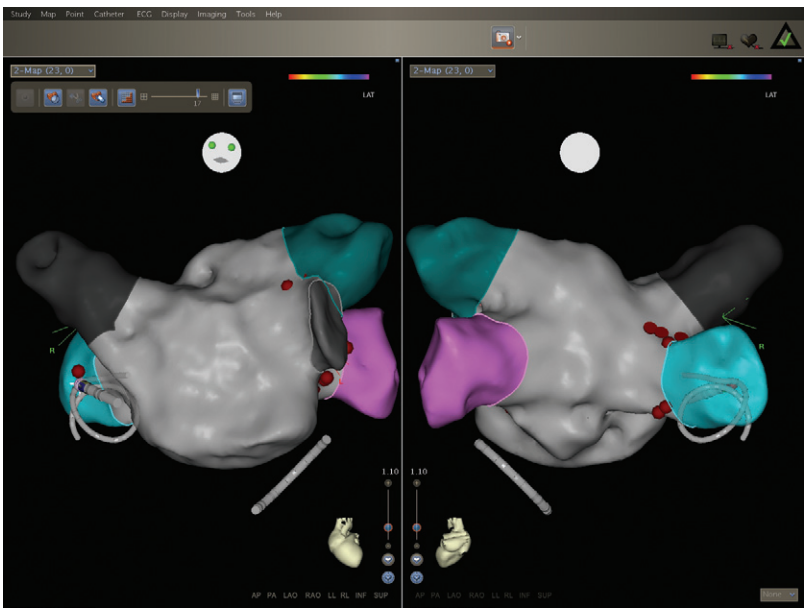

FIGURE 92-4 CARTO SOUND (Biosense Webster) integrating CARTO acquired geometry and real-time imaging with intracardiac echocardiography.

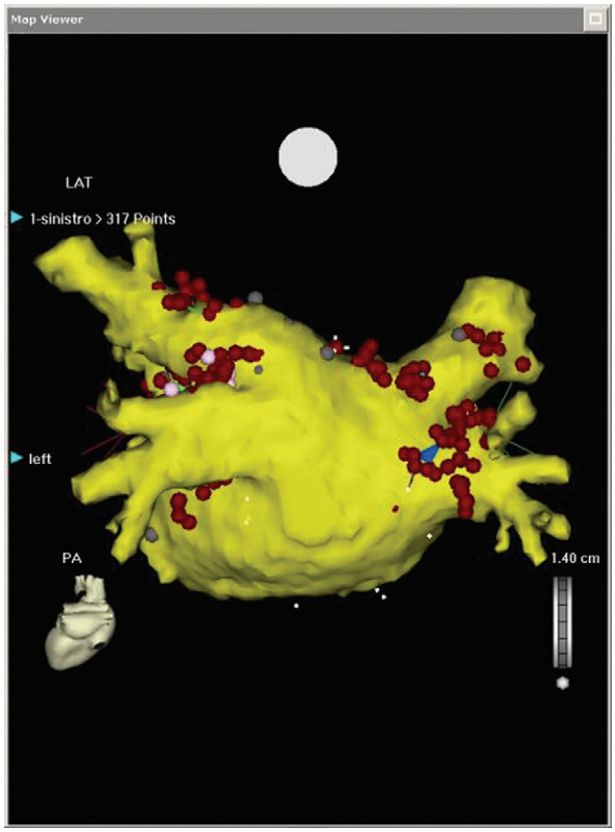

FIGURE 92-5 Posteroanterior and anteroposterior images of CARTO 3 (Biosense Webster) left atrial map, demonstrating simultaneous visualization of the circular mapping catheter, coronary sinus catheter and the ablation catheter, with pulmonary vein ablation lesions marked.

and vasculature. The system requires installation of two large Niobe magnets on either side of the catheter laboratory table. Once placed within the magnetic field, the ablation catheter can be manipulated and navigated remotely with the mouse and keyboard of the CARTO RMT system. Operators and other catheter laboratory staff therefore do not have to stand adjacent to the patient during the procedure, which significantly reduces x-ray exposure to staff. The catheters are very soft and flexible because they do not require torsional and deflectional rigidity. Not only does this make them potentially better at navigation to all regions of a cardiac chamber, but they also have significantly less potential to cause trauma. The CARTO RMT software enables automated geometry creation of a 100-point (or more) map using a predetermined algorithm. This is the first time this capability has been developed and may indicate the future direction of complex mapping technology.

EnSite system

Ensite NavX

The EnSite system (St Jude Medical, Inc., St Paul, MN) uses changes in impedance to calculate catheter position in three dimensions. This methodology is based on the principle that applying an electrical current across two surface electrodes creates a potential gradient along the axis between the electrodes. Six surface electrodes are placed on the patient's chest in three pairs: anterior to posterior, left to right lateral, and superior (neck) to inferior (leg). The three electrode pairs form three orthogonal axes (X-Y-Z), with the heart at the center. A 5-kHz signal is sent alternately through each pair of surface electrodes to create a voltage gradient along each axis, forming a transthoracic electrical field. As a catheter enters the transthoracic field, the voltage signal corresponding to 5 kHz is measured at each catheter

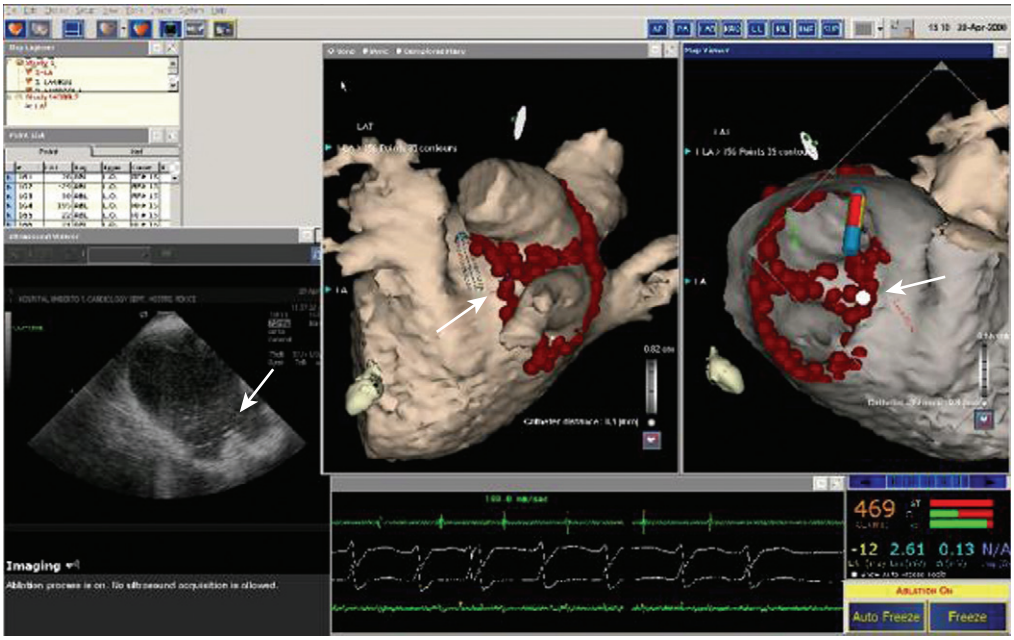

FIGURE 92-6 CARTO XP (Biosense Webster) geometry merged with left atrial segmentation from pre-ablation computed tomography (CT) angiography. Ablation lesions are shown at pulmonary vein ostia projected on to the new registered CT left anterior surface.

electrode, timed to the creation of the gradient along each axis. By using the sensed voltages compared with the voltage gradient on all three axes, the EnSite NavX software calculates the three-dimensional position of each catheter electrode. The calculated position for all electrodes occurs simultaneously and repeats 93 times per second. The EnSite System displays the located electrodes as catheter bodies with real-time navigation. It permits the simultaneous display of multiple catheter electrode sites and also reflects real-time motion of both ablation catheters and those positioned elsewhere in the heart.[1]

Three-dimensional chamber geometries are created by dragging an ablation catheter along the endocardial surface. The system logs points in three-dimensional space where the catheter electrodes have been and then interpolates between these points to create an endocardial shell. For complex chamber anatomies, such as the left atrium and pulmonary veins, separate endocardial geometries can be created for each structure so that false interpolation does not occur. This might happen, for example, between a distal part of a pulmonary vein and the body of the left atrium. Thus separate geometries are created for each pulmonary vein and the body of the left atrium. Although slightly more time consuming, this technique ensures that areas of false geometry are not created unintentionally. In the newer software versions, however, this is less of a problem and complex chambers can often be collected as a single chamber.

The relative positions of the electrodes are calculated by assuming that changes in the recorded field potential are only caused by changes in catheter position. Therefore changes in thoracic impedance can cause the system to "drift." Electrode positions are averaged over a few seconds to minimize the effect of cardiac motion. Respiratory compensation is also applied after recording the movement that occurs with respiration and correlating it with changes in thoracic impedance.

The latest user interface of the NavX system is called EnSite Velocity. One of the principal advantages of this system is its open platform. Catheters from any manufacturer can be used and displayed with this system, making it extremely versatile. NavX was the first electroanatomic system that enabled visualization of all catheters on top of three-dimensional spatial information and mapping data. Another advantage of the latest iteration of this system is the OneMap Tool. This allows collection of anatomic and electrical data (voltage or activation) simultaneously from all electrodes from all catheters. This means that the operator has to navigate to each endocardial position only once to generate both an anatomic shell and an activation or voltage map (Figure 92-7). Previous software iterations would have required two separate mapping procedures, so this feature can significantly save procedural time. The EnSite System can also be integrated with the Sensei robotic catheter system (Hansen Medical, Mountain View, CA), allowing completely remote catheter navigation (Figure 92-8).

EnSite Verismo Segmentation Tool and EnSite Fusion

These software tools work in a similar way to the CARTO Merge software by converting two-dimensional CT or MR slice data into three-dimensional models. Anatomic data can be presented on the same screen, side by side with the mapping data, without registering it with an acquired geometry. This tool is useful as a guide to the operator while creating a chamber geometry, especially when the anatomy is unusual. Direct integration of mapping data with the CT- or MRI-derived images can also be registered or "fused." Once applied, EnSite NavX mapping and labeling functions can be applied to the model surface, including contact mapping, map labels, voltage data, and lesion and anatomic markers (Figure 92-9).

Global Data Acquisition from a Single Cardiac Cycle

Global mapping systems (basket catheter mapping and noncontact mapping) were developed to provide simultaneous data from an entire cardiac chamber from just a single beat of sinus rhythm or tachycardia.[2,3] This ability allowed rapid and detailed mapping of a single ectopic or entire VT circuit without the need for the tachycardia to be sustained; such systems are therefore ideally suited for mapping complex and poorly tolerated arrhythmias such as infarct-related VT. As previously mentioned, basket catheter mapping is not discussed in this chapter because this system is infrequently used outside of research studies. Noncontact mapping presented an ingenious solution to overcome the problem of having to be in all places at once. By avoiding the need to position contact electrodes across the whole of the endocardium, this system calculates electrograms at the endocardial surface by interpreting signals recorded from catheter electrodes within the cardiac chamber.

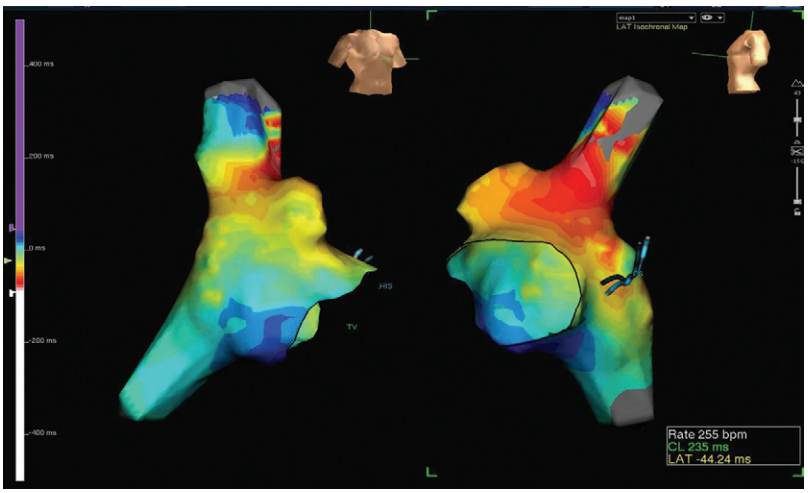

FIGURE 92-7 NavX Velocity (St Jude Medical, Inc.) geometry and activation map of the right atrium. *Red* areas represent the earliest activation and dark blue areas represent late activation; therefore there is a centrifugal activation pattern suggesting a focal right atrial tachycardia.

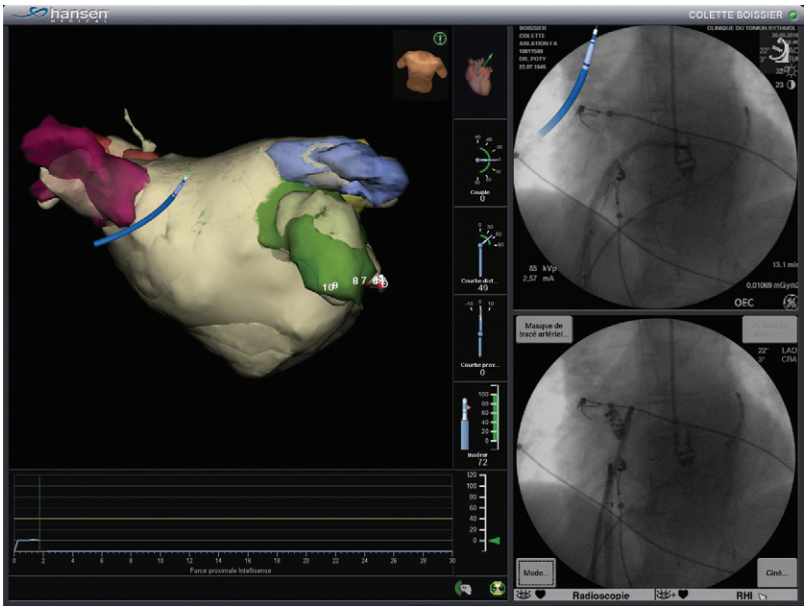

FIGURE 92-8 NavX (St Jude Medical, Inc.) left atrial geometry integrated via NavX Cohesion with the Sensei robotic catheter system (Hansen Medical).

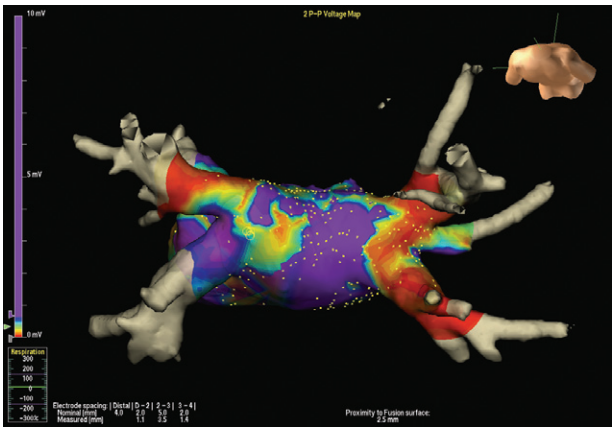

FIGURE 92-9 NavX (St Jude Medical, Inc.) geometry and voltage map fused with left atrial magnetic resonance imaging segmentation. Voltage points are projected onto the surface of the scan.

Noncontact Mapping

Noncontact mapping depends on three important mathematic principles: (1) the Laplace equation, (2) the boundary element method, and (3) the classic solid angle theory. Laplace calculated that the voltage measured at an outer boundary (e.g., the endocardium) can be applied to a formula that accurately calculates the voltage everywhere inside a chamber cavity. Cavitary potentials are a summation of the electric potential from around the entire endocardial surface and depend on the distance from each endocardial source point, a method known as *spatial averaging*.

The boundary element method, the process in which a simple formula is applied to multiple elements within a boundary and then combined, can provide an accurate assessment of information along the whole boundary. Thus, when calculating voltage from an endocardial surface, the endocardium is divided into multiple elements and a simple expression for voltage, and current is applied to each element to estimate the electric behavior within and between each element. These estimates are combined for an accurate measurement of the endocardial potential.

The classic solid angle theory describes the phenomenon that changes in cardiac potential are detected earliest by an electrode in closest proximity to the source of activation. This site has the greatest negative potential change and decreases with distance. If the position and orientation of each electrode are known, the site of origin and sequential activation within a cardiac chamber can be determined. The use of the boundary element method as an inverse solution to Laplace's equation has enabled the reconstruction of surface endocardial electrograms from intracavitary potentials and led to the development of multi-electrode intracavitary probes.

EnSite Array Catheter

The EnSite Array catheter uses a collapsible multi-electrode array with a braid of 64 wires woven around an 8-mL balloon. Each wire is insulated, apart from one small part that acts as the electrode. From the resulting 64 electrograms that are evenly distributed around the balloon, 3360 virtual endocardial electrograms are recreated on a geometry that has previously been created (per NavX above). A ring electrode on the proximal shaft of the 9 Fr array catheter in the inferior vena cava is used as a reference for unipolar electrogram recordings. This allows construction of high-resolution endocardial isopotential (akin to voltage) and isochronal (activation) maps. By using the same locator signal, the system can also guide the mapping catheter, without the need for fluoroscopy, to points on the virtual endocardium that may be suitable targets for ablation. Finally, it has the facility to rapidly delineate areas of low voltage (scar) using the Dynamic Substrate Mapping tool. This tool is especially useful in identifying islands of scar acting as borders in re-entrant arrhythmias.

The system has been used to help map macro–re-entrant VT complicating ischemic heart disease, where it has proven invaluable in identifying and guiding ablation to the region of the diastolic pathway, as well as other VTs. With the array deployed in the atrium, the noncontact system can delineate the circuits of focal, macro–re-entrant atrial tachycardia (AT), focally initiated AF, AF, and typical AFL.

Despite the ability to estimate cardiac activation of an entire cardiac chamber from a single beat, limitations to the noncontact mapping system remain problematic. The balloon may move within the cardiac chamber, especially in the structurally normal left ventricle, which can render electrogram data inaccurate. Electrogram fidelity is most accurate at sites in the equatorial plane of the balloon. Electrogram accuracy reduces as the controller progresses to sites at the polar ends of the balloon and also for electrograms recorded beyond 34 mm from the center of the balloon. Therefore, mapping large-volume chambers, such as the diseased left ventricle, can pose logistical problems. It is impossible to be less than 34 mm from the endocardial surface in some left ventricular cavities when using the currently available EnSite Array catheter. Another issue is the inability of this system to accurately reconstruct small or fractionated electrograms. This is especially important when mapping re-entrant atrial or ventricular circuits. These critical diastolic electrograms are sometimes too small to be identified and can be swamped by the repolarization artifact after activation of the systolic portion of the circuit or by ventricular far-field signal in the case of atrial mapping. Thus circuit maps can be incomplete, and the operator is left to estimate the exact location of diastolic pathways. In addition, small chambers such as the LA or RVOT are challenging areas for catheter manipulation around the balloon, and balloon-induced ectopy due to local trauma can also be problematic. New iterations of this catheter are designed to overcome these issues, although the new catheters are not yet commercially available.

Visualization of Electroanatomic Information

Visualizing Activation

The most widely used method for visualizing electroanatomic maps is isochronal mapping. For each electrogram, the local activation time (LAT) is determined by computer processing and manually verified, with adjustment, if necessary. LAT is measured relative to activation at another reference electrode, which is kept in the same location while the map is being created. By obtaining the LAT at a large number of points throughout the cardiac chamber, a map can then be created; the LAT is color coded and interpolated across the cardiac surface. The user must decide the "window of interest" before creation of the map—this is the anticipated timing of the first and last electrograms relative to the reference electrogram.

For focal tachycardias, isochronal maps demonstrate centrifugal activation with earliest activation at the focus, surrounded by later activation elsewhere. For macro–re-entrant tachycardias, isochronal maps demonstrate a pattern where "early meets late." Because of the cyclical nature of the mechanism, the latest point gives rise to the earliest point in the next cycle (where assignment of the "end" of a cycle is arbitrary). This is illustrated in Figure 92-10. Isopotential mapping is an alternative approach to visualization. Instead, activation is assumed to occur when the electrogram voltage reaches a user-defined value. A movie of active areas can then be played to give the user information about the pattern of activation (see Video 92-1).

Although isochronal and isopotential mapping have provided great enhancement of the understanding of arrhythmias in the clinical setting, these methods do have limitations. Isochronal mapping requires a single, correct value of LAT to be determined, and isopotential mapping also makes simple assumptions about the relationship between electrogram voltage and time. In complex arrhythmias, electrograms of key significance often do not have discrete, single points of activation. Instead, they may be

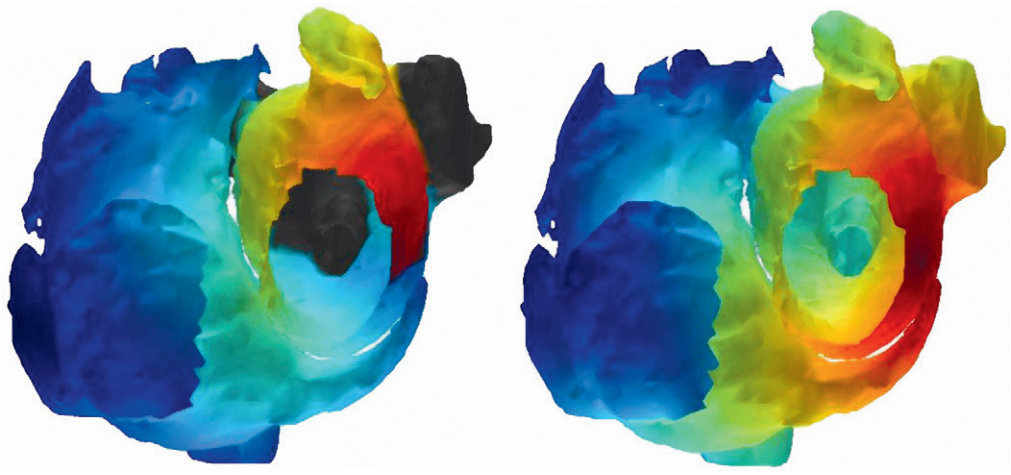

FIGURE 92-10 Isochronal maps comparing peri-mitral macro–re-entry (*left*) with focal macro–re-entry (*right*). Early points are red and late ones are blue. The maps are produced from simulated tachycardias. In the macro–re-entrant tachycardia, "late meets early" at the mitral isthmus, and the entire cycle length can be mapped around the circuit. Therefore "early" activation occurs immediately after the latest activation from the preceding cycle. Focal tachycardia (*right*) demonstrates centrifugal activation from the lateral mitral isthmus.

fractionated or have double potentials and be of low amplitude. Because of interpolation between points, a single incorrect assignment of activation time can invalidate an isochronal map, even if hundreds of other points exist.

A new method for electroanatomic visualization of arrhythmias has recently been described. Ripple mapping aims to remove the need for an operator-determined window of interest, manual verification of activation times, and interpolation of information into unmapped areas.[4] The method is best illustrated by example (see Video 92-1). Electrograms are displayed as bars on the cardiac surface. Each electrogram is represented as a dynamic bar (on a video), where the length varies according to the electrogram voltage-time relationship. This allows the appreciation of overall cardiac activation and of the properties of the electrogram such as fractionation and low amplitude. A preliminary study has demonstrated the concept in the mapping of ventricular as well as atrial arrhythmias.[4]

Visualizing Other Data

The collection of electrical information and where it has been obtained allows other information to be represented on the anatomic surface, not only information about activation. For example, during AF, electrograms can be analyzed to assess the degree of fractionation at each site. Proponents have demonstrated alterations in the left atrial electrophysiological properties after ablation at these sites, some instances of restoration of sinus rhythm, and higher long-term freedom from AF.[5]

Other investigators have used electroanatomic mapping systems to color code the representation of the atrial surface according to postpacing intervals, following the entrainment of macro–re-entrant arrhythmias.[6,7] This has assisted with research into the tachycardia mechanisms and also may have some application for clinical diagnosis.

Clinical Application of Electroanatomic Mapping

A comprehensive profile of the clinical application of electroanatomic mapping systems in mapping and guiding treatment of arrhythmias is beyond the scope of this chapter. Suffice it to say that they have been used for a range of supraventricular arrhythmias, including focal and re-entrant AT, AFL, and accessory pathway ablation.[8-10] In addition, they have also been extensively used in the treatment of unstable infarct-related VT with voltage maps created during sinus rhythm, which hitherto had essentially been unmappable with conventional electrophysiological techniques.[11]

Atrial Mapping with Electroanatomic Systems

Ablation of Atrial Fibrillation

Perhaps the most widespread use of electroanatomic mapping systems is for the treatment of AF. Mapping systems such as CARTO 3 and EnSite Velocity provide anatomic guidance for pulmonary vein isolation, atrial defragmentation, and the creation of linear lesions. Most physicians achieve electrical isolation of pulmonary veins by a combination of anatomically guided ablation and electrically guided ablation, typically with a multi-polar circular mapping catheter placed within the veins.[12] However, electroanatomic mapping systems are used only for anatomic guidance in this process.

As outlined above, some investigators have reported techniques for ablation of persistent AF, which involves targeting fractionated electrograms. With some electroanatomic mapping systems, color-coded maps of fractionation can be created with proprietary software.

Ablation of Atrial Tachycardia

In the setting of ablation for persistent AF, AT is frequent and can be challenging to diagnose. Electroanatomic mapping systems allow the creation of activation maps that can assist with this process, although good results can also be obtained with conventional methods.[13,14] For patients with congenital heart disease or previous cardiac surgery, electroanatomic mapping systems may be more important for diagnosis of macro–re-entrant tachycardias.[15] This is because the best targets for ablation are highly dependent on the patient's individual atrial anatomy and electrical function. In addition, entrainment maneuvers are less useful because they are more likely to disrupt the tachycardia in this patient group.[15]

Noncontact Atrial Mapping

The EnSite Array has been used to study atrial activation during sinus rhythm as well as during AF. By using two EnSite Array catheters, Lemery and colleagues studied inter-atrial conduction from data collected simultaneously in both atria.[16] They found that conduction across the muscular connections, consisting of Bachmann's bundle and the coronary sinus, was more prominent than across the true atrial septum. Simultaneous bi-atrial mapping has also been used to study patients with AF.[17,18] These studies have indicated the presence of non–pulmonary vein drivers of fibrillation, in addition to ectopic beats arising from the pulmonary veins. Additionally, patients with persistent fibrillation had a more extensive distribution of tachycardia origins as well as coexistence of multiple tachycardias. Noncontact mapping has also been used successfully for the mapping of AT during ablation procedures.[19,20]

Ablation of Ventricular Tachycardia by Using Complex Mapping Systems

Mapping and Ablation of Hemodynamically Stable Ventricular Tachycardia

Conventional Electroanatomic Mapping

The CARTO system was used by Soejima et al to generate voltage maps during sinus rhythm to target VT ablation.[11] VT was induced and, if possible, a re-entrant isthmus was identified. If VT was hemodynamically unstable, pacemapping along the low-voltage border of the scar was performed to look for a pacematch identical to that of the induced VT in addition to a stimulus to QRS delay of greater than 40 ms. Standard radiofrequency (RF), irrigated, or cooled-tip catheter energy was delivered to these sites during sinus rhythm, followed by short ablation lines, which were created extending from these sites parallel to the scar border zone over 1 to 2 cm until pacing at 10 mA at 2-ms stimulus strength failed to capture in that region. If the target site was within 2 to 3 cm of the mitral annulus, lesions were extended to the annulus to interrupt a potential submitral isthmus, as first demonstrated by Wilber et al.[21] In their study, programmed stimulation was repeated, and

if VT was re-induced, further mapping and ablation were repeated with RF lines extended. Electrically unexcitable scar was identified in all 14 patients, and all 20 VT circuit isthmuses were located adjacent to these regions. However, it was difficult to discriminate between low amplitude, fractionated electrograms that represented scar and those that indicated the diastolic pathway. Nevertheless, RF ablation lines connecting selected electrically unexcitable scar regions abolished all inducible VTs in 10 patients (71%), and spontaneous VT was markedly reduced during follow-up (142 ± 360 to 0.9 ± 2.0 episodes per month).

Noncontact Mapping

Initial data from series using noncontact mapping to target VT for ablation have been encouraging. Schilling et al used noncontact mapping to target VT and achieved an initial success rate of 77% in VTs for which diastolic pathway activity was mapped.[2] Careful optimization of filter settings is important to reveal these diastolic pathways.[22] Strickberger's group successfully ablated 15 (78%) of 19 targeted VTs.[23] The remaining four VTs could not be ablated because of inability to maneuver the catheter to the target site, proximity of the target site to the bundle of His, or a complication causing termination of the procedure. On follow-up, VT recurrence was significantly reduced, as was the requirement for defibrillator therapy. In the 12 patients with implantable cardioverter-defibrillators (ICDs) implanted before ablation, defibrillator therapy frequency was reduced from 19 ± 32 per month to 0.6 ± 1.4 per month at 1 month of follow-up.

The studies described above have predominantly investigated patients with VTs relating to coronary artery disease. Other studies have reported successful outcomes of ablation in some patients, the majority of whom did not have organic heart disease.[24] These included patients with sustained VT or with frequent premature ventricular contractions.

Mapping and Ablation of Hemodynamically Unstable Ventricular Tachycardia

As described above, conventional mapping is not feasible for unstable ventricular arrhythmias. Several groups have published series on the use of substrate mapping during sinus rhythm and noncontact mapping of unstable VT followed by rapid termination.

Conventional Electroanatomic Mapping

Marchlinski et al used the CARTO system to produce voltage maps of the left ventricle with the creation of linear ablation lines from areas of dense scar (defined by a voltage amplitude of <0.5 mV) to areas of normal endocardium or anatomic boundaries.[25] In addition, elctrocardiographic morphology during VT and pacemapping in sinus rhythm were used at sites of ablation. Nine of 16 patients had VT in the context of healed myocardial infarction, and the remainder had dilated cardiomyopathy. Thirteen patients had poorly tolerated VT; of these, seven had VT inducible after ablation, five of which were fast VTs only. All patients had ICDs, and during a median follow-up of 8 months (range, 3 to 36 months), only two patients with unstable VT had a recurrence, giving a success rate of 85% in this subset. Up to 87 RF lesions were required per patient, with a mean of 54.6 ± 24.1 per patient.

Arenal et al studied 18 patients considered to have unmappable VT, either because the target VT was not inducible or mapping was not tolerated.[26] A further six patients with well-tolerated VT were studied to enable activation mapping and entrainment for comparison. The authors hypothesized that low-amplitude electrograms with an isolated, delayed component (E-IDC) along the scar border were more specific for VT isthmus slow conduction compared with low-amplitude electrograms alone (commonly found along the scar border). Such electrograms were characterized by double or multiple components separated by very-low-amplitude signals and could be found in sinus rhythm. Again, the CARTO system was used to generate voltage maps (complete scar defined as voltage ≤0.1 mV, dense scar as voltage ≥0.1 and ≤0.5 mV); and E-IDCs located during sinus rhythm or right ventricular apical pacing were marked on the map for rapid location, with areas up to 1 cm around these sites then explored and labeled. When this was completed, pacemapping was performed, starting at sites with the latest E-IDC and moving to adjacent sites when pacemapping was not identical to clinical VT. Attempts at VT induction were performed at E-IDC sites with an identical pacematch to look for presystolic or mid-diastolic electrograms during VT and to examine the stimulus-QRS (S-QRS) interval. Concealed entrainment was attempted when the VT was sufficiently well tolerated. Ablation was then performed at all sites with E-IDC at which pacemapping reproduced the target VT and the S-QRS interval was 50 ms or longer, or at any E-IDC site that became mid-diastolic during VT. Between one and 35 RF lesions were applied per patient, and none of the six patients with hemodynamically unstable VT was inducible after ablation. Of the 18 patients with unmappable VT, two patients had a recurrence of their clinical VT during follow-up, and five more patients had recurrence of a previously unrecorded VT.

Most recently, Brunckhorst et al used another marker of slow conduction to identify targets for VT ablation during sinus rhythm.[27] Twelve patients were studied, in whom 51 VTs were inducible; all clinical VTs were resistant to drug therapy, producing ICD shocks in all. S-QRS delays were analyzed during pacemapping at multiple areas in the left ventricle. Pacing was performed at 890 sites (74 ± 23 per patient), of which 93% achieved capture. No S-QRS delay occurred at 56% of pacing sites, a delay of 40 ms or more occurred at 44%, and a delay of 80 ms or more occurred at 15% of sites, the latter two groups usually being clustered together. The areas of conduction delay were compared with locations of target areas (areas within 2 cm of a re-entrant isthmus, defined by entrainment and ablation) and overlapped in 13 of 14 cases. Sites with delay of 80 ms or more were more frequent in a target area, although a close pacematch was only seen in 41% of sites in these areas and an exact match in only 9%. Furthermore, 46% of sites with a close pacematch were outside the target area, emphasizing the limitations of pacemapping of VT in patients with structural heart disease. Ablation was performed at a mean of 10 ± 3 sites in the target area, rendering seven patients noninducible at the end of the procedure, and at least one VT was abolished in five more patients. Over 6 months of follow-up, three patients died, and VT recurred at the time of death in two of these patients. The remaining nine patients remained free from VT despite a mean of 18 ± 16 VT episodes in the 6 months before ablation.

Epicardial mapping is also now widely used in conjunction with substrate mapping of the endocardium for infarct-related VT.[28] Nonsurgical access to the epicardium is typically via the subxiphoid approach. In patients without previous cardiac surgery, navigation of the pericardial space with a standard ablation catheter is usually straightforward. However, catheter stability is an issue. Electrophysiological data can be obtained and

recorded by using an electroanatomic system, and endocardial and epicardial maps can be seen concurrently. It is interesting to see that in some patients or in some conditions, one surface can appear completely normal while another shows diffuse areas of low voltage, scar, and abnormal electrograms. Care must be taken to avoid injury to the coronary arteries, but even this information can be readily seen if prior cardiac CT scanning can provide three-dimensional reconstructions of the coronary anatomy. A reconstruction can then be overlaid on the epicardial geometry by using the registration processes previously described. The advent of nonsurgical epicardial mapping greatly enhances the electrophysiologist's ability to accurately characterize the arrhythmogenic substrate. Only the mid-myocardium remains elusive.

The use of these techniques has produced excellent results in patients unsuitable for conventional ablation and has also improved the understanding of the subtleties of the underlying substrate that support scar-related VT.

Noncontact Mapping

Della Bella et al have reported on the use of noncontact mapping to guide ablation of hemodynamically unstable VT in 17 patients, of whom 11 had infarct-related VT.[29] VT was induced and terminated after 15 to 20 seconds and activation analyzed offline. Ablation was performed in sinus rhythm, either by a line across the diastolic pathway (DP) (if identified) or around the exit point. If the patient was noninducible at the end of the procedure, an ICD was not implanted. After separating the different underlying etiologies, an exit point was defined in all 21 post–myocardial infarction VTs, and DP activity was identified in 17 (80%). Successful ablation was achieved in 67% of VTs and in 53% of patients, and a partial success was achieved in one patient. Ablation was not performed, or was unsuccessful in 42% of patients; importantly, the success rate of ablation was higher with linear lesions across the DP (78%) compared with encircling lesions around the exit (16%).

During follow-up, seven of nine successfully ablated patients remained free from arrhythmia recurrence, as did the patient with a partial success, and all remained free of the target VT. ICD shock frequency was significantly reduced. The results from this study demonstrate that noncontact mapping–guided ablation of unstable VT is feasible, with success highly dependent on the identification of DP activity, as with stable VT.[2] However, in patients with frequent ICD shocks from rapid, hemodynamically unstable VT, this technology does provide a therapeutic option if drug therapy is limited.

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CHAPTER 93

Curative Catheter Ablation for Supraventricular Tachycardia: Techniques and Indications

Dipen Shah

The current popularity of radiofrequency (RF) catheter ablation is, in large part, attributed to its contribution to the management of supraventricular tachycardias (SVTs). The electrophysiologist is able to ablate as well as analyze mechanisms, evaluate the results of ablation, and re-ablate, if necessary, all with minimal morbidity.

This chapter briefly reviews the basic principles of performing curative catheter ablation for SVTs. The arrhythmias considered below include arrhythmias involving accessory atrioventricular (AV) connections, AV nodal re-entry tachycardia (AVNRT), atrial tachycardia (AT), including typical flutter and other macro–re-entrant right and left AT (atypical flutters), and non–re-entrant AT.

Accessory Atrioventricular Connections

The anatomic substrate of accessory AV connections is the myocardium bridging the AV annuli, which, in normal individuals, are fibrous and electrically insulating (Box 93-1).[1] The sequence of normal initial ventricular septal depolarization is altered by conduction through these connections inserting into the ordinary myocardium and bypassing the normal insulated and septally conducting His-Purkinje system. The relatively slow spread of activation through the ordinary myocardium contrasts with the coordinated septal endocardial breakthrough of Purkinje ramifications and results in the δ-wave in the surface electrocardiogram (ECG). In addition to providing an additional route for impulse conduction between the atria and the ventricles, nearly all accessory connections exhibit conduction properties different from the AV node. Decremental conduction is not ordinarily seen; that is, with increasing frequency or shortening coupling intervals, the conduction time across the pathway does not significantly increase.

Ventricular Pre-excitation and Its Mechanisms

Pre-excitation is defined as ventricular myocardial activation by a pathway other than the His-Purkinje system during sinus rhythm or atrial pacing. The normal H-V interval includes the time required for activation to proceed from the bundle of His recording site down the bundle branches to the distal ramifications of the Purkinje fibers before exiting to depolarize the working myocardium. Therefore pre-excitation is inferred if the H-V interval is abnormally short during sinus rhythm or atrial pacing. The H-V interval may be normal if too little myocardium is pre-excited (consequently generating feeble voltage) to be evident on the surface ECG. With an increased frequency of supraventricular impulses, more of the ventricular myocardium is pre-excited through the accessory connection (with a progressive widening of the QRS and shortening of the H-V interval) because of decremental conduction through the AV node and nondecremental conduction through accessory AV connections. Incremental atrial pacing is an integral part of the evaluation of accessory AV connections and increases pre-excitation, thus allowing the optimal surface ECG localization of pathway insertion. Pre-excitation may be difficult to discern on the surface ECG in sinus rhythm in case of accessory connections with long anterograde conduction times or short conduction times through the AV node. Pre-excitation should, however, be detectable by rapid pacing or slowing conduction through the AV node.

An accessory pathway with a long antegrade conduction time can manifest with an isoelectric interval separating the end of the P wave from the onset of ventricular activation, which may persist even during atrial pacing or AT. An electrical connection between the AV node and the ventricular myocardium bypassing the His-Purkinje system has also been postulated to be responsible for such an ECG but has not been conclusively demonstrated. The so-called *fasciculoventricular connections* can also produce similar ECG manifestations with a high septal breakthrough from the normally insulated bundle of His or bundle branch being the anatomic correlate. Interestingly, no clinical arrhythmia correlate has been described for what may be no more than an anatomic variant.

Electrophysiological Characteristics of Accessory Pathways

Normal retrograde (ventriculoatrial [VA]) activation over the AV conduction system depolarizes the atria from the septal region and decrements by at least 20 ms with faster stimulation. Nondecremental free wall activation (the so-called *eccentric activation*) suggests VA conduction over an accessory AV connection. Dynamic maneuvers are required to distinguish between septally situated accessory pathways and normal routes of VA conduction.

Box 93-1 Checklist for Catheter Ablation of Accessory Atrioventricular Connections

PRE-PROCEDURAL ASSESSMENT

1. Symptoms, physical examination
2. ECG: intermittent vs. constant pre-excitation vs. no pre-excitation
3. Associated heart disease, previous cardiac surgery

SETUP

1. Three to four multi-polar diagnostic catheters
2. Catheter positioning: high right atrium, right ventricular apex, coronary sinus, roving map, and ablation catheter
3. Signal analysis:
   - Bipolar recordings: 30-500 Hz bandpass filters; notch filters to be avoided, if possible
   - Unipolar recordings: 0.05-500 Hz bandpass filters, limited to distal electrode of ablation catheter, indifferent either Wilson's central terminal or preferably, an electrode in the IVC

EVALUATION

1. Baseline: H-V intervals and pre-excitation
2. Assessment of AV conduction:
   - Decremental atrial pacing (until 200-ms pacing cycle length, AV Wenckebach pattern) mainly to potentiate subtle pre-excitation. Induction of atrial fibrillation to be usually avoided (see later) because irregular activation precludes sequential mapping.
3. Assessment of VA conduction:
   - Decremental ventricular pacing (until VA Wenckebach or VA dissociation or approximately 250-300 ms pacing cycle length)
4. Evaluating the refractory period of the accessory pathway:
   - Decremental atrial pacing, programmed atrial stimulation, and the shortest pre-excited R-R interval during atrial fibrillation
5. Detection of a concealed accessory AV connection:
   - Nondecremental VA conduction pattern, VA intervals during apical and basal right ventricular sites, para-Hisian pacing
6. Tachycardia evaluation:
   - SVT evaluation: exclude other SVT mechanisms (AVNRT and atrial tachycardia)
   - Analysis of antegrade tachycardia limb (H-V interval, ventricular reset by late atrial extrastimuli)
   - Analysis of retrograde tachycardia limb (atrial activation sequence, atrial reset by ventricular extrastimuli coincident with the His, overdrive ventricular pacing)
7. Techniques and catheter options:
   - Left-sided AP: retrograde transaortic versus trans-septal access
   - Para-Hisian AP: jugular or subclavian access
   - Right free wall AP: large-curve long sheath to improve contact and stability against tricuspid annular free wall
   - Irrigated catheter for resistant APs (in case of inefficacy attributed to low RF power delivered)
   - Cryoablation: To be considered for mid-septal or para-Hisian APs
8. RF ablation parameters:
   - Temperature-controlled, power-limited conventional RF: 65°-70° C target temperature on the right side and 50°-60° C on the left side
   - Open-tip irrigated RF: maximum 40-45 W power-controlled RF delivery.
   - Ablation in the coronary sinus or cardiac veins at low RF power to ensure safety
9. AP ablation target parameters:
   - Earliest V-δ timing, earliest retrograde
   - AV or VA bipolar electrogram continuum
   - Unipolar QS morphology in case of ventricular pre-excitation
   - Presumptive AP
   - Absence of bundle of His electrogram at ablation site
10. Ablation endpoint:
    - Tachycardia termination coincident with AP conduction block (if ablation performed during tachycardia)
    - Tachycardia noninducibility
    - Absence of demonstrable antegrade and retrograde conduction through the AP
    - Stability of above endpoints for 20-40 min
11. Follow-up:
    - Clinical and ECG follow-up
    - Exercise stress test
    - Event monitor in case of symptoms

ECG, *Electrocardiogram;* IVC, *inferior vena cava;* AV, *atrioventricular;* VA, *ventriculoatrial;* SVT, *supraventricular tachycardia;* AVNRT, *atrioventricular nodal re-entrant tachycardia;* AP, *accessory pathway;* RF, *radiofrequency.*

During sinus rhythm, ventricular extrastimuli resulting in atrial activation preceding retrograde bundle of His activation indicate an accessory connection. If moving the ventricular pacing site from the apex toward the septum decreases the stimulus to atrial activation time instead of increasing it, an accessory VA connection should be considered. Moving away from the apex increases the conduction time to the normal AV conduction system through the distal Purkinje myocardial interface, whereas it decreases the conduction time to the annular insertion of an accessory pathway.[2] Similarly, high output–dependent capture of the insulated right bundle or the bundle of His contrasted with lower output ventricular myocardial capture at the same site can show changes in atrial activation sequence, retrograde His to atrial activation time, and stimulus to atrial activation timing, which suggest the presence of more than one retrograde pathway of VA conduction.[3] Unchanged atrial activation sequence coupled with a constant H-A interval and prolongation of the stimulus-A interval resulting from loss of His–right bundle capture indicate the presence of the normal VA conduction alone. Conversely, the absence of change in any of the intervals and sequences indicates the sole presence of accessory pathway retrograde conduction. If the accessory pathway is remote from the pacing site or is captured only with a long conduction time or if conduction through the AV node is very rapid, conduction through the accessory pathway may be completely masked. In practice, left free wall pathways remote from a right ventricular pacing site may fulfill these conditions and are therefore likely to be masked.

During a tachycardia, evidence of conduction through an accessory AV connection can be obtained by delivering late ventricular extrastimuli coincident with or 10 ms before activation of the bundle of His, thus ensuring the encountering of complete refractoriness within the bundle of His. If the extrastimulus is earlier than the His electrogram, the lack of anticipation of the ventricular electrogram, the bundle of His electrogram, or both confirms His-Purkinje refractoriness. The presence of conduction through an accessory connection is indicated if the ventricular extrastimulus advances or delays atrial activation or terminates the tachycardia without conduction to the atria.[4] Tachycardia termination by a His-synchronous ventricular extrastimulus without conduction to the atria or with anticipation of the

succeeding ventricular or bundle of His electrogram indicates participation of the accessory pathway in the tachycardia.

In addition to establishing the presence of an accessory connection, the electrophysiological study (EPS) allows assessment of the arrhythmogenic potential of the accessory connection. The indications for curative ablation of accessory pathways chiefly depends on their proven threat—pre-excited AF degenerating to VF—or their potential threat, indicated by R-R intervals shorter than 200 to 250 ms during AF or the presence of clinical tachycardias using the accessory pathway.[5]

Successful ablation of an accessory AV connection requires precise localization, and the surface ECG is a vital starting point. Although many algorithms have been described, those using the δ-wave vector are more difficult to use compared with the mean QRS vector during full or maximal pre-excitation. ECG pattern recognition allows the planning of a strategy specific to the presumed location.

Left Lateral Atrioventricular Accessory Connections

Left free wall pathways are found in the arc extending from approximately the 12 o'clock position to the 7 o'clock position on the mitral annulus, as viewed in the left anterior oblique view. The anteroseptal aspect of the mitral annulus is the region of aortomitral fibrous continuity established in early embryonic life, which means that accessory pathways do not occur in this area. Left free wall pathways have been considered to be the most straightforward locations for catheter ablations because they are far away from the AV conduction axis and are easily pinpointed by a multi-electrode coronary sinus catheter. In contrast, the proximity of the mitral valve and the circumflex coronary artery and the possibility of a true mid-myocardial pathway can represent significant technical challenges.

Retrograde Transaortic Approach

In our laboratory, a retrograde arterial approach is preferred, whereas the trans-septal approach is used secondarily. Trans-septal access is the first-line approach in case of aortic or arterial abnormalities, such as the presence of prosthetic valves; aortic stenosis; or severe aortic, femoral, or iliac atherosclerosis. In pediatric patients, the trans-septal approach may be preferred to avoid injury to the aortic valve.

Entering the left ventricle in a retrograde fashion across the aortic valve is an important part of the retrograde arterial approach. When the catheter is brought down to the root of the aortic valve, it meets the resistance of the aortic valve, and catheter flexion combined with continued gentle pressure facilitates the formation of a loop. The loop generally crosses the aortic valve into the left ventricular cavity before a 180-degree flexion. This may be facilitated by gentle torquing. It is imperative to avoid the catheter tip entering a coronary artery, and the catheter should be promptly withdrawn in case of any doubt. Rare instances of complications resulting from an unrecognized position within the left coronary system have been reported. The catheter can also easily enter the right coronary artery ostium, particularly if it has a downward takeoff. Entry into the left ventricle occasionally produces mechanical trauma and block within the normal AV conduction axis, which does not become apparent until the accessory pathway conducting in an anterograde fashion has been ablated. Fortunately, spontaneous recovery of normal conduction is the most common outcome. After crossing the aortic valve, the catheter should be straightened before it is gently advanced toward the posterolateral left ventricular free wall. Progressive flexion of the catheter tip as it touches the free wall brings the catheter tip near or at the level of the mitral annulus and under the mitral valve leaflet, as indicated by the recording of a significant atrial electrogram. The posterior and lateral mitral annulus should be mapped at this level.

Although catheter stability is the strong suit of the retrograde left-sided approach, this same characteristic renders mapping the mitral annulus difficult. Moving from one position to another requires catheter withdrawal from under the leaflet and repositioning it anew. Clockwise rotation positions the catheter tip more laterally and anteriorly, whereas counterclockwise rotation brings the tip around more medially. The size of the catheter curve is important; a large curve does not allow the catheter tip to reach the annulus level, and a small curve means that the catheter tip "floats" or bounces without stable contact. A more atrial position (where the catheter tip makes contact with the atrial side of the mitral leaflet) can be achieved by torquing the catheter counterclockwise so that it slips medially onto the atrial side through the posterior commissure. The further anterior the accessory pathway, the more difficult it is to reach the atrioventricular annulus with the catheter tip from the retrograde approach. This situation may call for a larger curve or a trans-septal approach. The catheter tip can be much more freely moved to map the annulus on the atrial side of the mitral leaflet but, typically, is less stable than when positioned under the leaflet. Ectopy, not uncommon during RF delivery in this position, can easily dislodge the catheter.

Trans-septal and Other Approaches

The trans-septal route probably offers greater freedom in mapping the left AV annulus and allows the use of bipolar electrogram polarity reversal to bracket the atrial insertion of accessory pathways. Long sheaths improve catheter stability and facilitate precise mapping. Anterolaterally located pathways can be directly accessed, whereas septal pathways are difficult to access trans-septally. A left free wall pathway ordinarily calls for both femoral venous and arterial access. An anteroseptal pathway pattern should suggest the requirement for subclavian or jugular vein access, a right free wall pattern, the need for a long sheath, and posteroseptal pathways suggest the possible need for coronary sinus angiography.

Electrophysiological Localization

A multi-catheter approach can cover both AV annuli and provide corroboration of localization rapidly. Successful and equally rapid ablation can, however, be achieved with fewer catheters—typically two or three. In the case of evident pre-excitation, a single ablation catheter may be successfully used, which may be followed by an adenosine test; but the assessment of retrograde VA conduction usually requires an additional intracardiac catheter.

When even the best unipolar and bipolar endocardial electrograms are not good enough, an epicardial or intramyocardial

pathway insertion may need to be evaluated or considered. Ventricular electrograms close to or at the site of insertion can be late, not only because the insertion may be far from the endocardium but also because of the endocardial insertion of an oblique pathway. Changing the pacing site (e.g., from the right ventricular apex to the lateral left ventricular or the right ventricular infundibulum) can help distinguish apparently early atrial electrograms (during ventricular pacing) because of an oblique pathway course. Simultaneous comparison of endocardial and epicardial recordings obtained from within the coronary sinus is useful; bracketing, as well as electrogram timing and dv/dt (rate of ventricular electrogram depolarization) comparison, can provide valuable clues. Ablation within the coronary sinus may be necessary (Figure 93-1), although conventional RF delivery achieves only low power and is frequently ineffective. Ablation in the coronary sinus and veins with a catheter with an open irrigated tip can achieve good results; however, stepwise increments in RF power (a cautious maximum of 25 W) are prudent. Pops in the thin-walled coronary venous structure can be devastating; damage to adjacent coronary arteries has also been reported.

Localizing a pathway conducting in an antegrade fashion involves sampling the annulus of interest for the shortest local AV intervals and the earliest V (local ventricular electrogram)-δ intervals. Some posteroseptal pathways exhibit long AV times at successful sites, which suggests slow conduction through the accessory pathway. The correct assessment of the timing of ablation catheter electrograms requires comparison with the surface ECG lead showing the maximum pre-excitation.

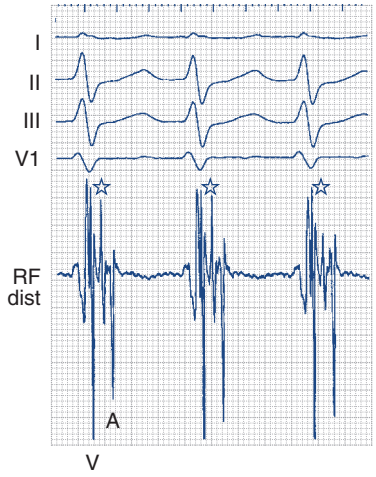

FIGURE 93-1 An epicardial concealed left-sided accessory atrioventricular connection successfully ablated within the distal coronary sinus at about the 2 o'clock position in the left anterior oblique (*LAO*) view; coronary sinus angiogram with catheter position (*arrow*) is shown below. *Top*, The recording at the ablation site within the coronary sinus (*RF dist*). The *star* marks the accessory pathway potential, which was found to be dissociated from atrial and ventricular activity in sinus rhythm after successful ablation.

Local Electrogram Characteristics

Bipolar and unipolar electrograms should both be used for mapping (Figure 93-2)—the former because of their higher signal/noise ratio and the latter because of their simple morphologic pattern recognition–based analysis.[6] Localization based on bipolar electrograms requires distinction of atrial electrograms from ventricular electrograms by using late-coupled ventricular and atrial extrastimuli. However, these maneuvers can be difficult to perform or analyze and may even induce arrhythmias. The contribution of the proximal ring electrode to bipolar electrograms from the distal bipole can be misleading. Atrial electrograms can be distinguished from ventricular electrograms by using unipolar electrograms from the distal electrode.

Unipolar electrograms with a steep QS morphology are particularly useful for localizing the site of ventricular insertion on the basis of a steep QS morphology (the absence of an initial R wave) during sinus rhythm, pacing, or even ongoing AF and also in patients with Ebstein's anomaly who exhibit low-amplitude, fractionated bipolar electrograms on the tricuspid annulus. Unipolar electrograms should be recorded with wide band filters—0.05 to 500 Hz—because the low-frequency content makes important contributions to the generation of RS or QS patterns. Instead of Wilson's central terminal, a remote cutaneous or inferior vena cava (IVC) electrode may be useful as a ground, allowing common mode rejection of contaminating 50- or 60-Hz line noise. Notch filters should also be used with caution, if at all. Once the atrial and ventricular electrograms have been recognized, the intervening deflections represent presumptive accessory pathway potentials (see Figure 93-1).[7] Certainly, the best validation is the prompt abolition of accessory pathway conduction by RF ablation at this site (assuming appropriate power delivery and contact). In practice, accessory pathway potential validation often is a retrospective exercise.

For patients without pre-excitation, the target of choice is the shortest VA interval during orthodromic AVNRT because this effectively rules out the fusion of activation through the normal AV axis with activation through the accessory connection. Ablation during ongoing AVNRT can, however, lead to dislodgment of the ablation catheter at tachycardia termination. Prompt initiation of ventricular pacing after tachycardia termination has been advocated to minimize or prevent instability. If no tachycardia is inducible and retrograde conduction through the normal AV axis can be excluded or distinguished, earliest atrial activation during ventricular pacing is a reasonable target. In the presence of an obliquely coursing accessory pathway, changing the ventricular pacing site is useful in evaluating electrogram timing as pointed out above.

Individual Pathway Locations

Right Free Wall Atrioventricular Accessory Connections

Right free wall pathways are defined by a location within the arc of the tricuspid annulus extending from approximately the 12

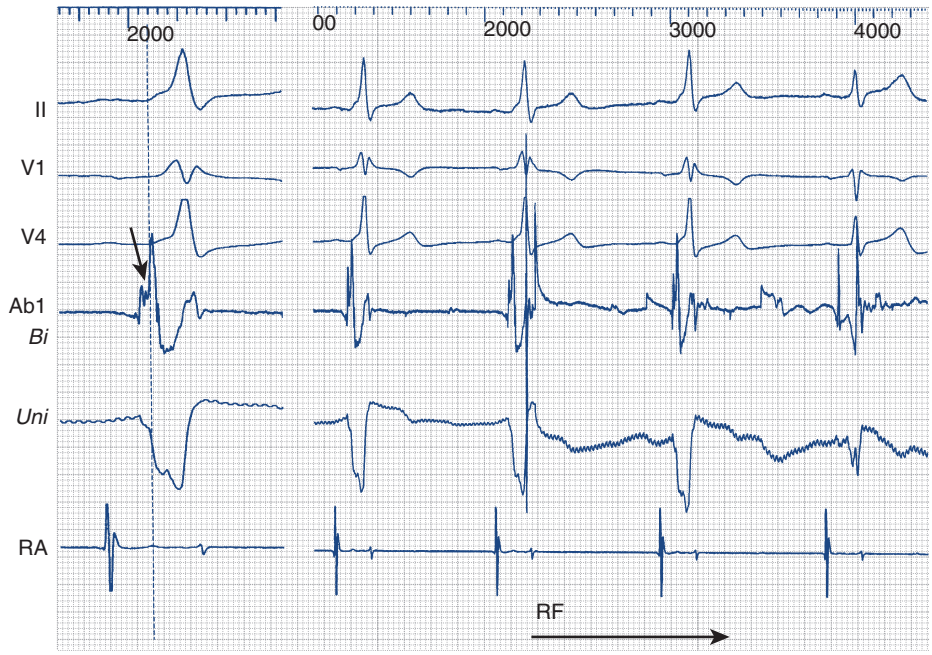

FIGURE 93-2 *Left*, Site of successful ablation for a pre-excited left lateral accessory atrioventricular connection. *Right*, Prompt elimination of pre-excitation during radiofrequency (*RF*) delivery. Vertical *dashed line* marks intrinsic deflection of ventricular electrogram preceding δ-wave onset by less than 10 ms. Note QS morphology in the unipolar electrograms. The *arrow* indicates presumptive accessory pathway potential interposed between atrial and ventricular deflections identified, respectively, by comparison after ablation (atrial electrogram) and correlation with unipolar (*uni*) electrogram (ventricular electrogram).

o'clock position to the 6 o'clock position, as viewed from the left anterior oblique 45-degree view. The tricuspid annulus has a much more vertical orientation compared with the mitral annulus, the right ventricle is much thinner than the left ventricle, and there is no counterpart of the coronary sinus. Access to the right AV annulus is much more direct than on the left side, but a position on the annulus is more difficult to achieve, particularly from the femoral route. Right atrial free wall contraction tends to dislodge the catheter tip and long sheaths or large curve catheters facilitate ablation by improving stability. The radiolucent shadow of annular fat is a useful clue to the level of the tricuspid annulus, particularly when annular electrograms are fractionated and of low amplitude, as in Ebstein's anomaly. Unipolar electrograms can be of help, and recordings from within the right coronary artery have been used, although the latter run the risk of significant complications. Unlike the usual QS morphology at successful ablation sites of other pathway locations, the ventricular electrogram has a two-stepped deflection; the first steeper deflection indicates local right ventricular activation, and the second represents far-field activation probably originating from the septum and the left ventricle.

The typical successful ablation site for right free wall pathways shows ventricular electrograms with timings approximately 20 to 30 ms earlier than for left free wall pathways. The atrial insertion of the pathway is activated before the end of atrial activation so that right ventricular pre-excitation actually begins within the P wave, and pre-excitation of the thin-walled right ventricle does not become evident on the surface ECG as early as for pathways inserting into the thicker left ventricle. Local ventricular activation of −10 to −20 ms (preceding the QRS) is therefore usually not "early enough" for pathways in this location. Ablation at this location is characterized by the lower electrode temperatures during RF delivery—related to catheter contact, electrode orientation, and stability and high-power delivery during temperature-controlled RF applications. Mechanical block of accessory pathway conduction may be frequent, and an eventual recurrence is more likely for pathways at this location despite the "security" RF applications.

Septal Atrioventricular Accessory Connections

Septally situated pathways have been divided into anteroseptal, mid-septal, and posteroseptal pathways. The anteroseptal pathways are located on the tricuspid valve (TV) annulus (because of the aortomitral fibrous continuity on the left side) between the 12 o'clock position (in the left anterior oblique view) and the bundle of His region—with the provisio that any His potential recorded at the site be less than 0.1 mV. A larger His deflection defines the pathway as para-Hisian. Posteroseptal pathways are defined by a location between the coronary sinus ostium to approximately the 6 o'clock position on either AV annulus. The mid-septal pathways are more difficult to define in terms of location and are broadly considered to be between the His and coronary sinus ostial locations, excluding the para-Hisian pathways. Except for the anteroseptal pathways, the septal pathways have in common the possibility of being accessible from either annulus and proximity to the AV node or the bundle of His. An epicardial location is more frequent for the posteroseptal pathways; therefore mapping of the coronary sinus and the middle cardiac vein is often necessary.

The anteroseptal pathways can be ablated with advantage from the superior vena cava (SVC) approach, with active catheter flexion bringing the catheter tip in contact with the annulus; with the femoral approach, relaxing the catheter tip flexion is required to achieve contact, and unless the catheter is bi-steerable, this is a passive movement providing much less stable contact. It may also be easier to achieve a position under the tricuspid valve by making a loop in the right ventricle using an approach from above.

The main concern with regard to the mid-septal pathways is to avoid damage to the AV node and the normal conduction axis. As for the para-Hisian pathways, proximity to the bundle of His allows an estimation of this risk. Proximity to the compact AV node is, however, difficult to estimate in the absence of an electrogram marker. The appearance of junctional rhythm is a clear warning that should prompt cessation of RF delivery, and a narrow QRS complex without a preceding P wave should not be mistaken for loss of pre-excitation. Using conventional RF, the strategy for pathways estimated to be close to the AV node or the bundle of His should center around careful mapping for the best electrograms and delivering low RF power at sites thought to be farthest from the conduction axis, usually on the ventricular side of the AV ring. At prospective ablation sites, it is useful to verify the presence and the amplitude of a bundle of His deflection concealed by pre-excitation by using programmed stimulation to induce antegrade pathway block or sustained orthodromic AVNRT. RF power may be increased cautiously in steps of 5 W, but energy delivery should be terminated immediately in case of junctional rhythm or if loss of pre-excitation does not occur promptly. Cryoablation offers the theoretical advantage of reversible cryomapping. In practice, although a greater margin of reversible lesion creation with cryoablation and therefore a lower risk of AV block may exist, this energy source has a clearly higher risk of recovery of pathway conduction.[8]

The posteroseptal pathways have a higher likelihood of an epicardial course or insertion. Moreover, the anatomic boundaries of the posterior pyramidal space frequently require a choice to be made between the right or left endocardial sites and the sites within the proximal coronary sinus or the middle cardiac vein. A steep QS complex in lead II or an rS complex in leads V5-V6 during pre-excitation may be a clue to an insertion into the middle cardiac vein.[9] If endocardial mapping is not good enough or the ablation is unsuccessful, mapping within the coronary sinus and the middle cardiac vein is performed under the guidance of a coronary sinus angiogram. Occlusion balloon angiography provides the best opacification of the great cardiac vein and related branches, but adequate visualization of the proximal coronary sinus and the middle cardiac vein can be achieved from the femoral approach by using an Amplatz catheter. Successful ablation sites are frequently clustered in proximity to venous anomalies such as aneurysms or diverticula. A superior approach from the internal jugular vein provides a relatively straight and vertical catheter course to the middle cardiac vein and should be considered in case of difficulty with the femoral approach. Ablation within the coronary sinus or cardiac veins with a conventional nonirrigated ablation catheter is frequently ineffective because of low delivered powers and high electrode temperatures as a consequence of limited blood flow around the electrode. Ablation in the middle cardiac vein can damage the posterior descending and posterior left ventricular branches of the distal right coronary artery. Ineffective low power delivery can be overcome by using an irrigated tip catheter that allows power to be titrated up to a limit of 25 to 30 W to avoid pops or damage to nearby coronary arteries (within 2 to 3 mm of the site of ablation).

Specific Situations

During an ablation procedure, sustained AF is not infrequent, which renders mapping difficult. No alternative to electrical cardioversion may be available because type I or III antiarrhythmic drugs may alter the accessory pathway properties and may even eliminate pre-excitation. Mapping the earliest ventricular activation during the widest QRS (indicating maximum pre-excitation) is feasible, as is ablation, particularly when guided by unipolar electrograms. Verification of bi-directional conduction block (assessment of VA conduction) is not possible during AF.

Multiple pathways are not common but may be encountered, particularly in association with Ebstein's anomaly. Changing patterns of pre-excitation and VA intervals and sequences are important clues. However, the same principles of mapping and ablation described above are usually effective.

The substrates of the "Mahaim" pathways (decremental atriofascicular or atrioventricular pathways) and permanent junctional reciprocating tachycardias are both thought to be accessory pathways with long conduction times—antegrade in case of the atriofascicular or AV Mahaim pathways and retrograde in case of persistent junctional reciprocating tachycardia (PJRT). In addition, these two accessory pathway variants share another characteristic—that of one-way conduction only. The few available histologic studies suggest that the anatomic substrate of PJRT is a long and tortuous muscular fascicle, whereas in the case of the Mahaim fiber, an accessory node–like structure is thought to exist at its atrial origin.[10] Atriofascicular and AV Mahaim fibers are most effectively ablated by targeting the pathway potentials at the level of the annulus; they resemble the bundle of His potentials but continue to precede ventricular activation even during pre-excitation. PJRT is ablated by targeting the earliest atrial activation during the tachycardia, and, as with every ablation within that posteroseptal area, care must be taken to ensure a reasonable distance from the normal AV conduction axis.

An accessory pathway with a large insertion or an insertion with multiple branches may occasionally be encountered.[11] Multiple coalescent lesions, each of which modifies local electrogram parameters, have been used.

Another uncommon variant is an appendage to the ventricular connection characterized by an insertion bridging the appendage tip to the ventricle away from the annulus.[12] Careful mapping, aided by three-dimensional mapping as needed, can clarify the exact location of the insertion. Similarly, the unusual variant of surgically acquired pre-excitation is encountered rarely after right atrial appendage anastomosis to the right ventricular outflow tract (RVOT) (historically performed as a palliative procedure for tricuspid atresia). In the appropriate surgical context and with the pre-excited QRS resembling an RVOT tachycardia, careful mapping has allowed successful ablation.

An additional arrhythmia substrate such as AVNRT or AT may coexist. The electrophysiological maneuvers described above can assist in deciding whether the accessory pathway participates in the tachycardia.[13] However, in practice, elimination of the accessory pathway substrate typically unmasks the AVNRT or AT, which can then be ablated in the standard fashion.

Indications for catheter ablation include the following:

- Wolff-Parkinson-White (WPW) syndrome and AF with rapid conduction
- Poorly tolerated AVNRT
- Well-tolerated WPW syndrome (pre-excitation + symptomatic arrhythmias)
- Infrequent AVNRT (no pre-excitation; offered as one among a group of roughly equivalent treatments)

Atrioventricular Nodal Re-entrant Tachycardias

AVNRT is the result of a re-entry circuit in the AV junctional region (Box 93-2), although debate about anatomic delimitations continues. The functional heterogeneity of AV junctional tissues, primarily with respect to conduction velocity and refractory periods, permits the sustenance of an excitable gap re-entry circuit. Because of anatomic factors and the lack of distinct electrophysiological markers of activation, it is difficult to delineate the anatomic extent of the circuit. Nevertheless, available evidence suggests that the peri-nodal atrium, the compact AV node, and possibly a part of the proximal bundle of His are involved. Although no significant anatomic abnormalities have been found in patients with AVNRT, multiple posteriorly situated pathways or approaches to the AV node have been described.[14]

At least three different types of AVNRT have been described: (1) slow antegrade/fast retrograde, (2) fast antegrade/slow retrograde, and (3) slow antegrade/slow retrograde. In addition to differences in conduction velocity and refractory periods, the fast and slow pathways manifest relatively disparate anterior and posterior retrograde exit sites, which helps delineate the different types of AVNRT. Most laboratories today establish baseline evidence of antegrade "slow" pathway conduction in the form of a long A-H interval (>200 ms) with or without a discontinuity (50-ms increments in A-H for a 10-ms decrement in coupling interval). In addition, an H-A interval ranging from 25 to 80 ms during tachycardia is indicative of a typical slow-fast AVNRT. Variants of AVNRT (fast-slow or slow-slow) can be distinguished from AVNRT and AT by the response to ventricular extrastimuli introduced during the AV nodal refractory period, by rapid ventricular stimulation, and by the atrial activation sequence and tachycardia behavior during AV block.[13]

Earliest retrograde activation at the anterosuperior tricuspid annulus during typical AVNRT localizes the fast pathway exit site, and retrograde activation near the posteromedial tricuspid annulus during fast-slow AVNRT localizes the slow pathway exit site. Techniques of AV nodal modification have therefore targeted these sites to produce selective fast or slow pathway ablation.

The fast pathway exit can be approached by slow withdrawal of the catheter a few millimeters from the bundle of His position while concurrently applying clockwise torque to maintain good contact. A monitoring catheter kept in the bundle of His–recording position is a convenient reference. Because no accepted electrogram markers of fast pathway activation exist, indirect parameters such as an A/V electrogram amplitude ratio greater than 1 and a His deflection less than 0.05 mV are used to ensure relative separation from the bundle of His. RF energy applied for a short period at such sites results in P-R interval prolongation and elimination or marked attenuation of retrograde VA conduction. A junctional tachycardia is frequently noted; this may require atrial pacing to allow monitoring of AV conduction. P-R interval prolongation by more than 50% or AV block make prompt discontinuation of RF energy delivery (which should be titrated in steps of 5 W) mandatory.

Evaluation after fast pathway ablation typically reveals abolition or marked attenuation of VA conduction accompanied by an

Box 93-2 Checklist for Catheter Ablation of AV Nodal Re-entrant Tachycardia

PRE-PROCEDURAL ASSESSMENT
1. Symptoms, physical examination
2. Associated heart disease, prior heart surgery

SETUP
1. Three to four multi-polar diagnostic catheters
   - High right atrium, right ventricular apex, coronary sinus, bundle of His recording, roving map, and ablation catheter
   - Similar setup to that for APs (unipolar recordings not useful)

EVALUATION
1. Baseline assessment
2. AV conduction assessment:
   - Decremental atrial pacing
   - Programmed atrial stimulation
   - Demonstration of AV nodal duality
3. VA conduction assessment:
   - Confirmation of concentric and decremental VA conduction
   - Earliest retrograde atrial breakthrough: Peri-Hisian or mid-septal or posteroseptal (near or in the CS)
4. Assessment of induced tachycardia:
   - Exclude septal AP-mediated AVNRT (see preceding sections) and atrial tachycardia (ventricular overdrive pacing)
5. Technique:
   - Slow pathway ablation in sinus rhythm
   - Avoid damage to antegrade AV conduction: anatomy—relation to bundle of His electrogram, junctional rhythm (rate and VA conduction during junctional rhythm), stop RF ablation to verify antegrade AV conduction
   - If atypical AVNRT, conventional slow pathway ablation in sinus rhythm often effective. Alternative or secondary target earliest retrograde atrial activation (avoid para-Hisian or mid-septal region); typically coronary sinus ostium or proximal coronary sinus, rarely posterior mitral annulus
6. Endpoint:
   - Slow pathway modification or elimination
   - Tachycardia noninducible, maximum two nodal echoes with intravenous isoprenaline
   - Endpoint stability for 20-40 minutes
7. Follow-up:
   - Clinical assessment
   - Event monitor in case of symptoms

AP, *Accessory pathway;* AV, *atrioventricular;* VA, *ventriculoatrial;* CS, *coronary sinus;* RF, *radiofrequency;* AVNRT, *atrioventricular nodal re-entrant tachycardia.*

increase in the A-H interval and elimination of dual AV nodal physiology. VA conduction is eliminated in more than one third of patients, whereas the VA block cycle length is increased in the remainder. Similarly, the A-H interval is prolonged markedly (<50%) but without significant change in the H-V interval, AV nodal effective refractory period (ERP), or anterograde Wenckebach cycle length.

Although fast pathway modification is successful in more than 90% of patients, complete heart block occurs in up to 21%.[15] In case of transient conduction block, in-patient telemetric monitoring may be advisable for 1 to 2 days after ablation to watch for delayed complete heart block. The high incidence of AV block and the efficacy of slow pathway ablation have led to this technique being abandoned.

The slow pathway has been targeted by selective ablation, and because of the greater distance from the compact AV node, the incidence of complete heart block is consistently lower. Slow pathway ablation or modification has become the therapeutic procedure of choice.

Two approaches have been used: anatomic and electrophysiological. The anatomic approach uses fluoroscopic landmarks to guide the positioning of the ablation catheter, with the target area being the junction of the middle and posterior thirds of the medial inter-atrial septum at the level of the tricuspid annulus or in the vicinity of the ostium of the coronary sinus. Arrhythmia re-induction is attempted after each RF delivery (for 30 to 60 seconds) followed by slow pathway assessment. If AVNRT remains inducible, subsequent RF energy is delivered nearer the AV node; however, the most posterior (inferior) successful ablation site is the safest.

One electrophysiological approach targets the earliest atrial activation during retrograde slow pathway conduction during fast-slow AVNRT or ventricular pacing but is limited by the difficulty in inducing consistent retrograde slow pathway conduction. This is possible in only approximately 10% of patients. More commonly, characteristic electrograms representative of slow pathway conduction have been used to guide RF energy application. Two distinct types of slow pathway potentials have been described. One is a sharp, spikelike potential (Asp) preceded by a lower frequency, lower amplitude potential (A) during sinus rhythm.[16] Asp usually follows A by 10 to 40 ms; such double potentials are recorded in the vicinity of the coronary sinus ostium near the tricuspid annulus. During retrograde conduction over the slow pathway, the sequence of these double potentials is reversed, that is, Asp now precedes A. RF energy applied to the latest Asp potential close to the tricuspid annulus successfully eliminated AVNRT in 99% of patients (with only one AV block). Experimental data have shown that similar double potentials are produced by asynchronous activation of muscle bands flanking the mouth of the coronary sinus.[17]

Other types of the slow pathway potentials are characteristically low-amplitude, low-frequency signals that are concealed within or follow the atrial electrogram and occupy some or all of the A-V interval in sinus rhythm.[18] They are easily found by withdrawing the catheter posteriorly from the bundle of His position. In the posterior septum, they are usually hump shaped, whereas more anteriorly they are rapid, narrower, often biphasic, and with a superimposed bundle of His deflection. They are typically recorded at the junction of the anterior two thirds and the posterior one third of the area between the bundle of His and the coronary sinus ostium. During incremental atrial pacing, these slow potentials characteristically separate from the atrial electrograms, are prolonged in duration, and decline in amplitude. They fractionate and disappear at rapid pacing rates so they are not discernible during tachycardia. Animal studies indicate that the low-frequency deflections coincide with the activation of the cells around the tricuspid annulus possessing AV node–like properties. During reverse ventricular echoes, these cells are activated before the earliest atrial activation during retrograde slow pathway conduction but fail to be activated during antegrade conduction over the fast pathway. In view of their wide recording area, they may represent dead-end pathway activation overlying the actively participating cells. Activation of the posterior part of the slow atrionodal approaches may give rise to the Asp potential, and the (transitional) tissue anteriorly (beyond the coronary sinus ostium) gives rise to low-frequency slow potentials.

After successful ablation of the slow pathway, an increase in the antegrade AV block cycle length and the AV nodal ERP is usually noted without a change in baseline A-H intervals or retrograde conduction. The maximum A-H interval during incremental atrial pacing is characteristically curtailed. However, in approximately 50% of patients, residual slow pathway conduction, in the form of persistent antegrade AV nodal duality, single AV nodal echoes, or both, is evident, although AVNRT typically remains noninducible even with intravenous infusion of isoproterenol.

RF ablation guided by either approach offers essentially equivalent results, although fewer applications may be required when ablation is guided by low-frequency potentials. Complete AV block during slow pathway ablation is definitely uncommon but may be related to an abnormally posteriorly situated fast pathway.

To avoid AV block, a careful search should be made for the most posterior site with typical slow potentials, without His deflections, of course, but also avoiding sites that exhibit slow potentials that persist and coincide with the end of the A-H interval during rapid pacing. Junctional ectopy is elicited at 70% to 90% of effective sites, and it is important to monitor VA conduction during this rhythm. VA block—even intermittent—and faster rates of junctional rhythm are useful markers of impending AV block. In case of doubt, it may be wise to stop RF delivery to check the P-R interval during sinus rhythm. Atrial pacing may be helpful, although the flip side is that it may mask junctional rhythm and prevent monitoring of VA conduction, which is an early sign of encroachment on antegrade conduction. In the event of AV block, early recovery (within 2 to 3 minutes) indicates a good prognosis.

Recurrence after successful ablation is uncommon (approximately 2%) and may be lower if complete elimination of the slow pathway is achieved. However, tachycardia noninducibility in spite of isoproterenol infusion is an adequate endpoint.

The lower incidence of AV block (approximately 1%) has made slow pathway ablation the technique of choice, although fast pathway ablation may be considered if the slow pathway approach is ineffective. Cautious ablation of the slow pathway is usually effective even in patients with prolonged P-R intervals at baseline because of the persisting so-called "intermediate" pathways that permit AV conduction. Cryoablation is theoretically attractive but has not been shown to be superior and, in fact, has a high incidence of recurrence.[19]

Symptomatic patients who do not wish to have drug therapy or cannot tolerate standard drug therapy may be offered this intervention. The ablation should probably not be performed for initial or infrequent episodes of AVNRT because of the small but definite risk of AV block. This risk is thought to be higher in small children.

Indications for catheter ablation include the following:

- Poorly tolerated AVNRT (hemodynamic intolerance)
- Recurrent symptomatic AVNRT
- Infrequent or single episode of AVNRT in patients who desire complete arrhythmia control

Atrial Flutter

Negative sawtooth flutter waves in leads II, III, and aVF between 200 and 350 beats/min characterize typical atrial flutter (Box 93-3). The absence of a diastolic isoelectric baseline distinguishes it from other SVTs. A typical flutter includes the counterclockwise as well as the clockwise form of the cavotricuspid isthmus–dependent flutter. Beyond this characterization, macro–re-entrant ATs are often considered to be forms of atrial flutter, although they are termed *atypical* to distinguish them from cavotricuspid isthmus–dependent (typical) flutter.

Typical Atrial Flutter

The key to the widespread use of catheter ablation for the treatment of typical atrial flutter has been the realization that the anatomically limited and easily accessible cavotricuspid isthmus is critical for maintenance of the arrhythmia. The understanding that stable isthmus conduction block is a clearly demonstrable endpoint in sinus rhythm and the absence of significant adverse effects have contributed to the popularity of this treatment.

Modern mapping techniques have merely confirmed the data derived more than 20 years ago that the macro–re-entrant circuit of typical atrial flutter is confined to the right atrium, resulting in counterclockwise or clockwise activation when viewed in the left anterior oblique perspective, with the tricuspid valve en face. In analogy with Mines' ring models, the tricuspid valve is the outer boundary, and the posterior intercaval right atrium–crista terminalis complex is the inner boundary of a ring of re-entrant activation.[20]

The surface ECG morphology of counterclockwise typical flutter is remarkably consistent, allowing effective ablation even without proof of the participation of the cavotricuspid isthmus. In contrast, the surface ECG morphology of clockwise flutter is variable and difficult to distinguish from non-isthmus-dependent flutters. Intracardiac activation and entrainment mapping often are necessary for confirming the diagnosis. Because the cavotricuspid isthmus is a critical segment of the circuit of both clockwise and counterclockwise forms, the strategy of cavotricuspid isthmus ablation is effective for both forms.

Box 93-3 Checklist for Catheter Ablation of Typical Atrial Flutter

PRE-PROCEDURAL ASSESSMENT
1. Symptoms and clinical examination
2. Associated heart disease
3. Associated atrial fibrillation
4. Adequacy of anticoagulation
5. Transesophageal echocardiography
6. Confirmation of ECG diagnosis of typical flutter

SETUP
1. One multipolar, preferably deflectable, diagnostic catheter
2. One ablation catheter (open tip, irrigated)

EVALUATION
1. During atrial flutter:
   a. Activation mapping
   b. Entrainment mapping to confirm cavotricuspid dependence

TECHNIQUE
1. Point-by-point or drag ablation from ventricular to IVC edge of cavotricuspid isthmus: up to 40 W RF power with the open-tip irrigated catheter
2. Flutter termination by intra-cavotricuspid isthmus block during RF delivery
3. Evaluation of cavotricuspid isthmus conduction:
   a. Activation mapping (sequential mapping or multipolar catheter around tricuspid valve annulus)
   b. Double potential mapping
   c. Differential pacing
4. Ablation of residual conducting gaps
5. Verification of stability of cavotricuspid isthmus block for 20-40 minutes

FOLLOW-UP
1. Oral anticoagulation for at least 1-3 months
2. Clinical follow-up for symptomatic arrhythmias
3. Holter surveillance for asymptomatic atrial fibrillation or flutter

ECG, *Electrocardiogram;* IVC, *inferior vena cava;* RF, *radiofrequency.*

Ablation of Typical Atrial Flutter

The aim of catheter ablation for typical atrial flutter is to create complete and stable bi-directional cavotricuspid isthmus block because terminating or interrupting the flutter is not enough as an endpoint and because recurrences are frequent if isthmus conduction persists. The ablation procedure involves (1) creation of linear lesion, (2) elimination of residual conducting gaps, and (3) verification of isthmus conduction block.

Creation of Linear Lesion

We use a 4-mm ablation catheter with an open irrigated tip for temperature-controlled, sequential, point-by-point RF applications at the isthmus between the IVC and the tricuspid annulus, although ablation catheters with an 8-mm tip have been shown to provide good results as well. A series of linear and contiguous point lesions need to be created to expeditiously achieve complete conduction block. The lesions may be delivered under fluoroscopic guidance, alone or supplemented by nonfluoroscopic navigation (e.g., the Biosense system), with or without the use of long sheaths for superior stability. During counterclockwise flutter, RF may be delivered point by point from the TV annulus on electrograms within the isthmus region coinciding with the center of the surface ECG flutter wave plateau, all the way from the TV annulus to the IVC edge. This ensures a lesion perpendicular to the advancing wavefront and allows catheter displacement to either side to be recognized by the altered timing of the recorded electrogram; for example, in case of lateral displacement, the electrogram coincides with the beginning of the surface ECG plateau, and in case of medial displacement, it coincides with the end of the plateau. During low lateral right atrial pacing in sinus rhythm, sequential RF may be similarly delivered at the 6 o'clock position in the left anterior oblique view in the isthmus on electrograms with a constant stimulus electrogram time from the TV annulus to the IVC edge.[21]

Merely delivering RF energy at a given location does not guarantee a transmural lesion; the lesion-making ability of RF varies

according to contact, local blood flow, delivered power, and myocardial thickness. During unidirectional activation in the atrial myocardium (e.g., in the isthmus during typical flutter or during pacing from the low lateral right atrium or from the ostium of the coronary sinus), a local transmural RF lesion of significant size (comparable with the distal bipole) often can be recognized by double potentials separated by an isoelectric interval; the second potential is produced by activation detouring around the lesion.[22]

The created lesion size depends on tissue heating, which, in turn, is determined by the current density over a given area. RF power, target temperature, or both may need to be manipulated to achieve transmural lesions at each delivery site. Conventional temperature-controlled RF delivery is subject to variations in local convective cooling, which limits the delivered power either by achievement of the target temperature, by coagulum formation and impedance rise, or by both. Irrigating the ablation electrode substantially reduces the electrode temperature and coagulum formation, thus permitting the delivery of desired (and relatively higher) mean RF power, irrespective of variations in convective cooling. This results in consistent electrogram changes, that is, splitting into double potentials. The use of irrigated-tip catheters with a relatively limited power ceiling (40 W) has been shown to be clinically effective and safe for typical flutter cases resistant to conventional catheter ablation and as a first-line strategy. A significant reduction in procedure and fluoroscopy durations is achieved using irrigated-tip catheters compared with conventional 4-mm tip catheters.[23]

Identification and Ablation of Residual Gaps

Because of variations in isthmus anatomy and the inability to create consistent continuous transmural lesions, isthmus conduction frequently persists despite anatomically sufficient ablation, flutter termination during RF delivery, or both. Locating and ablating residual gaps in the ablation line is therefore necessary. During typical atrial flutter, such residual gaps can be identified with local electrograms, with a single or a fractionated potential centered on or spanning the isoelectric interval of adjacent double potentials (Figure 93-3). This allows targeted ablation of flutter that recurs after previous ablation. The same approach has been used during pacing from either side of the isthmus, targeting single or fractionated potentials adjacent to double potentials and centered on their isoelectric intervals, with the aim of establishing a continuous corridor of double potentials with isoelectric intervals across the full width of the isthmus.[21]

Assessment of Isthmus Conduction

Termination of flutter during RF delivery is not a sufficient endpoint because in more than 50% of instances, conduction through the cavotricuspid isthmus persists, resulting in frequent recurrence.[24] Transient block or conduction slowing within the isthmus (or ectopics) may be enough to terminate flutter without eliminating the substrate. During pacing from one side of the ablation lesion, a delay in activation on the opposite side and an activation sequence demonstrating a 180-degree change in direction of activation on the other side have been used to diagnose isthmus block. This can be documented sequentially by using rove mapping and simultaneously with a duodecapolar electrode catheter during low lateral atrial or coronary sinus pacing. Local electrogram–based criteria (double potentials) have been shown to be highly sensitive markers of block in the cavotricuspid isthmus.[21]

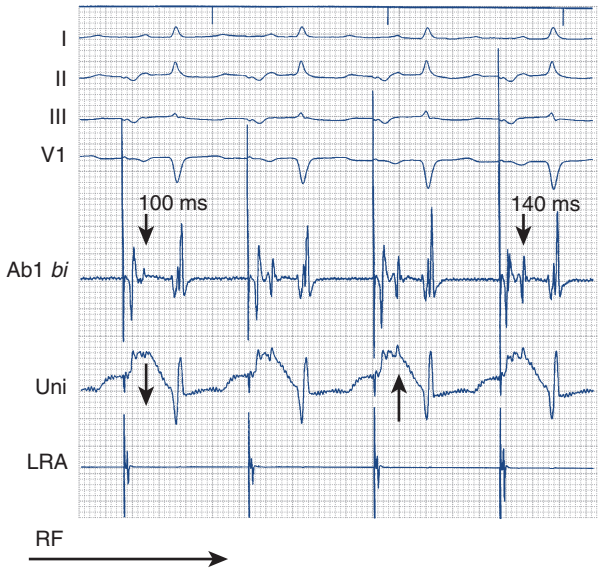

FIGURE 93-3 Ablation of the final gap in the cavotricuspid isthmus ablation line completes the block in a patient undergoing ablation for typical atrial flutter. A fractionated continuous electrogram is recorded from the distal bipole of the ablation catheter (*Ab1 bi*), which correlates with a multi-deflection negative unipolar electrogram (*uni*) and radiofrequency (*RF*) delivery at this site splits the electrograms into two components: the second with a prolonged timing of 140 ms and a completely positive deflection in the unipolar electrogram, together indicating the achievement of complete isthmus block. *LRA*, Low right atrium.

A high recurrence rate was observed when flutter termination and noninducibility were considered sufficient endpoints, but the demonstration of isthmus block with local electrogram-based criteria—mapping double potentials supplemented with differential pacing—has reduced recurrence rates to less than 5%.

The sensitivity of double potential–based local electrogram criteria derives from being assessed on the linear lesion, and their specificity relates to relative independence from catheter positioning as well as from posterior intercaval conduction. The presence of posterior intercaval conduction may shorten the timing to the second component of double potentials but cannot produce false-positive gap electrograms on the ablation line. The activation detour suggestive of isthmus block can be demonstrated by standard multi-electrode multi-catheter techniques, basket catheters, electroanatomic sequential mapping, and noncontact mapping.

The choice of pacing site is instrumental in maximizing the sensitivity and specificity for complete isthmus block and must be as close as possible to the line of block to maximize the sensitivity for detecting slow conduction through the line and avoid it being concealed by the wavefront going around the lesion with a relatively shorter conduction time. This can be easily assessed by the stimulus to the first potential time (st-DP1) on the line; an st-DP1 of 30 ms or less is considered optimal.[25] Isthmus block that produces a change in the surface ECG P wave during pacing is greater when pacing from the low lateral right atrium compared with pacing from the coronary sinus ostium. Left atrial activation from the coronary sinus input acts as a surface ECG amplifier of P-wave change during pacing from the low lateral right atrium.

Differential pacing assesses the response of local electrograms (including double and fractionated potentials) to advancing toward or withdrawing the pacing site away from the ablation line.[25] If activation on both sides of the line (indicated by local double potentials) is directly linked by a conducting gap, withdrawing the pacing site will increase the activation time to both sides and by roughly the same magnitude. However, if no conducting gap across the line exists, withdrawing the pacing site will certainly increase the activation time upstream of the line. It will either shorten the activation time on the other side of the line or leave it unchanged, but it will not increase it.

The demonstration of functional linking by changing the pacing sites depends on the relative conduction times to both flanks of the ablation line and therefore will be affected by the pacing position, relative conduction velocities, length of the activation detour, and intervening areas of slow conduction or block that affect only one of the two pacing positions. The pacing catheter should be positioned as close as possible to the lesion line and the magnitude of displacement of the pacing position limited (15 mm) so that the stimulus to the first potential time is approximately 40 ms during distal pacing and 60 ms during proximal pacing. To detect very slow conduction through the isthmus (e.g., ≤0.05 m/s), both pacing sites may need to be even closer to the ablation line, that is, with shorter stimulus to the first potential times. Very slow conduction through the isthmus, however, cannot be ruled out by any technique or criteria.

Differential pacing is best used as a complement to local electrogram assessment to evaluate double or triple potentials or fractionated potentials without having to move the recording ablation catheter from the recording site or perform supplemental mapping. A gap-like electrogram, if validated to represent persistent conduction through the ablation lesion (by differential pacing), requires prompt ablation. Because very slow conduction ultimately cannot be excluded, the gold standard for complete (and stable) isthmus conduction block is only the absence of recurrence of typical atrial flutter.

Stable conduction block is necessary to avoid recurrence. The probability of conduction recovery across a composite lesion can be estimated by the number of constituent lesions (mean of 6 to 10 point lesions) multiplied by the individual probability of recovery. If the latter is estimated to be 2% (based on data from WPW ablation, the so-called *point ablation*), this works out to 12% to 20%. Recent data have indicated high rates of conduction recovery after the achievement of complete block (as also after the termination of flutter by RF delivery in the cavotricuspid isthmus). This mandates monitoring of the stability of isthmus conduction block after ablation. The exponential reduction in the incidence of recovery with time suggests an empirical cutoff for the duration of the monitoring period. An extended duration of monitoring (15 to 20 minutes at least) is compatible with the current low recurrence rates observed in our laboratory.[24]

The ablation of typical flutter, as described above, is very well tolerated, and few adverse effects have been reported. As a result, indications have been expanded so that RF catheter ablation is being offered to all patients with symptomatic and atrial flutter refractory to at least one drug. It may even legitimately be considered an alternative first-line therapy.

Indications for catheter ablation include the following:

- Recurrent or poorly tolerated typical atrial flutter
- Type IC (atrial fibrillation converted to typical atrial flutter under treatment with type I/III antiarrhythmic drugs)
- First episode of sustained typical flutter

Atypical Atrial Flutter

Macro–re-entrant ATs other than cavotricuspid isthmus–dependent atrial flutter are termed *atypical atrial flutter* (Box 93-4).

Box 93-4 Checklist for Catheter Ablation of Atypical Atrial Flutter

PRE-PROCEDURAL ASSESSMENT
1. Symptoms and clinical examination
2. Associated heart disease, atrial fibrillation
3. Previous heart surgery, previous catheter ablation
4. Anticoagulation
5. Transesophageal echocardiography

SETUP
1. Two multipolar (octapolar or decapolar) diagnostic catheters: right atrial free wall and coronary sinus
2. Rove mapping and ablation catheter (open tip, irrigated) in the left atrium by transseptal puncture

EVALUATION
1. Establish cavotricuspid independence:
   a. Cycle length in the right atrium < 60% of tachycardia cycle length
   b. Entrainment from the right atrial free wall (and, if necessary, cavotricuspid isthmus)
2. Localize atrium and region of interest:
   c. Activation mapping
   d. Entrainment mapping
3. Map reentry circuit:
   e. Three-dimensional activation mapping
   f. Entrainment mapping
4. Choice of target isthmus:
   g. Narrowest, safest, accessible isthmus

TECHNIQUE
1. Point-by-point or drag ablation in case of wide isthmus
2. Punctual ablation in case of narrow isthmus
3. Monitor
   a. Local double potentials
   b. Tachycardia cycle length
   c. Activation sequence
4. Tachycardia transformation
   a. Repeat assessment with activation and entrainment mapping
   b. Ablation of new isthmus if necessary

ENDPOINT
1. Tachycardia termination
   a. Verify noninducibility
   b. Conduction block in target isthmus
   c. Stability for 20-40 minutes

FOLLOW-UP
1. As for typical atrial flutter

Diagnostic Criteria

The diagnosis of atypical flutter is based on excluding cavotricuspid isthmus dependence for maintenance of the re-entry circuit. This is indicated by bi-directional activation of the isthmus from opposing directions during tachycardia resulting in collision or fusion. The recording of double potentials, separated by an isoelectric and constant interpotential interval through the full extent of the isthmus during tachycardia, also reflects the presence of isthmus block. The demonstration of stable isthmus conduction block during sinus rhythm is strong evidence of exclusion as is the demonstration by entrainment of the isthmus being out of the circuit. Entrainment mapping at non–right atrial locations—within the coronary sinus or in the left atrium—serves to elucidate their participation, and documentation of activation spanning the full re-entry cycle length in the right atrium provides support for the right atrium being the locus of the re-entry circuit.

Documentation of less than 60% of the cycle length in the right atrium and evidence of intermittent dissociation of the right atrial free wall from the tachycardia also support the diagnosis of left atrial re-entry.[26] Passive activation of the right atrium by septally originating wavefronts colliding on the right atrial free wall is also characteristic. However, conduction block in the cavotricuspid isthmus can mask the lower, septally originating wavefront.

Barriers in the Atria

Some form of fixed or functional central barrier is a prerequisite for re-entry. The wavefront of typical atrial flutter circulates around the posterior intercaval crista terminalis complex. Other naturally occurring barriers in the right atrium include the IVC and the SVC. Acquired barriers in the right atrium include surgical incisions or patches, as well as "mute" regions devoid of electrical activity of uncertain origin.[26,27] The role of functional activation inhomogeneities in the right atrium is unclear, although the crista terminalis region has been shown to permit conduction across it during sinus rhythm (as well as during certain forms of re-entry). Each of the above barriers or inhomogeneities—whether functional or fixed—can potentially support a re-entry circuit around it, provided that an appropriate trigger is present and the conditions of sufficient conduction times (wavelength) around it are met.

The left atrium has little evidence of a naturally present zone of block or slow conduction and certainly lacks the anatomic equivalent of a crista terminalis. Perhaps as a result, left atrial macro–re-entry in the absence of structural heart disease, surgery, or catheter ablation is far less common than typical atrial flutter. Left atrial flutter occurs in predominantly two situations: (1) as a sequel to ablation in the left atrium and (2) in subjects with left-sided structural heart disease.[26] Characteristically, most patients have more than one ECG arrhythmia morphology (hence circuit) of re-entry, correlating with the frequent demonstration of multiple loop re-entry. Anatomic obstacles such as the pulmonary veins or the mitral valve, buttressed centrally or laterally by linear ablation lesions, form the core of the circuit. Although these macro–re-entrant circuits are large in diameter (approximately 5 cm), other small (1- to 1.5-cm diameter) re-entrant circuits have been observed around a pulmonary vein ostium or an incomplete lesion at the pulmonary vein ostium.[28] In patients without prior left atrial ablation, macro–re-entrant circuits frequently are anchored around relatively large electrically silent areas, in addition to anatomic obstacles such as the pulmonary veins and the mitral valve. Although the exact nature of these "mute zones" remains to be determined, infarction or a myocarditic inflammatory scar have been evoked. Coronary angiography has, however, failed to show an appropriately located coronary occlusion (or lesion), and in the absence of other evidence of myocarditis, other, perhaps hemodynamic (related to elevated pressures), reasons may be operative.

Clinical Clues

History of a surgical procedure involving an atriotomy (other than cannulation atriotomies), a successful ablation of the cavotricuspid isthmus with demonstrated complete conduction block, or an ECG tracing obviously different from typical flutter should suggest the diagnosis of atypical flutter. Clockwise cavotricuspid isthmus–dependent flutter as well as, more rarely, counterclockwise isthmus-dependent flutter with an atypical ECG tracing (probably because of altered left atrial activation)—pseudo–atypical flutter—should be excluded.

Left atrial flutters should be suspected in a patient with structural heart disease affecting the left side of the circulation—particularly if the ECG exhibits low voltages, especially in the limb leads. Lead V1 commonly shows a dominantly or completely positive deflection, reflecting passive activation of the right atrium. Pseudo–typical flutter is a left atrial flutter resembling typical flutter in morphology and requires intracardiac mapping for diagnosis.

Intracardiac Mapping

In the electrophysiology lab, a stable and sustained arrhythmia allows the sequential acquisition of data—both anatomic and electrical—to enable the reconstruction of a three-dimensional activation map. Entrainment mapping (which is a sequential data acquisition technique) is also very useful. However, an arrhythmia with varying activation sequences, conduction times, or both does not lend itself to sequential analysis; accordingly, data acquired simultaneously from multiple sites (by multi-electrode catheters) must be used to determine the chamber of interest. Detailed three-dimensional electroanatomic mapping can be pursued after cardioversion in sinus rhythm to locate fixed barriers. In patients without inducible arrhythmia, the same strategy may also have to be followed.

Ideally, the aim of mapping is to determine the complete re-entrant circuit. This is defined as the spatially shortest route of unidirectional activation returning to the site of earliest activation and encompassing the complete cycle length of the tachycardia in terms of activation timing. Double-loop or multiple-loop re-entry is defined by the presence of more than one activation front fulfilling the above conditions. Limited mapping may lead to an incomplete loop being mistaken for a complete one because of software interpolation. High-density mapping or entrainment mapping can clarify this situation by documenting wavefront collision and long postpacing intervals, respectively. Multiple fixed barriers produce multiple isthmuses, and recurrence may result from a completely different arrhythmia or transformation to a circuit dependent on another of the multiple isthmuses.

The tachycardia behavior can also provide some clues as to its nature. A single-loop tachycardia with a fixed barrier as its core typically remains stable and unchanged during catheter manipulation and can even be difficult to pace terminate. Mechanical "bump" termination (without extrasystoles) suggests a restricted and relatively fragile isthmus. A change in ECG morphology without change in cycle length may be caused by a transformation of a multi-loop tachycardia by interruption of one loop or by a change in bystander activation sufficient to be visible

on the surface ECG or in activation of the same circuit in the opposite direction. A significant change in activation within the circuit distinguishes between circuit transformation or antidromic activation around the same circuit and changes in bystander activation. Similarly, variations in cycle length can suggest variations in activation pathways resulting from circuit transformation or simply changes in conduction time, the latter usually manifesting as cycle length alternans. ECG changes may not occur despite changes in activation sequences because of distance from the recording electrodes or insufficient electrically active tissue.

Critical isthmuses can be identified during sustained stable re-entry by activation mapping supplemented by entrainment mapping. However, it is not possible to identify a critical isthmus during sinus rhythm. Significantly large (in two dimensions) areas devoid of electrical activity can be easily recognized as electrical scars, provided that catheter contact is verified, but narrow lines of block (thinner than the recording field of clinically used bipoles) may easily be missed unless the conduction delay across them is maximized by the appropriate choice of optimal pacing sites. It may be necessary to perform mapping during more than one form of activation, for example, during both proximal coronary sinus pacing and low lateral right atrial pacing to identify the majority of potential isthmuses.

In the absence of sustained stable re-entry (allowing sequential mapping), it is important to evaluate the potential of scars or barriers to support re-entry. In a study of 22 consecutive patients with AT after surgical closure of an atrial septal defect, three-dimensional electroanatomic mapping of the right atrium was performed during stable sustained tachycardia and in sinus rhythm to study the properties of electrical scars.

The characteristics of the line of block resulting from the surgical atriotomy on the right atrial free wall played a significant role in determining the kind of arrhythmia circuit that developed.[29] A right atrial free wall peri-atriotomy re-entry circuit was more likely to occur if the scar was relatively long, resulting in a restricted isthmus bounded inferiorly by the IVC, and if the scar was vertical or oblique and relatively anteriorly placed. Nearly all these patients with a free wall circuit also had peri-tricuspid re-entry. Isolated peri-tricuspid re-entry was observed when no electrophysiological evidence of a right atrial free wall atriotomy was found or if this scar was too small or posteriorly placed. If the right atrial free wall atriotomy is long enough to extend to the IVC inferiorly, thus eliminating the inferior isthmus, peri-atriotomy re-entry cannot occur. It is not clear whether the near-universal presence of peri-tricuspid re-entry in this cohort of patients is caused by diffuse substrate alterations or results from the presence of a (posteriorly placed) atriotomy buttressing the often-functional block zone of the crista terminalis.

These data suggest that in a right atrial free wall line of block, even if sustained re-entrant arrhythmias are not inducible in the electrophysiological laboratory, both isthmuses (inferior end of scar to IVC and the cavotricuspid isthmus) should be ablated with the endpoint of complete and stable block to eliminate the occurrence of both peri-tricuspid as well as peri-atriotomy flutter.

Patients with pronounced hemodynamic loads, for example, after corrective or palliative surgery such as the Fontan procedure, have the substrate for re-entry in the form of small channels or isthmuses in the altered milieu of a low-voltage area of the right atrial free wall.[30] It may be difficult to distinguish multiple small channels within this low-voltage area without three-dimensional mapping, and mapping during different rhythms may be necessary to detect as many potential isthmuses as possible. Despite the frequent presence of surgical incisions in the septum, re-entry in this anatomic location is infrequent.

The remaining minority of atypical right atrial re-entrant tachycardias include the so-called *peri-crista re-entry* as well as small and functional re-entry circuits in various parts of the right atrium. It is likely that block within the cavotricuspid isthmus facilitates the occurrence of this form of re-entry. Mapping during re-entry is useful to document the circuit, and RF delivery at the site of conduction across the crista region of block or more medially between the ostium of the coronary sinus and the posterior intercaval region can be effective.

Left Atrial Substrate

Re-entry within the left atrium typically is related to scars from surgery or catheter ablation or is associated with structural heart disease. A detailed account of the surgical or catheter ablation procedure is useful to allow optimal mapping within a particular region of interest. Gaps of persisting conduction across linear or isolating lesions are the typical substrate of isthmuses and can be easily recognized by fractionated "diastolic" electrograms coinciding with synchronous isoelectric intervals in all 12 ECG leads.[28] These isthmuses usually support small-diameter (1 to 1.5 cm) re-entrant circuits. Less frequently, large re-entrant circuits depend on such small, slow conducting isthmuses. Large circuits typically are the result of wide isthmus re-entry around anatomic barriers or anatomic plus lesion-based barriers. In our experience, they are typically associated with severe left atrial dilation, linear lesions in the left atrium, or both. Multiple linear lesions in the left atrium frequently are associated with the greatest likelihood of multi-loop re-entry.

Ablation Procedure

Ideally, detailed mapping is necessary to determine the full re-entrant circuit to plan and achieve interruption by ablation. An accurate knowledge of the anatomy is very useful in estimating the anatomic extent of isthmuses. Three-dimensional electroanatomic mapping, which combines electrical activation in an anatomic setting, is the strategy of choice. It is often possible to limit mapping to the detection of the critical isthmus, estimate its width, and target it by ablation to eliminate the tachycardia even without knowledge of the complete circuit. It may be possible to eliminate some circuits by using double potential and entrainment mapping, usually the subset of right atrial free wall macro–re-entries, in which the position and extent of the atriotomy scar are well standardized. Once the circuit has been mapped, the safest, narrowest, and most convenient access to the isthmus is chosen for ablation. Entrainment mapping is helpful in choosing between various isthmuses. The anticipated difficulty of creating a complete conduction block across the chosen site also needs to be considered; areas of catheter instability caused by mechanical contraction (e.g., the right atrial free wall in the region of the tricuspid valve annulus) or regions of thick tissue (particularly in patients with congenital heart disease before or after surgical repair) render ablation that much more difficult.

The width of the targeted isthmus, which significantly affects both the duration of the procedure and its success rate, is commonly estimated by anatomic and electrophysiological landmarks. Local electrograms, including double potentials indicating a line of block and long-duration fractionated electrograms suggesting a protected corridor of slow conduction, can be particularly useful. Single-deflection electrograms suggest a wider and

relatively large ablation target. Electrophysiological signals are a necessary supplement to anatomic guidance because the electrically active isthmus may be smaller than an anatomically defined one. High-density mapping can reveal that a given segment of the circuit is, in fact, functionally narrower than the anatomy would suggest by demonstrating the presence of lateral boundaries in the form of zones of block.

With the same principles as for typical atrial flutter, RF energy can be delivered sequentially point by point to span the targeted segment or by dragging during continuous energy administration. Lesion contiguity and continuity depend on the coalescence of multiple transmural lesions, best ensured by documenting the breakdown of the target electrogram (at each site) into double potentials and continuing RF delivery at this point for approximately 30 to 40 seconds more to ensure a stable lesion. An irrigated-tip catheter is preferable to permit the delivery of higher power necessary for consistent transmural lesions and to avoid generating char.

Assessment of Outcome

During the delivery of RF lesions, the tachycardia may terminate, or its cycle length may increase, transiently or permanently. Both phenomena indicate that the delivered lesions have slowed conduction within the re-entry circuit and should be followed by continuation of RF or extension of the lesion to achieve complete conduction block.

The inability to re-induce the original arrhythmia is a clearly desirable endpoint but may reflect only conduction delay or variations in autonomic parameters. Complete stable conduction block within the re-entry path is the most objective endpoint for ablation of large-diameter re-entrant arrhythmias, as for accessory AV connections, or typical atrial flutter. The achievement of complete conduction block clearly correlates with lower rates of recurrence in the population with re-entrant tachycardias in the left or right atrium.

An inversion of the activation sequence downstream of ablation, local electrogram changes, or both are characteristic of conduction block in the targeted isthmus. The sensitivity of assessing conduction block depends on the choice of pacing site as for assessment of cavotricuspid isthmus conduction.

To ensure the stability of the block, re-verification is advisable after a waiting period; because careful three-dimensional mapping may be time consuming, an initial assessment by local electrogram criteria followed approximately 15 to 20 minutes later by mapping is an effective and time-saving strategy.

The subset of small re-entrant circuits requires careful mapping for their recognition and can be difficult to distinguish from non–re-entrant arrhythmias. Because of their characteristic dependence on a fragile, narrow, and slow-conducting isthmus (which gives rise to fractionated low-amplitude electrograms coinciding with 12-lead isoelectric intervals), they are relatively easy to ablate with one or few RF current applications. However, their small circuit dimensions render it difficult to use activation mapping to demonstrate block through the ablated isthmus. Tachycardia noninducibility is the only available endpoint.

The different re-entrant circuits encountered in the right and left atria require ablation to be individually tailored. Multiple isthmuses may require ablation. An empiric linear lesion—Maze-like solution, including multiple lesions to block all anatomic isthmuses—may be necessary, although with current ablation techniques, it is difficult to achieve conduction block across long linear lesions. At present, success rates for ablation of typical atrial flutter remain significantly higher than for atypical flutter. When keeping in mind the complexity of atypical flutter, this is perhaps not so difficult to understand.

Symptomatic and drug-refractory atypical flutters usually are considered for ablation, although the threshold typically is lower in the presence of tachycardiomyopathy, postoperative congenital heart disease, or left ventricular dysfunction. However, the complexity of mapping and ablation means that the experience and success rates of individual centers should be considered.

- Indications for catheter ablation include the following:
- Poorly tolerated or antiarrhythmic drug–refractory symptomatic atypical flutter
- Presumed tachycardiomyopathy

Non–re-entrant Atrial Tachycardias

This arrhythmia subset must be distinguished from re-entrant AT because the approach to successful ablation is clearly different (Box 93-5).

The major difference is a radial pattern of activation during these tachycardias.[31] For practical purposes, the atria, unlike the ventricles, can be considered to be two dimensional. The absence of electrical activity spanning a significant part of the cycle length indicates a diastolic pause characteristic of abnormal impulse generation resulting from triggered activity or abnormal automaticity. This deduction presupposes an adequate and complete

Box 93-5 Checklist for Catheter Ablation of Non–Re-entrant Atrial Tachycardia

PRE-PROCEDURAL ASSESSMENT
1. Symptoms, clinical examination
2. TEE in case of associated atrial fibrillation or suspected left atrial origin

SETUP
1. Two multipolar diagnostic catheters: RA free wall and coronary sinus
2. Rove mapping and ablation catheter
3. Trans-septal access to be anticipated based on ECG findings
4. Unipolar electrograms from ablation catheter useful

EVALUATION, TECHNIQUE
1. Sustained tachycardia is critically important:
   a. Burst or programmed atrial stimulation
   b. Isoprenaline infusion or combinations
2. Localization:
   a. Activation mapping: earliest atrial activation
   b. Unipolar QS morphology
3. Ablation:
   a. Point ablation at earliest activation site
   b. Segmental or circumferential isolation (great veins only)
4. Endpoint:
   a. Tachycardia termination and noninducibility
   b. Isolation in sinus rhythm in case of great vein origin (SVC, persistent LSVC or pulmonary veins)
5. Follow-up:
   a. Clinical evaluation
   b. Event monitor if needed

TEE, *Transesophageal echocardiography;* RA, *right atrial;* ECG, *electrocardiogram;* SVC, *superior vena cava;* LSVC, *left superior vena cava.*

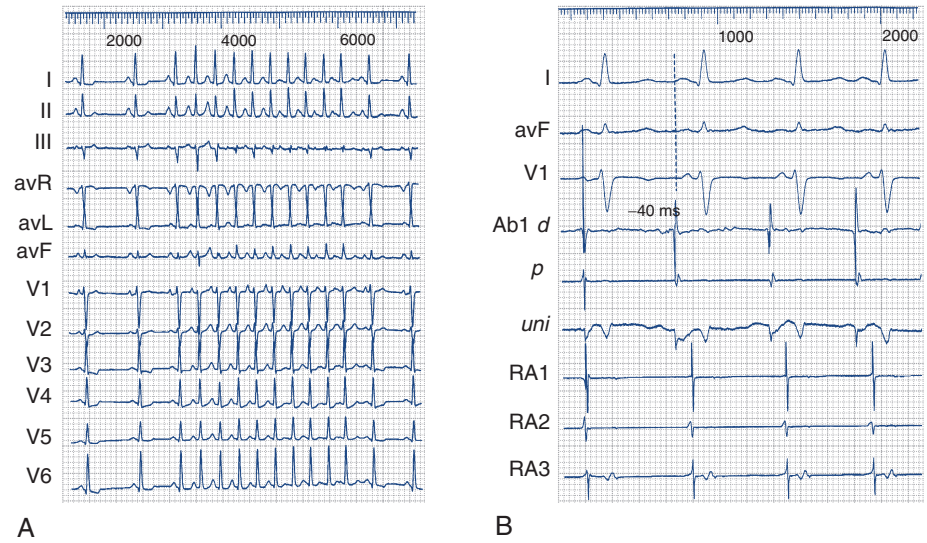

FIGURE 93-4 Non–re-entrant left atrial tachycardia that exhibited characteristic warm-up and stop-start behavior. *Left*, A 12-lead electrocardiogram. *Right*, The successful ablation site, which was at the junction of the right superior pulmonary vein with the right inferior pulmonary vein. The first is a sinus beat; the remaining are atrial tachycardia beats. Note the characteristic distal (*d*) to proximal (*p*) activation sequence in the two bipoles of the ablation catheter (*abl*) along with a sharp QS-type morphology of the unipolar atrial electrogram (*uni*).

exploration of the endocardium, including the great thoracic veins; the coronary sinus should not be considered a surrogate for the left atrium. Mapping reveals radial atrial activation confined to electrical systole, that is, coinciding with the surface ECG P wave. The sequence of activation of the two bipoles of the rove mapping and ablation catheter can be useful; a distal-to-proximal activation persisting with catheter advancement indicates a vector originating from that direction, whereas a proximal-to-distal activation sequence suggests that the wavefront originates from the direction of the proximal bipole. An iterative mapping sequence documenting the transition from the former to the latter activation direction is characteristic of the source of radial activation and requires returning to the initial catheter position.

The inference of a non–re-entrant mechanism is further strengthened by a pattern of arrhythmia bursts with cycle length irregularity, warm-up behavior, or both, unlike a stable re-entrant mechanism (see Figure 93-4). Identical activation sequences for the first and subsequent beats of the tachycardia further support a non–re-entrant mechanism. If the arrhythmia is sustained, demonstration of entrainment is supportive of re-entry. If the re-entry circuit is small, radial activation of the rest of the atria cannot be distinguished from a non–re-entrant mechanism. Therefore recognition of small re-entry circuits depends on the mapping resolution. If the arrhythmia source is confined to an unmapped area (e.g., in the left atrium or within the SVC), the arrhythmia mechanism may be difficult to recognize. Unlike re-entry, pacing maneuvers—typically overdrive—suppress the non–re-entrant tachycardia without demonstrating the classic features of entrainment with progressive fusion. In the experimental laboratory, termination of the tachyarrhythmia by sectioning a critical part of the circuit is a highly specific evidence of re-entry, but clinically, the difficulty in consistently achieving a completely transmural incision such as a lesion by RF delivery reduces the value of this criterion.

The surface ECG with a clearly visible P wave in all 12 leads is highly valuable for localizing the origin of the tachycardia. A clear isoelectric baseline separating individual P waves is compatible with non–re-entrant mechanisms; however, some very rapid non–re-entrant tachycardias may not exhibit a baseline. P-wave polarity in leads V1, I, and aVL is important in assigning the atrium of origin.[32] A late positive, dominantly positive, or completely positive P wave in lead V1 indicates left atrial origin.[33] Septally originating tachycardias exhibit narrower P waves, and the frontal plane axis is helpful as it indicates a superior or inferior origin. Localization can be further refined with the help of pace-mapping by using both the surface ECG as well as patterns of intracardiac activation.

Multi-catheter activation mapping allows quicker assessment of approximate localization, although the selection of an appropriate ablation site still requires careful mapping and sufficient arrhythmia. The optimal ablation site is one with the earliest bipolar and unipolar activation, although the issue of determining the early enough timing remains. A timing preceding the surface ECG onset of the P wave with a QS morphology on the unipolar electrogram and that does not precede bipolar activation at that site is usually necessary (see Figure 93-4).

Sites on or close to the inter-atrial septum as well as the posterior mitral annulus may need to be mapped from more than one side to choose the better site—the former from the right and the left atria and the latter from the endocardium as well as the epicardium (coronary sinus).

In most instances, focal ablation suffices and arrhythmia elimination and noninducibility are the only endpoints. Venous tachycardia (which can be either re-entrant or non–re-entrant) is a specific situation, particularly a pulmonary vein tachycardia, which can even trigger and maintain AF. An expeditious solution is to disconnect the vein from the left atrium (right atrium in case of the SVC), making sure that the disconnection is proximal to the source of the arrhythmia.[34] This endpoint is useful even with arrhythmia that is difficult to induce.

The role of three-dimensional mapping systems in understanding and ablating these arrhythmias is unclear. Systems that rely

on sequential data acquisition require sufficient reproducible arrhythmia, whereas simultaneous data-acquiring techniques such as multi-electrode basket arrays or the Ensite noncontact system have an advantage if fewer arrhythmias are available for analysis. The resolution of noncontact mapping systems is, however, not good enough at present to allow selection of the ablation site in the absence of ambient arrhythmia.

Indications for catheter ablation include the following[35]:

- Recurrent symptomatic atrial tachycardia
- Incessant atrial tachycardia

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CHAPTER 94

Catheter Ablation for Atrial Fibrillation: Clinical Techniques, Indications, and Outcomes

Pasquale Santangeli, Luigi Di Biase, J. David Burkhardt, Javier Sanchez, Rodney Horton, G. Joseph Gallinghouse, Shane Bailey, Jason D. Zagrodzky, and Andrea Natale

The prevalence of atrial fibrillation (AF) in Western countries continues to rise, with 30 million patients estimated to be affected by 2050 across the United States and Europe alone.[1] Catheter ablation of AF is currently an established treatment to achieve cure in a substantial proportion of patients.[2] Multiple randomized clinical trials have demonstrated a clear superiority of catheter ablation over antiarrhythmic drug therapy to achieve lasting sinus rhythm maintenance, improve symptoms and quality of life, and possibly reverse the AF-associated risk of thromboembolic complications.[3-5]

To achieve such important outcomes and develop highly effective ablation techniques, intense research has been directed toward the discovery and validation of electrophysiological and anatomic targets fundamental for triggering and maintaining the arrhythmia.[6-10]

After the pivotal demonstration that focal discharges from the pulmonary veins (PVs) are implicated in the initiation of AF, empirical PV isolation has been performed with the highest procedural success in patients with paroxysmal AF, in whom spontaneous PV firing is frequently the only trigger for AF paroxysms.[4,9,11] Patients with AF of longer duration, such as those with persistent and longstanding persistent AF, may require targeting additional sites for successful ablation, including the entire left atrial posterior wall and complex fractionated atrial electrograms (CFAE).[12,13] Moreover, targeting other sites of AF initiation has been demonstrated to offer incremental benefit to patients presenting for repeat ablation procedures.[14]

This chapter summarizes state-of-the-art AF ablation techniques, discussing the evidence underlying different approaches in different patients. The present and future contributions of remote navigation systems and other ablation technologies is also reviewed.

Patient Selection and Pre-procedural Management

The 2011 edition of the American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) guidelines for the management of AF gives a class I indication with the highest level of evidence to catheter ablation in patients with symptomatic paroxysmal AF who have not responded to treatment with an antiarrhythmic drug.[15] Of note, updated guidelines have also introduced new recommendations for catheter ablation in patients with persistent AF, significant left atrial dilation, and left ventricular dysfunction (Tables 94-1 to 94-3).[15-21] Evidence suggests that catheter ablation is successful in patients not yet included in guideline recommendations, such as those with previous cardiac surgery or valvular heart disease, and subgroups such as older adults and women (Table 94-4).[22-30] Accordingly, catheter ablation should be offered to nearly all patients with symptomatic drug-refractory AF.

In our institution, all patients are required to undergo ablation under therapeutic warfarin, which is initiated in an outpatient setting at least 2 months before the scheduled procedure. All patients receive weekly international normalized ratio (INR) monitoring during the 4 to 6 weeks preceding the procedure with a target INR of 2 to 3. Pre-procedural transesophageal echocardiography (TEE) is performed only in patients showing subtherapeutic INR values in the month before the procedure. Patients who demonstrate INR values consistently above 2 in the month before the procedure directly undergo ablation.

This approach has been demonstrated to decrease peri-procedural complications compared with warfarin discontinuation and bridging with heparin.[31] In a large cohort study, including 6454 patients undergoing ablation in nine different centers, 2488 underwent ablation with an 8-mm ablation catheter and pre-procedural warfarin discontinuation (group 1), 1348 underwent ablation with an open irrigated catheter and pre-procedural warfarin discontinuation (group 2), and 2618 underwent ablation with an open irrigated catheter without pre-procedural warfarin discontinuation (group 3). Overall, peri-procedural thromboembolic complications occurred in 39 (0.6%) patients, with a rate of 1.1% in group 1 and 0.9% in group 2. Of note, none in group 3 had peri-procedural thromboembolism (Figure 94-1). These data also support the finding that pre-procedural TEE does not add much if therapeutic INR is present on the day of the procedure and has been verified every week in the month preceding the ablation.

Importantly, the anticoagulation strategy of ablation with a therapeutic INR was confirmed to be a strong and independent

Table 94-1 Current Recommendations for Catheter Ablation of Atrial Fibrillation

CLINICAL SCENARIO	CLASS OF RECOMMENDATION	LEVEL OF EVIDENCE
Symptomatic paroxysmal AF, failed treatment with an AAD	I	A
Symptomatic persistent AF	IIa	A
Symptomatic paroxysmal AF, significant left atrial dilation or LV dysfunction	IIb	A

AAD, *Antiarrhythmic drug;* AF, *atrial fibrillation;* LV, *left ventricular.*

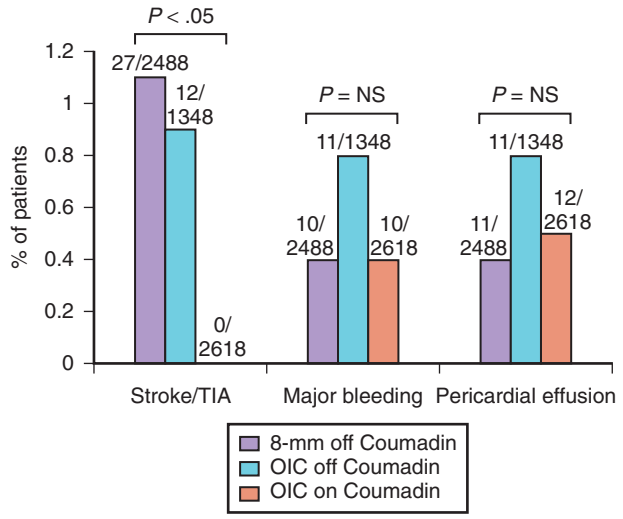

FIGURE 94-1 Complications of radiofrequency catheter ablation of atrial fibrillation according to the peri-procedural anticoagulation strategy adopted. *TIA*, Transient ischemic attack; *8-mm*, 8-mm nonirrigated ablation catheter; *OIC*, open irrigated ablation catheter; *off/on Coumadin*, peri-procedural discontinuation or maintenance of therapeutic oral anticoagulant therapy with warfarin (Coumadin). *P*, from multiple comparison between OIC on Coumadin and 8-mm and OIC off Coumadin. *(Modified from Di Biase L, Burkhardt JD, Mohanty P, et al: Periprocedural stroke and management of major bleeding complications in patients undergoing catheter ablation of atrial fibrillation: The impact of periprocedural therapeutic international normalized ratio,* Circulation *121:2550–2556, 2010.)*

predictor of lower peri-procedural thromboembolic events at multivariable analysis (odds ratio, 0.54; 95% confidence interval, 0.32 to 0.89; $P = .017$). With regard to bleeding, the pooled rate of major bleeding complications (e.g., bleeding requiring interventions, including transfusions, hemopericardium, hemothorax, and retroperitoneal bleeding) and pericardial effusion in patients who discontinued warfarin before the ablation procedure (groups 1 and 2) was 1.1%, whereas in group 3 it was 0.8% (see Figure 94-1).[31]

In our institution, all patients undergoing AF ablation are type matched and cross-matched; packed red blood cells and fresh frozen plasma are made available for infusion in case of

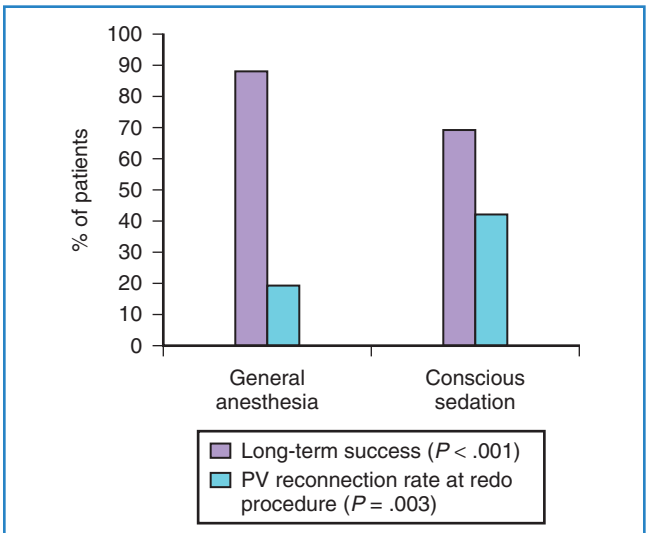

FIGURE 94-2 Impact of general anesthesia on catheter ablation success rate at a mean follow-up of 17 ± 8 months and rate of pulmonary vein (*PV*) reconnection at repeat procedure. *(Modified from Di Biase L, Conti S, Mohanty P, et al: General anesthesia reduces the prevalence of pulmonary vein reconnection during repeat ablation when compared with conscious sedation: Results from a randomized study,* Heart Rhythm *8:368–372, 2010.)*

hemorrhagic complications under therapeutic INR. If the pre-procedural INR is above 3.5, we partially reverse the anticoagulant effect with one to two units of fresh frozen plasma.

The anesthesia protocol adopted during ablation can affect the procedural results. In a randomized trial, 257 consecutive patients undergoing the first AF ablation were allocated to general anesthesia (n = 129) or conscious sedation (n = 128).[32] General anesthesia was initiated with propofol (2 mg/kg) and fentanyl (1 to 2 μg/kg), followed by a neuromuscular blocking agent (usually rocuronium 0.6 to 1 mg/kg) and by endotracheal intubation, with intermittent positive-pressure ventilation. Conscious sedation was obtained with fentanyl or midazolam. At 17 ± 8 months of follow-up, 88 (69%) patients assigned to conscious sedation were free of atrial arrhythmias off antiarrhythmic drugs compared with 114 (88%) patients randomized to general anesthesia ($P < .001$) (Figure 94-2). 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 ($P = .003$).[32] Therefore current evidence supports the adoption of general anesthesia or other strategies to achieve better catheter stability, such as jet ventilation.[33]

Techniques and Results of Ablation in Paroxysmal Atrial Fibrillation

Pulmonary Vein Isolation

PVs are the trigger site for paroxysmal AF in the majority of patients. Over the years, catheter ablation of PV triggers has undergone a profound evolution. Initial attempts at focal PV ablation involved longitudinal mapping of triggers of AF in the PVs and focal ablation.[11,34,35] The clinical outcome of such an approach,

Table 94-2 Randomized Controlled Trials on Catheter Ablation of Atrial Fibrillation

REFERENCE	NO. PATIENTS	INCLUSION CRITERIA	KEY EXCLUSION CRITERIA	ABLATION TECHNIQUE	ENDPOINT	FOLLOW-UP (mo)	% PAF	SUCCESS RATE (RFCA VS. CONTROL)	NOTES
Krittayapong et al, 2003[91]	30	Drug-refractory AF >6 mo	Valvular heart disease	CPVA, MIL, CTIL, RA linear	Freedom from AF at 12 mo	12	67	78.6% vs. 40%	Amiodarone controlled trial
Wazni et al, 2005[4]	70	Monthly symptomatic AF	h/o AFL and heart surgery	PVAI	Freedom from AF/AT at 12 mo	12	96	87% vs. 37%	First-line therapy vs. IC AADs or amiodarone controlled trial
Stabile et al, 2005[92]	137	Drug-refractory AF	LVEF ≤35%, LA diameter >6 cm, h/o heart surgery	CPVA, MIL, CTIL	Freedom from AF/AT at 12 mo	12	67	55.9% vs. 8.7%	Amiodarone controlled trial
Oral et al, 2006[93]	146	AF >6 mo	LA diameter >5.5 cm, valvular heart disease	CPVA, LA roof, MIL	Freedom from AF/AT at 12 mo	12	0	74% vs. 58%	Amiodarone controlled trial
Pappone et al, 2006[94]	198	Drug-refractory AF >6 mo	LA diameter >6.5 cm, LVEF <35%, valvular heart disease	CPVA, MIL, CTIL	Freedom from AF/AT at 12 mo	12	100	93% vs. 35%	Flecainide, sotalol, or amiodarone controlled trial
Calo et al, 2006[95]	80	Drug-refractory NPAF	Not reported	CPVA, MIL, CTIL, PICL, SVCL	Freedom from AF at follow-up	14	0	85% vs. 61%	LA vs. LA + RA ablation
Jais et al, 2008[96]	112	Drug-refractory AF ≥6 mo	Prior AF ablation	PVAI, CTIL, LA linear discretional	Freedom from AF/AT at 12 mo	12	100	89% vs. 23%	AAD controlled trial
Khan et al, 2008[20]	41	NYHA II/III HF patients, LVEF ≤40%	h/o heart surgery	PVAI	Change in LVEF, distance at 6MW test, MLWHF score	6	52	LVEF 35% vs. 28%; 6MW 340 m vs. 297 m; MLWHF 60 vs. 82	AV node ablation with biventricular PM as control group
Wilber et al, 2010[5]	167	>3 drug-refractory AF episodes in <6 mo	LVEF <40%, h/o ablation, cardiac surgery, valvular heart disease	PVAI, CTIL and LA linear discretional	Protocol-defined treatment failure*	9	100	66% vs. 16%	AAD controlled
Packer et al, 2010[97]		≥2 drug-refractory AF ≥1 h + risk factors†	Ineligible for RFCA or medical Rx	PV isolation + adjunctive (discretional)	Freedom from AF/AT at 12 mo	12	32	61% vs. 38%	RFCA vs. rate or rhythm control Rx
Packer et al, 2010[80]	245	>2 drug-refractory AF episodes in <2 mo	NR	Cryoballoon PV isolation	Freedom from AF at follow-up	12	100	69.9% vs. 7.3%	AAD controlled

6MW, Six-minute walk; AADs, antiarrhythmic drugs; AF, atrial fibrillation; AT, atrial tachycardia; CPVA, circumferential pulmonary vein ablation; CTIL, cavotricuspid isthmus line; AFL, atrial flutter; h/o, history of; HF, heart failure; LA, left atrial; LVEF, left ventricular ejection fraction; MIL, mitral isthmus line; MLWHF, Minnesota Living With Heart Failure questionnaire; NPAF, nonparoxysmal AF; NYHA, New York Heart Association; PAF, paroxysmal AF; PICL, posterior intercaval line; PM, pacemaker; PVAI, pulmonary vein antrum isolation; RA, right atrial; RFCA, radiofrequency catheter ablation; Rx, medical therapy; SVCL, septal vena cava line toward the fossa ovalis and isolation of the superior vena cava.

**Any documented symptomatic AF episode, repeat ablation >80 days after the initial ablation, absence of entrance block confirmed in all pulmonary veins at the end of the ablation procedure, or changes in specified drug regimen after a 3-month blanking period.*

†≥65 years of age or <65 years with ≥1 of the following: hypertension, diabetes, heart failure, prior cerebrovascular accident or transient ischemic attack, LA diameter >5 cm, LVEF ≤35%.

Table 94-3 Effect of Ablation for Atrial Fibrillation in Patients with Left Ventricular Dysfunction

TRIAL NAME	NO. PATIENTS	LVEF	NYHA CASS	FOLLOW-UP (MO)	% PAF	CHANGE IN LVEF (%)	RANDOMIZED
Hsu et al, 2003[19]	58	<45%	≥II	12	9	21*	No
Chen et al, 2004[16]	94	<40%	≥II	14	39	5†	No
Gentlesk et al, 2007[18]	67	≤50%	NR	6	70	14*	No
Khan et al, 2008[20]	41	≤40%	II-III	6	49	8*	Yes
Efremidis et al, 2008[17]	13	≤40%	I-IV	12	0	23*	No
Tondo et al, 2006[21]	40	<40%	≥II	12	25	14*	No

AF, *Atrial fibrillation;* LVEF, *left ventricular ejection fraction;* NYHA, *New York Heart Association;* PAF, *paroxysmal AF.*
*P < *.05*
†P = *not significant*

Table 94-4 Clinical Studies on Catheter Ablation for Atrial Fibrillation in Older Adults

TRIAL NAME	NO. PATIENTS	AGE (YEARS)	LVEF	FOLLOW-UP (MO)	% PAF	FREEDOM FROM AF (%)
Corrado et al, 2008[26]	174	>75	53% ± 7%	20 ± 14	55	73
Bhargava et al, 2004[25]	323	≤50 (n = 106) 51–60 (n = 114) >60 (n = 103)	56% ± 7.6% 53% ± 7.6% 51% ± 9.8%	14.9 ± 5.3 14.8 ± 5.4 14.7 ± 5.2	61 49 52	85 83 82
Kusumoto et al, 2009[28]	240	<65 (n = 91) 65–75 (n = 88) >75 (n = 61)	NR NR NR	12 12 12	76 66 34	94 84 61
Zado et al, 2008[30]	1165	<65 (n = 948) 65–74 (n = 185) ≥75 (n = 32)	<50% (n = 114) <50% (n = 13) <50% (n = 5)	27.6 ± 13.8 27.7 ± 13.6 23.8 ± 11.3	65 62 53	66 53 50
Hsieh et al, 2005[27]	37	72 ± 4	40 ± 10	52 ± 6	100	81
Nademanee et al, 2008[29]	635	67 ± 12	50 ± 13	27.9 ± 20.2	40	71

AF, *Atrial fibrillation;* LVEF, *left ventricular ejection fraction;* PAF, *paroxysmal AF; NR, not reported.*

which often required multiple electrical cardioversions during the ablation procedure because of the necessity of repeat induction of AF for mapping, was fairly disappointing.[11,34,35] Moreover, radiofrequency (RF) delivery within the PVs for focal ablation increased the risk of PV stenosis.[36,37]

The procedure evolved to target the ostium of the tubular portion of the PVs to isolate electrically the myocardial connections between the PV and the left atrium. This procedure is commonly referred to as *segmental ostial ablation*.[6] Also, with segmental ostial ablation, initial attempts were aimed at ablating only the PVs that had evidence of arrhythmogenic activity. However, it became rapidly appreciated that empirical isolation of all PVs was necessary to increase the procedural success because more than 85% of patients actually have multiple arrhythmogenic PVs.

Although the results achieved by segmental ostial PV ablation were good, symptomatic PV stenosis remained an important and frequent risk. Moreover, AF triggers localized in the more proximal antral region of the PV were not targeted with such strategy.

Therefore subsequent evolution of PV ablation involved further movement downstream in the atrium, targeting the so-called *PV antrum*.[8,37,38] To achieve PV antrum isolation (PVAI), 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 intracardiac echocardiography (ICE) or angiography.[8,9,37-40]

Our current approach consists of PVAI guided by a circular mapping catheter and ICE. This approach has been demonstrated to be superior to other ablation techniques in studies of direct comparison and is one of the most reproducible and standardized techniques to achieve PVAI because it has reproducible effectiveness in different institutions and with different operators (Figures 94-3 and 94-4).[2,38,41,42]

In particular, our experience with circumferential PV ablation guided by nonfluoroscopic three-dimensional mapping systems (CARTO, Biosense Webster, Diamond Bar, CA) has been disappointing.[37,41] In a previous study, we evaluated such an approach in 71 patients with early recurrence of AF after electrical cardioversion. After a mean follow-up of 29 months, 17% of patients had AF recurrences refractory to antiarrhythmic drug therapy, and 62% remained on antiarrhythmic drugs. These suboptimal results were associated with a rate of PV stenosis of 36%, which was severe in nearly one third of cases, and with a rate of

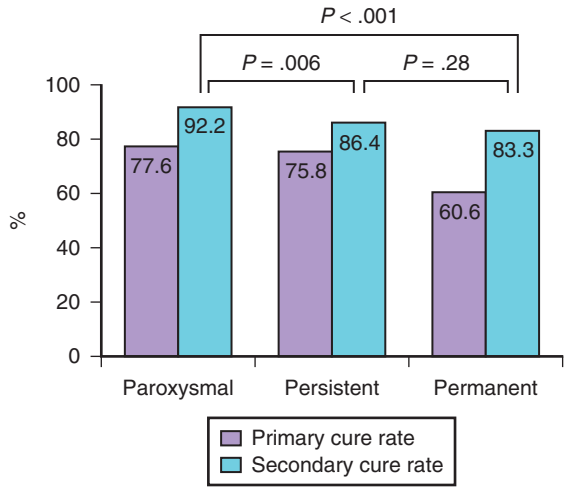

FIGURE 94-3 Primary and secondary cure rates (freedom from atrial fibrillation recurrence) in 1404 patients undergoing pulmonary vein antrum isolation guided by a circular mapping catheter and intracardiac echocardiography at four different institutions with 12 different operators. *(Modified from Bhargava M, Di Biase L, Mohanty P, et al: Impact of type of atrial fibrillation and repeat catheter ablation on long-term freedom from atrial fibrillation: Results from a multicenter study,* Heart Rhythm *6:1403–1412, 2009.)*

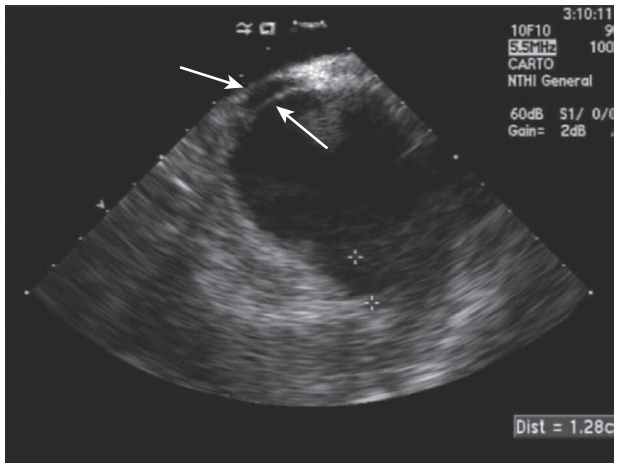

FIGURE 94-4 Intracardiac echography (ICE) image obtained before trans-septal puncture showing a double septum. This highlights the importance of ICE while performing trans-septal access in cases with unusual anatomy.

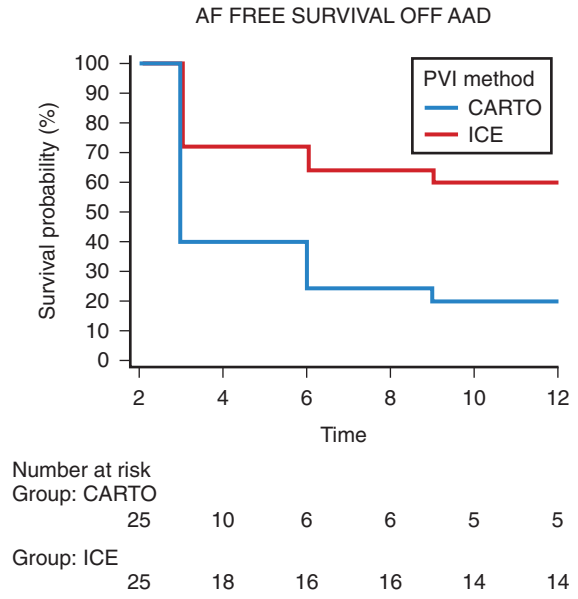

FIGURE 94-5 Evidence of superior effectiveness of pulmonary vein antrum isolation (*PVI*) guided by intracardiac echography (*ICE*) compared with circumferential pulmonary vein ablation guided by the three-dimensional electroanatomic mapping system (CARTO, Biosense Webster). *(From Khaykin Y, Skanes A, Champagne J, et al: A randomized controlled trial of the efficacy and safety of electroanatomic circumferential pulmonary vein ablation supplemented by ablation of complex fractionated atrial electrograms versus potential-guided pulmonary vein antrum isolation guided by intracardiac ultrasound,* Circ Arrhythm Electrophysiol *2:481–487, 2009.)*

PV reconnection of 69%.[37] Recently, we reported the results of a randomized direct comparison between CARTO-guided circumferential PV ablation and PVAI using ICE and a circular mapping catheter.[41] Overall, 60 patients with drug-refractory AF underwent randomization. The endpoint assessed was long-term procedural success, defined as absence of atrial tachyarrhythmias off antiarrhythmic drugs. The mean procedural time was comparable between the two approaches, although PVAI was associated with longer fluoroscopy time. At a mean follow-up of 24 ± 12 months, PVAI was more likely to achieve control of atrial tachyarrhythmias off antiarrhythmic drugs (57% vs. 27%, $P = .02$) (Figure 94-5).[41]

The superiority of PVAI guided by circular mapping catheter over electroanatomic mapping–guided circumferential PV ablation has been confirmed by other groups.[43] Karch et al conducted a randomized study on 100 patients, comparing circumferential PV ablation and segmental PVAI guided by a circular mapping catheter.[43] In that study, PVAI guided by circular mapping catheter was associated with shorter procedural time compared with circumferential PV ablation (256 ± 72 min vs. 284 vs. 86 min; $P = .02$), although the fluoroscopy time with a circular mapping–guided approach was confirmed to be longer (72 ± 26 min vs. 45 ± 21 min, respectively; $P < .01$). At 6-month follow-up, 42% of patients allocated to circumferential PV ablation and 66% of those receiving PVAI were free of atrial tachyarrhythmia episodes ($P = .02$ for comparison).

Putting together these results, electroanatomic mapping–guided circumferential PV ablation appears unreliable in completely isolating the PVs, which supports a circular mapping–guided technique to achieve effective PV ablation. The latter approach also offers the potential advantages of shortening the procedural time, limiting the delivery of RF energy to discrete areas showing the earliest PV potentials.[38,40] Moreover, because with circumferential PV ablation, contiguous lesions are created without necessarily achieving complete conduction block, post-incisional re-entrant atrial tachycardia (AT) has been reported with this approach in up to 20% of patients.[44]

As far as techniques for PVs imaging are concerned, ICE has been demonstrated to be of incremental value compared with other techniques such as PV angiography.[9] We have reported the outcome of PVAI in 315 patients: 56 underwent ablation-guided

by circular mapping catheter and PV angiography (group 1), 107 patients underwent circular mapping catheter and ICE-guided ablation (group 2), and 152 patients received circular mapping–guided ablation with titration of RF energy based on visualization of microbubbles by ICE (group 3). After a mean follow-up of 13 ± 4 months, 19.6% of patients in group 1 had AF recurrence compared with 16.8% of those in group 2 and 9.8% in group 3 ($P < .01$ vs. group 1). Fluoroscopy and procedure times were significantly lower in groups 2 and 3 compared with group 1, and no cases of severe PV stenosis were observed in group 3 patients compared with a rate of 3.5% in group 1 and 1.8% in group 2.[9]

At the end of PVAI, we systematically challenge patients with isoproterenol infusion up to 30 μg/min for 15 minutes to increase the chance of disclosing early PV reconnection or latent non-PV triggers of AF. Mapping during the isoproterenol challenge is performed by positioning the circular mapping catheter at the ostium of the left atrial appendage (LAA) and the ablation catheter in the right superior PV. Differential activation between the distal coronary sinus and the circular mapping catheter can distinguish LAA firing versus left PV firing. In the presence of rapid conduction through the Bachmann bundle, the circular mapping catheter positioned at the ostium of the LAA is of invaluable aid in correctly detecting LAA firing, which, in this case, is usually associated with rapid septal–right atrial activation. In case of right-sided atrial ectopy, the site of origin can be detected by analyzing the activation sequence of the duo-decapolar catheter, which is similar to sinus rhythm.

In this way, the site of origin of any significant ectopic atrial activity can be mapped and targeted for ablation.

Adjunctive Non–Pulmonary Vein Targets

As an adjunct to PVAI, patients in our institution undergo systematic isolation of the superior vena cava (SVC) as well. This approach is supported by robust clinical evidence.[45,46] In a randomized study of 320 consecutive patients with AF (46% paroxysmal, 23% persistent, 31% permanent), we assessed the incremental value of systematic isolation of the SVC as an adjunctive strategy to PVAI versus PVAI alone. At 12-month follow-up, a significant difference in procedural success between the two approaches was found solely in patients presenting with paroxysmal AF (77% in the PVAI alone vs. 90% in the PVAI plus isolation of the superior vena cava; $P = .04$ for comparison).[46] The technique adopted for SVC isolation is similar to that for PVAI—a circular mapping catheter–guided technique with ICE assistance. Caution should be exercised when isolating the lateral portion of the SVC because of its proximity to the right phrenic nerve. In this case, high-voltage pacing (>30 mA) is used to check for phrenic nerve stimulation before delivering RF energy.

Extending ablation beyond the PV antra and SVC in patients with paroxysmal AF is unnecessary.[42] In a recent randomized study, we aimed to assess whether adding bi-atrial ablation of the CFAE to PVAI in patients with paroxysmal AF presenting in the electrophysiology laboratory improved the procedural success compared with PVAI alone. At a follow-up of 1 year, no difference in terms of success rates was found between PVAI alone and PVAI plus ablation of CFAE (89% vs. 91%).[42]

Therefore, in paroxysmal AF, ablation beyond the PV antrum or the SVC should be guided by the documentation that additional triggers exist.

Techniques and Results of Ablation in Persistent and Longstanding Persistent Atrial Fibrillation

Current guidelines define persistent AF as either lasting longer than 7 days or requiring termination by cardioversion. Persistent AF is defined as longstanding when it has lasted for 1 year or longer despite cardioversion and antiarrhythmic therapy.[15]

In patients with persistent AF, as an adjunct to PVAI and SVC isolation, we extend ablation to the entire left atrial posterior wall down to the coronary sinus and the entire left side of the septum (Figure 94-6). CFAE in the left atrial chamber and within the

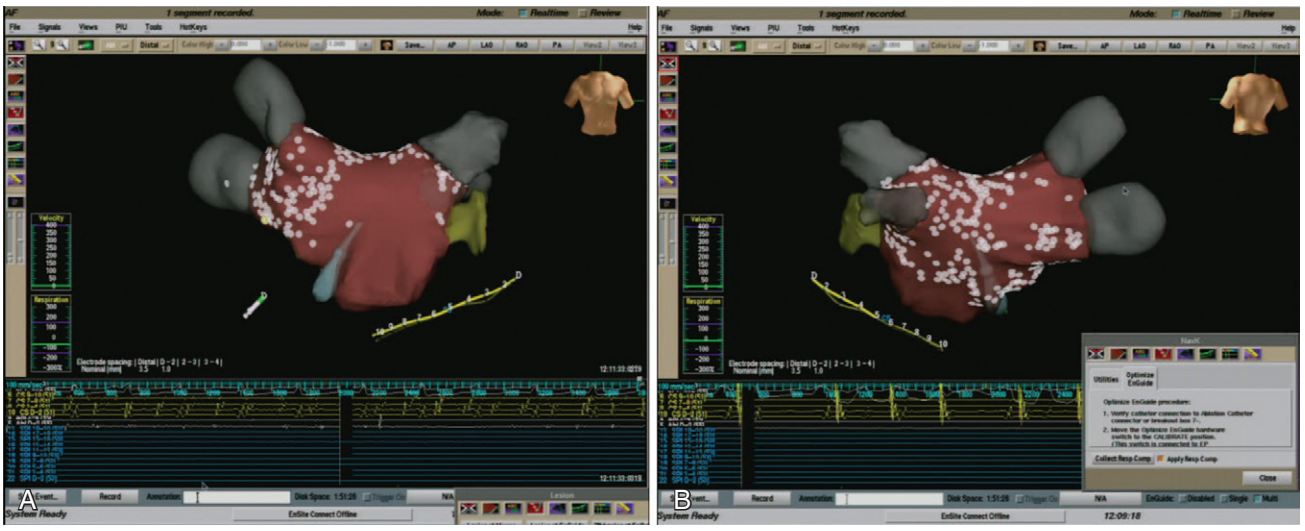

FIGURE 94-6 Anteroposterior (**A**) and posteroanterior (**B**) views of a three-dimensional electroanatomic left atrial map (EnSite NavX, St Jude Medical, Inc.) in a patient with paroxysmal atrial fibrillation. *Dots* indicate ablation lesions at the level of the pulmonary vein antra and the posterior wall between the pulmonary veins.

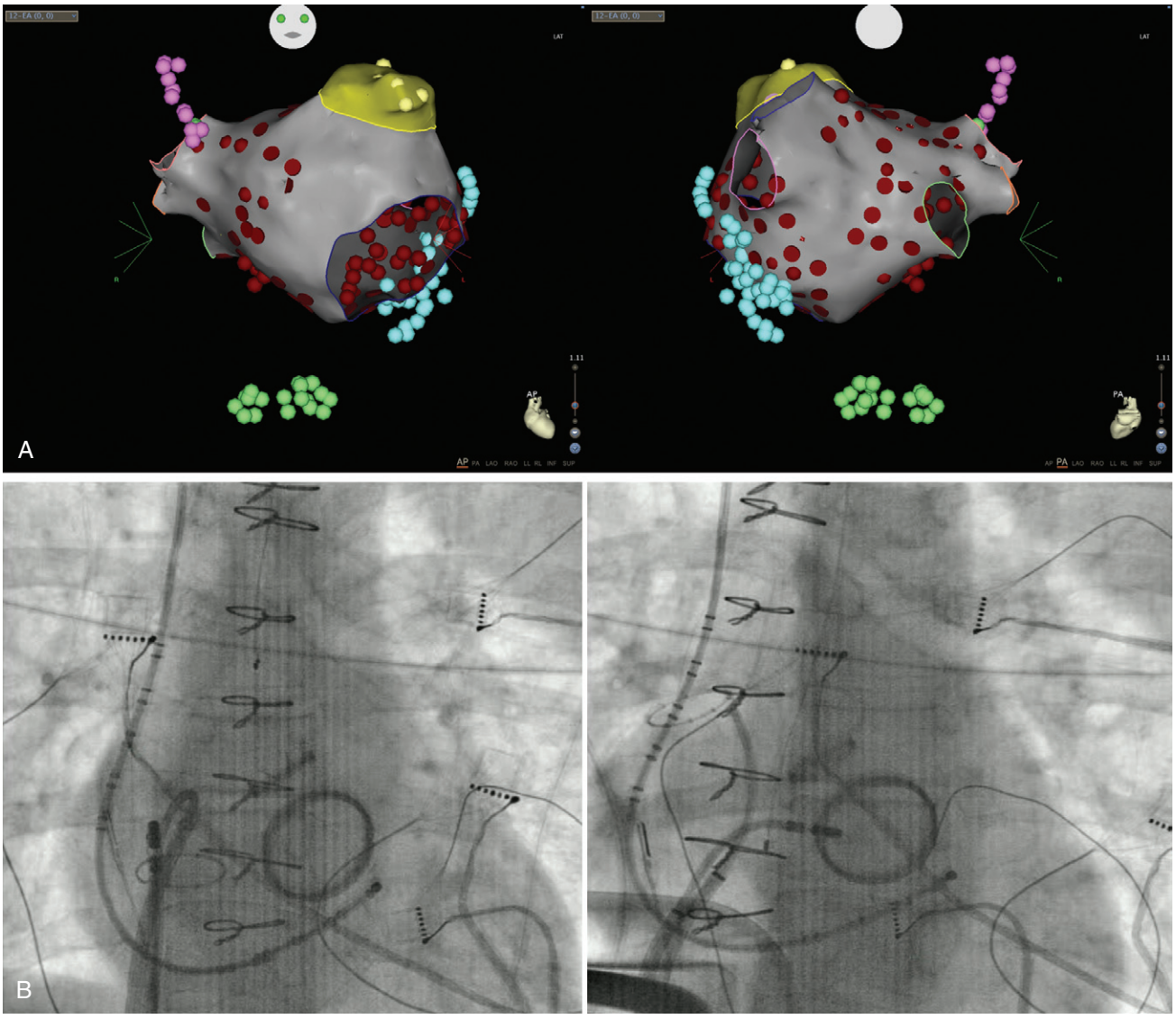

FIGURE 94-7 Anteroposterior and posteroanterior (**A**) views of a three-dimensional electroanatomic left atrial map (CARTO 3, Biosense Webster) in a patient with longstanding persistent atrial fibrillation with mechanical mitral valve (**B**). *Red dots* indicate lesions at the level of the pulmonary vein antra and the entire posterior wall down to the coronary sinus. Lesions within the coronary sinus are depicted as *blue dots*. *Green dots* depict lesions at the level of the cavotricuspid isthmus. *Yellow dots* indicate ablation lesions at the ostium of the left atrial appendage. *Pink dots* indicate ablation lesions at the level of the superior vena cava.

coronary sinus are targeted as well.[12,47] This approach is well supported by available evidence.[48]

Isolation of the Left Atrial Posterior Wall

From an embryologic, anatomic, and electrophysiological standpoint, the posterior left atrial wall should be considered an extension of the PVs (Figure 94-7).[49] Rotors and high-frequency sources of AF have been demonstrated within the posterior left atrial wall in preclinical studies, and sentinel observations from intraoperative AF ablation have confirmed a significant role of the posterior wall for triggering and maintaining the arrhythmia.[50] In this regard, AF localized to the posterior wall and dissociated from sinus rhythm has been reported after en bloc encircling of all PVs and the posterior wall.[51,52]

In patients with persistent and longstanding persistent AF, significant changes in atrial structure and electrophysiological function (i.e., atrial remodeling) further increase the chance that non-PV sites are involved in triggering and maintaining the arrhythmia. This supports the inadequacy of PV isolation alone as an effective ablation strategy.[12,13,47,53,54] Ablation of the posterior wall has been suggested to be of equal effectiveness compared with circumferential PV ablation in patients with chronic AF. In a randomized trial, 80 patients with chronic AF were assigned to circumferential PV ablation or to non-encircling linear ablation of the posterior wall. At a mean follow-up of 9 months, AF recurred in 28% of patients who underwent circumferential PV ablation compared with 25% of those who received posterior wall linear ablation (P = .8 for comparison).[55]

Substrate-Modifying Approaches: Ablation of Complex Fractionated Atrial Electrograms

The concept of targeting the left atrial electrophysiological substrate to cure AF derives from early surgical experience on AF mapping, which demonstrated critical sites of slow and discontinuous conduction characterized by strikingly fractionated atrial electrograms.[56]

Endocardial mapping and ablation of areas displaying CFAEs as a curative approach for AF has been firstly described by Nademanee et al.[13] In their original contribution, CFAE were defined by visual criteria as low-amplitude potentials (0.06 to 0.25 mV) with consistent temporal and spatial stability and either fractionated atrial electrograms (composed by two or more deflections) or atrial electrograms with cycle length of 120 ms or greater. Applying a substrate-based approach targeting only areas with CFAE to patients with all forms of AF, Nademanee et al reported quite high success rates (91% at 1-year follow-up).[13]

After the report by Nademanee et al, investigators have been evaluating the adjunctive role of CFAE ablation to PVAI. Haissaguerre et al described a stepwise sequential ablation approach for patients with longstanding persistent AF, which included PVAI, linear ablation across the roof of the left atrium between the left and right upper PVs and at the mitral isthmus, ablation at the inferior left atrium toward the coronary sinus and the base of the LAA, and left atrial ablation guided by CFAE mapping.[53,54] With this fairly extensive ablation strategy with the procedural endpoint of AF termination, the authors described a consistent prolongation of AF cycle length followed by either organization in ATs (87% of cases) or conversion to sinus rhythm (13% of cases) (Figure 94-8).[54] The ATs were subsequently mapped and ablated.

Our group has evaluated the role of CFAE ablation as an adjunct to PVAI in a prospective randomized trial.[47] Overall, 144 patients with longstanding persistent AF were randomly assigned to circumferential PV ablation (group 1), PVAI guided by a circular mapping catheter (group 2), or ablation of CFAE followed by PVAI (group 3). After a mean follow-up of 16 months, 11% of group 1 patients achieved sinus rhythm off antiarrhythmic drugs compared with 40% of group 2 and 61% of group 3 patients. Success rates reached 28% in group 1, 83% in group 2, and 94% in group 3 after the second procedure (see Figure 94-8).

In a meta-analysis of six randomized controlled trials on catheter ablation of nonparoxysmal AF that included 360 patients, adjuvant CFAE ablation in addition to PVAI was confirmed to increase the rate of sinus rhythm maintenance (relative risk, 1.35; 95% confidence interval, 1.04 to 1.75; $P = .022$).[48]

In our laboratory, procedural termination of AF is not sought as an endpoint.[12] In a prospective study on 306 patients with longstanding persistent AF undergoing the first procedure of PVAI plus CFAE ablation, only 6 (2%) patients converted directly to sinus rhythm during ablation, whereas in 172 (56%), the AF organized into AT, which was mapped and ablated, and 128 (42%) patients remained in AF and were cardioverted at the end of the procedure.

Interestingly, after a mean follow-up of 25 ± 6.9 months, 69% of patients remained in sinus rhythm without significant differences between those who had procedural termination or organization of AF and those who remained in AF and received cardioversion. Of note, procedural organization of AF predicted the mode of recurrence, with a significant association with recurrence of AT ($P = .022$).[12]

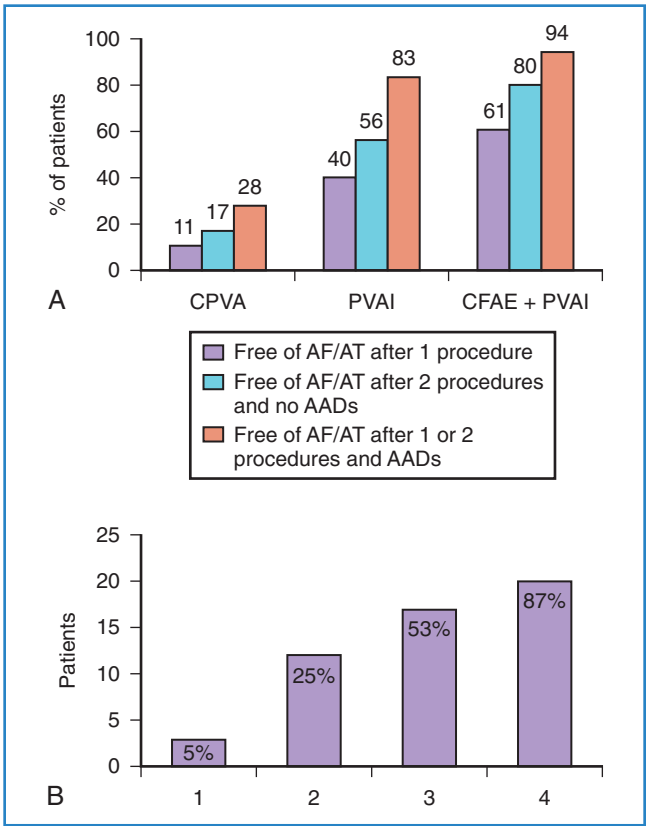

FIGURE 94-8 **A,** Randomized comparison of circumferential pulmonary vein ablation (*CPVA*), pulmonary vein antrum isolation (PVAI), and PVAI plus ablation of complex fractionated atrial electrograms (*CFAE*) in patients with longstanding persistent atrial fibrillation (*AF*). **B,** Percentage of conversion to sinus rhythm or atrial tachycardia (*AT*) during each step of the stepwise ablation approach in patients with longstanding persistent AF. *AAD*, Antiarrhythmic drug. (***A,*** *Modified from Elayi CS, Verma A, Di Biase L, et al: Ablation for longstanding permanent atrial fibrillation: Results from a randomized study comparing three different strategies,* Heart Rhythm *5:1658–1664, 2008.* ***B,*** *Modified from Haissaguerre M, Sanders P, Hocini M, et al: Catheter ablation of long-lasting persistent atrial fibrillation: Critical structures for termination,* J Cardiovasc Electrophysiol *16:1125–1137, 2005.)*

In conclusion, we deliver an extensive set of ablation lesions in patients with longstanding persistent AF. PVAI with SVC isolation is associated with ablation of the entire left atrial posterior wall, isolation of the coronary sinus, and left atrial ablation of CFAE.

Other Targets

Nakagawa et al have evaluated the role of ganglionated plexi ablation as an adjunct to PVAI.[57,58] This approach was derived from preclinical and clinical observations that autonomic nervous system modulation is an important mechanism for triggering and maintaining AF.[59,60] In a randomized trial, 67 patients with paroxysmal AF were assigned to PV isolation or ganglionated plexi ablation followed by PV isolation.[61] In this study, PV isolation was sought through a circular ablation catheter, which is a nonirrigated ablation technology. After a mean follow-up of 10 months, 45.5% of those receiving PV isolation remained free from AF recurrence compared with 73.5% in the ganglionated plexi ablation plus PV isolation group ($P = .022$ for comparison). It is

important to emphasize that the adoption of a nonirrigated circular ablation catheter for PV isolation may have reduced the procedural effectiveness in the PV isolation only arm (see below) and skewed the trial results toward a greater benefit of ganglionated plexi ablation.[61]

Other authors have been investigating different methods for targeting the neural connections to the atria relevant for triggering and maintaining AF. Pachon et al have developed a system for real-time spectral mapping using fast Fourier transformation in sinus rhythm.[10] This method identifies the myocardial areas where unfiltered atrial bipolar electrograms contain high frequencies (i.e., AF nests). Our group has evaluated the adjunctive role of AF nest ablation to PVAI and isolation of the SVC in a prospective randomized study.[62] Overall, 157 patients underwent randomization; AF nest ablation was shown to reduce AF recurrence rate, with an absolute risk reduction of 9% in paroxysmal AF and 10% in patients with persistent AF.[62]

Of interest, the distribution of autonomic nervous targets for AF ablation seems correlated with the distribution of CFAE at the level of the PV antra. Therefore autonomic ganglia can be targeted as bystanders during PVAI or CFAE ablation.[58,63]

The benefit of ablating thoracic venous structures other than the PVs and SVC is a matter of increasing interest. These include the coronary sinus and the ligament of Marshall.[64,65] At the present time, ablation within the coronary sinus is performed in case of CFAE recording or significant ectopy arising from this structure.[47] The ligament of Marshall usually can be ablated from the endocardial aspect of the left atrium inferior to the ostium of the left inferior PV, although it rarely requires direct catheterization from within the coronary sinus.[64]

Recently, ethanol infusion in the vein of Marshall through an angioplasty wire and balloon has been demonstrated as an attractive strategy to achieve effective ablation of this structure throughout its course between the mitral annulus and the left superior PV.[66,67] Of note, ethanol infusion in the vein of Marshall was associated with effective isolation of the left inferior PV in 40% of patients.[66]

Notwithstanding such promising data, the clinical relevance of ablation of the ligament of Marshall is still undefined and warrants investigation in further studies.

Special Considerations for Patients Presenting for Repeat Procedure

As techniques advance and operators become more experienced with AF ablation, arrhythmia recurrence caused by reconnection of the PV antrum becomes less frequent, and non-PV trigger sites will play an increasing role in AF recurrence, especially in nonparoxysmal AF.[68] One of these trigger sites is the LAA.

In a recent study, we reported the prevalence of AF triggers from the LAA in a series of 987 patients (29% paroxysmal AF, 71% nonparoxysmal AF) referred to our institution for repeat catheter ablation.[14] LAA firing was assessed only after all the potential sites of reconnection, including the PV antra, the posterior wall, and the septum were checked and targeted, if reconnected.

Overall, 266 (27%) patients showed firing from the LAA at baseline or after administration of isoproterenol; in 8.7% of patients, the LAA was found to be the only source of arrhythmia. LAA firing was defined as consistent atrial premature contractions with the earliest activation in the LAA, or as AF or atrial tachyarrhythmia originating from the LAA. In these cases, a complete isolation of the LAA is the ablation strategy that provides the best long-term outcome.

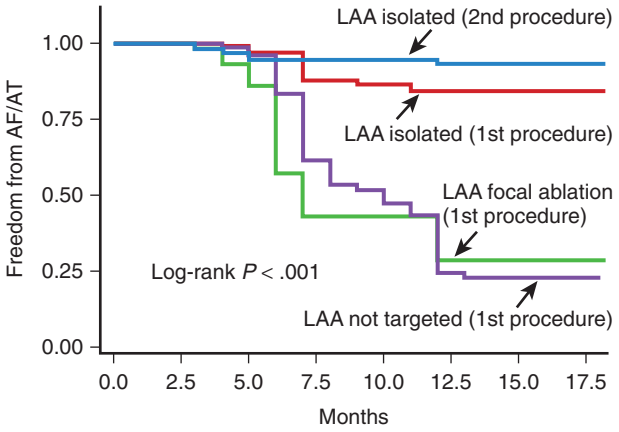

FIGURE 94-9 Impact of left atrial appendage (*LAA*) isolation on long-term freedom from atrial fibrillation (*AF*) or atrial tachycardia (*AT*) in patients presenting with firing from the LAA at repeat catheter ablation of AF. *(Modified from Di Biase L, Burkhardt JD, Mohanty P, et al: Left atrial appendage: An underrecognized trigger site of atrial fibrillation,* Circulation *122:109–118, 2010.)*

Of the 266 patients presenting with LAA firing, 43 were not ablated (group 1), 56 received a focal ablation (group 2), and 167 underwent LAA isolation guided by a circular mapping catheter and ICE (group 3). After a mean follow-up of 1 year, AF recurred in 74% of group 1 patients compared with 68% of group 2 and 15% of group 3 ($P < .001$ for multiple comparison) (Figure 94-9).[14]

The technique used for LAA isolation is similar to that adopted for PVAI, although the procedure requires more ablation time. Moreover, since the LAA has a very thin wall and may be prone to perforation, extreme caution should be exercised when isolating this structure.

Of interest, isolation of the LA does not appear to significantly alter its mechanical function. We found a preserved contractility at TEE 6 months after ablation in more than 60% of patients. However, further prospective studies are necessary to disclose the clinical relevance of LAA isolation and its consequences with respect to potential complications.

Postprocedural Care and Follow-up

Postprocedural management in our institution involves strict monitoring for outcome and complications during overnight hospital stay and on the following day prior to discharge using symptom assessment, serial neurologic examinations, and puncture site checks. All patients are instructed to call in case of any symptom development and to send weekly trans-telephonic electrocardiogram (ECG) transmissions for the first 5 months after ablation. Progress of recovery and symptoms are assessed as well by dedicated nurses. Moreover, all patients present for follow-up 3 to 4 months after ablation, and 7-day Holter monitor readings are obtained every 3 months for 1 year.

With regard to out-of-hospital long-term anticoagulation management, patients are referred to dedicated anticoagulation clinics with the aim of maintaining a stable therapeutic INR level. We follow a standard, uniform, and validated protocol of

long-term postprocedural anticoagulation management.[3] In brief, oral anticoagulation is discontinued, regardless of the $CHADS_2$ score, if patients do not have any recurrence of atrial tachyarrhythmias, severe PV stenosis (PV narrowing >70%), and severe left atrial mechanical dysfunction, as assessed by transthoracic echocardiography.

Patients with a $CHADS_2$ score of 1 or greater and early recurrence of AF are maintained on warfarin for at least 6 months. In these patients, warfarin is discontinued in the absence of AF recurrence without antiarrhythmic drugs, and 81 to 325 mg of aspirin is started. In case of new AF recurrence after warfarin discontinuation in patients with a $CHADS_2$ score of 1 or greater, oral anticoagulation is resumed.

In addition to the above criteria, patients who have undergone LAA isolation are managed with TEE 6 months after the procedure to decide if anticoagulation should be discontinued. If the LAA contractility is deemed preserved and the flow velocity is normal (>0.3 ms), warfarin is discontinued.

Remote Navigation Technologies for Ablation of Atrial Fibrillation

Two remote navigation systems are currently available for clinical use: the magnetic navigation system (Niobe; Stereotaxis, St Louis, MO) (Figure 94-10), and the robotic navigation system (Sensei; Hansen Medical, Mountain View, CA) (Figure 94-11).

With the magnetic navigation system, two focused-field permanent magnets are placed on either side of the operating table to generate a magnetic field. The magnetic field is used to direct the tip of specialized mapping or ablation catheters. These catheters are extremely flexible and have magnets embedded at their

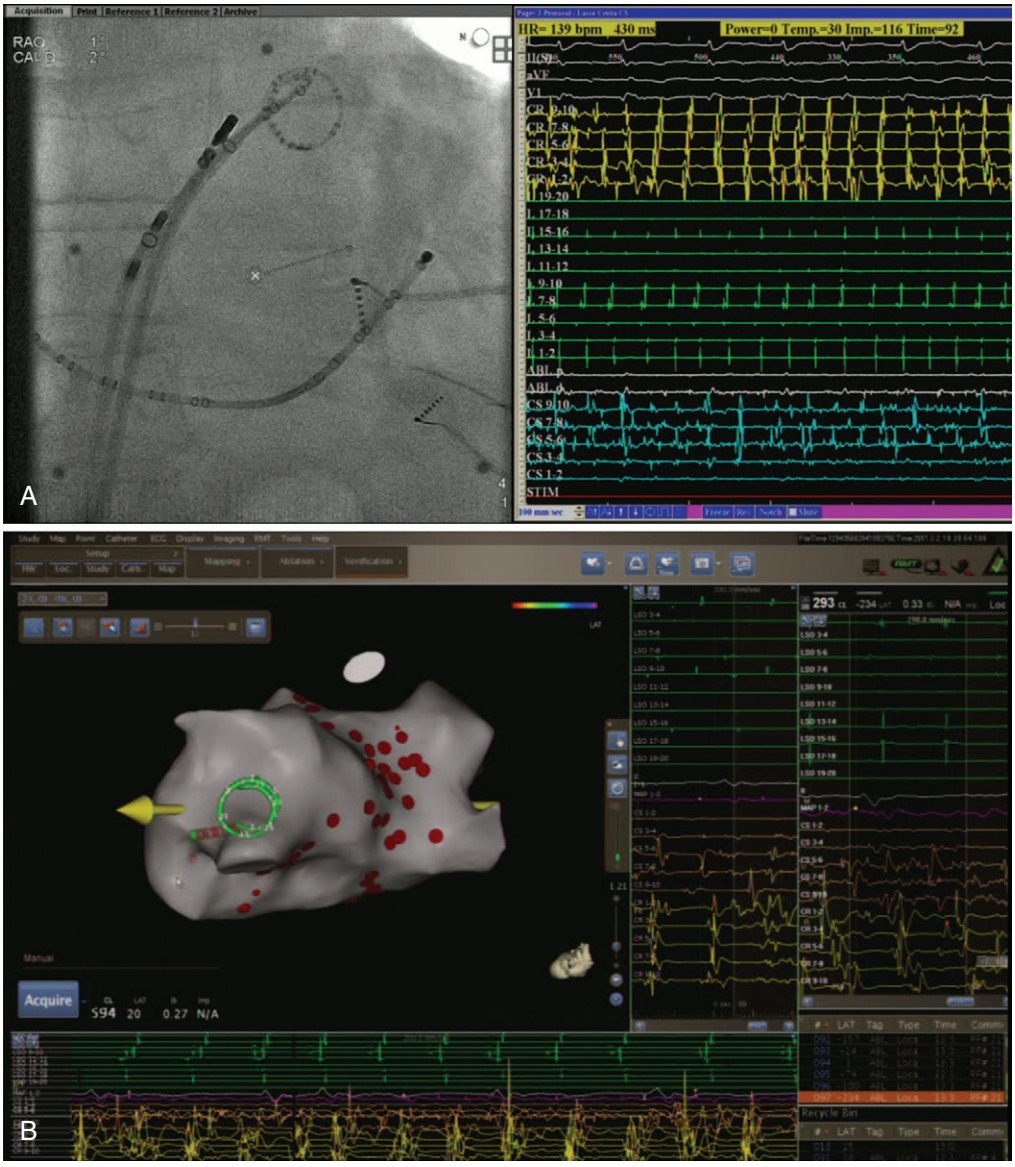

FIGURE 94-10 Pulmonary vein antrum isolation with the Niobe remote magnetic navigation system (Stereotaxis). **A,** Left anterior oblique image of a left superior pulmonary vein antrum ablation. **B,** CARTO RMT (Biosense Webster) reconstruction of the left atrium, with the *arrow* showing the direction of the magnetic field.

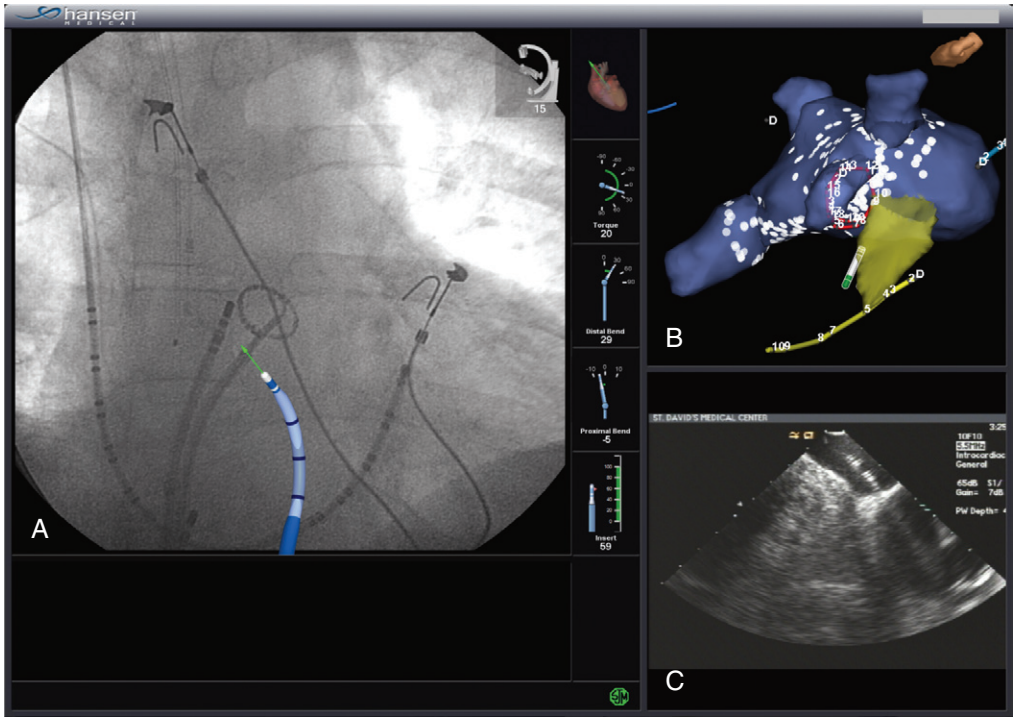

FIGURE 94-11 Posterior wall isolation using the Sensei (Hansen Medical) robotic system. **A,** Fluoroscopy image showing the virtual catheter and the real Artisan (Hansen Medical) catheter at the level of the posterior wall guided by the circular mapping catheter. **B,** EnSite NavX (St Jude Medical, Inc.) map obtained during the procedure showing ablation (*white dots*). **C,** Intracardiac echocardiography image obtained during the procedure showing the Artisan catheter in the posterior wall.

tip to allow navigation. The operator directly manipulates the external magnetic field at the level of the video workstation, which results in different orientations of the catheter tip. Advancement or retraction of the catheters is guided by a computer-controlled advancer system (Cardiodrive unit, Stereotaxis) directly connected at the catheter shaft outside the sheath at the venous insertion site. Therefore the video workstation with the Cardiodrive unit allows precise orientation and advancement or retraction of the catheter by 1-mm or greater increments. The system includes both a coordinate remote control and a wand remote control. The wand remote control is a single-hand control system with a joystick that controls both the orientation and advancement of the catheter. The coordinate control of the catheter is a two-hand control system that includes a joystick to control the advancement or retraction of the catheter, and a mouse to control the orientation. The cursor is represented as an arrow with a circle. The arrow represents the direction of the magnetic field as projected onto the respective fluoroscopic imaging plane.

The magnetic navigation system is integrated with a nonfluoroscopic three-dimensional electroanatomic mapping system (CARTO RMT, Biosense Webster). Integration with the CARTO RMT allows the implementation of automatic mapping algorithms once some anatomic landmarks have been identified by the operator, such as the PV ostia, the left atrial roof, and the mitral annulus. However, the reliability of the automatic navigation software remains to be established.

The role of the magnetic navigation system in AF ablation has been evaluated by different authors with controversial results.[69,70] Pappone et al reported the results of a circumferential PV ablation using the remote magnetic navigation system and a 4-mm-tip nonirrigated ablation catheter.[69] In this study, remote magnetic navigation was effective in 38 of 40 patients in achieving greater than 90% reduction in the bipolar electrogram amplitude, peak-to-peak bipolar electrogram amplitude or both to less than 0.1 mV inside the circumferential ablation line.[69] Although this study was important in demonstrating the feasibility of remote magnetic navigation for left atrial ablation, the procedural endpoint considered to define effective ablation is of unclear electrophysiological significance.

Our group has evaluated the efficacy of remote magnetic navigation with a nonirrigated 4-mm-tip ablation catheter for PV ablation.[70] In this study, 45 patients underwent a stepwise ablation protocol, which sequentially included circumferential PV ablation as described by Pappone et al, circular mapping catheter–guided PVAI, and manual PVAI. Interestingly, none of the PVs targeted with circumferential ablation was isolated at the end of the procedure, as assessed by a circular mapping catheter. Even after the second step of our protocol, 92% of patients failed to reach the endpoint of PV antrum isolation, which was effectively met by manual PVAI using an open-irrigated 3.5-mm ablation catheter.[70] Moreover, at the end of the procedure, we found evidence of tip charring on the 4-mm ablation catheter in 33% of cases.

The results of our study have demonstrated that remote magnetic navigation with a 4-mm-tip nonirrigated ablation catheter is ineffective in achieving PVAI and has significant risk of catheter tip charring.

Recently, an open-irrigated ablation catheter has become available for remote magnetic navigation. Arya et al have retrospectively compared the outcome of AF ablation with remote magnetic navigation (n = 70) with that of a matched control group undergoing manual ablation (n = 286). The authors reported similar success rates (57.8% vs. 66.4% at 6 months, respectively; $P = .19$) with markedly reduced fluoroscopy times. However, both RF and procedural times were longer in the remote magnetic navigation group. Moreover, the rate of PV disconnection was significantly lower in the remote magnetic navigation group (87.6% vs. 99.6%; $P < .05$).

Miyazaki et al have evaluated the safety and efficacy of this newly available catheter for PV isolation in a consecutive series of 30 patients.[71] PV isolation was performed with a circular mapping catheter–guided approach and was achieved in 114 (94%) of 120 veins. Again, this was associated with significantly longer RF and procedural times compared retrospectively with a similar group of patients undergoing manual ablation.[71] These results have been largely confirmed by other groups (Table 94-5).[72,73]

In particular, the RF and procedural times with remote magnetic navigation have been consistently reported to be longer, which is likely caused by the limited contact force achievable with this system (maximum 10 to 15 g). Although this might increase the safety of this system, it may act as a limiting factor for achieving adequate lesion size.

In the future, technical modifications to increase the tissue-catheter contact force and wider clinical experience will likely further increase the effectiveness of AF ablation with the remote magnetic navigation system.

The robotic navigation system (Sensei) consists of a workstation that includes the instinctive motion controller, a remote catheter manipulator, and a setup joint mounted on a table at the patient's side. The system is based on multiple pullwires that control a robotic hollow catheter with an internal steerable guide sheath system (Artisan Catheter, Hansen Medical). The control is provided via a master-and-slave electromechanical system, in which the operator movements at the instinctive motion controller are updated constantly with resultant motion of the catheter. This system allows for a broad range of motion in virtually any direction. In contrast to the remote magnetic navigation, most standard ablation catheters can be used with the robotic system, since the sheath can accommodate any catheter up to 8.5 Fr diameter. Extreme caution should be exercised when advancing the robotic sheath into the right atrium; the robotic sheath is stiff and has to be advanced through a 14-Fr vascular sheath, which may cause vascular dissection. To minimize the risk of vascular complications, we currently first insert an 8-Fr sheath with gradual upsizing to 11 Fr and 14 Fr. A long (30 cm) 14-Fr sheath is then inserted to reach the inferior vena cava in its immediate subdiaphragmatic portion; the robotic sheath is then inserted with the ablation catheter leading by at least 10 cm into the right atrium. At this level, the ablation catheter is withdrawn into the sheath with only the distal electrodes protruding.[74] By adopting this technique, we have had no vascular complications.

Once positioned in the right atrium, the Hansen system is advanced in the left atrium through a trans-septal access in three steps: (1) a manual trans-septal puncture is performed with a standard trans-septal sheath and needle; (2) the needle is replaced

Table 94-5 Studies on Catheter Ablation of Atrial Fibrillation with Remote Magnetic Navigation

STUDY	ENDPOINT	RESULTS	CONCLUSION
Pappone et al, 2006[69]	Feasibility of RMNS with NIC ablation	RMNS ablation successful in 38 of 40 patients without complication Ablation time longer in first 12 patients (192.5 min vs. 148 min; $P = .012$); longer procedure time with remote ablation than control patients undergoing manual ablation ($P < .001$)	RMNS for AF ablation is safe and feasible, with a short learning curve.
Di Biase et al, 2007[70]	Feasibility and efficacy of RMNS and ablation with NIC	PVs remained electrically connected in 100% of circumferential PV ablation and in 92% after circular mapping catheter–guided approach	RMNS with NIC could not achieve PV antrum isolation.
Arya et al, 2010[98]	Efficacy at 6 months of OIC RMNS vs. manual RFCA	RF time = 75.4 ± 20.9 vs. 53.2 ± 21.4 min ($P < .001$) Procedure time = 223 ± 44 vs. 166 ± 52 min ($P < .001$) Fluoroscopy time = 13.7 ± 7.8 vs. 34.5 ± 15.1 min ($P < .001$) Success rate = 57.8% vs. 66.4% ($P = .196$)	OIC RMNS is effective and safe; procedure times were longer in RMNS compared with manual.
Chun et al, 2010[72]	Safety and efficacy of OIC RMNS vs. a redesigned catheter	Procedure time = 270 vs. 243 min ($P < .001$) Fluoroscopy time = 24 vs. 16 min ($P = .011$)	OIC RMNS is feasible; procedure times were longer in RMNS compared with manual.
Miyazaki et al, 2010[71]	Feasibility and safety OIC RMNS vs. manual RFCA in PAF	RF time = 60 ± 27 vs. 43 ± 16 min ($P = .0019$) Procedure time =246 ± 50 vs. 153 ± 5 min ($P < .001$) Fluoroscopy time = 40 ± 14 vs. 58 ± 24 ($P < .001$)	OIC RMNS backed up with manual ablation is feasible in PAF but requires longer procedure, RF, and fluoroscopy times.
Pappone et al, 2011[73]	Safety and long-term efficacy of OIC RMNS	At 15.3 ± 4.9 months, success rate: PAF = 81.4%, NPAF = 67.3% ($P = .035$) No major complications	RMNS ablation with OIC magnetic catheters is safe and effective.

AF, *Atrial fibrillation;* RMNS, *remote magnetic navigation system;* NIC, *nonirrigated ablation catheter;* NPAF, *nonparoxysmal atrial fibrillation;* OIC, *open irrigated ablation catheter;* PAF, *paroxysmal atrial fibrillation;* PV, *pulmonary vein;* RF, *radiofrequency;* RFCA, *radiofrequency catheter ablation.*

Table 94-6 Studies on Catheter Ablation of Atrial Fibrillation with Remote Robotic Navigation

STUDY	ENDPOINT	RESULTS	CONCLUSION
Saliba et al, 2008[75]	Feasibility and efficacy of RN ablation in AF (n = 40; 23 with concomitant AFL)	Procedure time = 163 ± 88 min Fluoroscopy time = 64 ± 33 min PV antrum isolation + isolation of the SVC successful in all patients Cavotricuspid ablation with bidirectional block achieved in all 23 patients 1-year procedural success = 86%	RN ablation is feasible and effective.
Di Biase et al, 2009[76]	Efficacy and safety of RN ablation vs. manual ablation	At mean follow-up of 14 months, success rates were 74% vs. 78% off AADs and 81% vs. 85% on AADs	RN ablation has similar effectiveness compared to manual ablation.
Wazni et al, 2009[74]	Safety of RN ablation and evaluation of approach modification	No procedure-related deaths Six intraoperative complications (vascular = 4, cardiac tamponade = 2) Six late complications (PV stenosis = 5, gastroparesis = 1)	Approach modification reduces complications.
Kautzner et al, 2009[99]	Efficacy and safety of RN ablation in PAF vs. manual	Procedure time = 207 ± 29 vs. 250 ± 62 (P = .007) Fluoroscopy time = 15 ± 5 vs. 27 ± 9 (P < .001) At 5 ± 1 month follow-up: AF free rate = 91% vs. 81% No major complications	RN ablation is safe, effective, and associated with reduced procedure and fluoroscopy times.
Schmidt et al, 2009[77]	Feasibility and efficacy of RN ablation in PAF (n = 43) and NPAF (n = 22)	Procedure time 195 ± 40 min At 8 months: single-procedure success = 73% (76% in PAF and 68% in NPAF)	RN ablation is feasible and effective.
Hlivak et al, 2010[78]	Safety and efficacy of RN ablation in PAF	At median of 15 months: single-procedure success rate = 63%; 86% after mean of 1.2 procedures No major complications	RN ablation is safe and effective in PAF.
Willems et al, 2010[100]	Efficacy of RN ablation in PAF	At 3 months: success rate = 67%; 81% 1 year after repeat ablation of recovered PVs	RN ablation is safe and effective in PAF.

AAD, *Antiarrhythmic drug;* AF, *atrial fibrillation;* AFL, *atrial flutter;* NPAF, *nonparoxysmal atrial fibrillation;* PAF, *paroxysmal atrial fibrillation;* PV, *pulmonary vein;* RN, *robotic navigation.*

with a long guidewire positioned in a left PV; and (3) the robotic sheath is then advanced across the septum by using the guidewire as a marker for the trans-septal access, and the guidewire is finally withdrawn.

Our initial experience with the robotic navigation system included 40 patients with drug-refractory AF (23 with concomitant typical atrial flutter). PVAI plus isolation of the SVC was successfully performed in all patients, and cavotricuspid ablation with the endpoint of bi-directional conduction block was added to those with history of typical atrial flutter. At 1-year follow-up, 34 patients (86%) and 5 patients were free from atrial arrhythmia off and on antiarrhythmic drugs, respectively.[75] Such encouraging results have been replicated in larger series of patients. Our most recent report included 390 patients, of whom 193 underwent ablation with the remote robotic navigation system (group 1), and 197 underwent conventional manual ablation (group 2).[76] After a mean follow-up of 14 ± 1 months, the success rate in group 1 was 85% compared with 81% in group 2 (P = .264 for comparison). Overall, fluoroscopy time was significantly shorter in group 1 (48.9 ± 24.6 min vs. 58.4 ± 20.1 min; P <.001), and was statistically reduced after 50 procedures (P <.001).[76]

The results from other groups are quite similar to our experience (Table 94-6). Schmidt et al have recently reported a single-procedure success rate of 73% at a median follow-up of 20 months.[77] Hlivak and colleagues reported their experience with robotic navigation in 100 patients with paroxysmal AF undergoing circumferential PV ablation with an open irrigated ablation catheter.[78] After a median follow-up of 15 months, single-procedural success was of 63%, and increased to 86% after a mean of 1.2 procedures.[78]

With regard to procedural safety, preliminary data from a worldwide survey that included more than 1000 patients showed complications similar to those of manual ablation.[79]

Other Technologies for Ablation of Atrial Fibrillation

Balloon-based ablation technologies and multi-electrode ablation catheters have been developed with the aim of achieving successful PV isolation in a shorter time and with less dependency on operator experience. The major drawbacks of such technologies are that they allow targeting only the PVs and that switching to conventional ablation catheters is required to target non-PV structures. Even in the setting of PV ablation, the significant intra-patient and interpatient variability in PV anatomy may hamper

the efficacy of balloon-based ablation across the wide spectrum of patients with AF.

Balloon-Based Technologies

The most advanced experience with balloon-based technologies is that with cryoenergy (Cryocath Technologies, Inc., Point Claire, QC, Canada). Cryoablation is carried out through a pressurized refrigerant (e.g., nitrous oxide), and the rapid evaporation of the refrigerant in a chamber localized at the tip of the ablation catheter delivers freezing energy to the underlying tissue. One of the main advantages of cryoenergy is that when freezing is applied at temperatures between 0° C and –40° C, tissue lesions are reversible; this is of particular interest when ablating close to critical structures such as the conduction system or vessels.

The cryoablation balloon catheter (cryoballoon) is available for clinical use in two diameter sizes: 23 mm and 28 mm. Once the balloon is inflated at the ostium of the PVs, it is capable of achieving PV isolation within a single cryoablation. The most important clinical study evaluating the effectiveness of the ablation of AF with the cryoballoon has been the Sustained Treatment of Paroxysmal Atrial Fibrillation (STOP-AF) trial.[80] In this study, 245 patients with at least two documented episodes of paroxysmal AF in the previous 2 months resistant to at least one antiarrhythmic drug were randomized in a 2:1 ratio to cryoablation or antiarrhythmic drug therapy. Over 12 months of follow-up, 70% of patients treated with cryoablation were free of AF compared with only 7% of the antiarrhythmic drug group ($P < .001$). Serious adverse events related to the cryoablation procedure or to the device occurred in five patients, including four strokes and one death. Twenty-nine patients (11.2%) developed postprocedural phrenic nerve palsy, which persisted beyond 12 months in four patients.[80] In conclusion, cryoballoon ablation is the first balloon-based technology with a demonstrated effectiveness in a large randomized trial. The rate of adverse events, however, is significant, and further experience and technical advancements are warranted before the widespread adoption of this technology for AF ablation can be considered appropriate.

The high-intensity focused ultrasound (HIFU) balloon catheter (ReCor Medical, Ronkonkoma, NY) includes a transducer with a piezo-electric crystal that generates sound waves in the frequency range of 500 kHz to 20 MHz. Because sound waves are mechanical energy, they propagate within the medium and, once absorbed by the myocardium, result in heating. The main advantage of ultrasound energy is its independence on contact. Furthermore, ultrasound energy can be collimated to a desired target, theoretically without damage to the intervening tissue. We have evaluated the efficacy of the HIFU balloon catheter in 15 patients with drug-refractory AF.[81] After 35 weeks, five patients had AF recurrence, three responded to previously ineffective antiarrhythmic medications, and two remained in AF.[81] Despite the encouraging results of our early study, the HIFU balloon is no longer evaluated in clinical trials because of the severe complications reported in other studies, mainly related to phrenic nerve paralysis and fatal atrioesophageal fistula.[82]

The Cardiofocus (Marlborough, MA) balloon-based laser ablation system is a 12-Fr balloon catheter with a 2-Fr endoscope at the proximal end of the balloon. Once positioned in the left atrium, the balloon should be occlusively inflated at the ostium of the PV to deliver circumferential ablation. The first generation of the laser balloon catheter was available in three diameter sizes: 20, 25, and 30 mm. The endoscope allows the operator to visualize the internal face of the balloon and correctly identify areas of tissue-balloon contact. These areas appear in white (i.e., left atrial wall), whereas areas of poor contact are characteristically stained with red blood. The generator of laser energy is an optical fiber located within the central shaft of the catheter, which projects an arc of light onto the tissue in contact with the balloon face.

Our initial experience with the first-generation laser balloon included 30 patients with paroxysmal AF. Successful isolation of the PVs occurred in 105 (91%) of 116 PVs, corresponding to a single-procedure 1-year success rate of 60%. Adverse events included one cardiac tamponade, one stroke, and one asymptomatic phrenic nerve palsy.[83] Of note, the first-generation laser balloon ablation technology was limited in its ability to deliver optimal lesion because of poor balloon-tissue contact caused by the noncompliance of the system and a large ablative arc that increased the risk of thrombus formation when targeting areas with poor contact.

A new version of the endoscopic ablation system housed in a compliant, sizeable balloon with the capability of delivering spot laser lesions over a wider range of energies is being actively investigated in clinical trials. Preliminary reports suggest that with this system PV isolation can be achieved in an effective and safe manner.[84]

Multi-electrode Ablation Catheters

Multi-electrode catheters deliver unipolar or bipolar RF energy and are available in different shapes to suit specific target areas. Circular and mesh array–shaped catheters are used for PV isolation, with reported good success rates at short-term follow-up.[85] Other configurations such as cross- and Y-shaped catheters have been developed for linear ablation. However, exchanging the configurations of catheters during the procedure may be time consuming and costly and may increase the risk of procedural complications.

The major limitation of this technology is the lack of available irrigation platforms and the dependency on tissue-electrode contact. The latter is a major issue with this technology because the maneuverability of multi-electrode catheters appears inferior to that of circular mapping catheters.[86]

Force-Sensing Technologies

The possibility to have real-time information on tissue-catheter contact force is invaluable. Contact force is an important contributor of lesion size and depth and, importantly, can predict major procedure-related complications such as steam pop, perforation, and coagulum formation.[87]

Recently, open-irrigated catheters with contact force sensors (TactiCath, Endosense, Inc., Geneva; ThermoCool SmartTouch, Biosense Webster) have been made available (Figures 94-12 and 94-13). Two sensors give real-time information on tissue-catheter contact force and on the angle between the catheter tip and the underlying tissue. These catheters will allow the operator to apply the appropriate force and deliver optimal lesions without the risk of pressure-related complications. Importantly, data exist demonstrating a poor agreement between electrogram amplitude and electrode-tissue contact force in catheter ablation of AF, which further supports the clinical importance of force-sensing technology.[88]

In a multi-center European feasibility and safety study, the Touch+ for Catheter Ablation (TOCCATA) trial, 76 patients with

supraventricular arrhythmias (42 right supraventricular arrhythmias, 34 paroxysmal AF) underwent ablation with the TactiCath catheter. The preliminary results of the TOCCATA have demonstrated good safety and efficacy profiles of this novel ablation technology in the setting of supraventricular arrhythmias.[89] Notably, recurrence rate and PV reconnection appeared higher when energy was delivered with poor contact (≤5 g).[90] Ongoing prospective multi-center trials are further evaluating the performance of force-sensing catheters in the setting of AF ablation.

Other technologies aimed at assessing the degree of tissue-catheter contact are being actively investigated. Among these, novel open irrigated ablation catheters with incorporated temperature-sensing chips are able to measure and interpret microwaves emitted from heated tissue during ablation (i.e., microwave radiometry technology, Tempasure, Advanced Cardiac Therapeutics, Laguna Beach, CA), which provide indirect assessment of tissue–catheter contact. In addition, microwave radiometry has the capacity of providing a real-time feedback on tissue temperature and lesion growth. This novel technology should enter clinical investigation soon.

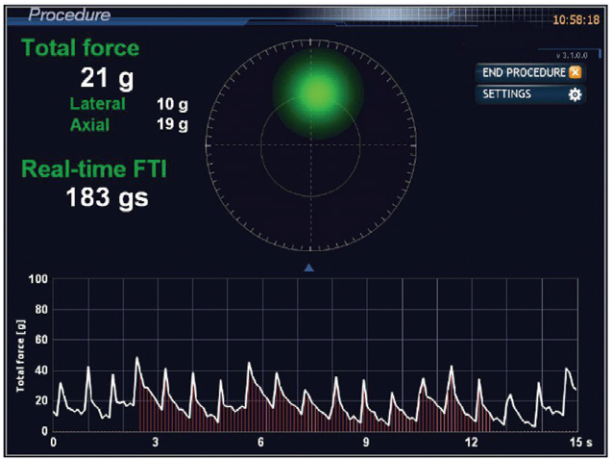

FIGURE 94-12 Real-time contact force information provided by the TactiCath (Endosense, Inc.) ablation catheter. The time-contact force diagram at the bottom shows phasic variation of contact pressure caused by the beating of the heart and respiration.

Conclusion

Ablation is an effective, safe, and established treatment for AF that offers the possibility of a definite cure. The mainstay of AF ablation techniques is achieving a permanent PVAI. Our approach to PVAI, which is guided by a circular mapping catheter and ICE, has been demonstrated to be superior to other techniques of PV ablation in multiple studies. Proven strategies to increase procedural efficacy and safety include the adoption of general anesthesia, targeting additional non-PV sites in selected patients (SVC, CFAE, coronary sinus, or the LAA), and performing procedures under therapeutic oral anticoagulation.

Manual ablation, however, is affected by a significant degree of operator dependency. Technologies such as remote navigation systems, balloon-based ablation systems, multi-electrode ablation systems, and novel catheters with force-contact sensors have the potential to overcome the operator dependency of manual ablation and will likely further increase the adoption of ablation in the treatment of AF.

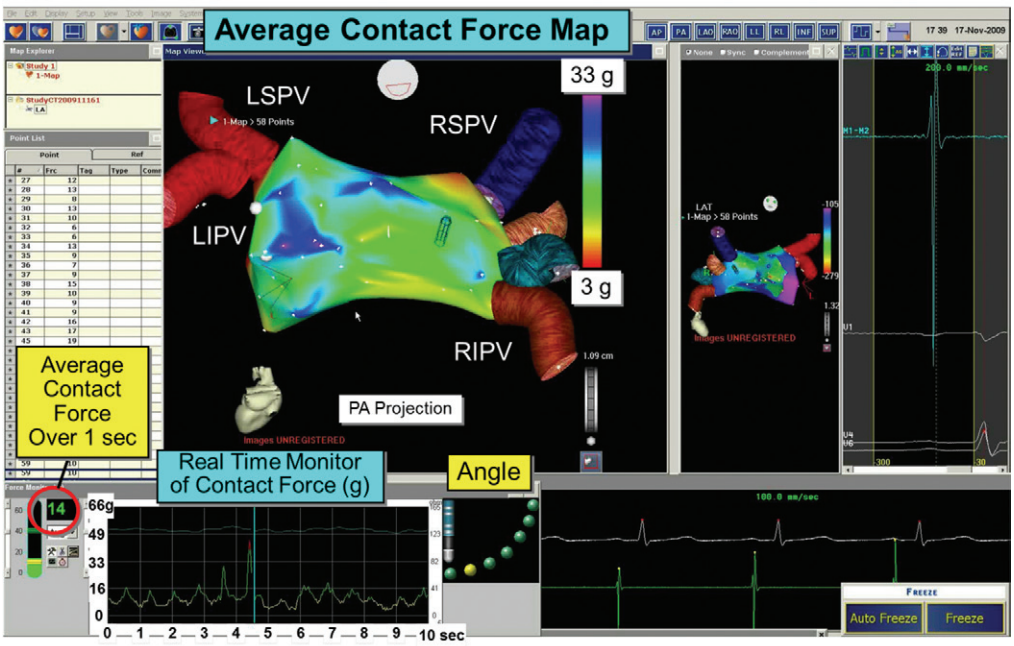

FIGURE 94-13 Real-time contact force information provided by the SmartTouch (Biosense Webster) ablation catheter. The average contact force, its variation over time, and the angle between the catheter tip and underlying myocardium are shown.

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CHAPTER 95

Catheter Ablation of Ventricular Tachycardia: Current Techniques and New Technologies

Indrajit Choudhuri, Jasbir Sra, and Masood Akhtar

Introduction and Historical Perspective

The surgical techniques first described between the late 1950s and early 1980s served as the foundation for ventricular arrhythmia surgery, and the mapping techniques developed during that period are at the core of contemporary catheter mapping and ablation of ventricular tachycardia (VT). Before the advent of catheter ablative techniques, management of drug-refractory VT required open-chest surgical exploration with intraoperative mapping, followed by encircling ventriculotomy, endocardial resection, or cryoablation.[1-6]

Perioperative arrhythmia mapping employed nonsurgical catheter-based techniques to localize the arrhythmogenic myocardium, as well as intraoperative mapping with handheld roving electrodes and electrode arrays to precisely localize the site of VT origin. Mapping was performed in sinus rhythm (SR) to identify complex fragmentation of the local electrogram, indicating regions most likely to harbor latent micro–re-entrant circuits; mapping was also performed during VT to sequence temporal activation through isochronous maps.[7]

Recognition of three dominant activation patterns—focal, circumferential re-entry, and "figure-of-8" re-entry (Figure 95-1)—subsequently defined the approach to VT surgery targets: (1) the earliest site of activation, (2) the scar border zone, and (3) critical segments of the re-entrant circuit.[8]

In 1982, a nonsurgical technique by which an electrode catheter, percutaneously positioned endocardially, could deliver a direct-current defibrillatory shock for the purpose of local tissue destruction was described.[9] The technique proved successful, ushering in the era of percutaneous catheter ablation. Later that year, the technique was successfully applied to treat VT.[10]

Since the first description of VT surgery more than a half century ago, the methods pioneered in the surgical era have evolved through advanced mapping technologies, novel catheter design, and methods of cardiac access for percutaneous techniques, and the preferred energy source has transitioned to radiofrequency (RF) current. In this chapter, these now well-established approaches will be reviewed, as well as recent advances in catheter ablative techniques for the management of VT.

Role of Catheter Ablation in Management of Ventricular Tachycardia

While the foundations of ablation for VT lie in the surgical arena, VT surgery today is reserved for patients in whom the catheter-based approach has failed. RF catheter ablation is the preferred approach to the management of symptomatic, drug-refractory monomorphic VT and ventricular ectopy.

Catheter ablation is considered when VT causes significant symptoms and is refractory or as an alternative to medical therapy. In the absence of overt structural heart disease, ablation may be offered as *primary* and *curative* therapy, as no contributory progressive myocardial disease that promotes VT recurrence exists. The clinical scenario may be complicated, however, by the potential to develop ectopy-mediated and tachycardia-mediated left ventricular (LV) dysfunction, when the use of an implantable cardioverter-defibrillator (ICD) may be difficult to justify after seemingly successful ablation, but deferring may yet have dire consequences.

In patients with structural heart disease, the ICD remains the mainstay, though ablation is an important *adjunct* to prevent recurrent defibrillation discharges, which occur in 20% of patients in primary prevention and 40% to 60% of patients in secondary prevention.[11] VT ablation offers effective symptom control but is at best *palliative*, as targeting existing myocardial circuits does not alter the potential for new circuits to manifest from progressive and continuous myocardial remodeling due to the underlying disease process.

VT involving the His-Purkinje system (HPS) poses a unique clinical scenario in which ablation may serve as stand-alone therapy in patients without structural heart disease. However, VT involving the HPS is more prevalent in valvular heart disease, idiopathic dilated cardiomyopathy and intrinsic neuromuscular disease, where HPS disease develops as an associated manifestation. In these patients, ablation should again be considered adjunctive and palliative therapy, as conduction abnormalities and scarring are not limited to the HPS and involve the myocardium as well. Since ablation targeting the HPS will not circumvent the risk of myocardial VT in these patients, ICD implantation becomes necessary.

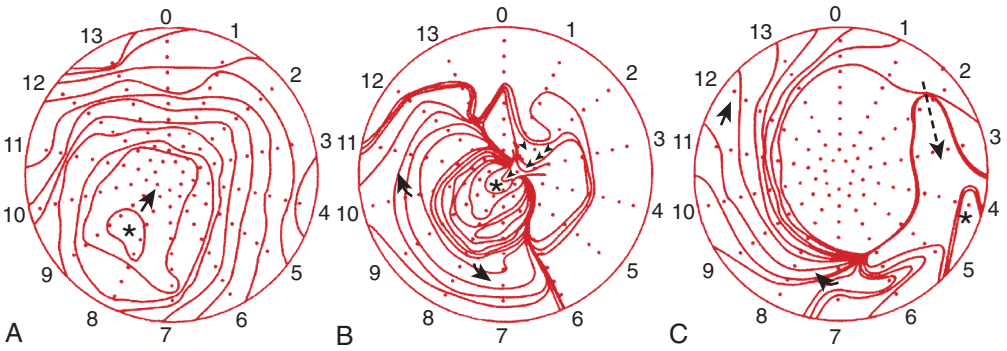

FIGURE 95-1 Patterns of activation observed through trans-atrial balloon mapping. **A,** Focal or mono-regional activation radiates from well-defined focus indicated by an *asterisk*. **B,** Figure-of-8 re-entry with earliest site of endocardial activation indicated by an *asterisk* and propagation in two directions around arcs of block. An area of slow conduction, identified by crowding of isochrones, is identified between two areas of block and is directly contiguous with the site of earliest endocardial activation. **C,** Circular re-entry, in which a large portion of myocardium is involved in a sweeping circular front of activation. Earliest site of endocardial activation is indicated by asterisk and the direction of revolution is "clockwise," with the latest activated areas indicated by *broken arrows* at a site of slow conduction, directly contiguous with the site of earliest activation. Also, note that the center of the circuit path is not activated because of anatomic or functional conduction block. *(From Mickleborough LL, Harris L, Downar E, et al: A new intraoperative approach for endocardial mapping of ventricular tachycardia,* J Thorac Cardiovasc Surg *95:271, 1988.)*

Table 95-1 Mechanisms of Ventricular Tachycardia

MECHANISM	MYOCARDIAL CHARACTERISTICS	VT TYPE
Re-entry occurring within the myocardium	Structural heart disease with myocardial scarring	CAD, DCM, RVD, CHD, HCM, Chagas' disease, cardiac sarcoid
Re-entry involving HPS	Normal heart Normal heart and structural heart disease HPS disease, structural heart disease, or both	ILVT Interfascicular re-entry Bundle branch re-entry, interfascicular re-entry
Triggered	Normal hearts (valves and perivalvular structures)	Outflow tract VTs or PVCs
Automaticity	Normal hearts	Fascicular automaticity, some LVOT VT

CAD, *Coronary artery disease;* CHD, *congenital heart disease;* DCM, *dilated cardiomyopathy;* HCM, *hypertrophic cardiomyopathy;* HPS, *His-Purkinje system;* ILVT, *idiopathic left ventricular tachycardia;* LVOT, *left ventricular outflow tract;* PVCs, *premature ventricular contractions;* RVD, *right ventricular dysplasia;* VT, *ventricular tachycardia.*

Table 95-1 categorizes the most common VTs by mechanism and critical structures involved. The indications for catheter ablation of VT are outlined in Table 95-2.[12]

Mechanistic Targets for Catheter Ablation

Strategies for mapping VT are multiple and complementary and should be tailored to the clinical presentation and putative mechanism. Detailed pathophysiological and clinical evaluation, including the morphology and behavior of spontaneous VT, and recognition of the strengths and limitations of various electrophysiological techniques facilitate and expedite ablation.

VT that is uniform in morphology and localizable, either within a re-entrant circuit or to a focus, is amenable to electrophysiological study (EPS) and catheter ablation. Automatic VTs are rare and generally arise from underlying physiological stress such as myocardial ischemia or sepsis and are poor candidates for study, as the VT often has multiple forms and generally is not responsive to traditional electrophysiology techniques. More importantly, ablation in these patients does not address the underlying predisposing condition that continues to provoke VT. Ablation may prove effective in the rare instance in which automatic VT arises from isolated and identifiable structures or foci.

Re-entry

Histologic changes in the myocardium and the HPS (scar, calcification, patchy fibrosis, surgical incisions) or functional changes without overt structural heart disease may alter myocardial conduction to permit wavefront propagation along a continuously excitable path such that re-entrant activation may produce tachycardia if the time for a single complete revolution is greater than the longest refractory period in the circuit. The normal fibrous skeleton of the heart may also play a role in promoting re-entry by providing anatomic barriers (e.g., valve annuli) that not only create conduction block but, when in proximity to such altered myocardium, also create corridors of conduction that confine the propagating wavefront, slow impulse conduction, and restrict the direction of wavefront propagation, again facilitating re-entry.

Theoretical Basis for Re-entrant Circuits Associated with Myocardial Scarring

The majority of VTs associated with myocardial scarring arise from re-entrant circuits involving the interface between the

Table 95-2 Recommendations for Ablative Therapy

CLASS I

Ablation is indicated in patients who are otherwise at low risk for SCD and have sustained predominantly monomorphic VT that is drug resistant, who are drug intolerant, or who do not wish long-term drug therapy. (level of evidence: C)

Ablation is indicated in patients with bundle-branch re-entrant VT. (level of evidence: C)

Ablation is indicated as adjunctive therapy in patients with an ICD who are receiving multiple shocks as a result of sustained VT that is not manageable by reprogramming or changing drug therapy or who do not wish long-term drug therapy. (level of evidence: C)

Ablation is indicated in patients with WPW syndrome resuscitated from sudden cardiac arrest caused by AF and rapid conduction over the accessory pathway causing VF. (level of evidence: B)

CLASS IIA

Ablation can be useful therapy in patients who are otherwise at low risk for SCD and have symptomatic nonsustained monomorphic VT that is drug resistant, who are drug intolerant or who do not wish long-term drug therapy. (level of evidence: C)

Ablation can be useful therapy in patients who are otherwise at low risk for SCD and have frequent symptomatic predominantly monomorphic PVCs that are drug resistant or who are drug intolerant or who do not wish long-term drug therapy. (level of evidence: C)

Ablation can be useful in symptomatic patients with WPW syndrome who have accessory pathways with refractory periods less than 240 ms in duration. (level of evidence: B)

CLASS IIB

Ablation of Purkinje fiber potentials may be considered in patients with ventricular arrhythmia storm consistently provoked by PVCs of similar morphology. (level of evidence: C)

Ablation of asymptomatic PVCs may be considered when the PVCs are very frequent to avoid or treat tachycardia-induced cardiomyopathy. (level of evidence: C)

CLASS III

Ablation of asymptomatic relatively infrequent PVCs is not indicated. (level of evidence: C)

AF, *Atrial fibrillation;* ICD, *implantable cardioverter-defibrillator;* PVCs, *premature ventricular contractions;* SCD, *sudden cardiac death;* VF, *ventricular fibrillation;* VT, *ventricular tachycardia;* WPW, *Wolff-Parkinson-White.*

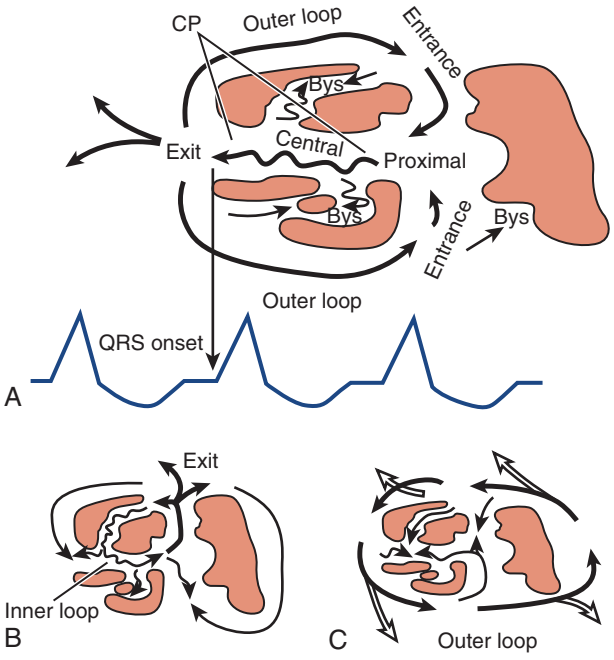

FIGURE 95-2 Theoretic re-entrant circuits developing in a post-infarction model. The re-entry circuit is indicated by the *black arrows*, while *open arrows* indicate excitation wavefronts leaving the circuit and depolarizing tissue not in the circuit or scar (*red regions*). **A,** Circuit that contains two outer loops and a central common pathway (*CP*) or isthmus of slow conduction creating a figure-of-8 re-entry configuration. The QRS is inscribed when the excitation wavefront leaves the common isthmus through the exit and then proceeds along the outer loop. The excitation wavefronts then re-enter the infarct region at the proximal portion of the common isthmus. Regions that are passively activated but do not participate in the tachycardia circuit are labeled as bystanders (*Bys*). **B,** The circuit is contained entirely within the chronic infarct. This circuit consists of an exit and central, proximal, and inner loop regions. **C,** Single outer loop circuit, in which the excitation wavefront circulates around the margins and in the paths within the chronic infarct (bystanders). *(From Stevenson WG, Friedman PL, Sager PT, et al: Exploring postinfarction reentrant ventricular tachycardia with entrainment mapping,* J Am Coll Cardiol *29:1180, 1997.)*

normal myocardium and the abnormal myocardium. Initial in vivo evidence for re-entry came from epicardial recordings in dogs 3 to 7 days following acute infarction. El-Sherif and colleagues recorded electrical activity over infarcted tissue bridging the diastolic interval between consecutive VT beats, providing compelling evidence for re-entry.[13] The clinical relevance of re-entry was subsequently confirmed by intraoperative mapping studies of human VT, using high-density endocardial electrode arrays.[14]

Stevenson and coworkers proposed a theoretical model that clarified the components of VT re-entrant circuits and provided a useful framework to analyze the appropriateness of ablation targets (Figure 95-2). In their model, re-entrant circuits contain a region of slow conduction, representing activation of a relatively small mass of ventricular tissue, critical to the initiation and propagation of tachycardia.[15] Mapping studies in canine models and in humans have suggested that these slowly conducting components are often localized to narrow isthmi, isolated from the adjacent myocardium by arcs of anatomic or functional block and that during VT, impulse propagation through these regions occurs in diastole.[16,17] In fact, Wilber and associates demonstrated that in 4 of 12 patients with VT and prior inferior wall infarction, the isthmus defined by the mitral valve annulus and infarct served as a region of slow conduction critical to the re-entrant circuit.[18] Because these isthmi of slow conduction are anatomically narrow and physiologically essential to re-entry, they provide attractive targets for ablation.

When the excitation wavefront emerges from a region of slow conduction to depolarize the remainder of the myocardium at a site designated by Stevenson's model as the "exit," the QRS complex is inscribed on the surface electrocardiogram (ECG). Subsequently, the re-entrant wavefront may propagate through

normal tissue along the border of the scar (outer loop), through the infarct region (inner loop), or through excitable tissue within the infarct not essential to the circuit (bystander), eventually returning to the proximal segment of the central isthmus of slow conduction.

Re-entrant circuits may be complex. Downar and colleagues observed that strands of surviving myocardial fibers within infarct zones comprise the region of slow conduction required for re-entry and may use alternative entry and exit points during tachycardia.[19,20] The multiplicity of potential re-entrant pathways that result may produce spontaneous changes in the tachycardia cycle length and VT morphology. Moreover, the lack of a single defined exit point suggests that exit sites are poor ablation targets.

Triggers

Triggered activity refers to induced ionic flow across myocyte membranes that stimulate action potential formation linked to, or *triggered* by, a preceding action potential. This nonstimulated response is referred to as "*after-depolarization*," which may occur *during* (phase II or III) or *after* (phase IV) the action potential, termed *early* after-depolarization (EAD) and *delayed* after-depolarization (DAD), respectively. VT may result from a single after-depolarization that initiates re-entry or from repetitive after-depolarizations that maintain the tachycardia.

Repetitive DADs from the ventricular outflow tracts and associated structures manifest as outflow tract VTs and premature ventricular contractions (PVCs). The focal nature of these tachycardias makes them ideal for study and catheter ablation. Programmed stimulation with rapid pacing or administration of catecholamines is often required for induction and provides a suitable endpoint following ablation. Recognition of the susceptibility of triggered activity to menstrual phases facilitates optimal scheduling for EPS and ablation. VT related to digitalis toxicity also occurs because of DADs but is not an indication for catheter ablation.

EADs contribute to the development of polymorphic VT in the setting of increased transmural dispersion of repolarization (e.g., short QT syndrome [SQTS], long QT syndrome [LQTS], Brugada syndrome). These VTs generally do not lend themselves to study because initiation is often related to secondary factors such as bradycardia, electrolyte derangement, or stress; maintenance is not limited to critical structures but rather may involve the entire biventricular myocardium, providing no specific anatomic or physiological targets for ablation. Further, ablation does not address underlying predisposition to VT.

Preoperative Evaluation

Clinical Assessment of Myocardial Scarring and Other Considerations

As part of the clinical evaluation of VT, an assessment for structural heart disease is a prerequisite. Identifying the sites of healthy and scarred myocardium is paramount, recognizing that islands of scar tissue may reside within viable myocardium, and islands of viable myocardium may reside within areas of scar tissue.[21] Coronary stenoses should be identified to predict scar distribution, though scarring may not correlate with regions subtended by coronary arteries if the process is, in fact, idiopathic, dysplastic, or infiltrative. Also, true infarcts may vary in severity in relation to collateral circulation, involvement of watersheds, and availability of dual blood supply, impacting the size, distribution, and transmurality of scar tissue as well as the development of Q waves as seen on ECG. Scarring may be related to prior surgery such as repair of congenital heart disease (CHD) or valvular surgery. In addition, bipolar voltage mapping may not accurately delineate the extent of myocardial scarring, not only because of sampling error but also because anatomically scarred myocardium with overlying hypertrophy, for instance, may be identified as electrically normal.[21]

Intracardiac thrombi should be definitively excluded. Antiarrhythmics should be discontinued or converted to short-acting intravenous (IV) preparations to be discontinued before the EPS, unless these agents slow VT to the point of hemodynamic tolerance that facilitates mapping. Finally, it must be kept in mind that the VT may be epicardial in origin, requiring a pericardial approach that may be hindered in the presence of prior cardiac, thoracic, or abdominal surgery with resultant adhesions within the intended approach trajectory and tissue planes.

Electrocardiogram in Sinus Rhythm and in Ventricular Tachycardia

The approach to VT ablation begins with analysis of a 12-lead ECG obtained during sinus rhythm and in tachycardia. The sinus rhythm ECG is useful in identifying the presence of structural heart disease, particularly (1) prior myocardial infarction (MI) suggested by Q waves, (2) scarring suggested by low-voltage and wide "splintered" QRS morphology arising from delayed and meandering cell-to-cell myocardial conduction, (3) HPS disease suggested by fascicular blocks and increased QRS duration, and (4) alteration in structural geometry with aneurysm formation suggested by persistent ST-segment elevation in the region of a prior MI. An entirely normal ECG is also important as it may suggest an idiopathic type of VT, though structural heart disease must still be excluded. All of these observations aid in anticipating the underlying tachycardia mechanism and provide clues to sites of involvement.[22]

When telemetry is available, evaluation of VT onset may provide insight into the mode of initiation, especially if PVCs with a particular morphology initiate the VT, making them important targets for ablation. In the absence of a 12-lead ECG rhythm of VT strips are useful in determining the cycle length (CL) and approximate morphology for comparison with tachycardias induced in the electrophysiology suite to confirm clinical relevance. In patients with implanted rhythm monitors, including permanent pacemakers (PPM) and ICDs, if no recordings are available to assess the morphology for localization, the device may be programmed to detect, but not deliver, therapy once in the electrophysiology suite. The electrograms from VTs induced during EPS may be compared with device recordings of spontaneous VTs. Similarities between electrograms and CL suggest induction of clinical tachycardia, which may then be localized on the basis of 12-lead ECG of VTs recorded during the study.

Electrocardiogram Features Suggesting Epicardial Origin of Ventricular Tachycardia

The normal sequence of myocardial depolarization initiates endocardially within the specialized conduction system and rapidly activates a relatively large amount of myocardium, accounting for

a steep intrinsicoid deflection. The spread of activation in VT of *endocardial* origin is related to cell-to-cell transmission with eventual HPS activation, delaying the intrinsicoid deflection. Depolarization that originates in the epicardium must activate the myocardium through cell-to-cell transmission *alone* without HPS contribution, further slowing QRS inscription and accounting for the "pseudo–δ-wave" pattern often seen. In VT of right bundle branch block (RBBB) morphology that is successfully ablated at the epicardium as well as during LV epicardial pacing, a duration of pseudo–δ-wave 34 ms or longer and intrinsicoid deflection in V2 of 85 ms or greater is highly sensitive (83% and 87%, respectively) and specific (95% and 90%, respectively) for identifying an epicardial origin. Similarly, QRS *width* is also related to the contribution of the HPS to global LV activation, though QRS width alone may not discriminate epicardial sites from endocardial sites because myriad factors affect ventricular conduction and activation.[23] However, the overall contribution of intrinsicoid deflection to absolute QRS width is greater for the epicardially activated ventricular depolarization than for the endocardially activated ventricular depolarization.[24] A delayed precordial maximum deflection index (MDI, intrinsicoid deflection/QRS width) 0.55 or greater identifies epicardial VT with 100% sensitivity and 98.7% specificity, with best discrimination according to MDI in lead V2 (Figure 95-3).[24]

It is important to appreciate that the role of ECG in the approach to VT ablation is to *estimate* sites of involvement and that the ECG may vary with scar burden and distribution, use of antiarrhythmic agents, and the variable position of the heart within the thorax, either as normal variant or because of intrathoracic pathology causing mediastinal shifting.

Considerations for the Diagnostic Suite

The Mapping System

The contemporary approach to VT ablation involves three-dimensional electroanatomic mapping for (1) the creation of a virtual ventricular geometry, (2) the evaluation of the presence of scar tissue and macro–re-entrant circuits, (3) activation sequence assessment, (4) facilitation of the return of the catheter tip to specific targets that may be physiologically important (e.g., for entrainment and pacemapping, and assessment of local electrograms), and (5) labeling of the sites of ablation with respect to chamber geometry and delivery of contiguous ablation lesions. Current mapping systems provide nonfluoroscopic navigation capabilities to permit detailed substrate mapping and analysis without excessive radiation exposure. In VTs involving the HPS, mapping systems may not be required as the bundle branch, fascicular, and Purkinje potentials may be mapped directly.

Vascular Catheterization

Vascular access is required for the placement of at least one diagnostic electrode catheter to deliver programmed stimulation, generally from the right ventricle. Additional access may be required

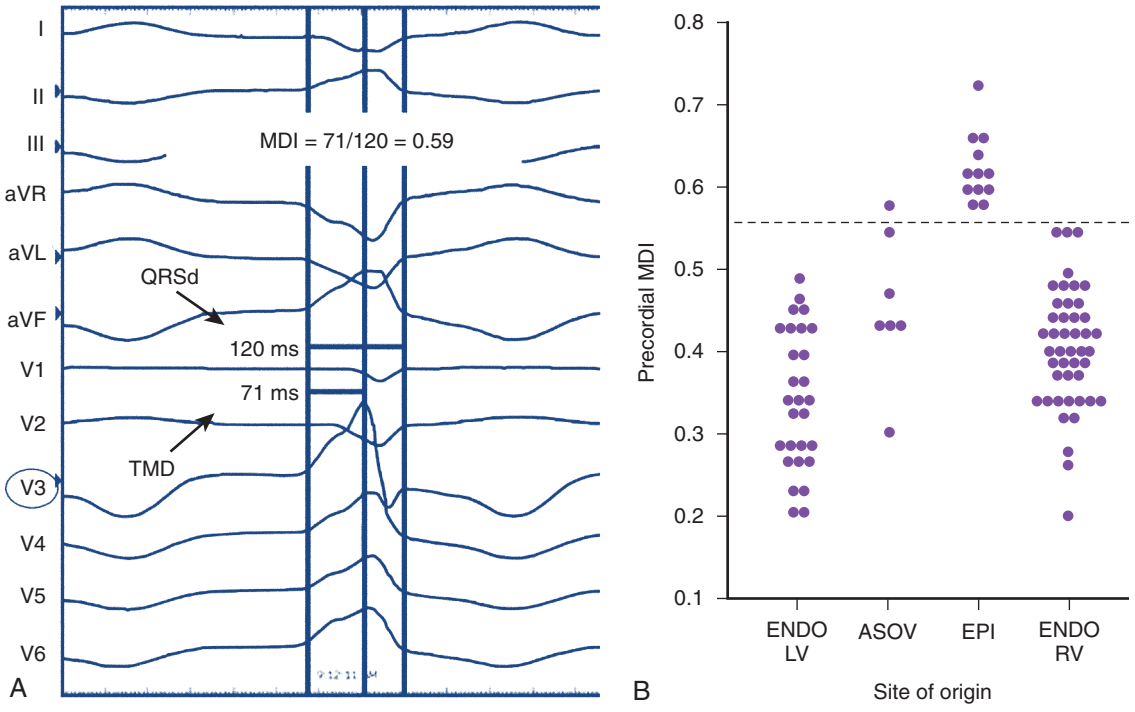

FIGURE 95-3 Assessment of the precordial maximum deflection index (*MDI*). **A,** The MDI is given by the earliest time to maximum deflection (*TMD*) in any precordial leads (in this example, lead V3) divided by total QRS duration (*QRSd*). **B,** Distribution of precordial MDI values in patients with various types of idiopathic ventricular tachycardia (VT). With a cut-point of 0.55, there is excellent discrimination between epicardial (*EPI*) VT and endocardial (*ENDO*) and aortic sinus of Valsalva (*ASOV*) VTs. *LV,* Left ventricle; *RV,* right ventricle. *(From Daniels DV, Lu YY, Morton JB, et al: Idiopathic epicardial left ventricular tachycardia originating remote from the sinus of Valsalva: Electrophysiological characteristics, catheter ablation, and identification from the 12-lead electrogram,* Circulation *113:1659, 2006.)*

for atrial programmed stimulation to entrain fascicular re-entrant VTs, to record the His and bundle branch potentials in idiopathic and bundle branch re-entry VTs, to permit coronary sinus cannulation as a guide to epicardial origin, and to introduce an inferior vena cava (IVC) catheter to serve as a reference for unipolar recordings. Additional femoral venous access may be required for intracardiac echocardiography (ICE), which is useful in guiding trans-septal puncture, identifying aneurysms, demonstrating endocardial catheter contact, and observing for thrombus formation. And, of course, one femoral access is required for the introduction of the mapping or ablation catheter into the presumed chamber of VT origin; this may be venous if the right ventricle is being mapped or if the trans-septal approach is used to map the left ventricle and arterial if a direct retrograde trans-aortic approach is used.

A dedicated arterial line should be placed for close hemodynamic monitoring. If the retrograde aortic approach is employed, the arterial line may be foregone, and the side port of the vascular sheath transduced; however, unless the sheath is 1 Fr size larger than the ablation catheter, the signal may be dampened with insertion of the ablation or mapping catheter, producing spuriously low pressure recordings. After all the vascular access has been obtained, anticoagulation with bolus heparinization, with or without repeat bolus dosing or continuous infusion, should be administered for prophylaxis against thrombus formation, particularly if left intracardiac chambers will be entered.

Approach to the Left Ventricle

No systematic studies have compared the trans-septal approach with the retrograde transaortic approach in VT ablation; however, a few generalizations may be made. The aortic approach, which is simpler and requires no additional hardware, is the preferred first-line method of access to the left ventricle. Aortic catheter advancement should be performed delicately to avoid damaging or engaging and occluding the coronaries and damaging the aortic valve. In patients with severe aortic atherosclerosis, the risk of atheroemboli as well as traumatic intramural hematoma or frank dissection may be increased. The natural curvature of the catheter as it enters the left ventricle facilitates approaching the posterior wall because of the posteromedial relation of the left ventricular outflow tract (LVOT) to the aortic root. The retrograde aortic approach may rarely limit access to the basal anterolateral wall in very tall or large patients, particularly if smaller curve mapping or ablation catheters are used. The decision to use the retrograde trans-aortic approach should be reconsidered in patients with severe peripheral arterial disease and is contraindicated in patients with mechanical aortic valve prostheses and arterial conduits at the femoral puncture site.

In contrast, the trans-septal approach affords access to the left ventricle in these very patients. The orientation of the catheter may facilitate approaching the septal left ventricle, as the catheter tends to follow the natural curve of the trans-septal sheath. Further, it may provide extended catheter availability to reach the anterolateral left ventricle. The trans-septal approach provides additional stability and may be less arrhythmogenic with respect to the mechanical induction or suppression of VT but requires specific expertise, more hardware, and possibly additional personnel, which prolongs and complicates the procedure.[25] Finally, the trans-septal approach is contraindicated in patients with mechanical mitral valve prostheses and may be challenging if closure of an atrial septal defect (ASD) or a patent foramen ovale (PFO) has been performed.

In patients with mechanical aortic *and* mitral prostheses or other contraindications to both vascular approaches to the left ventricle, an epicardial approach may be considered.

Technique of Pericardial Access

Epicardial ablation may be required in specific instances such as with an ECG suggestive of epicardial origin, failed endocardial ablation, or contraindications to endocardial ablation (for example, presence of mechanical aortic *and* mitral prostheses, or LV thrombus). Further, it should be considered for patients with nonischemic cardiomyopathy or Chagas' disease, in which epicardial VTs occur with higher frequency.

Pericardial access, as described by Sosa et al, is obtained under fluoroscopic guidance by advancing an epidural needle or pericardiocentesis needle at 30- to 45-degree angulation toward the scapula while maintaining negative pressure with the plunger of a syringe containing x-ray contrast.[26] As the needle tip approaches the cardiac silhouette, the contrast medium is repetitively "puffed," and will be observed to stain the extracardiac space and structures until the pericardium is breached. Contrast instillation within the pericardial space will layer and outline the cardiac silhouette. Myocardial contact may demonstrate ECG evidence of the injury current, and ventricular penetration will yield bloody aspirate. In the case of right ventricular puncture, usually simple withdrawal of the needle will suffice; the myocardial wall at the site of the puncture will generally collapse and occlude the puncture site, though close observation for hemodynamic compromise is always prudent. In the case of LV puncture, more aggressive management and serial echocardiography to exclude growing pericardial effusion may be required, even in the absence of initially compromised hemodynamics.

When the contrast medium layers along the cardiac silhouette, signifying the position of the needle tip within the pericardial space, a guidewire is advanced far in to maintain pericardial access, observing for a course along the cardiac silhouette or over the cardiac surface and contained by the pericardium and its reflections and not an intracavitary course. A retaining sheath is then advanced over the guidewire to permit introduction and manipulation of the mapping/ablation catheter within the pericardial space (Figure 95-4). If open-irrigated ablation is desired, care must be taken to periodically drain the irrigant or permit continuous drainage via the side port. After the procedure, all intrapericardial hardware must be removed; no specific closure devices are required. A short course of oral nonsteroidal anti-inflammatory drugs, colchicine, or steroids may be prescribed to prevent reactive pericardial inflammation in response to the instilled contrast.

If a history of prior cardiac surgery, myocarditis, or prior pericardial instrumentation for any reason exists, pericardial adhesions may hinder smooth pericardial access. In such instances, surgical dissection in the electrophysiology suite may be required.

Epicardial ablation should not be performed without prior knowledge of the location and distribution of the coronaries. Intraoperative intermittent coronary angiography may be required to visualize ostia or segments that are proximal to the ablation sites; more than 0.5 to 1 cm is considered a safe intervening distance between the closest coronary segment and ablation catheter tip. An alternative is to perform preoperative coronary angiography in the electrophysiology suite using views predetermined

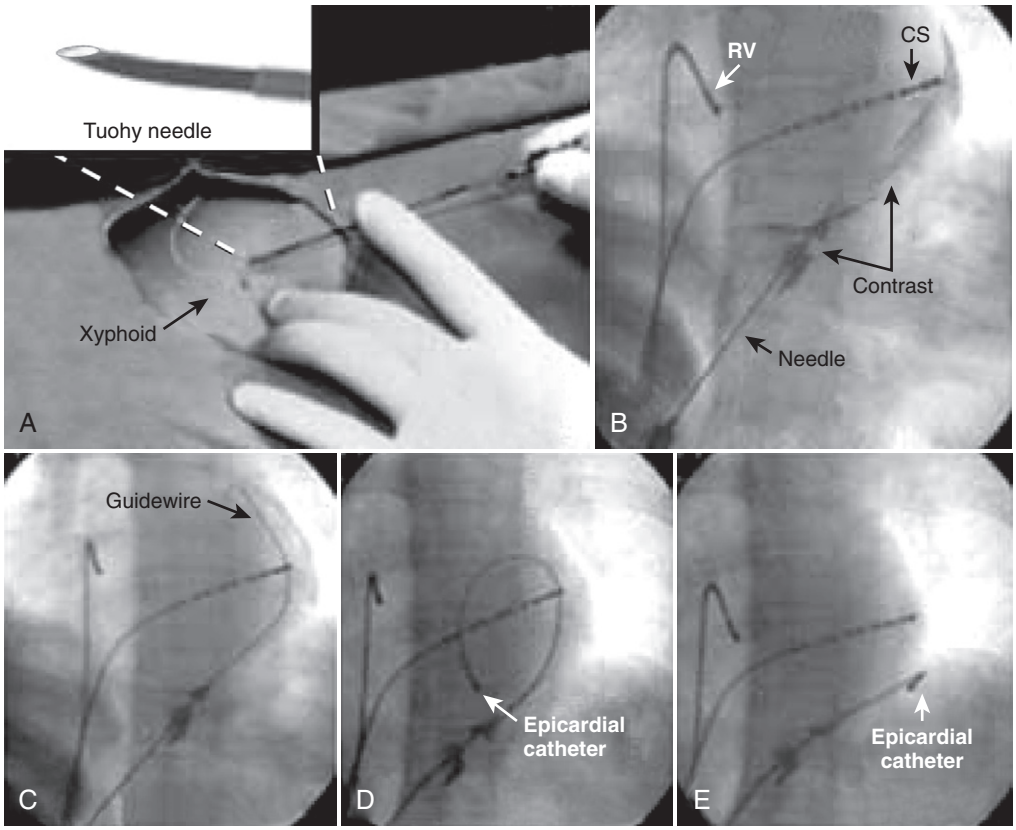

FIGURE 95-4 A, Technique utilized to perform sub-xyphoid approach. A regular Tuohy needle (*upper left, inset*) is used to reach the pericardial space. **B,** Left anterior oblique (LAO) image position showing the exact moment when the contrast medium is layering the heart silhouette. **C,** Guidewire around the heart silhouette correctly positioned inside the pericardial space. **D** and **E,** LAO images of catheter into the pericardial space. *CS*, Coronary sinus; *RV*, right ventricular. *(From Sosa E, Scanavacca M: Epicardial mapping and ablation techniques to control ventricular tachycardia,* J Cardiovasc Electrophysiol *16:449, 2005.)*

to be those used for ablation, which permits comparison of anticipated ablation sites and coronary distribution on stored angiographic views; however, only simultaneous visualization of the coronaries during RF delivery can exclude intraprocedural coronary injury.

Irrigated Radiofrequency Delivery: Clinical Considerations in Ventricular Tachycardia Ablation

While the evolution of ablation catheter technology has seen much progress, a particularly significant advance with respect to VT ablation has been the development of irrigation methods to cool the catheter tip, avoiding excessive heating at the tissue-electrode interface, and preventing coagulum and char formation but improving energy delivery deep within tissue.

Clinical experience with irrigated RF ablation has demonstrated its benefit in VT resistant to ablation with nonirrigated catheters.[27] Of relevance is the fact that the lesions are large and may penetrate scar tissue and effectively ablate surviving myocyte bundles deep to the regions of fibrosis.[28] However, in patients with structural heart disease, particularly LV or right ventricular dysfunction, congestive failure may develop because of excessive volume overload from mismatch of irrigant volume and urine output. In contrast, inadequate irrigant flow rate may fail to prevent char or coagulum formation, thereby preventing effective ablation because of increased impedance and increasing risk of thromboembolism. In addition, intramural boiling can lead to eruption of steam through the myocardial wall, also known as *steam pops*, with a potential for cardiac perforation.

In the first report on internally cooled RF ablation in humans with VT related to structural heart disease, cerebrovascular events and cardiac tamponade occurred more frequently than in the Multicenter European Radiofrequency Survey (MERFS) and the North American Society of Pacing and Electrophysiology (NASPE) survey, though differences in study design and study population may have been contributing factors. The mortality rate related to heart failure was no different from the reported procedure-related mortality rate (2.7%). The overall mortality at 1 year in this cohort was 25%, with 73% related to heart failure, and the majority sustaining recurrent VT.[29]

In a multicenter prospective study of patients with VT associated with prior MI undergoing open-irrigated RF ablation, a similar major complication (10%) and procedure-related mortality rates (3%) were reported. The overall mortality at 1 year in this cohort was 18%, with 79% of those deaths attributed to recurrent VT. Of note, no clinically evident thromboembolism occurred, and better flow and electrode surface cooling afforded by open-irrigation systems were offered as explanations.[30,31]

While irrigated RF ablation potentially improves lesion transmurality, this may not be necessary and may increase risk of perforation in patients with structurally normal hearts, requiring ablation of overlying thin myocardial walls (e.g., right ventricular outflow tract [RVOT]).

Catheter Ablation of Specific Ventricular Tachycardias

The specific approach to catheter ablation of VT hinges on whether VT provokes hemodynamic embarrassment. Techniques for mapping *during* VT are employed when the rhythm is well tolerated, while sinus rhythm *substrate* mapping is performed for poorly tolerated VT. In most cases, VT must be induced in the diagnostic suite at least once, if even for brief duration, for comparison with clinical tachycardia to apply mapping techniques, and to offer an endpoint of noninducibility following ablation. Clinically stable VT may become unstable in the electrophysiology suite as a consequence of relative volume depletion from the lack of oral intake and the vasodilatory and hypotensive effects of anesthesia, making familiarity with multiple ablation techniques critical.

Ventricular Tachycardia Caused by Myocardial Scarring

The most common pathophysiology underlying VT is re-entry caused by myocardial scarring, with post-MI VT representing the most prevalent and most clinically significant form. As re-entrant arrhythmias lend themselves to study, re-entrant VT in the setting of ischemic heart disease is the most common form of VT targeted with contemporary ablation techniques.

Electrocardiography in Ventricular Tachycardia Associated with Prior Myocardial Infarction

A standard 12-lead ECG recorded during VT provides an important tool to localize the myocardial *exit site* and aids in procedure planning to limit the amount of the myocardium that is mapped. While VT localization in the setting of prior MI has its limitations, the methods of Miller et al afford some localization based on the region of prior infarction, QRS morphology in V1 (left bundle branch block [LBBB] or RBBB), pattern of R-wave progression (RWP), and QRS axis.[32] In patients with inferior infarction, these authors found LBBB VT with left superior axis and progressive RWP mapped in most cases to the inferobasal septum. RBBB VTs with a superior axis generally arose from the inferobasal free wall, whereas a leftward axis suggested a more medial exit. RBBB VTs with a right inferior axis usually originated from the inferolateral free wall. In patients with anterior infarction, LBBB VTs with a left superior axis were associated with an inferoapical septal exit, whereas VTs with an inferior axis mapped to the anteroapical septum, though RBBB VTs with a right inferior axis also exited from the anteroapical septum. In general, the site of myocardial exit in LBBB VTs was largely confined to the interventricular septum, and VTs associated with inferior infarction commonly exited from the inferobasal left ventricle.

Disregarding the site of prior infarction, Segal et al found that all LBBB VTs arose from the mid- and basal-interventricular septum, whereas RBBB VTs arose away from the septum; RBBB VTs with a superior axis arose posteriorly, and RBBB VTs with an inferior axis arose apically, or anteriorly from the mid- and basal-interventricular septum.[33]

Overall, the findings from these studies are concordant and generalize VT exit site localization in structural heart disease along the septal-lateral and anterior-inferior axes: LBBB VTs exit septally or rarely from the right ventricle, whereas RBBB VTs may exit septally or away from the septum in the left ventricle. VTs with an inferior axis exit anteriorly, whereas VTs with a superior axis exit inferiorly or posteriorly.

Pacemapping studies also confirmed these findings and further refined VT localization by contributing the third axis—apical-basal—in which dominant precordial R waves (V1-V5) suggest a more basal exit, dominant R in V3 and V4 suggest an exit between apex and base, and dominant precordial S waves suggest an apical exit (Figure 95-5).[34]

Specific Catheter Mapping and Ablation Techniques and Their Relationship to Clinical Presentation

Ablation of re-entrant VT targets critical conducting corridors bounded by nonconducting or poorly conducting tissue—whether it is myocardial scar tissue, abnormal but functional tissue, or anatomic barriers. Ablation targeting these conducting corridors eliminates VT. Ablation of VT in the setting of prior inferior MI affords a model of macro–re-entry that illustrates the ablation strategy in structural heart disease.

Remote Inferior Infarction: A Paradigm for Ablation of Scar-Related Ventricular Tachycardia

The basal inferior or posterior wall receives dual circulation from the distal left circumflex (LCX) and from the proximal right posterolateral branch and the atrioventricular (AV) groove branches of the right coronary artery; this often spares this myocardial territory in the setting of inferior infarction, whether from right or left coronary occlusion. This creates an isthmus of viable tissue between the superior border of an inferior wall scar and the posterior mitral annulus.

As described previously, VT in the setting of remote inferior infarction may be associated with both *LBBB VTs with a left superior axis* and *RBBB VTs with a right superior axis*, suggesting propagation within the same circuit around the scar but in opposite directions, with an inferobasal *septal* exit and an inferobasal *lateral* exit, respectively. From the surgical experience, successful ablation of VT after remote inferior infarction often included cryolesion delivery within this isthmus of surviving myocardium between the mitral valve annulus and the infarct border.[35]

Wilber et al examined the frequency at which slow conduction within this mitral isthmus was critical to the maintenance of VT associated with remote inferior infarction in patients undergoing catheter ablation.[36] Two morphologies of VT were inducible in their patients—*LBBB left superior axis* and *RBBB right superior axis* (Figure 95-6). They observed that single RF energy applications across the mitral isthmus eliminated the inducibility of both morphologies of VT without recurrence over 1 to 11 months of follow-up.

The paradigm of transecting corridors of conducting tissue underlies the approach to ablation of re-entrant scar-mediated VT. Capitalizing on specific features of the substrate, the associated VT morphologies, and regional anatomy facilitates efficient and expeditious ablation.

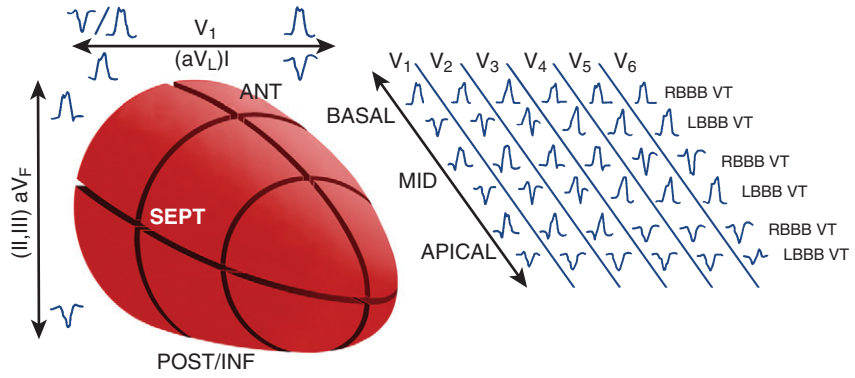

FIGURE 95-5 Depiction of anticipated ventricular tachycardia (*VT*) exit site based on 12-lead electrocardiogram morphology. Cut planes divide heart schematic into 12 segments: septal versus lateral segments; basal, mid, and apical segments; and anterior versus posterior or inferior segments. Bundle branch block morphology in lead V1 suggests a septal (LBBB or RBBB) versus lateral (RBBB) exit site. Note that the RBBB-type morphology may arise from septal and lateral segments but may be distinguished by morphology in lead I (and aV_L). VT QRS axis as determined by inferior leads indicates anterior (inferior axis) versus inferior (superior axis) exit sites. Precordial R-wave transition or progression can be highly variable but suggests basal-to-apical axis exit site, with more basal sites manifesting predominant R-wave pattern in patients with RBBB VT and progressive R-wave increase in patients with LBBB VT. Apical sites manifest dominant QS or S-wave pattern in patients with LBBB VT, whereas patients with RBBB VT develop dominant S waves and transition pattern intermediate between apical and basal pattern for mid-left ventricular exit sites. *ANT*, Anterior wall; *LBBB*, left bundle branch block; *POST/INF*, posterior/inferior wall; *RBBB*, right bundle branch block; *SEPT*, left ventricular septum (lateral wall not labeled).

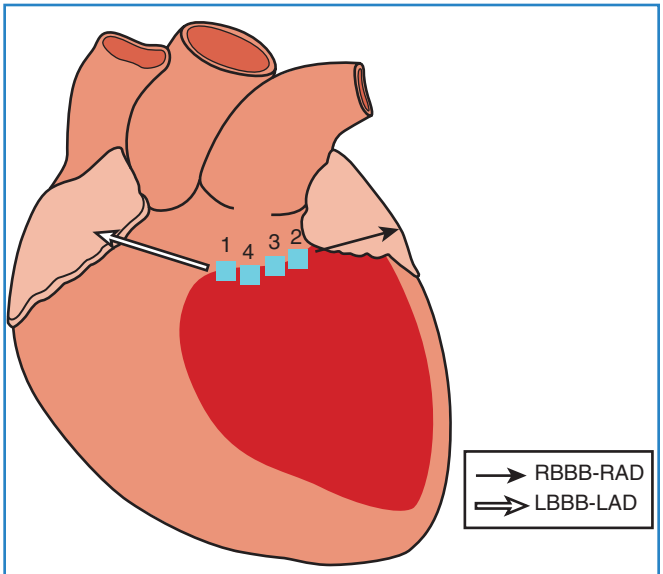

FIGURE 95-6 Schema of mitral isthmus ventricular tachycardia (VT) related to remote inferior myocardial infarction. VTs using the band of tissue between the superior border of an inferior scar (*red region*) and the mitral annulus may have two different QRS morphologies related to the direction of propagation through this isthmus. Both VT morphologies were successfully eliminated with ablation within the mitral isthmus (four patients studied and the location of their ablation delivery shown with numbered *blue* squares). *RBBB-RAD*, Right bundle, right-axis deviation; *LBBB-LAD*, left bundle, left-axis deviation. *(From Wilber DJ, Kopp ED, Glascock DN, et al: Catheter ablation of the mitral isthmus for ventricular tachycardia associated with inferior infarction,* Circulation *92:3481, 1995.)*

Scar Mapping

Knowledge of the distribution of scar tissue permits focus of the mapping process and shortens procedure time. Bipolar voltage mapping using a three-dimensional electroanatomic mapping system is now standard for delineating the extent of VT scarring in the diagnostic electrophysiology suite.[37] Mapping is usually performed during sinus rhythm and the appropriate electrogram amplitudes that adequately discriminate tissue types, typically healthy tissue and scar tissue. The width of the voltage window defines electrogram amplitudes that are felt to represent specific tissue histology and conduction characteristics. Histologic studies have demonstrated that the VT circuit comprises viable tissue bundles embedded within and bordering the scar. Voltage mapping allows the identification of these tissue types, which can then be visualized as a color-coded map based on the electrogram amplitudes.

The map is created through point-by-point collection of position and local bipolar electrogram amplitude data, until a sufficient number and distribution of locations have been sampled to permit reliable reconstruction of the ventricular geometry. The positional data are used to construct an anatomic shell of the endocardium. The electrogram amplitudes, expressed as a color spectrum across the operator-defined voltage window, color code the shell creating a colorized *voltage map*. Current mapping systems use similar display spectra: regions with electrogram amplitude below the lower bound of the voltage window are displayed as *red* or *white*, whereas regions with electrogram amplitude above the voltage window upper bound are displayed as *violet*. Regions with intermediate-amplitude electrograms are displayed in the remaining colors spanning the visible spectrum between red and violet. The resultant maps depict islands of dense scar as red or white, surrounded by a multicolored border of viability, in a violet-colored "sea" of normal myocardial tissue.

Based on porcine infarct model bipolar voltage mapping studies from the University of Pennsylvania, borders of akinetic

myocardium, defined by intracardiac echocardiography, correlated with 2.0-mV isopotential lines, whereas 1.0 mV isopotential lines were consistently adjacent to the scar border on pathologic analysis.[38] The same group used the CARTO system (Biosense Webster Inc., Diamond Bar, CA) to map the LV myocardium in people without structural heart disease and identified that more than 95% of sampled sites had electrograms greater than 1.55 mV. On the basis of their prior work, electrogram voltage less than 0.5 mV was arbitrarily designated as "dense scar." Though few studies have validated these values against more traditional definitions of scarring, the thresholds continue to be applied, with reasonable clinical success, in contemporary ventricular mapping studies.

Mapping Hemodynamically Tolerated Ventricular Tachycardia

Activation Mapping

When VT does not cause hemodynamic instability, the arrhythmia may be allowed to sustain for EPS. Mapping during VT permits observation and study of the activation sequence of the various intracardiac sites at which recording electrode catheters have been positioned; therefore, it is referred to as *activation mapping*. This affords an opportunity to directly evaluate the regions and structures that participate in the VT circuit, as well as the relationships among the circuit anatomy, associated electrograms, and physiology critical to its maintenance, which may identify potential sites for ablation.

Sites of earliest activation (at least 50 ms presystolic) have been postulated to represent exit routes from the circuit to the ventricles and were assumed to be close to regions necessary for the maintenance of re-entry.[4,39] However, the success rate of ablation at these sites has been modest. The limitations with this approach include difficulty identifying the QRS onset from which to reference sites of diastolic, early activation, as well as diastolic or presystolic activation occurring in bystander sites not critical to the VT circuit.[40] Subsequently, diagnostic stimulation methods *applied* at sites of diastolic activity—termed *isolated diastolic potentials* (IDPs)—have proven useful in identifying the sites that are truly integral parts of the re-entrant circuit.[41]

Isolated Diastolic Potentials

Slow conduction through an isthmus bounded by lines of functional or anatomic block during re-entrant VT may produce low-amplitude IDPs preceding the QRS onset by as much as hundreds of milliseconds (Figure 95-7).[42-44] Although "bystander" regions may generate IDPs, potentials that cannot be dissociated from VT despite repeated induction of arrhythmia may signify essential components of the re-entrant circuit and important ablation targets. Fitzgerald and coworkers isolated such potentials in 7 of 14 post-infarct VTs. In each case, ablation at the site of these IDPs was successful.[45] Subsequently, Bogun and associates observed uniform concordance between sites of IDPs that could not be dissociated from post-infarct VTs and sites of concealed entrainment, providing additional evidence that isolated diastolic potentials originate in critical regions of slow conduction.[43]

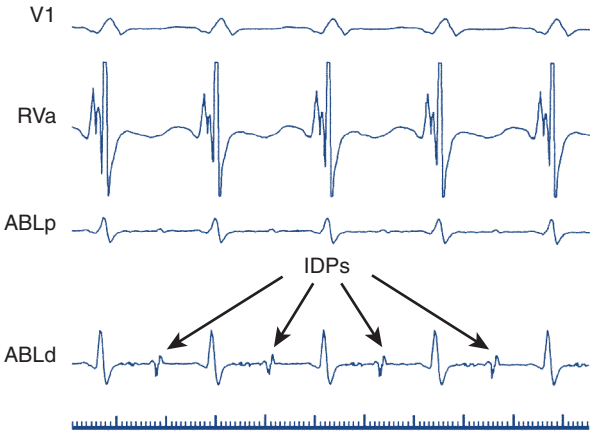

FIGURE 95-7 Catheter mapping during ventricular tachycardia reveals potentials separated from other intervening signals by an isoelectric phase during ventricular diastole—isolated diastolic potentials (*IDPs*). The relation between the IDPs and intervening ventricular electrograms is fixed, suggesting 1 : 1 activation. Identification of IDPs signifies regions of slow conduction that may participate in the re-entrant circuit.

Entrainment with Concealed Fusion

Entrainment mapping depends on the presence of an "excitable gap" in re-entrant circuits.[46] During tachycardia, an interval exists when the myocardium within a discrete portion of the re-entrant circuit has recovered from the preceding activation wavefront but has not yet been depolarized by the next orthodromic wavefront. When a train of pacing stimuli is applied to a re-entrant circuit during tachycardia at a CL less than the tachycardia CL such that each stimulus falls within this "excitable gap," the orthodromic wavefronts initiated by pacing propagate through the circuit, whereas the antidromic wavefronts collide with the returning orthodromic impulses. The resulting acceleration of QRS complexes to the pacing rate during tachycardia constitutes entrainment.

During VT, entrainment from a site outside the tachycardia circuit results in fusion of the paced and tachycardia QRS morphologies, producing a blended intermediate QRS morphology. When pacing from within the circuit, the paced and tachycardia QRS morphologies appear identical, so entrainment results in the fusion of identical QRSs. This absence of *apparent* fusion is termed *concealed fusion* and suggests pacing from within the tachycardia circuit (Figure 95-8).

To verify concealed fusion, it is essential to pace at several CLs during entrainment.[15] Pacing at slower rates outside the re-entrant circuit may produce minimal QRS fusion and masquerade as concealed fusion, as wavefronts propagating away from the pacing site and wavefronts emerging from the tachycardia circuit collide close to the pacing site. Pacing at faster rates in these regions, however, should produce progressive fusion as the point of wavefront collision moves away from the pacing site.

Entrainment with concealed fusion alone, however, does not specifically localize critical regions of slow conduction within re-entrant circuits. Theoretically, pacing adjacent bystander sites may produce entrainment with concealed fusion (Figure 95-9). Supporting this concept, Bogun and colleagues observed that in

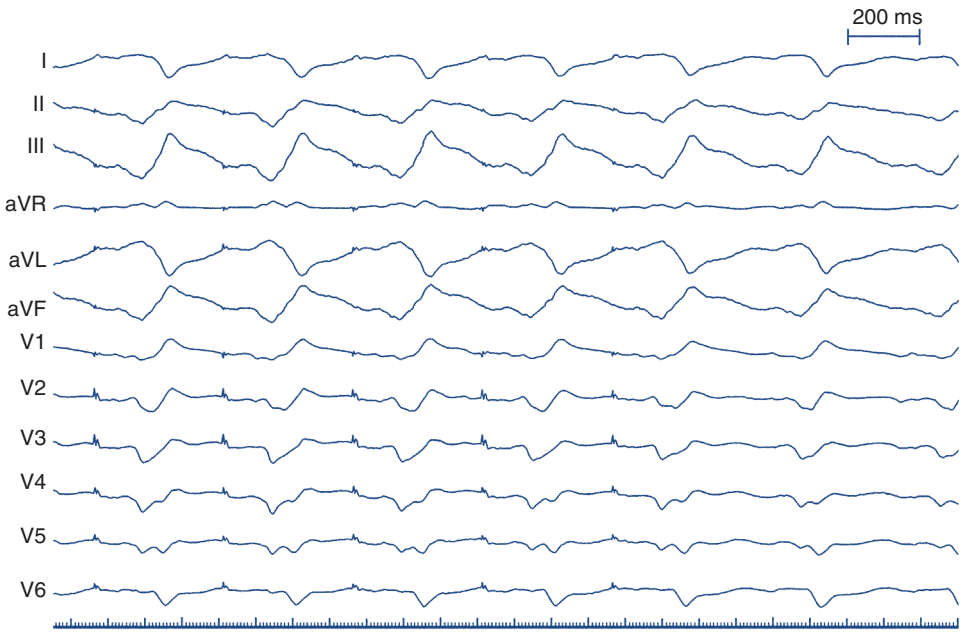

FIGURE 95-8 Concealed entrainment. Ventricular pacing through the mapping catheter at a cycle length just shorter than ventricular tachycardia (VT) cycle length accelerates VT to the pacing cycle length. Cessation of pacing permits continuation of VT at the spontaneous or intrinsic cycle length. Note that the entrained VT morphology is identical to spontaneous VT. Entrainment is achieved without manifest fusion, hence "concealed."

14 patients with post-infarct monomorphic VT, the positive predictive value of concealed entrainment for localizing successful RF ablation targets was only 54%.[47] Therefore, additional criteria have been developed to enhance specificity.

Postpacing Interval

After demonstration of concealed entrainment, the further demonstration of a postpacing interval (PPI) equal to the tachycardia cycle length suggests that a pacing site represents an essential portion of the re-entrant circuit.[42] After pacing within a re-entrant circuit, the stimulated orthodromic wavefront makes one revolution through the circuit before returning to the pacing site, where a local electrogram is recorded. The time from the last captured pacing stimulus in a pacing train to the next local electrogram recorded at the pacing site—the PPI—should equal the tachycardia CL. When a site outside the re-entrant circuit is paced, the paced wavefront must propagate into the circuit, around the circuit, and back to the pacing site. This would result in a PPI exceeding the tachycardia CL by the conduction time to and from the VT circuit (see Figure 95-9).

The approximation of the tachycardia CL by the PPI depends on the maintenance of a consistent re-entrant pathway and stable conduction velocities during tachycardia and pacing. Slowing of conduction or the development of functional block will prolong the PPI, irrespective of the pacing site. In canine models of VT, these confounding factors were demonstrated to occur during rapid pacing.[48,49] Therefore, it is critical to use the slowest stimulus trains, usually 10 to 40 ms shorter than the VT cycle length, for analysis of PPI.[15]

Errors in the measurement of the PPI may also arise from stimulation and recording techniques.[50] Unless unipolar stimulation during entrainment is used, the point from which excitation spreads remains uncertain. Although the same distal electrode used for pacing should ideally be used to record the unipolar electrogram for measurement of PPI, the unipolar stimulation artifact often obscures this signal, necessitating the substitution of unipolar or bipolar signals recorded from more proximal poles. When closely spaced electrodes are used for stimulation and recording, minimal error is introduced to the measurement.[51] If the recording and stimulation electrodes are farther apart, particularly in the presence of depressed myocardial conduction velocity, substantial error may result. Finally, the predictive accuracy of the PPI depends heavily on the ability to differentiate near-field from far-field recordings.

Stevenson and coworkers reported that a PPI within 30 ms of the VT cycle length was strongly associated with successful RF ablation–mediated termination of tachycardia.[42] This finding was not confirmed by Bogun and associates who found that the prevalence of PPI within 30 ms of the VT CL did not differ substantially between effective and ineffective ablation target sites.[52] These conflicting findings may have been caused by important methodologic differences, and while the statistical correlation with clinical success remains controversial, PPI is broadly applied in evaluating tachycardias and assessing proximity to critical sites within re-entrant circuits.

S-QRS Interval

During entrainment with concealed fusion, the interval between the pacing stimulus and the QRS onset (S-QRS interval) represents the conduction time from pacing site to the exit site for a re-entrant circuit. When pacing within a circuit, the time from the local electrogram recorded at the pacing site to the QRS onset

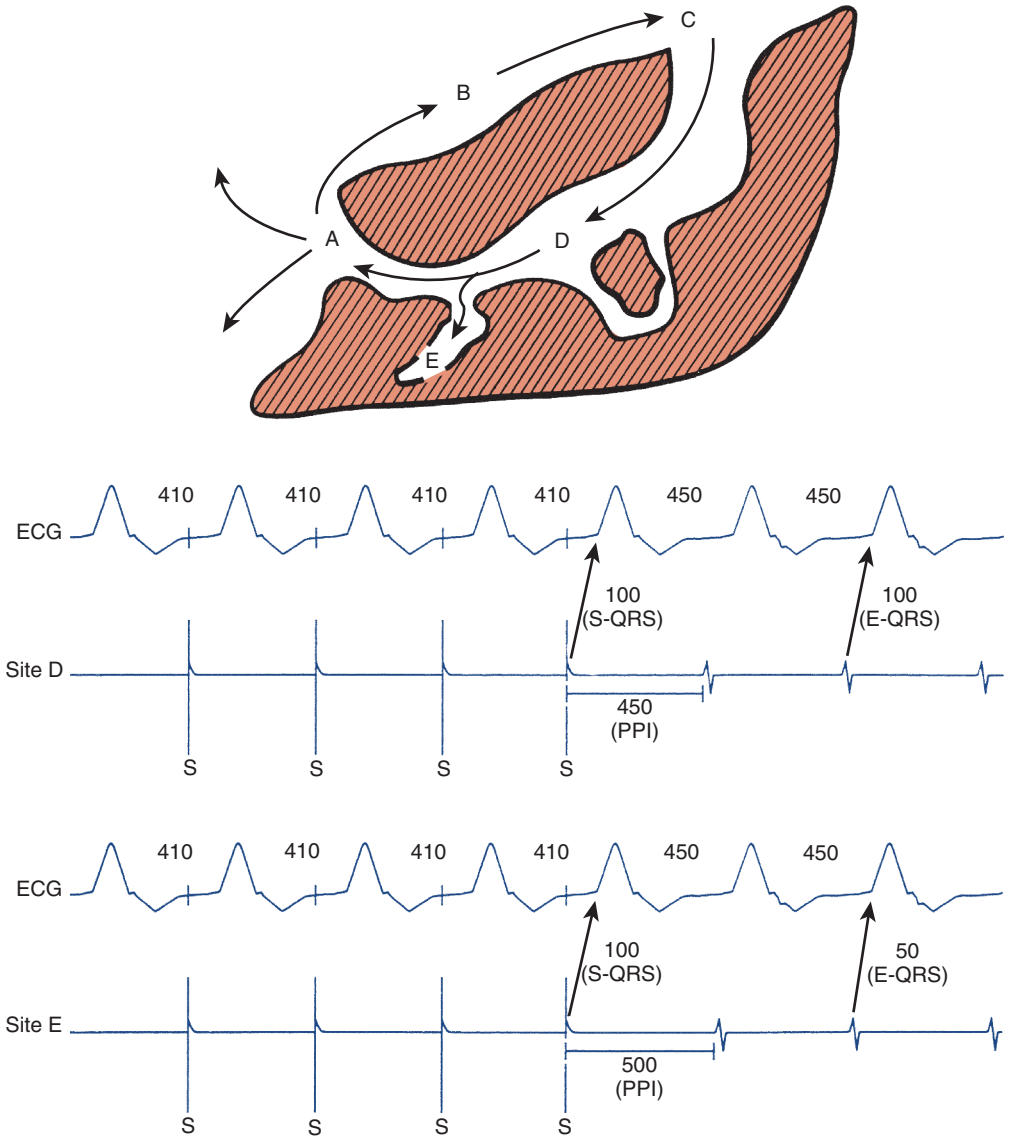

FIGURE 95-9 Schematic contrasting entrainment with concealed fusion at a site within a theoretical re-entrant circuit (*site D*) and at a bystander site (*site E*). The circuit contains a protected region bounded by inexcitable tissue from site C to sites D and A. Tachycardia wavefronts exit the protected region at site A. A stimulus at site D or E produces an orthodromic wavefront that propagates toward site A, where it exits the protected isthmus to activate the remainder of the myocardium and propagate through the circuit from site A to sites B and C, resetting the tachycardia. Whether the stimulated wavefront originates at site D or E, the impulse exits the circuit at site A, the tachycardia exit site. Therefore, QRS intervals during pacing and tachycardia are identical, as demonstrated in the tracings below the schematic. The postpacing interval (*PPI*) and S-QRS intervals may be used to differentiate sites within the tachycardia circuit and bystander regions. Following entrainment at site D, the stimulated wavefront propagates from the pacing site to sites A, B, and C, returning to site D resulting in a PPI equal to the tachycardia cycle length. After stimulating site E, in contrast, the orthodromic wavefront must travel into the tachycardia circuit, traverse the circuit, then return to site E before a local electrogram is recorded at the tip of the pacing catheter. The PPI would, therefore, exceed the tachycardia cycle length. The interval between the stimulus and the onset of the QRS (*S-QRS*) represents the conduction time from the pacing site to the exit site (*site A*). When stimulating within the circuit at site D, the time from the local electrogram recorded during tachycardia at the pacing site to the QRS onset (*E-QRS*) approximates the S-QRS interval. Pacing bystander site E produces an S-QRS interval that exceeds the E-QRS interval.

during tachycardia is ordinarily within 20 ms of the S-QRS interval. In contrast, pacing a bystander site does not produce an S-QRS interval that approximates the local electrogram to QRS (E-QRS) interval during tachycardia (see Figure 95-9).[15,42] Also, according to the Stevenson model of entrainment mapping, when S-QRS is 30% to 70% of the VT CL, it suggests a location central or proximal within a slowly conducting isthmus. S-QRS intervals less than 30% of the VT CL suggest distal sites within the isthmus, or exit sites and sites that exceed 70% of the VT CL, represent inner loops (Figure 95-10). Entrainment of VT is shown in Figure 95-11. Application of the Stevenson algorithm suggests that the mapping catheter is located at an exit site.

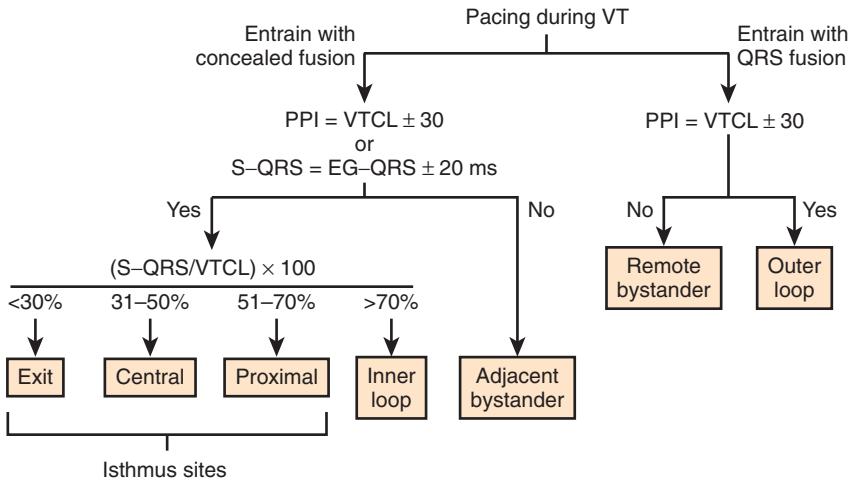

FIGURE 95-10 Ventricular tachycardia (*VT*) entrainment response interpretation algorithm. If pacing entrains tachycardia with concealed fusion, the postpacing interval (*PPI*) or S-QRS interval is assessed to determine whether the site is in the re-entry circuit. If the site is not in the circuit, it is classified as an *adjacent bystander*. If the site is in the circuit, the S-QRS interval expressed as a percentage of the tachycardia cycle length is used to classify the site relative to the circuit exit. Sites with an S-QRS interval 70% of the VT cycle length (*VTCL*) have the highest incidence of tachycardia termination and are referred to collectively as *isthmus sites*. If pacing entrains the tachycardia with QRS fusion and the PPI is consistent with a re-entry circuit site, the site is classified as an *outer loop*. Sites where pacing entrains the tachycardia with QRS fusion and the PPI exceeds the tachycardia cycle length are *remote bystanders*. The EG-QRS interval from the electrogram is recorded at the pacing site during VT to QRS onset. *(From Stevenson WG, Friedman PL, Sager PT, et al: Exploring postinfarction reentrant ventricular tachycardia with entrainment mapping,* J Am Coll Cardiol *29:1180, 1997.)*

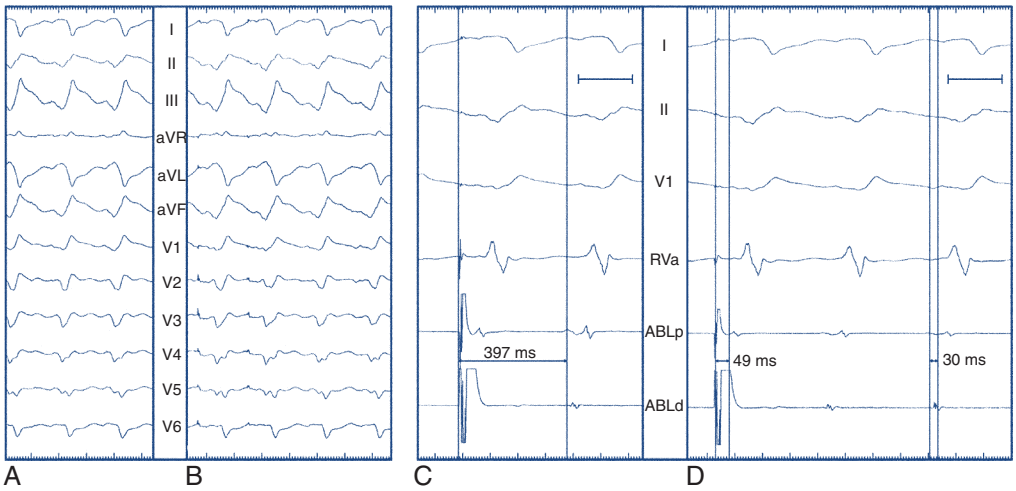

FIGURE 95-11 Example applying entrainment mapping criteria (Stevenson algorithm). **A,** Sustained ventricular tachycardia cycle length (VTCL) 380 ms. **B,** Overdrive pacing at 30 ms shorter than VTCL accelerates the tachycardia to the pacing CL with paced morphology identical to clinical tachycardia (concealed entrainment), and cessation of pacing results in continuation of tachycardia at clinical CL. **C,** Measurement of the postpacing interval (PPI)—interval from the last pacing stimulus to the first electrogram on the pacing channel (PPI = 397 ms). **D,** Measurements of intervals between pacing stimulus and associated paced QRS, and electrogram to associated QRS; difference between these intervals (S-QRS less E-QRS) is 19 ms. All findings thus far suggest that the pacing site is within the tachycardia circuit. Ablation at this location fails to terminate the tachycardia. Note that that the S-QRS interval is only ~13% of the VTCL, suggesting that the catheter location is actually at an exit location and not within a conducting isthmus of tissue inside the scar.

Recently, El-Shalakany and colleagues evaluated the accuracy of entrainment mapping criteria for predicting the termination of VT by a single RF lesion. In 15 consecutive patients with coronary artery disease, they attempted RF ablation of 20 monomorphic VTs. They looked for the following at each potential ablation site: (1) exact QRS match during entrainment; (2) PPI approximating VT cycle length; and (3) E-QRS interval (during VT) equal to S-QRS interval (during pacing/entrainment), but less than 70% of VT CL. At all of the 19 sites that met all three criteria, tachycardia terminated with a single RF application. In contrast, ablation

failed to terminate VT at 24 of 25 sites not meeting all three criteria.[53] Bogun and coworkers prospectively evaluated the predictors of effective ablation in the presence of concealed entrainment. Studying 14 patients with coronary artery disease and hemodynamically stable monomorphic VT, they found that concealed entrainment alone carried a positive predictive value (PPV) of 54% for successful ablation. This increased to 72% when the S-QRS/VT CL ratio was less than 70% and increased to 82% when the S-QRS interval matched the E-QRS interval. The finding of mid-diastolic potentials associated with VT further enhanced the PPV to 89%.[47]

Pacemapping

Unipolar pacing from the tip of the mapping catheter (cathode) during sinus rhythm permits comparison between paced QRS complexes and the QRS complexes during clinical VT, referred to as *pacemapping*.[54-56] This technique is applicable to both stable and unstable VTs, as pacing is performed during SR for brief periods and should not provoke hemodynamic embarrassment. Pacing is performed at a rate similar to that of clinical tachycardia because local myocardial conduction velocities and refractory periods may change with the frequency of activation, altering the surface ECG morphology. The ECGs during pacing and tachycardia are then compared. Optimal pacemaps are those with the closest match between QRS morphologies, including both R wave/S wave ratio and fine notching, in each of the 12 leads (Figure 95-12).

Pacemapping in structural heart disease is limited primarily because pacing may produce QRS patterns grossly disparate from VT despite their proximity to a VT exit. This occurs because the spread of ventricular activation from a pacing site may be different from the sequence of activation during VT exiting from the same site. In addition, the amount of myocardium initially activated, which determines the QRS morphology, may differ significantly between pacing and VT. Excessive pacing current and use of a bipolar pacing configuration rather than a unipolar pacing configuration, both of which increase the size of the virtual electrode, may also significantly impact the QRS morphology. Such observed QRS differences between pacing and VT would divert the operator away from a potentially important VT exit site. Therefore, pacemapping should be performed at two times the diastolic threshold at the tachycardia CL. If unipolar pacing results in significant stimulus artifact obscuring the QRS itself, closely spaced bipolar pacing, which approximates unipolar pacing with a pacing area small enough to not significantly augment the virtual electrode or obscure the paced complex, can be used.

Mapping "Unmappable" Ventricular Tachycardia

More than 90% of clinically relevant VTs precipitate hemodynamic collapse and were previously deemed unmappable using techniques applied to patients with tolerated VT.[54] In addition, patients with clinical VT may be noninducible in the diagnostic suite. While the optimal approach to mapping unmappable VT has yet to be defined, the general approach relies on substrate analysis searching for surrogates of re-entrant pathways.

Complementary Use of Substrate and Pacemapping

The most widely applied approach involves voltage mapping during sinus rhythm and pacemapping around the perimeter of scar tissue to identify paced QRS matches most closely approximating the target VT morphology, thereby identifying exit sites of the scar that could be clinically relevant. Linear ablation lesions are then delivered at these sites, obliquely transecting the edges of the scar, with the expectation of interrupting a critical portion of the re-entrant circuit (Figure 95-13).

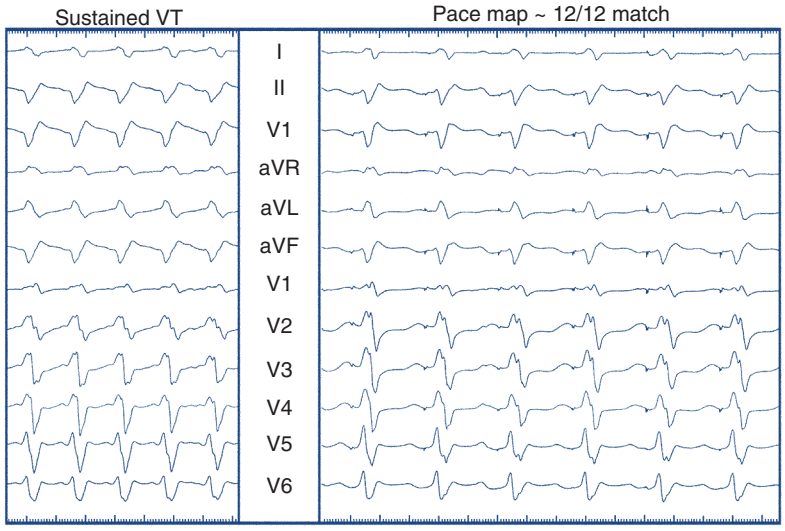

FIGURE 95-12 Pacemapping. Pacemapping, in this case of ventricular tachycardia (*VT*) (*left*), is undertaken by pacing through the roving mapping catheter (*right*) from various candidate myocardial locations in an effort to reproduce the morphology of the clinical arrhythmia. True pacemap matches must reproduce not only the overall polarities of the QRS, but its smaller undulations, notches, and minor details. Note how the paced QRS complexes reproduce not only the primary vectors of the Q, R, and S waves of the clinical VT but also the more subtle features, and that these characteristics are reproduced in all 12 leads of the standard electrocardiogram, that is, a "12 of 12" match.

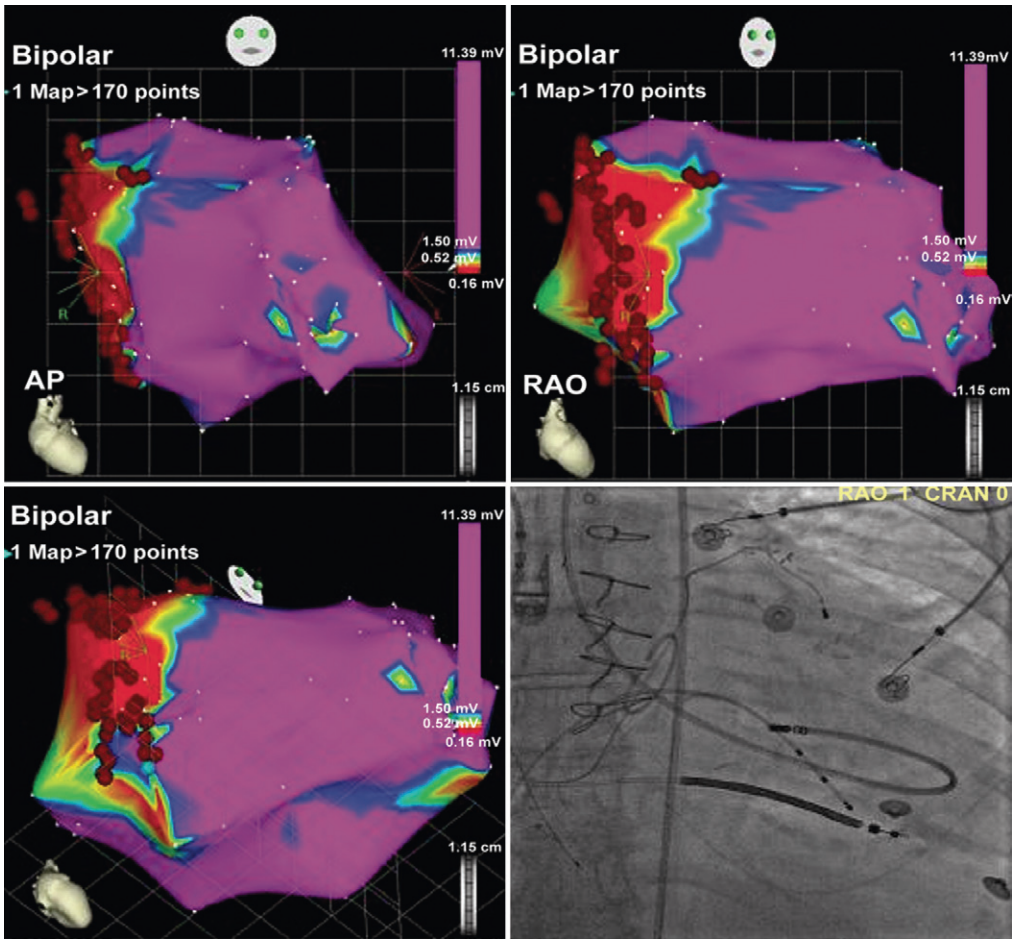

FIGURE 95-13 Electroanatomic map (CARTO) of the left ventricle in multiple projections (*upper left:* anteroposterior [AP]; *upper right:* right anterior oblique [RAO]; *lower left:* RAO caudal) demonstrating perimitral annular dense scar (*red*) involving the basal septum, and healthy myocardium (*purple*) elsewhere. Pacemapping performed at the blue annotation (*lower left*) produced a "12 of 12" match (see Figure 95-12). Radiofrequency was delivered in a linear fashion just inside the scar border from the site of pacemap match, believed to represent a scar exit site, to the mitral annulus to prevent reentry. *Lower right,* A fluoroscopic projection of the ablation catheter positioned at the site of pacemap patch is shown.

Marchlinski and associates first applied this approach in 16 patients with drug-refractory monomorphic VT not amenable to conventional mapping on the basis of associated hemodynamic instability or inability to sustain tachycardia during mapping. Between 8 and 87 RF lesions were applied per patient, with the creation of between 1 and 9 linear lesions. During a median follow-up of 8 months, 12 patients (75%) remained free of VT.[57]

Wilber et al evaluated the relationship of the scar geometry to the slowly conducting channels, defined by entrainment criteria, and found them oriented perpendicular or tangential to the scar border.[58] Exit sites generally resided within 1 to 1.5 cm of the scar border. Marchlinski et al modified their technique to incorporate this relationship, with delivery of 3- to 4-cm linear lesions 1 to 2 cm within the scar border zone "to avoid the potential 'fanning out' of the slow conduction channel at its junction with normal myocardium," and improved outcomes in patients with unmappable VT, with more than 90% of patients experiencing complete elimination of VT or more than 90% reduction in monthly VT episodes over long-term follow-up.[57]

Unstable Ventricular Tachycardia

While scar mapping followed by ablation at VT pacemap-matched sites was revolutionary in its applicability to a large clinically relevant population—patients with unstable VT—the need to offer ablation to this growing population of patients has driven investigation that yielded a deeper understanding of the VT substrate and subsequently translated into hybrid techniques targeting the various pathophysiological components of the re-entrant circuits in patients with unmappable VTs, without exposing patients to excessive ablation or prolonged procedures.

Late Potentials and Fractionated Local Electrograms During Sinus Rhythm and Pacemapping

As impulses propagate slowly through islands of viable myocardium within infarcted regions during sinus rhythm, low amplitude, fractionated endocardial potentials result, consistent with asynchronous activation of myofiber bundles.[59] This slow,

fractionated local depolarization may even persist beyond the QRS complex to produce the *late potentials* that are sometimes recorded endocardially.[60] Stevenson and associates demonstrated that pacing in regions exhibiting late potentials commonly results in S-QRS intervals of less than 40 ms—evidence that t hese electrograms are associated with slow conduction that may permit re-entrant VT.[60] In their study of 24 patients with re-entrant VT, Harada and coworkers recorded late potentials in 71% of sites classified by entrainment mapping as appropriate targets for ablation. The incidence of late potentials at bystander sites approached 33%, particularly with long S-QRS intervals, and short S-QRS intervals were found at critical sites close to the scar exit, limiting their usefulness as sole predictors of successful ablation sites.[60] Late potentials may be identified throughout the myocardial scar and are not specific for re-entry channels critical to the operative VT circuit. Further, many re-entry circuit sites do not exhibit late potentials in SR, impairing both their sensitivity and specificity for identification of critical conducting channels.[60]

Electrograms with Isolated Delayed Components

Instead of SR mapping, changing the direction of activation wavefront propagation with right ventricular pacing allowed Arenal et al and others to unmask diastolic potentials that were isolated, delayed, and not always appreciated in SR (Figure 95-14).[61,62] Ninety-two percent of sites exhibiting electrograms with isolated delayed components (E-IDCs) were related to clinical VT, according to traditional pacemapping and entrainment criteria. Ablation was delivered until all E-IDCs were eliminated, resulting in noninducibility of clinical VTs in all but one patient, in whom re-inducibility was not tested.[62]

Dense Scar and Electrical Unexcitability

The most widely held definition of a scar from the perspective of cardiac mapping is tissue with bipolar electrogram amplitude less than 1.5 mV and that of dense scar less than 0.5 mV. Studies have shown, however, that areas of dense scar tissue defined by the 0.5-mV threshold may be traversed by viable, excitable tissue bundles with recordable, albeit very low-voltage, electrograms that are important to the central common pathways or critical isthmi of VT circuits in patients with remote MI. To that end, the infarct substrate has been described on the basis of physiological parameters, designating "electrically unexcitable scar" regions with electrical noncapture at pacing current of 10 mA at 2-ms pulse width according to Soejima, or "dense scar" regions with no recordable electrograms and no local capture in response to pacing according to Kottkamp.[63,64] In their studies, these regions of physiologically dead tissue were close to, and often bounded by, the conducting channels critical to the VT substrate, facilitating an ablation strategy that transected such channels.

Mapping the Channels Within the Scar

Arenal et al attempted to further define the composition of scar tissue in patients with sustained monomorphic VT after MI; they evaluated the impact of narrowing the electrogram voltage window and stepwise reduction in the less than 0.5-mV arbitrary definition of a dense scar to 0.05 mV on the basis of data, thus demonstrating a wide variation in electrogram amplitudes within the scar below less than 0.5 mV.[65] As compared with maps created with traditional voltage settings (Figure 95-15, *A*), their approach identified at least one complete conducting channel (Figure 95-15, *B*) contributing to re-entry circuits in 77% of cases, with the

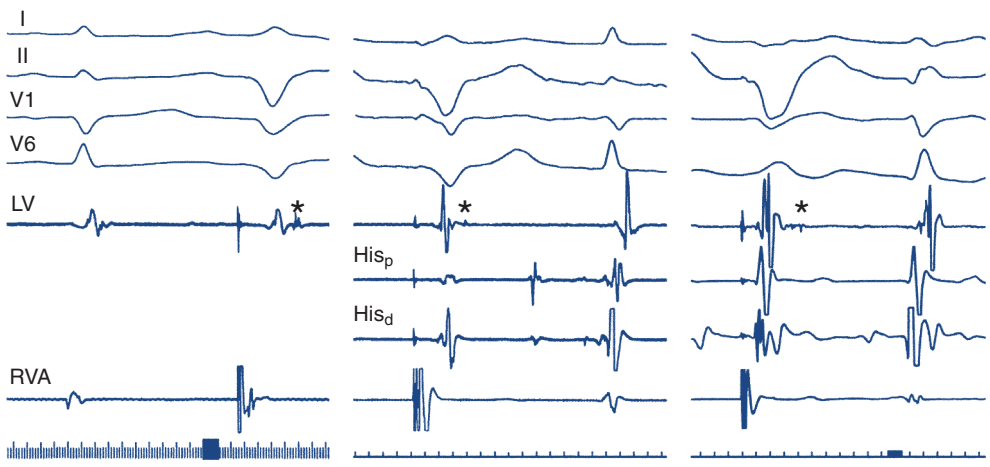

FIGURE 95-14 Ventricular pacing to identify isolated diastolic potentials (IDPs) not otherwise appreciated during sinus rhythm (SR). Examples of ventricular myocardial mapping to identify components of ventricular tachycardia circuits demonstrates that ventricular pacing allows identification of IDPs (*asterisk*) not detected from the same location when the ventricular myocardial activation is during SR (adjacent beat in each panel). This is explained by SR activation of the left ventricle through the His-Purkinje system that activates multiple myocardial regions almost simultaneously with resultant wavefront collision, preventing unimpeded propagation through the slowly conducting channels. Right ventricular pacing slows the activation of the left ventricle and provides a degree of unidirectionality that permits engagement and propagation through the slowly conducting channels without collision of multiple wavefronts, thereby permitting detection of the IDPs.

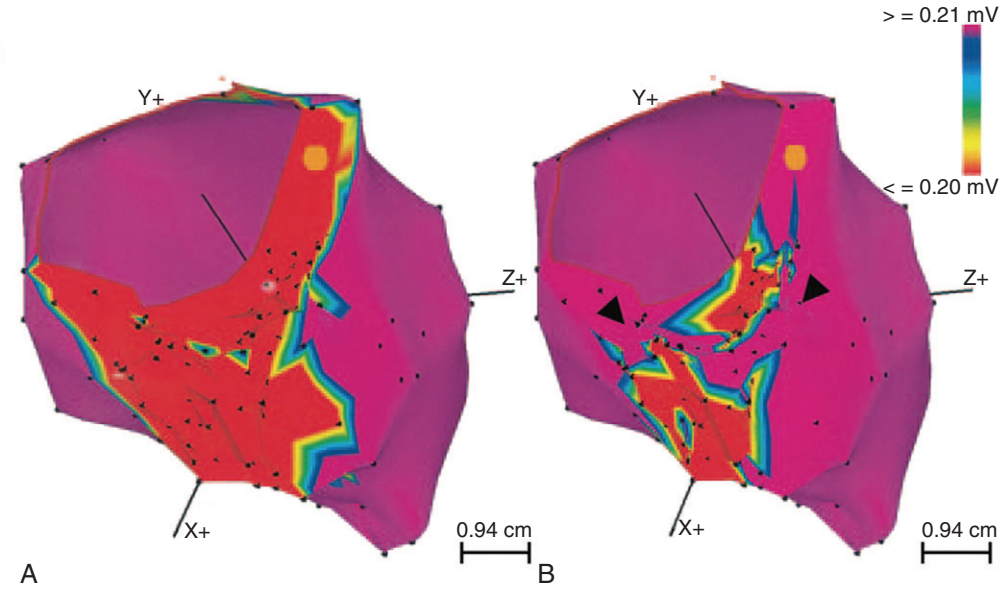

FIGURE 95-15 Mapping conducting channels. A voltage map of the left ventricle showing effect of scar voltage definition on identification of conduction channels. The color range represents voltage amplitude, and red denotes dense scar according to each definition. View of the inferior wall during right ventricular apical (RVA) pacing when scar definition was set at 0.5 mV (*A*) and at 0.2 mV (*B*), which demonstrated a complete channel spanning from septum to lateral wall (*black arrows show* limits of channels). *(From Arenal A, del Castillo S, Gonzalez-Torrecilla E, et al: Tachycardia-related channel in the scar tissue in patients with sustained monomorphic ventricular tachycardias: Influence of the voltage scar definition,* Circulation *110:2568, 2004.)*

majority being identified when the scar voltage was defined as 0.2 mV or less. Eighty-seven percent of conducting channels were related to clinical or induced VTs by various mapping techniques, and RF delivered over the channels terminated the arrhythmia in 14 patients with tolerated VT. In 4 patients with inducible unstable VT, RF delivered in SR rendered VT noninducible in 3 (1 patient not retested). The technique did not identify conducting channels in one quarter of patients, and IDPs were targeted in a fraction of patients with or without conducting channels. A 23% rate of recurrent VT was noted. The three VTs in 2 patients were possibly a recurrence of the clinical VT targeted at the time of ablation.

Hsia et al incorporated this technique in a series with patients who underwent mapping and ablation of stable VT and identified conducting channels (Figure 95-16) fulfilling traditional entrainment criteria in 56% of VTs. They did not analyze the specific impact of this approach prospectively, as the channels were not specifically targeted for ablation. However, a post hoc analysis demonstrated that ablating critical isthmi, defined by entrainment criteria with linear lesions along the scar border zone and at exit sites, resulted in ablation within the conducting channels in all 18 patients in whom such channels were identified and in acute termination of VT in 16 of them.[66]

Catheter Ablation in the Treatment of Electrical Storm

Electrical storm (ES), defined as 3 or more episodes of sustained VT/ventricular fibrillation (VF) within 24 hours, is independently associated with increased mortality in ICD recipients, with the greatest risk imparted during the first 3 months following its occurrence.[67] Unstable ES can pose the greatest clinical challenge to ablation, as patients may be critically ill—possibly in shock—require intravenous support agents, and are intolerant to VT inductions.

Carbucicchio et al performed catheter ablation in 95 patients with ES from scar-related VT, more than half of whom developed cardiogenic shock and more than 10% of whom required cardiopulmonary support.[68] After substrate mapping, in which standard definitions of scar tissue and healthy tissue were used, the voltage threshold window was modified to 0.2 mV and 0.5 mV to assess for conducting channels that were identified in 55% of their patients. Physiological significance was confirmed by entrainment criteria in those with stable ES and by pacemapping from within the conducting channel, which produced a QRS match with long S-QRS time in patients with unstable ES. Ablation was delivered across the conducting channels, from the scar to the healthy myocardium, transecting the border zone and encircling the entire scar, depending on the substrate map. Complete noninducibility was achieved in 62 patients (65%), whereas inducibility of nonclinical VTs occurred in 19 (20%), and clinical VTs remained inducible in 14 (14.7%). ES was suppressed in all patients, as evidenced by stable rhythm over 7 days of in-hospital monitoring. Over a median follow-up of 22 months, ES recurred in 8 patients (8%), with 6 of these in the first 3 months after the index storm. Sudden cardiac death (SCD) was statistically significantly higher in patients with ES recurrence, suggesting that successful catheter ablation of ES is not only feasible but may impact prognosis.

In a "rescue" approach in critically ill patients with severely impaired LV function from ischemic cardiomyopathy intolerant to VT, the ventricles were mapped during SR or right ventricular pacing, targeting areas in which the VT exits were anticipated. Pacemapping was performed in areas of scar tissue to identify the best QRS match to the clinical VT. Ablation targeting all discrete,

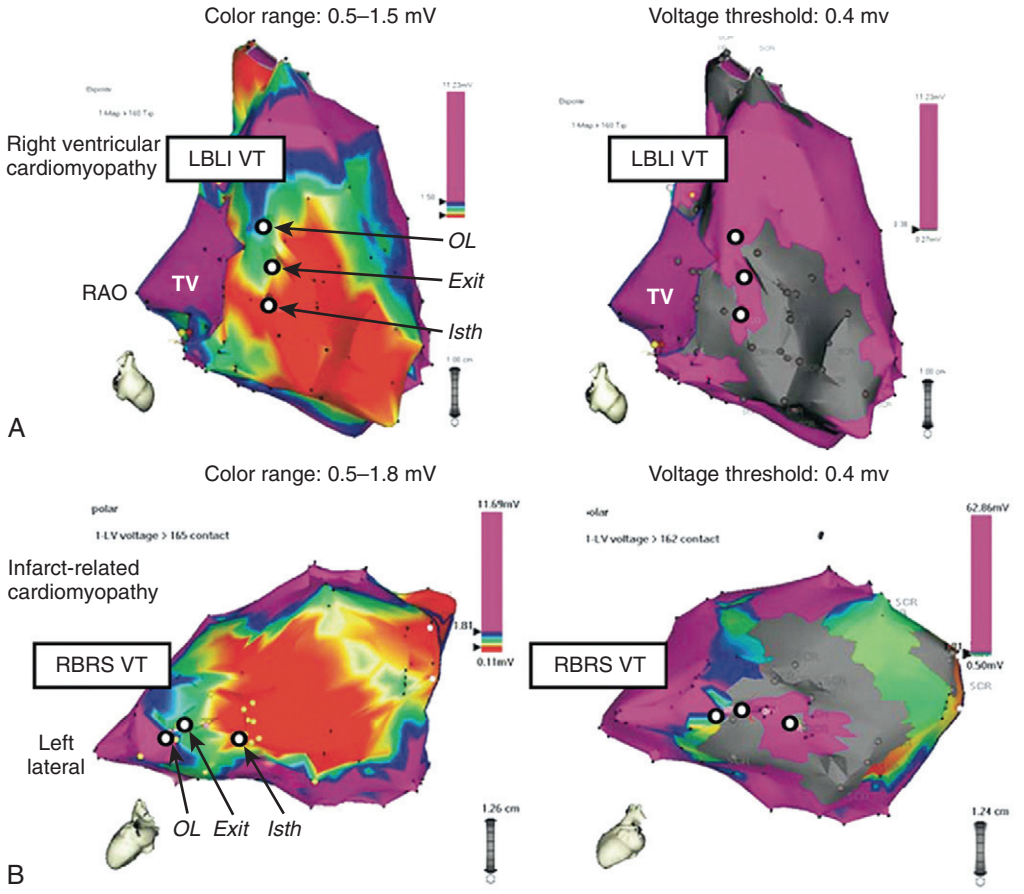

FIGURE 95-16 Identification of the conducting channels of ventricular tachycardia (VT) re-entrant circuits. Bipolar voltage maps in two patients with monomorphic VT are shown. The standard color range for the voltage maps are depicted on the left, and the maps after voltage-threshold adjustment are depicted on the right. **A,** Right ventricular maps in a patient with a right ventricular cardiomyopathy and sustained left bundle, left-inferior (LBLI) axis VT. At a voltage threshold of 0.4 mV (dense scar depicted by *gray* at 0.38 mV), a conduit characterized by a higher voltage follows the path defined by orthodromically activated VT sites. **B,** Left ventricular maps in a patient with an ischemic cardiomyopathy and prior infarction, who presented with a right bundle, right-superior (RBRS) axis VT. At a voltage threshold of 0.5 mV (dense scar depicted by *gray* at 0.4 mV), evidence of a conduit with a higher voltage that follows orthodromic activating sites during re-entrant VT was identified. *Isth,* Isthmus; *OL*, outer loop; *RAO,* right anterior oblique; *TV*, tricuspid valve. *(From Hsia HH, Lin D, Sauer WH, et al: Anatomic characterization of endocardial substrate for hemodynamically stable reentrant ventricular tachycardia: Identification of endocardial conducting channels,* Heart Rhythm *3:503, 2006.)*

highly fractionated delayed potentials found within scar tissue (defined as signal <1.5 mV) was the EPS endpoint.[69] Despite the critically ill condition of the patients, the arrhythmia burden was reduced dramatically over their follow-up period of 19.0 ± 7.7 months, with 66% of patients being VT free and 33% with less than 1 VT episode per month. Of particular interest is the fact that they achieved these results targeting specific electrogram characteristics, without linear lesions.

Other Forms of Scar-Related Ventricular Tachycardia

VT in the setting of coronary disease serves as the paradigm for catheter ablation of scar-mediated VT. The techniques described in the previous sections are applicable to all forms of scar-related VT, as the physiology is related to the presence of fibrosis, its impact on conduction, and the creation of re-entry circuits, and is not specific to the underlying disease process. The remainder of this section will focus on the outcomes of VT ablation related to myocardial scarring in different disease states, highlighting the technical challenges and modifications to the described techniques when applicable.

Ventricular Tachycardia in Idiopathic Dilated Cardiomyopathy

Idiopathic dilated cardiomyopathy represents a heterogeneous group of disorders, and the mechanisms of VT in these patients are equally diverse and include intramyocardial re-entry, HPS re-entry, and focal automaticity. Intramyocardial re-entry is the most common VT mechanism and is almost always associated with scarring that is often perivalvular and can be greater in epicardial extent than endocardial.[70] Isolated scar potentials may be identified in approximately 50% of patients undergoing ablation, presenting an attractive target for pacemapping and entrainment.[71]

In patients with nonischemic heart disease who undergo RF ablation of recurrent sustained monomorphic VT, scar-related

re-entry will account for up to two thirds of VTs, and ablation in this population may render up to two thirds of VTs acutely noninducible.[72] Noninducibility of all VTs may be acutely achievable in up to 70% of patients, with complete suppression of VT in approximately 60% of patients and improved control in up to 70% over longer-term follow-up.[71]

As scar-related VT accounts for the majority, but not all, of VTs, it is essential to exclude HPS re-entry in these patients. Seen in 10% to 20% of patients with nonischemic heart disease, this entity may account for a significant number of tachycardias and is readily amenable to catheter ablation.[73]

Ventricular Tachycardia in Ventricular Dysplasia

Arrhythmogenic ventricular dysplasia is an idiopathic cardiomyopathy characterized by fibro-fatty atrophy and ventricular arrhythmias. It most commonly involves the right ventricle (ARVD) in isolation or, less commonly, both ventricles, though it rarely manifests as a primary LV form that, like the RV form, has been linked to desmoplakin disease.[74-76] In ARVD, the scar characteristically involves diaphragmatic, apical, and infundibular regions and spares the interventricular septum. Left ventricular involvement has not been well characterized, but early experience suggests apical and septal involvement, most commonly in the left dominant variant.[76] Knowledge of typical regional involvement permits localization of potential ablation targets.

The dysplastic process is gradual, progressive, patchy, and diffuse in its involvement despite a certain regionality—an important distinction from the infarcted myocardium. Voltage mapping characteristics therefore would not be the same, and applying the typical voltage thresholds to discriminate between dense scar tissue and healthy tissue often may lead to the identification of extensive areas of abnormal myocardium with intermediate bipolar electrogram characteristics; this may not identify a central area of scar with surrounding border—an important target for substrate mapping. In general, however, a border zone can be identified in most patients, permitting the application of traditional mapping techniques.

Short-term and long-term success rates of substrate mapping were evaluated by Verma et al in 22 patients with ARVD by using a substrate-based ablation technique that either delivered linear lesions to connect scar tissue or the abnormal myocardium to a valve continuity or another scar or encircled the scar or the abnormal region. Acute procedural success, defined as noninducibility of VT, was achieved in 82% of patients, though VT recurred in 23%, 27%, and 47% of patients after 1-, 2-, and 3-year follow-up, respectively.[77]

In a study of 24 patients with ARVD who underwent 48 VT ablations, the VT recurrence rate was 85% over a follow-up period of 32 ± 36 months despite elimination of all clinical VTs in 77% of procedures. The VT recurrence-free survival was only 25% at 14 months. These results may, in part, reflect an important procedural limitation—that electroanatomic mapping was used in only 10% of procedures, subjecting 90% of patients to a nonsubstrate-based approach that may be less effective, particularly in this population.[78]

Although mapping and ablation in ARVD appear feasible with good acute success rates, the progressive nature of the disease and the associated potential for developing new arrhythmias suggests that the role of ablation will remain a palliative one.[79] Ablation of the dysplastic myocardium, currently evaluated only in the right ventricle, poses particular challenges that distinguish it from myocardial scarring caused by ischemic heart disease. The diffuse nature of the disease and mapping using traditional voltage window settings may preclude identifying well-delineated dense scar tissue and the border zone, thereby contributing to substrate maps that may contain a large number of potential VT circuits. Ventricular thinning may increase the risk of perforation; some authorities, therefore, advocate avoidance of irrigated-tip ablation, particularly at the right ventricular apex. At the same time, irrigated-tip ablation in the thin-walled dysplastic myocardium may improve the ability to achieve complete transmurality, potentially contributing to acute success. Emphasis on the rigorous application of International Task Force criteria is critical in identifying appropriate patients, as the high early recurrence rate suggested by some studies calls into question the role of early catheter ablation as an effective antiarrhythmic strategy.[78]

Ventricular Tachycardia Following Surgical Correction of Congenital Heart Defects

Ventricular arrhythmias occur commonly late after repair of congenital heart disease, with most of the published experience and the highest risk reported in patients with tetralogy of Fallot (TOF) who have undergone ventriculotomy or ventricular septal defect (VSD) patching.[80,81] The prevalence of VT in this population ranged from 3% to 14% in several large series; with an incidence of 12%, the risk of SCD was estimated to be 2% per decade. The impact of antiarrhythmic drugs alone is limited, and therapy focuses primarily on ICDs and catheter ablation.[82]

VT with LBBB morphology, reflecting right ventricular or septal exit, is observed in more than 50% of cases.[83] The frequent co-localization of the tachycardia origin at the site of surgical correction implicates the surgical procedure itself in the genesis of these ventricular arrhythmias.[84-86] During catheter-based or intraoperative endocardial activation mapping, the site of earliest activation is usually found at the RVOT, at the healed ventriculotomy site, or close to the VSD patch.[87,88]

In various series, the acute efficacy of RF ablation guided by conventional mapping techniques has been reported at 80% to 100% in patients with mappable VTs; however, it was reported to be as low as 50% on the basis of intention-to-treat analysis, as a significant proportion have unmappable VT, high-risk sites of involvement, and anatomic obstacles precluding effective ablation and contributing to recurrence rates as high as 40%.[89,90] In one study evaluating unstable VT after surgical repair of TOF, the EnSite Array (St. Jude Medical Inc., St. Paul, MN) permitted mapping and ablation, which rendered VTs acutely noninducible in 100% of patients in the study (80% of all patients), though 25% experienced recurrence.[91]

Important considerations in this population are (1) altered and often distorted anatomy; (2) the presence of foreign material patches and conduit anastomoses creating obstacles to ablation; (3) the potential for VT to arise from sensitive areas, including the bundle of His region and in areas close to coronaries; and (4) the need for large (8-mm) and irrigated-tip ablation catheters to achieve effective lesions because of underlying myocardial thickening from long-standing pressure and volume load.

Catheter Ablation of Ventricular Tachycardia in Chagas' Disease and Cardiac Sarcoid

Chagasic and sarcoid cardiomyopathies are under-recognized, and only rare case reports and series describing VT ablation in

these patients exist. The indications are extrapolated from the broader experience with ischemic heart disease, and though the approach to ablation is the same as that described for scar-related VT, specific considerations should be noted.

Both disease entities produce a nonischemic cardiomyopathy because of an infiltrative scarring process that may lead to scar borders that are less than well defined, as in ventricular dysplasia. As such, the distribution of scarring and interwoven conducting tissue may be spatially highly complex, producing multiple VT morphologies that require both endocardial and epicardial approaches. VT isthmus and exit sites may be identified by using a hybrid mapping technique that may require entrainment, pacemapping, and substrate analysis. VT ablation can be expected to provide reduction in the VT burden, though in Koplan's experience with ablation of sarcoid-related VT, recurrence was seen in 75% within 6 months.[92] Over longer follow-up (up to 7 years), however, 50% of patients were completely free of VT after ablation and with the use of antiarrhythmic and immunosuppressive agents, although the other 50% required cardiac transplantation for recurrent and uncontrollable VT.

The experience with ablation of Chagasic VT suggests several distinguishing features. The inferolateral left ventricle is involved in 80% of patients, though an endocardial approach alone is likely to be unsatisfactory, as despite activation mapping meeting several diagnostic criteria, the VT isthmus may be identified and ablated in only 30% of VTs.[93] Sosa et al have demonstrated that epicardial circuits are highly prevalent within the inferolateral LV and that epicardial mapping may facilitate ablation.[94,95]

Catheter Ablation of Ventricular Ectopy and Tachycardia Arising in the Normal Ventricle

Idiopathic Ventricular Tachycardia

By definition, idiopathic VT occurs in individuals without heart disease. Though sustained VTs may occur, even rarely provoking hemodynamic collapse, they most often occur as repetitive salvos and isolated PVCs frequently enough to cause disabling symptoms and LV dysfunction. These tachycardias either are focal, arising from the outflow tracts and few other non–outflow tract regions because of triggered activity (adenosine-sensitive) or enhanced automaticity (propranolol-sensitive), or are re-entrant, involving the LV septum and the left bundle branch fascicles (verapamil-sensitive). The largest experience with ablation of idiopathic VT is for RVOT VTs and verapamil-sensitive VTs involving the posteroseptal left ventricle. The accumulated experience indicates that these VTs may be successfully ablated with a high degree of success and limited procedural morbidity (Table 95-3). Ablation is indicated when symptoms impact quality of life, are severe, and are not suppressed with—or in an effort to avoid—medications. In rare instances when VT or PVCs precipitate VF, adjunctive ICD implantation may be warranted.

Electrocardiogram in Idiopathic Ventricular Tachycardia

As idiopathic VTs are not associated with cardiac structural abnormalities, no surrogates (e.g., scar distribution) to guide

Table 95-3 Ablation of Idiopathic Ventricular Tachycardia

REFERENCE	METHOD	NO. OF PATIENTS	VT ORIGIN	ACUTE SUCCESS (% OF PATIENTS)	RISK FOR VT RECURRENCE (%)	DURATION OF FOLLOW-UP (MONTHS)	COMPLICATION
63	DC/RF	8	LV	100	13	17	None
16	RF	8	LV	100	25	10.1	1 AI2 RBBB
—	—	20	RV	85	6	9.9	1 perforation/death
64	DC/RF	7	RV	100	0	16	None
17	RF	31	LV	85	9	28	None
—	—	30	RV	84	19	28	None
18	RF	35	RV	83	14	30	None
—	—	13	LV	92	0	36	None
30	RF	8	LV	100	13	10.5	1 MR
19	RF	—	LV	91	13	41	None
—	—	—	RV	91	10	41	None
39	RF	5	LV	80	0	10	None
65	RF	20	RV	100	5	7	None

AI, *Aortic insufficiency;* DC, *direct current;* LV, *left ventricle;* MR, *mitral regurgitation;* RBBB, *right bundle branch block;* RF, *radiofrequency;* RV, *right ventricle;* VT, *ventricular tachycardia.*

localization exist, and therefore *clinical* identification of VT origin is based strictly on ECG morphology. However, unlike scar-related VT, in which limitless permutations of scar distribution and varying involvement of re-entrant circuits contribute to myriad ECG morphologies that must be mapped precisely to identify exit sites, the ECG morphologies in idiopathic VTs are finite and involve only a finite number of structures and locations, allowing reasonable identification of the mechanism and origin of VT based on QRS morphology and axis alone. Individual QRS morphologies in idiopathic VT have been described elsewhere and are not covered in detail here, though a few characteristics and localizing principles deserve mention, as they guide critical decisions for ablation.

Idiopathic VTs usually produce relatively high-voltage QRS of smooth contour—generally without splintering—though notching may be present from changes in vector of depolarization. The focality of tachycardia origin is associated with uniform QRS during tachycardia. Multiple and varying morphologies should suggest a re-entrant mechanism, warranting further investigation to exclude structural abnormalities, though regional ablation for *multifocal* RVOT VT has been described.[96] VTs arising from the inflow regions, generally more inferiorly, have a superior axis; outflow tract VTs, which are more superiorly located, typically have an inferiorly directed axis, with either LBBB or RBBB morphology in lead V1, which is helpful in distinguishing the chamber of origin. Outflow tract tachycardias may originate anywhere between the right ventricular inflow region and the lateral mitral annulus, following the "arc-like distribution" of perivalvular tissues and epicardial fat pads that contain ganglionated plexi.[97] The most rightward originating VTs arise from the posterolateral tricuspid valve and have a late precordial QRS transition. As the QRS transition moves to earlier precordial leads and then alters the morphology in lead V1 from LBBB to LBBB with "prominent R" to RBBB, the site of origin moves leftward and posterior to the extreme of lateral mitral annulus VTs that have monophasic R waves in V1 and positive-concordant QRS morphology precordially. Generally, precordial R-S transition earlier than lead V3 is suggestive of left-sided origin.

Re-entrant LV septal VT—the verapamil-sensitive idiopathic VT that involves the left posterior division of the left bundle branch as the retrograde limb—typically has RBBB QRS morphology with left superior axis, reflecting early activation of the posteroapical LV septum. The rarer variant involving the left anterior division is associated with RBBB QRS morphology and right inferior axis. An upper septal variant of fascicular VT exhibits a narrow QRS with normal axis.

Catheter Mapping and Ablation of Specific Idiopathic Focal Ventricular Tachycardias

Focal VTs may arise from the endocardium, paravalvular and vascular sites, or the epicardium. Successful mapping and ablation is dependent on (1) careful analysis of the 12-lead ECG VT morphology to precisely identify the potential sites of origin; (2) systematic and detailed mapping, sometimes of multiple regions, to locate the true origin identified by the earliest site of activation; (3) adequate delivery of RF energy; and (4) avoidance of sensitive structures such as the coronary arteries.

Left Bundle Branch Block Morphology Ventricular Tachycardia: The Right Ventricular Outflow Tract Ventricular Tachycardia Paradigm

VT of RVOT origin is the most common form of idiopathic VT and serves as the paradigm for ablation of idiopathic focal VTs. Exercise-induced or stress-induced LBBB left inferior axis tachycardia with precordial R-S transition between V3 and V4 is the hallmark, though ARVD and ischemic heart disease should be excluded. The methods described in this section are applicable to other focal idiopathic VTs as well; however, they are less well validated because of their relative rarity.

Clinical and Laboratory Considerations

When VT of RVOT origin is suspected—or in a more general sense, when focal idiopathic VT is suspected—the clinical behavior of the VT, QRS morphologies in SR and in VT, and behavior of the VT in the diagnostic suite should confirm the physiology of *triggered* activity before ablation is undertaken.

Evaluation of clinical precipitants such as exercise, stress, caffeine, theophylline or aminophylline, or atropine as well as the termination of VT with adenosine may suggest a triggered mechanism and identify patients more likely to be inducible with laboratory techniques—making the degree of spontaneous VT an important consideration before invasive evaluation is started. All suppressive medications should be discontinued for a minimum of 5 half-lives to improve the chances of spontaneous occurrence and induction. Association with menstrual cycle should be considered during procedure scheduling, as up to 60% of women will have a hormonal trigger, and more than 40% may only have VT during specific menstrual phases.[98]

During invasive testing, in the absence of spontaneous tachycardia, burst ventricular pacing or atrial pacing with 1:1 conduction to the ventricles—either in the baseline state or with isoproterenol facilitation using doses as high as 20 μg/min—may facilitate myocyte intracellular calcium loading and increase the propensity for triggered activity, as will concomitant adenosine triphosphate (ATP) administration. In some instances, phenylephrine or epinephrine may be required. Administration of atropine and, theoretically, aminophylline may also facilitate induction by *withdrawal or inhibition of inhibitory G-proteins* that suppress the conversion of ATP to cyclic adenosine monophosphate (cAMP), thereby *increasing* cAMP and facilitating triggered activity. Adenosine administration terminating VT suggests *activation* of this inhibitory mechanism again supporting triggered activity, a diagnostic distinction from re-entrant VTs. Extrastimuli are generally less useful for induction and termination, as the mechanism is not re-entrant. Anesthesia with benzodiazepines and propofol may suppress arrhythmia induction, requiring reduced doses or complete discontinuation of sedation.

Mapping and Ablation

The approach to mapping RVOT VT depends on whether VT is inducible and sustained in the diagnostic suite. If so, activation mapping, with or without employing a three-dimensional reconstruction system, is the method of choice. The region mapped should be constrained to only a few centimeters in diameter based on clinical ECG localization. After a site of early activation is identified, a high-density map of this area further defining the origin of earliest activation may improve precision. Once the

high-definition map is created, pacemapping at the tachycardia CL from the early site should reproduce the clinical tachycardia, confirming the site of origin. Again, either unipolar pacing or closely spaced bipolar pacing should be performed at output not greater than twice diastolic threshold.

With the VT origin defined as the successful ablation site, endocardial activation at the origin is only modestly early, preceding the QRS onset by 10 to 60 ms. Identification of diastolic potentials suggests a zone of slow conduction and should not only raise the suspicion of re-entrant idiopathic VT but also of local myocardial scarring and structural heart disease.[99] Ablation at appropriate sites may lead to acceleration of the tachycardia or may initiate repetitive responses characterized by salvos of VT with progressively shorter duration and longer CL, followed by termination and noninducibility.[100]

When the absence of sustained VT precludes activation mapping, pacemapping may be performed and compared with clinical tachycardia for identification of the presumed tachycardia focus. The resolution of pacemapping has been evaluated, suggesting that multiple sites with the best pacemapping scores may be identified with up to a mean of 18-mm separation and up to 24-mm separation from the successful ablation site. Compared with activation mapping, pacemapping provides comparable localizing ability, which appears to be directly correlated with the size of the earliest activation site. That is, the larger the size of earliest activation area—defined as the area contained within the 10-ms isochrone, found to be *broadened* by mapping on isoproterenol—the larger is the separation between the best pacemap sites and their separation from the successful ablation site, which suggests that precision is enhanced by mapping in the baseline state.[101]

The qualitative evaluation of resemblance between spontaneous and paced waveforms during stepwise pacemapping yields good clinical results when the optimal pacemapping site is targeted, usually with confirmation of early local activation at the site of ablation. Gerstenfeld et al applied an automated, off-line, template-matching algorithm to pace mapping and quantitated the degree of match at sites yielding a complete 12-lead ECG match by visual inspection in patients undergoing ablation of RVOT VT.[102] They observed less than 12% difference between clinical VT and paced QRS at successful ablation sites, with a negative predictive value of 100% for sites with more than 15% difference. Whether ablation guided by automated, real-time pacemap match quantitation has the potential to improve outcomes remains to be seen.

In most reported series using the CARTO mapping system and a combination of activation and pacemapping, acute success of ablation ranged from 83% to 100%, with recurrence rates of 0% to 19%. However, when sustained VT permits adequate study, success rates in excess of 90% may be achieved with recurrence rates less than 5%.[99] Comparable ablation results have been reported using a multielectrode ablation catheter and with noncontact balloon-array mapping of mappable and unmappable RVOT VT.[103-105]

An important asset of the noncontact system is the ability to map and localize the earliest site of activation from a single beat, which, as preliminary information suggests, may not coincide with the earliest ventricular activation site in RVOT VT. In a case report of RVOT VT ablation guided by noncontact mapping, potentials preceding myocardial depolarization were identified within the myocardial sleeves investing the pulmonary artery, much like pulmonary vein (PV) automaticity triggering AF. Targeting these potentials resulted in the successful elimination of VT, which had previously failed when the presumed exit site that met several favorable diagnostic criteria had been targeted.[106] Potential concerns with use of the noncontact system include obstruction of the outflow tract and mapping errors related to shape mismatch between the balloon surface and the right ventricle endocardial surface.

Both contact and noncontact mapping methodologies may result in trauma—stunning at the myocardial focus and rendering VT noninducible—potentially resulting in ablation failure. Other reasons for failure include inaccurate diagnosis (including non-RVOT VT and pre-excited or antidromic tachycardia involving a right-sided accessory pathway [AP]), insufficient localization of endocardial focus, and an intramural or epicardial focus. Although infrequent, wall perforation (particularly the free wall) and tamponade may complicate ablation of the RVOT. Coronary occlusion during ablation of RVOT and LVOT VT has been reported as well.[107]

Distinguishing Sites of Origin of Idiopathic Ventricular Tachycardias

VTs attributed to the RVOT may, in fact, not map to this region despite LBBB and inferior-axis QRS morphology. In patients with failed endocardial RVOT ablation, non-RVOT sites should be explored. This may require scanning multiple regions in both ventricles and associated valvular and vascular territories to identify earliest endocardial activation.

In a broader sense, LBBB inferior-axis VT with R-S transition in lead V3 has a wide differential that may involve any of several disparate regions, each of which requires a different approach to achieve successful ablation (Figure 95-17). In a series of 33 patients, 58% had precordial transition in lead V3; of these, 42% arose from non-RVOT sites, including the LVOT below the left coronary cusp close to the aortomitral continuity (16%), aortic sinus of Valsalva (11%), coronary sinus (CS) (5%), pulmonary artery (5%), and epicardial focus (5%).[108]

Tanner et al described a stepwise approach with activation mapping, pacemapping, or both to systematically investigate the regions associated with ECG morphology suggestive of an RVOT origin, particularly those with R-S transition at lead V3.[108] The RVOT should still be explored first, as more than half of such VTs will arise there. From there, the pulmonary artery and then the coronary sinus should be explored. Early activation in the CS may suggest an epicardial origin, also identifiable by positioning of a CS catheter at the time of diagnostic study.

The tricuspid annulus should also be explored carefully as it may account for up to 8% of idiopathic VTs with LBBB morphology, the majority of which have inferior-axis and precordial transition around lead V3.[109] Tricuspid annulus VT or PVCs have positive QRS polarity in leads V1, V5, and V6 and may be distinguished from VTs of RVOT origin by (1) the absence of a negative component and greater amplitude in lead V1; (2) positive QRS polarity and rarity of QS or rS pattern in lead aV_L, as well as greater Q-wave ratio of lead aV_R to aV_L; and (3) QRS axis being more leftward and more superior. While VT originating along the anterior tricuspid annulus usually has positive QRS polarity in the inferior leads, a posterior origin will be associated with a negative QRS polarity, which, by virtue of the obvious difference in axis, should not be mistaken for an RVOT origin. In the study by Tada, the majority (74%) of tricuspid annular VTs arose from septal origin close to the bundle of His and the main bundle branches;

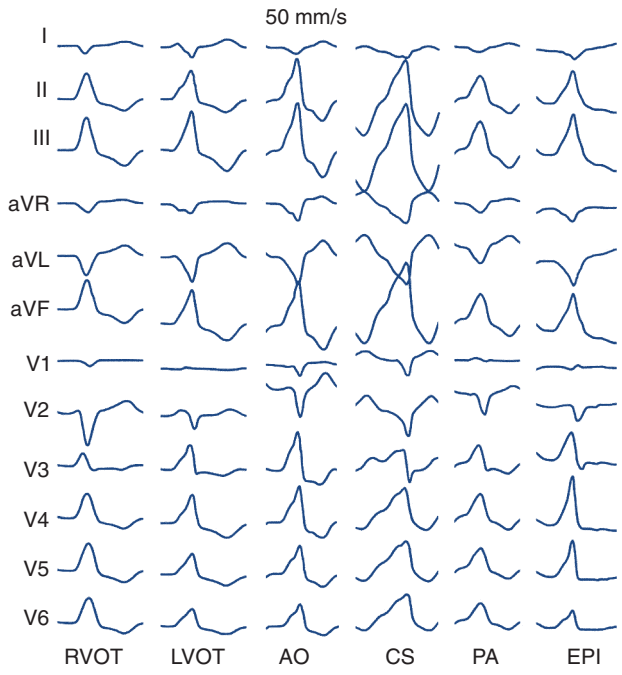

FIGURE 95-17 Twelve-lead surface electrocardiogram (ECG) from six different patients with idiopathic ventricular tachycardia (VT) that was successfully ablated in the right ventricular outflow tract (*RVOT*), in the left ventricular outflow tract (*LVOT*), in the aortic sinus of Valsalva (*AO*), in the coronary sinus (*CS*), in the main pulmonary artery (*PA*), and in the epicardial space via percutaneous pericardial access (*EPI*), respectively. Note that all ECGs present with left bundle branch block morphology, inferior axis, R wave/S wave transitional zone in the precordial leads V3, and negative QRS complex in lead I. *(From Tanner H, Hindricks G, Schirdewahn P, et al: Outflow tract tachycardia with R/S transition in lead V3: Six different anatomic approaches for successful ablation,* J Am Coll Cardiol *45:418, 2005.)*

this limited ablation because of the appearance of junctional rhythm and prolonged AV nodal conduction and resulted in 66% efficacy in this region, with just more than 20% of patients developing prolonged AV nodal conduction or RBBB. Alternatively, efficacy at nonseptal, and particularly lateral, sites was 90%. This has important clinical implications.

If transvenous mapping of idiopathic RVOT VT does not reveal early endocardial activation, the LVOT and sinus of Valsalva should be mapped via the retrograde transaortic approach. Ouyang et al described 7 patients with idiopathic LBBB inferior-axis VT demonstrating precordial R-S transition between leads V2 and V3; in these patients, local activation in the aortic sinus cusps preceded the onset of the QRS by 39.3 ± 24.2 ms. Further, late-diastolic or presystolic potentials could be identified in these VTs but not in RVOT VT beats. Additional characteristics strongly suggestive of VT arising from the aortic sinus cusp in patients with a typical LBBB inferior-axis VT were R wave duration index 50% or greater and R wave–S wave amplitude index 30% or greater.

Beyond the sinus of Valsalva, the LVOT may give rise to idiopathic focal VT 12% of the time, often with LBBB inferior-axis QRS and precordial R-S transition between V2 and V4. Triggered foci have been localized to the basal aspect of the superior LV septum, just inferior to the aortic valve, and these have been associated with precordial R-S transition before V3 and generally at V2.[110] A VT with relatively narrow (100 ms) QRS, LBBB inferior-axis morphology, and precordial R-S transition between V3 and V4 has been described; this is referred to as *upper septal fascicular tachycardia*, as the earliest endocardial activation occurs at the basal left ventricular septum and precedes the QRS by up to 30 ms, where a Purkinje potential may be seen in sinus rhythm. Ablation at the Purkinje potential eliminates this VT, characterized mechanistically as enhanced *automaticity* by its lack of response to ATP or oral verapamil.[111]

Ventricular Tachycardia with Right Bundle Branch Block Morphology

When VT exhibits an RBBB morphology in lead V1, that is, the precordial R-S transition has migrated to V1 or less, left ventricular sites away from the septum, in particular, VTs arising from the mitral valve annulus should be considered. All such VTs generally have an RBBB pattern in V6 and dominant Rs across the precordium. The anterior mitral annular location is associated with an inferior axis, whereas the posterior annular sites have a superiorly directed axis. Subtle differences in QRS morphology may be seen in lead V1, with a qR pattern from more septal locations such as the aortomitral continuity and the posteroseptal region, an isoelectric phase preceding the R wave at the anterior and posterior annular sites, and an almost δ wave–like upstroke at the onset of the QRS at the anterolateral mitral annulus.

Ventricular Tachycardia Arising from the Posterior Papillary Muscle

VT arising from the posterior papillary muscle has been described with several distinguishing features that aid in its recognition.[112] RBBB superior-axis QRS morphology characterizes the VT; it is believed to be automatic or triggered on the basis of (1) induction with catecholamines but not programmed stimulation, and (2) lack of termination with overdrive pacing.

Activation mapping is more useful than pacemapping because of a lack of catheter stability in contact with papillary muscles, which are constantly in motion. The focus resides deep within the papillary muscle, and cooled RF energy is required for ablation. The Purkinje system does not seem to be involved in its genesis of VT, given the lack of a Purkinje potential preceding local activation and QRS.

In Doppalapudi's experience, the site of successful ablation was along the inferior wall just off the septum, approximately one third the distance from the mitral valve annulus to the apex, at the base of the posterior papillary muscle. After meticulous catheter mapping and positioning to deliver RF focused at the base of the papillary muscle, ablation initiated at 30 W and gradually titrated up to a maximum of 50 W to effect an 8-ohm to 10-ohm fall in impedance, with temperature limited to less than 40° C, was successful in eliminating VT. Post-ablation follow-up should include surveillance for mitral regurgitation.

Despite systematic and detailed mapping of ventricles, valve annuli and leaflets, and associated vascular territories, the earliest site of activation may yet not be identified. In such cases, epicardial mapping may be required to adequately localize the origin and achieve elimination of VT.

Catheter Mapping and Ablation of Idiopathic Re-entrant Ventricular Tachycardia

This form of idiopathic VT involves the Purkinje network of the left bundle branch system to support re-entry. In contrast to re-entrant VTs that develop in the setting of hantavirus pulmonary syndrome, idiopathic re-entrant VTs occur in the *absence* of ostensible conduction disease; it should, however, be kept in mind that the region of slow conduction that contributes to re-entry may, *theoretically*, involve diseased or abnormal conduction system tissue along the upper interventricular septum. That its presence is not manifest on a standard 12-lead ECG or as H-V interval prolongation distinguishes idiopathic VT from bundle branch re-entry and interfascicular re-entry, with which hantavirus pulmonary syndrome, which manifests as H-V interval prolongation, intraventricular conduction delay (IVCD) and fascicular block, may be associated.

Earliest endocardial activation during fascicular VT commonly localizes to the ventricular septum—mid-to-distal posterior or anterior septum in the cases of VT involving the posterior or anterior fascicles, respectively—leading to relatively narrow QRS.[113-115] The posterior fascicular variant was the first to be characterized, typified by "Zipes' triad" of induction with atrial pacing, RBBB, and cardiac structural normality, and subsequently expanded by Belhassen with demonstration of verapamil sensitivity.[116,117]

Posterior Fascicular Idiopathic Ventricular Tachycardia

Patients without structural heart disease presenting with RBBB left superior-axis VT are presumed to have posterior fascicular VT, that is, re-entrant VT in which the posterior fascicle serves as a critical structure within the re-entrant circuit and poses an approachable target for ablation.

The tachycardia circuit has been deduced through observations made during VT and SR. In SR, Purkinje potential (PP) recordings demonstrate proximal-to-distal activation of the posterior fascicle, nearly fusing with the local ventricular potential preceding the QRS. Exiting of the wavefront through the Purkinje network termini in a retrograde fashion activates a specialized, decrementally conducting, verapamil-sensitive zone in the interventricular septum. Propagation through this zone toward the basal septum generates a high-frequency potential (P1) that may be obscured by concomitant anterograde myocardial activation but is identifiable in some patients after the ventricular activation.[118,119] Both P1 and PP may be recorded on a single multipolar catheter positioned along the left interventricular septum allowing the observation of the order of activation in both sinus rhythm and VT sinus rhythm (Figure 95-18, *A*).

Induction may be achieved with atrial-constant CL pacing and extrastimuli that block in the posterior fascicle and conduct along the upper-septal, specialized, verapamil-sensitive zone of slow conduction and then initiate VT by activating the posterior fascicle in a retrograde fashion. Induction may be achieved through ventricular programmed stimulation that captures the posterior fascicle in a retrograde fashion and then exits the left bundle to capture the slowly conducting basal septum in an anterograde fashion.

During VT (Figure 95-18, *B*), the basal interventricular septum is captured antidromically and serves as the anterograde limb of the re-entrant circuit, allowing P1 to emerge as an isolated late diastolic potential.[118] In the distal third of the septum, the anterograde wavefront penetrates the posterior fascicle of the left bundle branch system at the so-called *lower turn-around point* through the septal Purkinje network termini. This creates diverging wavefronts traveling to the myocardial exit site, with earliest activation seen at the posteroapical septum approximately 15 to 20 ms before inscription of the QRS in an anterograde fashion,[118,120] as well as activating the posterior fascicle in a retrograde, distal to proximal fashion, *reversing* the direction of Purkinje activation compared with SR, until the wavefront reaches the basal septum and exits the fascicle close to the main left bundle, the so-called *upper turn-around point,* and then re-enters the zone of slow conduction. Because P1 precedes PP in VT, P1 is also known as a *pre*-Purkinje potential (pre-PP) and PP is also referred to as P2. Some patients will not have a recordable P1, and only the PP that fuses with QRS activation may be identified.[119]

Involvement of slow calcium channel–dependent tissue may be demonstrated with as little as 1.5 mg verapamil administered intravenously during VT, which may prolong P1-P2, as this represents activation of the verapamil-sensitive region between the basal septum entrance and the point of posterior fascicle penetration; verapamil, however, should have no effect on P2-QRS, which depends on rapid fascicular fiber activation of the distal septum and myocardial depolarization—tissues where depolarization and conduction velocity are generally sodium channel dependent and not sensitive to calcium channel blockade.[119]

During VT, responses to spontaneous and stimulated events satisfy the diagnostic criteria of re-entry. Spontaneous sinus beats and atrial pacing may reset the tachycardia by capturing the anterograde limb of the circuit. Extrastimuli from the right ventricular apex may reset the tachycardia, and overdrive pacing just faster than the tachycardia from the right ventricular apex or the left ventricle proximal to the myocardial exit site results in manifest and concealed entrainment, respectively, with PPI similar to tachycardia CL.[119]

Successful ablation may be achieved through a variety of approaches. According to Nakagawa et al, apical-posterior septal sites exhibiting earliest activation and preceded by Purkinje-P2 potentials may be targeted; however, these authors identified such potentials over an area of the posterior half of the distal third to distal quarter of the interventricular septum measuring 2 to 3 cm^2.[120] In their experience, P2 preceded QRS by 27 ± 9 ms at successful ablation sites but only by 14 ± 6 ms at unsuccessful sites. Pacing from sites identifying the earliest P2 potential as well as from surrounding sites exhibiting later P2 produced QRS similar to VT morphology, which suggested activation of the Purkinje network with propagation to the exit site without identifying the precise exit.

Tsuchiya et al targeted basal-septal and mid-septal sites where a late-diastolic potential (LDP) analogous to P1, preceding P2, was identified.[118] They and others have demonstrated pressure termination of VT at these sites.[121]

Nogami and others targeted sites where P1 and P2 may be recorded or sites recording earliest P2 when P1 is not recorded, achieving tachycardia termination and noninducibility after ablation.[119,122] Such sites participated in and were critical to the re-entrant circuit and were associated with PPI 13 ± 13 ms or less longer than the tachycardia. At successful ablation sites, P1 preceded QRS by 60 ± 29 ms (18% ± 8% of VT CL) and when only P2 was recordable, it preceded QRS by 18 ± 6 ms (6% ± 3% of VT CL). Pacemapping at sites recording P1, P2, or both were associated with, at best, 10 of 12 ECG lead matches because of difficulty

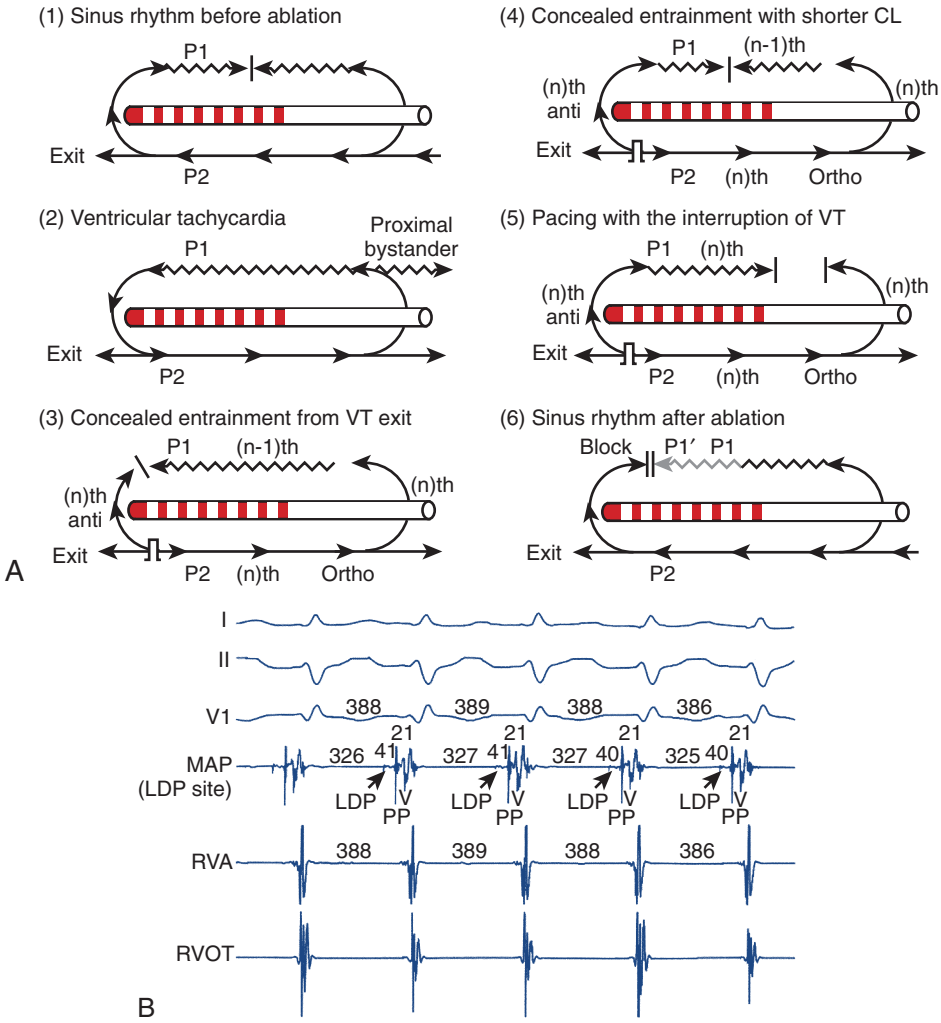

FIGURE 95-18 A, Schematic illustrating the mechanism of idiopathic verapamil-sensitive ventricular tachycardia (*VT*). (1) During sinus rhythm, activation proceeds along the Purkinje network and depolarizes P2, and then retrograde activation along the septum results in P1 being fused and buried within the local ventricular activation. (2) During VT, P1 precedes P2. (3) During concealed entrainment from the VT exit, antidromic wavefront (*anti*) block distal to P1 results in orthodromic activation (*Ortho*) of P2 and P1. The orthodromic wavefront of the preceding (n-1)th beat blocks in the connection between P1 and P2, encountering refractoriness caused by antidromic penetration from the (n)th pacing impulse, while the orthodromic wavefront from the last pacing impulse continues to reset the tachycardia. (4) Overdrive entrainment pacing with shorter cycle length (*CL*) advances the site of collision between the (n)th antidromic wavefront and the (n-1)th orthodromic wavefront to the middle portion of the area of slow conduction, with the interval from the last pacing stimulus to the orthodromically activated P1 prolonging because of rate-dependent conduction delay in the area of the slow conduction. (5) Overdrive pacing with yet shorter CL results in the antidromic wavefront blocking at the proximal portion of the area of slow conduction and the orthodromic wavefront from the previous paced beat blocking as well, thereby interrupting VT. Radiofrequency delivery between P1 and P2 eliminates VT, and P1 activation then proceeds orthodromically around the circuit and subsequently from a proximal to distal direction during sinus rhythm; hence, after ablation, P1 appears in the mid-diastolic period with the same activation sequence as during VT (6). *P1*, Diastolic potential; *P2*, presystolic Purkinje potential. **B,** Idiopathic verapamil-sensitive VT involving the posterior fascicle. Example of late diastolic potential (*LDP*) preceding a Purkinje potential (*PP*) recorded at the middle of the left ventricular septum during VT. Tracings are electrocardiogram leads I, II, and V1, and intracardiac electrograms recorded from the mapping catheter located at the middle of the left ventricular septum (*MAP*), the right ventricular apex (*RVA*), and the right ventricular outflow tract (*RVOT*). *V*, Ventricular potential. (***A,*** *From Nogami A, Naito S, Tada H, 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 *36:811, 2000.* ***B,*** *From Tsuchiya T, Okumura K, Honda T, et al: Significance of late diastolic potential preceding Purkinje potential in verapamil-sensitive idiopathic left ventricular tachycardia,* Circulation *99:2408, 1999.)*

in achieving isolated Purkinje capture without associated myocardial capture. In patients in whom both P1 and P2 were recordable and successfully ablated in the mid-septum, the distance between the successful ablation site and the myocardial exit was 7.5 ± 1.5 mm. Nogami et al found such sites close to the main left bundle and the bundle of His location and therefore targeted mid-septal sites where such potentials were still recordable, avoiding AV block and LBBB.

Pacemapping alone is generally less effective in mapping re-entrant idiopathic VT for a number of reasons: (1) differences between conduction characteristics during VT and pacing during SR; (2) disparity of locations, including bystander regions, from

which pacing may engage the fascicular system and thus produce excellent pacemap matches without identifying the true myocardial exit or the critical segment of the re-entrant circuit; and (3) as mentioned above, because the re-entrant circuit is located proximal to the myocardial exit, identification of the site of earliest activation may not terminate VT but only alter the exit site. In addition, selective capture of the fascicular system alone from sites recording P1, P2, or both is difficult, manifesting poor pacemap matches because of capture of the surrounding myocardium from sites demonstrated to be critical to the tachycardia circuit and to be successful at terminating VT.

Electroanatomic mapping studies have confirmed the re-entrant physiology of idiopathic posterior fascicular VT.[123] Retrograde activation of the septal region of slow conduction, as suggested by previous catheter mapping studies, has been confirmed with SR mapping studies in patients with idiopathic left ventricular tachycardia (ILVT) but was not seen in controls; this suggests that this difference is critical to the physiology that supports VT and provides a suitable ablation target.[118,119,124]

In patients with unmappable fascicular VT, electroanatomic mapping guided by Purkinje potentials and pacemapping has been used to deliver a contiguous linear lesion across the inferior mid-to-apical LV septum to transect the posterior fascicle for VT control (Figure 95-19).[125] The technique was effective in achieving acute and long-term arrhythmia control and required a mean of nine lesions per case. A similar technique was applied by Chen et al, who used the EnSite 3000 noncontact mapping balloon array (Endocardial Solutions Inc., St. Paul, MN) to guide ablation in patients with mappable, unmappable, and recurrent VT after prior failed ablation.[126] After mapping in SR to identify critical HPS structures and the sinus breakout (SBO), a linear lesion delivered perpendicular to the direction of propagation along the posterior fascicle, 1 cm above the SBO and guided by Purkinje potentials, was effective in preventing VT recurrence over a follow-up of 13 ± 4.8 months.

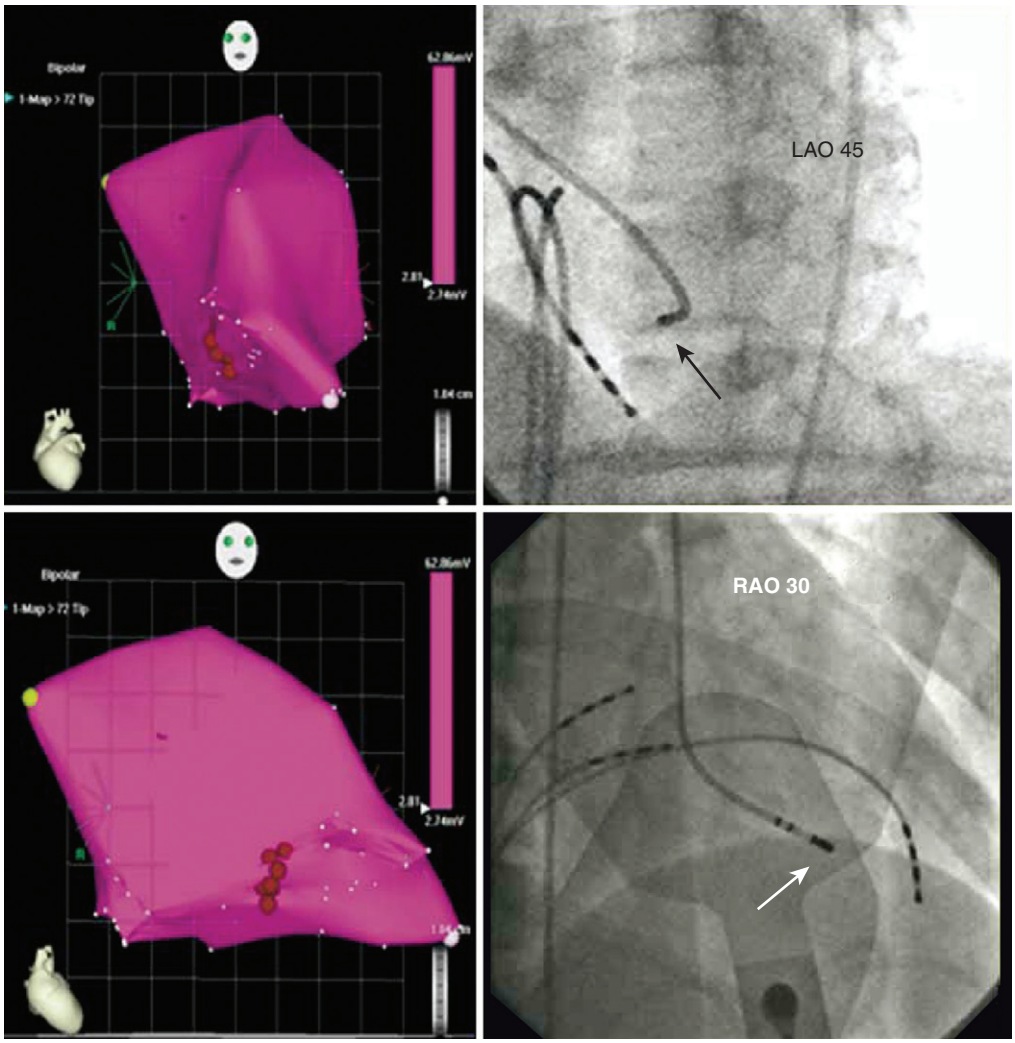

FIGURE 95-19 Three-dimensional electroanatomic map of the left ventricle from the left anterior oblique *(LAO)* and right anterior oblique *(RAO)* projections, and the corresponding fluoroscopic images at 45-degree LAO and 30-degree RAO. The line of *small red circles* represents the location of radiofrequency energy delivery in a linear fashion. *(From Lin D, Hsia HH, Gerstenfeld EP, et al: Idiopathic fascicular left ventricular tachycardia: Linear ablation lesion strategy for noninducible or nonsustained tachycardia,* Heart Rhythm *2:934, 2005.)*

Reliance on identifying the site of earliest activation alone does not appear to be a useful mapping approach, as there may be multiple sites of breakthrough, corresponding to the Purkinje-myocardial interface. Ablation at these sites was not successful in terminating VT in at least one case report.[127] Earliest ventricular activation sites were separated by up to 1.5 cm from sites exhibiting Purkinje potentials, which, when targeted for ablation, did eliminate VT.

Initial experiences reported a better than 80% acute success but up to a 25% recurrence rate after ablation for ILVT. Currently, improved understanding of tachycardia and its circuit, along with refinement in technique, has contributed to long-term success that exceeds 90%, with only rare recurrences. Complications are uncommon but include thromboembolic events, damage to valvular apparatuses, and potential for AV block or LBBB if ablating close to P1. As with all left-sided procedures, the potential for aorto-femoral injury and disruption, coronary damage, stroke, and perforation of the left ventricle must be considered.

Anterior Fascicular Idiopathic Ventricular Tachycardia

Analogous to left-posterior fascicular VT, the occurrence of VT with RBBB and right-axis deviation (RAD) in patients without structural heart disease is assumed to arise from the region of the anterior division of the left bundle (Figure 95-20, *A*). Idiopathic re-entrant tachycardia involves the basal interventricular septum

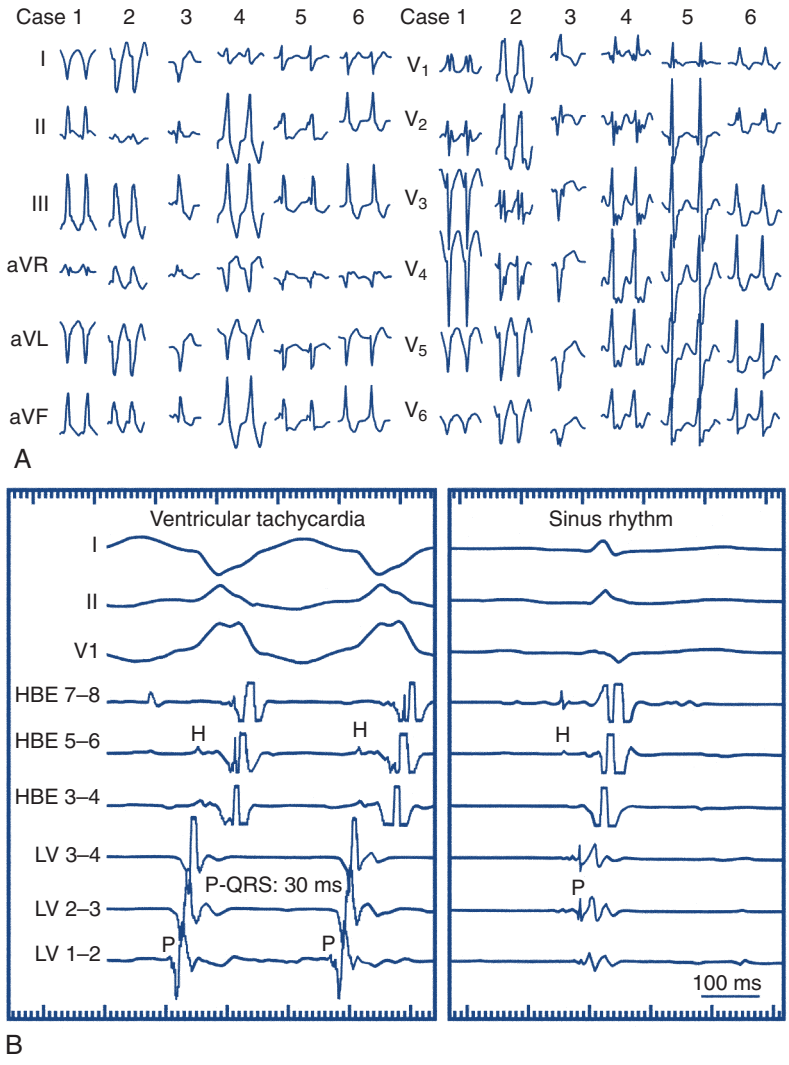

FIGURE 95-20 A, Twelve-lead electrocardiograms (ECGs) of the clinical ventricular tachycardia (VT) obtained in six patients with anterior fascicular variant of idiopathic verapamil-sensitive VT. **B,** Anterior fascicular idiopathic verapamil-sensitive VT: Purkinje potentials recorded during VT and sinus rhythm at the successful ablation site. Ablation catheter was positioned at the site of the earliest ventricular activation during VT (the VT exit site). A high-frequency potential (Purkinje potential) is fused with the earliest ventricular potential during VT, suggesting the VT exit. During sinus rhythm, recording from the left ventricular electrogram at the same site demonstrated a distinct Purkinje potential, which was recorded after the bundle of His potential (*H*) and before the onset of the QRS complex. Surface ECG leads I, II, and V, and intracardiac recording from the bundle of His region (*HBE*), the right ventricular apex, and the ablation catheter in the left ventricle (*LV*) were recorded simultaneously. *(From Nogami A, Naito S, Tada H, et al: Verapamil-sensitive left anterior fascicular ventricular tachycardia: Results of radiofrequency ablation in six patients,* J Cardiovasc Electrophysiol *9:1269, 1998.)*

and the anterior division of the left bundle, similar to the left posterior fascicular variant of ILVT, and may be mapped and ablated in comparable fashion.

In the largest experience, Nogami et al reported on 6 patients with RBBB RAD-morphology VT without ostensible myocardial scarring.[128] Four patients had no structural heart disease and had normal LV function; 1 patient had mitral stenosis and an ejection fraction (EF) of 45%, compatible with the listless LV performance seen in some patients with severe mitral stenosis; and 1 patient had hypertrophic cardiomyopathy (HCM) also with an EF of 45%. All patients exhibited verapamil sensitivity and lack of response to adenosine.

Re-entry was demonstrated to be the operative pathophysiological mechanism. VT was inducible with programmed stimulation in all but one patient in whom VT was nearly incessant. Overdrive pacing resulted in entrainment from the right ventricular apex, and VT termination was achievable with ventricular extrasystoles or burst pacing. In one patient, VT was induced with rapid atrial pacing.

Endocardial mapping during VT or PVCs demonstrates the earliest activation in the anterolateral left ventricle—the putative exit site—with local activation fusing with a PP (Figure 95-20, *B*). During VT, the PP precedes QRS by 20 to 35 ms. In 50% of patients, mapping the mid-interventricular septum in VT identifies an IDP, which precedes QRS by 56 to 66 ms and the local ventricular activation by 85 to 175 ms, suggesting a site of slow conduction remote from the VT exit site. Pacemapping from mid-septal sites exhibiting the isolated PP is associated with QRS morphology similar to pacing at the exit site as well as to the clinical VT, and the stimulus-to-QRS interval approximates the interval between the PP and the QRS in VT. However, in two patients, pacemapping at a site with the PP produced a QRS match in only seven ECG leads.

Ablation at the site of slow conduction along the mid-septum identified by an IDP or, when not identified, ablation at the site of earliest ventricular activation with a fused PP resulted in complete termination and noninducibility of VT without elimination of the PP or causing hemi-block.

Catheter Ablation of Ventricular Tachycardia Dependent on His-Purkinje System Disease

In patients with or without heart disease, the development of acute or chronic HPS disease may promote slow conduction and conduction block within the specialized conduction system, promoting re-entry that incorporates the bundle branches and intervening myocardium that is not itself necessarily diseased. Alternatively, as mentioned earlier, progressive myocardial disease may also involve the conduction system, permitting conduction slowing within both the myocardium and the HPS, promoting the development of HPS re-entry in isolation or in association with other forms of VT.

Electrophysiology of Bundle Branch Re-entrant Ventricular Tachycardia

Bundle branch re-entry is a common laboratory phenomenon. Ventricular programmed stimulation using the extrastimulus technique, particularly when preceded by a relative ventricular pause, may promote functional HPS refractoriness ipsilateral to the site of stimulation; this may be accompanied by *delayed* transventricular septal propagation and retrograde engagement of the contralateral bundle or fascicles, activating the bundle of His in a retrograde fashion and conducting along the functionally blocked bundle (Figure 95-21, *A*) in an anterograde fashion, resulting in the "V3 phenomenon" (Figure 95-21, *B*). A His deflection precedes each QRS, and the H-V interval usually exceeds baseline SR measurements. Re-entry is self-limited in the normal heart and most often manifests as a single beat. The absence of sustained re-entry appears to be related to a decrease in refractoriness from repeated ventricular depolarizations.[129] It also seems to be related to *rapid* trans-septal conduction and HPS engagement promoting the extinguishing of tachycardia caused by rapid return of the propagated wavefront to *still-refractory* tissue (Figure 95-21, *C*). When the HPS or the intervening myocardium is diseased, predisposition to conduction slowing may facilitate re-entry and manifest clinically as VT.[130]

In bundle branch re-entrant beats induced as *laboratory phenomenon only*, the direction of propagation is dependent on the site of stimulation, and QRS morphology is similar to paced complexes. "Counterclockwise" bundle branch re-entry is induced with right ventricular apical stimulation that results in VT with LBBB morphology, whereas "clockwise" re-entry, having a right bundle branch morphology, may be induced with LV stimulation.

Alternatively, *clinical* bundle branch re-entry, occurring in patients with evidence of conduction disease, manifests as a rapid VT with QRS in most cases similar to *sinus*, often with IVCD or typical bundle branch block morphology, the left side being more common than the right. QRS morphology in sinus is indicative of the bundle with superior conduction, a route of anterograde conduction and, thus, also the ventricle from which induction may be more likely.

Induction and Diagnosis of Bundle Branch Re-entrant Ventricular Tachycardia

Induction and diagnostic evaluation should be performed with a minimum of two multielectrode catheters in the bundle of His and right ventricular apical positions to evaluate the relationship during VT. A third catheter in the right bundle position permits evaluation of the direction of right bundle activation, in an anterograde fashion versus a retrograde fashion, to allow distinction from myocardial VT and supraventricular tachycardia (SVT) with RBBB aberration. A catheter positioned in the atrium permits atrial programmed stimulation for the distinction of SVT and induction of bundle branch re-entry when right ventricular stimulation is unsuccessful. LV pacing may be required for induction when VT has an RBBB morphology.

Though bundle branch re-entry, particularly the RBBB variant, may be induced with decremental atrial pacing—inducing functional block in the right bundle with slow propagation along the left bundle allowing recovery of the site of block in the right bundle—this mechanism is rare.[131,132] More commonly, bundle branch re-entry is induced through short ventricular bursts, constant CL ventricular pacing, or ventricular stimulation that introduces a pause—a "short-to-long" sequence—followed by extrastimuli, which provoke HPS and myocardial refractoriness ipsilateral to the site of stimulation; this permits slowed transseptal conduction and engagement of the contralateral bundle in a retrograde fashion. In addition, if the patient has inducible "counterclockwise" bundle branch re-entry VT but clinically has a right bundle branch VT compatible with "clockwise" VT, introduction of at least two ventricular extrastimuli *during* VT may block propagation and convert to bundle branch re-entry

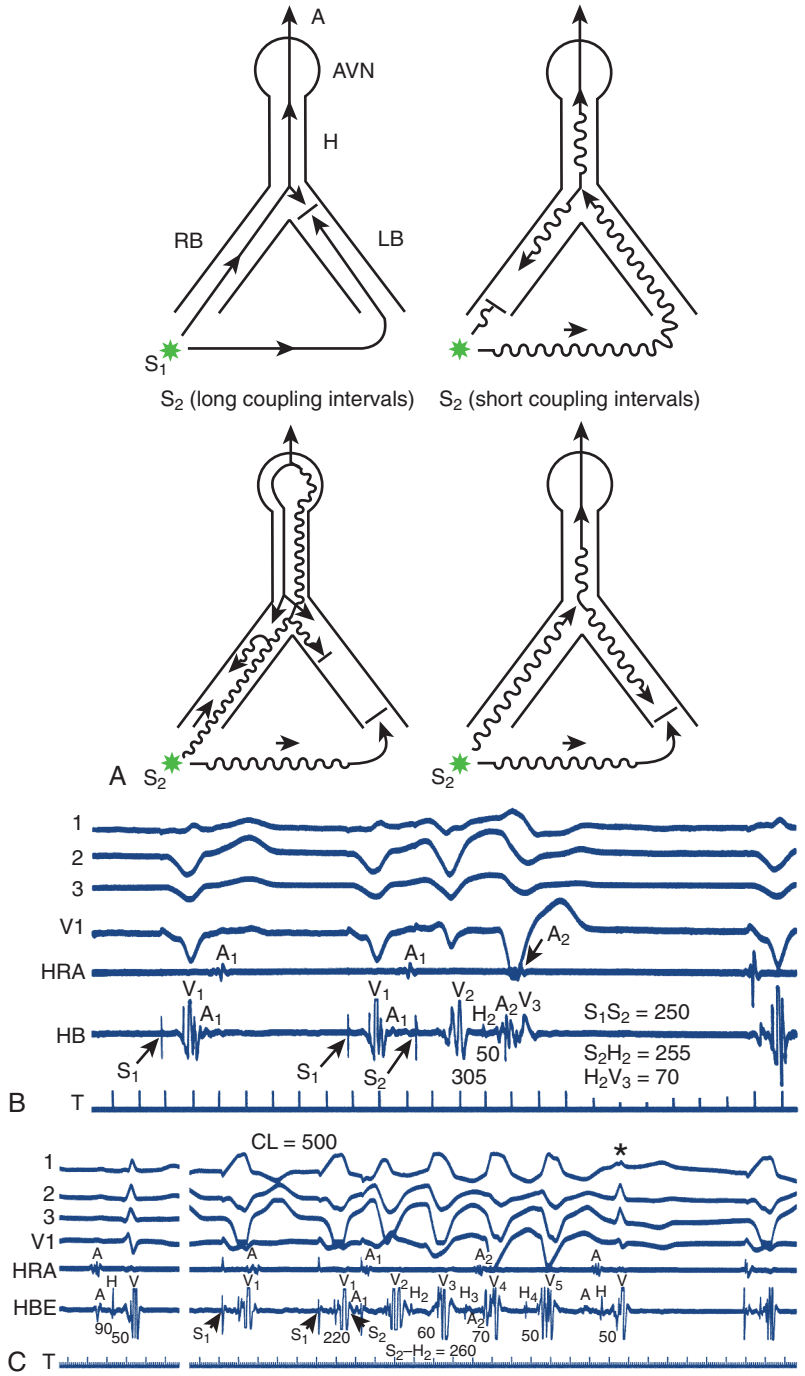

FIGURE 95-21 A, Bundle branch re-entry: Diagrammatic representation of possible events that follow right ventricular stimulation. The possible sites of block and the circuits of reentry are depicted. *A*, Atrium; *AVN*, atrioventricular node; *H*, bundle of His; *RB*, right bundle branch system; *LB*, left bundle branch system; S_1, basic ventricular drive stimulus; S_2, premature ventricular stimulus. **B,** Bundle branch re-entry: Tracings in each panel from top to bottom are standard electrocardiogram (ECG) leads I, II, III, V1; high right atrial (*HRA*) electrogram; bundle of His (*HB*) electrogram; and time lines recorded at 10 and 100 ms. All measurements are in milliseconds. *S*, *V*, and *A* represent stimulus artifact, ventricular, and atrial electrograms during the basic ventricular drive beats. Similarly, S_2, V_2, H_2, and *A* represent stimulus artifact, ventricular bundle of His, and atrial electrograms during the premature ventricular beat. **C,** Re-entry within the His-Purkinje system (HPS). **A,** The *left side* shows a reference sinus beat. **B,** The *right side* shows a premature ventricular beat coupled to the basic ventricular drive beat at an S, S_2 interval of 220 ms. S_2 conducts in a retrograde fashion with an S_2-H_2 interval of 260 ms, and a sustained re-entry is initiated. The H-V intervals of the three subsequent beats (i.e., V_3, V_4, V) measure 60, 70, and 50 ms, respectively. A_2 on the bundle of His region (*HBE*) coincides with the onset of H_2, and it is very unlikely that V4 is an A-V nodal re-entrant beat. The cycle of sustained re-entry within the HPS is followed by an AV nodal re-entrant beat (*asterisk*). The fact that the first beat on the *right side* does not capture the atria in a retrograde fashion should have no influence on the subsequent events, since it is unlikely that the sinus beat could have depolarized the HPS in an anterograde fashion. Similarity of V_5 to V_4 suggests their similar origin; however, AV nodal re-entry and aberrant conduction during V cannot be entirely excluded. *CL*, Cycle length. *(From Akhtar M, Damato AN, Batsford WP, et al: Demonstration of reentry within the His-Purkinje system in man,* Circulation *50:1150, 1974.)*

Table 95-4 Characteristic and Diagnostic Electrophysiological Features of Bundle Branch Re-entry Ventricular Tachycardia

- Evidence of baseline H-V interval prolongation in sinus
- Induction of monomorphic VT with extrastimuli consistently dependent on the development of critical HPS delay
- Typical right or left BBB monomorphic VT QRS morphology consistent with ventricular depolarization along the expected bundle branch
- H-V interval during VT different and usually longer than in sinus
- An RB potential preceding each local ventricular activation and QRS, and stable H-V and RB-V intervals in LBB morphology VT
- Spontaneous R-R interval changes during tachycardia preceded by similar H-H or RB-RB interval changes
- Evidence of macro–re-entry with a penetrable excitable gap, resetting with ventricular extrastimuli advancing the next RB deflection and associated shortening of the *next* V-V interval, and termination of tachycardia by spontaneous or induced HPS block
- Inducibility of a second VT morphology from the left ventricle with similar behavioral characteristics, demonstrating an *LB* recording preceding the local ventricular activation and QRS during VT
- Elimination of VT after effective bundle branch ablation

BBB, *Bundle branch block;* HPS, *His-Purkinje system;* LBB, *left bundle branch;* RB, *right bundle;* VT, *ventricular tachycardia.*

revolving in the opposite direction.[131] Characteristic and diagnostic electrophysiological features of bundle branch re-entry VT are listed in Table 95-4.[131,133]

Ablation of Bundle Branch Re-entry

In most patients, catheter ablation of the right bundle is the preferred mode of therapy because of the relative ease of access compared with the left bundle, although either target eliminates VT.[131,134] Despite ablation of a portion of the conduction system, pacemaker implantation is usually not required because of residual preserved anterograde conduction along the contralateral bundle. However, an H-V interval of more than 100 ms—in the baseline state, provoked with sodium channel blockade, or occurring after bundle branch ablation—necessitates permanent pacing. In such patients with clinical heart failure and left ventricle dysfunction, particularly an EF less than 35%, a bi-ventricular ICD should be considered.

To perform right bundle branch ablation, the catheter is positioned at the anterior interventricular septum to record a right bundle potential distally. An atrial potential should not be present in the distal bi-pole recording, and the His–right bundle potential interval should be at least 20 ms. RF ablation in this location should produce RBBB and terminate bundle branch re-entry VT (Figure 95-22).

In certain instances left bundle branch ablation should be considered. First, ablation of the right bundle may rarely be unsuccessful, and left bundle ablation is an alternative approach. However, an important consideration is the presence of severely impaired or complete LBBB, as right bundle ablation would result in further conduction impairment or complete AV block. The diseased bundle, in this case the left bundle, should be targeted, as it has little or no contribution to anterograde AV conduction; and, as mentioned earlier, ablation of either bundle will eliminate VT.[135] Finally, if the patient has intrafascicular re-entry as well (see the following section), left bundle ablation would eliminate *both* VTs.[135-137]

For left bundle branch ablation, using the transfemoral retrograde aortic approach in the anteroposterior fluoroscopic projection, the ablation catheter is advanced to the level of the aortic arch and then flexed to permit looping of the catheter tip as it traverses the arch posteromedially to the ascending aorta. Advancing the flexed catheter with clockwise torque should allow passage across the valve. Removing flexion then opens the catheter, and the catheter tip will naturally lodge against the anterior wall or prolapse more apically. Withdrawing the catheter partially allows any residual flexion to be removed, and at this point, counterclockwise torque will direct the catheter to assume a septal lie, which can be confirmed in the left anterior oblique (LAO) fluoroscopic projection. Torque and flexion may be required to maintain contact with the septum. While maintaining the LAO view, the catheter should be slowly withdrawn along the septum until the ablation catheter tip reaches the level of the His bundle catheter. The right anterior oblique (RAO) projection can then be used to fine tune the positioning of the ablation catheter until it fluoroscopically overlies the bi-pole on the His electrode that is recording the largest His potential (Bip_{His}), allowing recording of the left-sided His potential. As the left bundle branch is usually located within 1.5 cm of the aortic valve just below the membranous septum, the left bundle potential should be identifiable by slowly advancing the ablation catheter until the tip is approximately 5 to 10 mm inferior or anteroinferior to Bip_{His}. Similar to recording the right bundle potential, a high-frequency deflection with a left bundle–V interval measuring 20 to 30 ms and without a visible atrial electrogram signifies recording a left bundle potential. As the main left bundle branch is a broad structure, multiple high-frequency potentials may be obtained within that vicinity, and multiple contiguous lesions may be required to achieve effective ablation.

Three clinical possibilities exist if VT remains inducible: (1) The first is myocardial VT, which may be inducible in up to 43% of bundle branch re-entry patients, potentially requiring adjunctive ICD or antiarrhythmic drug therapy.[134] Myocardial re-entry should be distinguishable by the absence of the bundle of His preceding each QRS or, in the case of intact retrograde conduction, V-V interval variation preceding inter-His variability, as compared with bundle branch re-entry in which H-H variation precedes V-V changes. (2) The second possibility is, despite successful ablation of the local high-frequency bundle branch potential and development of bundle branch block morphology QRS in sinus, persistently inducible VT may yet be bundle branch re-entry if RF is delivered too distal along the bundle, thereby allowing the conducting impulse to exit proximal to the ablation site, provoking a change in the VT QRS morphology. This highlights an important principle—that a change in SR QRS does not imply adequate bundle ablation, that VT with a different morphology is not necessarily caused by a different mechanism, and that bundle branch re-entry should be sought and excluded.[138] (3) The third mechanism responsible for persistent VT, after confirmed right bundle ablation, is interfascicular re-entry.

Interfascicular Re-entry

A related though rare macro–re-entrant VT, interfascicular tachycardia uses left bundle branch fascicles as the anterograde and retrograde limbs of the re-entrant circuit, in contrast to

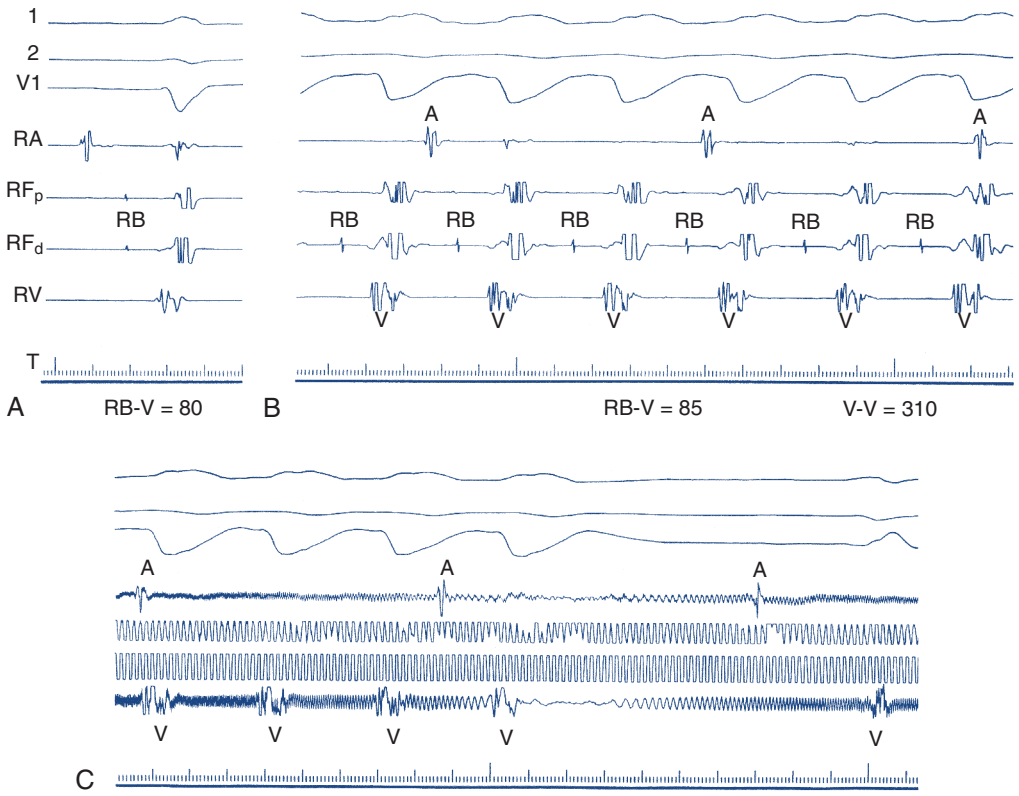

FIGURE 95-22 Termination of bundle branch re-entrant ventricular tachycardia (VT) during radiofrequency catheter ablation of the right bundle (*RB*). Shown (*top to bottom*) are surface electrocardiogram leads 1, 2, and V1, right atrium (*RA*), proximal and distal ablating catheters (RF_p, RF_d), right ventricular electrogram (*RV*), and time lines (*T*). All labeled intervals are in milliseconds. **A,** Activation of the right bundle (*RB*) is recorded in the proximal and distal bi-pole of the ablating catheter during sinus rhythm. **B,** Bundle branch re-entrant VT with a left bundle branch block QRS morphology. Activation of the RB is recorded from the distal pole of the ablation catheter. **C,** Termination of tachycardia within 6 seconds of energy application. Note the expected RB QRS morphology following the termination of the tachycardia. *(From Blanck Z, Dhala A, Deshpande S, et al: Bundle branch reentrant ventricular tachycardia: Cumulative experience in 48 patients,* J Cardiovasc Electrophysiol *4:253, 1993.)*

bundle branch re-entry and fascicular VT described earlier.[136,137] Again, conduction delay in the HPS is a prerequisite to the development of sustained tachycardia.

Electrophysiology and Diagnosis

Interfascicular re-entry has been described in the setting of anterior MI, myotonic dystrophy, and in association with, or after ablation of, bundle branch re-entry VT, with right bundle branch and left fascicular conduction delays being a common thread. Intact conduction along *both* bundle branches, particularly when right bundle conduction is superior to the left one, permits right bundle impulse propagation to spread trans-septally and invade the left bundle fascicles in a retrograde fashion; there, wavefront collision prevents re-entry, thereby "protecting" against the development of VT.[139]

Alternatively, anterograde conduction delay or block in the RBBB and one left bundle fascicle creates the unique situation in which A-V conduction proceeds down a *single* path only—the remaining functioning fascicle. In the absence of an arriving wavefront from the right ventricle to extinguish left bundle impulses, anterograde conduction along the functioning fascicle during sinus rhythm may then return along the fascicle that is blocked in an anterograde fashion with sufficient conduction delay to allow refractoriness from the previous depolarization to resolve, thus permitting re-entry (Figure 95-23). Ventricular extrasystoles may induce retrograde block in the functioning fascicle and engage the alternate fascicle to initiate re-entry.

In both sinus and interfascicular re-entry, anterograde conduction proceeds along the nonblocked, functioning bundle, leading to QRS morphology in VT that is identical to SR. The specific morphology is predicated by the particular fascicle serving as the limb that conducts in an anterograde fashion—RBBB right axis for anterior fascicular exit (because of posterior fascicular conduction impairment causing left posterior hemi-block pattern) or RBBB left axis for posterior fascicular exit (because of anterior fascicular conduction impairment causing left anterior hemi-block pattern).

When the propagating wavefront reaches the upper turnaround point at the bifurcation of the fascicles from the main left bundle and then continues in an anterograde fashion along the functioning fascicle, the impulse *also* propagates along the main left bundle and activates the bundle of His in a retrograde fashion. His activation occurring *in parallel* with anterograde conduction to the ventricle leads to an illusory shortening of the H-V interval—a diagnostic distinction from bundle branch

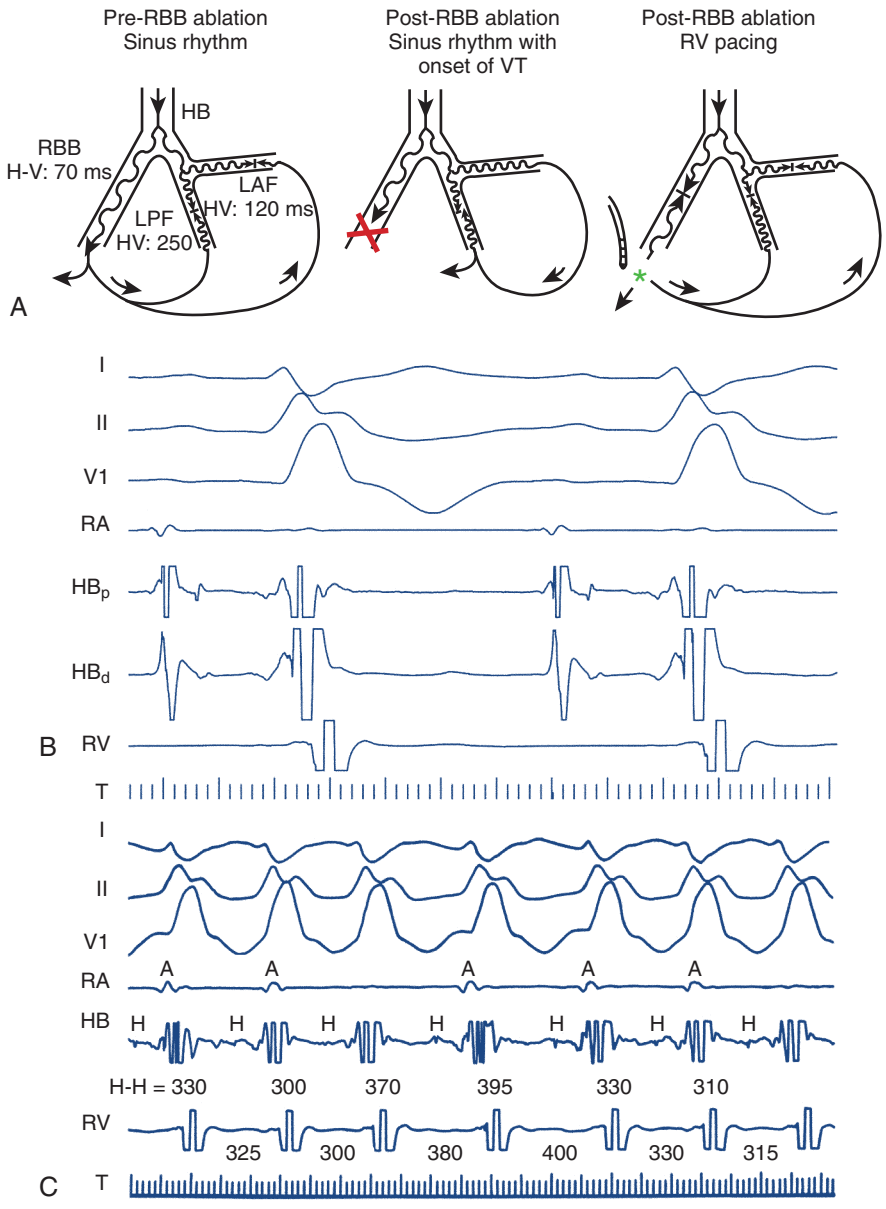

FIGURE 95-23 A, Proposed mechanism by which ablation of the right bundle branch (*RBB*) facilitates interfascicular re-entrant tachycardia. *Left*, During sinus rhythm and before RBB ablation, the faster antegrade conduction over the RBB (H-V interval 70 ms) allows the impulse to reach the right ventricle, cross the interventricular septum, and penetrate both left-sided fascicles in a retrograde fashion. *Middle*, After the RBB ablation, the sinus impulse reaches the left ventricle via the faster left anterior fascicle (*LAF*, H-V interval 120 ms) and intermittently blocks in the left posterior fascicle (*LPF*), setting the stage for the re-entrant mechanism, as shown. *Right*, Right ventricular pacing suppressing the re-entrant mechanism in the left-sided fascicles. **B,** The intracardiac electrograms during sinus rhythm after RBB ablation. *Top to bottom*, surface electrocardiogram (ECG) leads I, II, and V1, and electrograms from the right atrium (*RA*), bundle of His proximal and distal (HB_p and HB_d, respectively), and right ventricle (*RV*). Catheter ablation of the RBB prolonged the H-V interval to 120 ms (not labeled). **C,** Intracardiac electrograms during interfascicular reentrant tachycardia. *Top to bottom,* Surface ECG leads I, II, and V1, and electrograms from the bundle of His (*HB*). All intervals are in milliseconds. The H-V interval shortens from 120 ms in sinus rhythm to 70 ms during tachycardia (not labeled). In addition, changes in H-H intervals precede and dictate subsequent changes in RV-RV intervals, typical of His-Purkinje re-entry. *T*, Time lines. *(From Blanck Z, Sra J, Akhtar M: Incessant interfascicular reentrant ventricular tachycardia as a result of catheter ablation of the right bundle branch: Case Report and review of the literature,* J Cardiovasc Electrophysiol *20:1279, 2009.)*

re-entry. The wavefront may then also passively activate the right bundle branch system on the basis of its degree of functionality. The distance between the upper turn-around point and the bundle of His as well as the conduction velocities along the left bundle and the fascicle that is conducting in an anterograde fashion contribute to H-V interval shortening during VT, often more than 40 ms shorter than that recorded in sinus rhythm. The development of incessant VT after right bundle branch ablation, particularly in association with pronounced H-V interval shortening, should be considered interfascicular VT until proven otherwise.[139] Characteristic and diagnostic electrophysiological features of interfascicular re-entry are listed in Table 95-5.

Induction and Ablation of Interfascicular Re-entry

As in bundle branch re-entry, pacing trains with varied cadences may be required to produce functional block and conduction delay to induce interfascicular re-entrant VT. Unlike bundle branch re-entry, supraventricular impulses, including SR, may more readily induce VT.[139] As the activation sequence in VT may be preceded by a His deflection, behavioral characteristics should be analyzed and pacing maneuvers employed to confirm re-entry and exclude other forms of wide-complex tachycardia.

Catheter ablation is directed toward the fascicle that is conducting in a retrograde fashion, as targeting the normally functioning fascicle would result in advanced, if not complete, AV block. Therefore, in RBBB left-axis VT, the anterior fascicle is targeted, whereas in RBBB right-axis VT, the posterior fascicle is targeted. As for bundle branch re-entry, baseline, pharmacologically induced, or iatrogenic H-V interval prolongation greater than 100 ms necessitates permanent pacing, with consideration for bi-ventricular pacing and defibrillation capabilities in appropriate patients.

Frontiers in Ventricular Tachycardia Ablation

Remote Navigation

In conjunction with advanced three-dimensional mapping systems, mechanical catheter manipulation systems offer a number of enhancements to conventional ablation performed with manual catheter manipulation, which may be particularly pertinent to VT ablation. Most relevant is the greater degree of freedom of motion, which offers a broader range of catheter directability and enhanced stability facilitating the delivery of ablation to otherwise difficult to reach sites. By allowing remote catheter manipulation, the presence of the operator at the tableside is no longer obligatory, which reduces cumulative and excessive radiation exposure to the operator, particularly with complex and prolonged procedures such as ablation of VT. Finally, remote navigation helps eliminate the physical, particularly orthopedic, demands imposed by leaded aprons.[140]

The feasibility and efficacy of magnetically driven catheter ablation of VT was evaluated by Aryana et al by using the Niobe magnetic navigation system (Stereotaxis Inc., St. Louis, MO).[141] Right ventricular and epicardial mapping were achieved nearly exclusively using the remote system alone, whereas LV mapping required manual catheter manipulation in nearly one quarter of cases. Overall, the system demonstrated adequate ability to perform (1) substrate mapping, (2) maneuvers to identify zones critical to VT maintenance, and (3) ablation.

Mapping was performed with less than 2 minutes of fluoroscopy, less than 1 minute in most cases, because of the absence of any risk for cardiac perforation, as the remote magnetic technology catheter tips are easily deformable and less traumatic than conventional mapping catheters. The maps had less "tenting" of the chamber wall, thus producing depictions that were more accurate. As these catheters are not irrigated, supplemental manual irrigated ablation was performed in nearly all cases for enhanced safety and efficacy. Manual ablation was performed under fluoroscopy, which extended the total procedural fluoroscopy time to 21 ± 7 minutes. The single procedure success rate was 83%, and no VTs were documented over the 7 ± 3 months of follow-up—comparable with conventional methods, though procedural complications included the development of ulnar palsy and bilateral deep vein thrombosis.

In a limited series of patients with scar-related VT and electrical storm, magnetic navigation of an irrigated ablation catheter has been suggested to be safe and effective as well, with all clinical VTs acutely eliminated, no requirement of manual ablation, no development of complications or mortality, and no ICD discharges over a mean follow-up of 4.2 months.[142] The median total procedure and fluoroscopy times were 130 minutes (range, 100 to 150 minutes) and 6.7 minutes (range 5 to 9 minutes), respectively. Procedure duration was comparable in historical controls, but total fluoroscopy time was significantly less with magnetic navigation.

The system has also been employed successfully in ablation of idiopathic RVOT VT and left posterior fascicular tachycardia. In such VTs, where mechanical block may suppress inducibility, an important advantage to the magnetic navigation system is that the "soft tip" catheter appears to be less traumatic and is less associated with catheter-induced suppression and iatrogenic induction of PVCs and VT, which otherwise complicate mapping. Thornton et al found that the system permitted small increments of catheter movement, often difficult with conventional catheter manipulation, allowing precise catheter directability that facilitated ablation.[143,144] In their experience, as well as in Aryana's, manipulation was only slightly limited when the retrograde transaortic approach was used and entirely unencumbered when a trans-septal approach was used.[141]

The capabilities of the Sensei X Robotic Catheter System (Hansen Medical, Mountain View, CA) in VT ablation were still not described at the time of this writing, largely because of limitations in delivering the sheath system into the left ventricle and the pericardial space.

Table 95-5 Characteristic and Diagnostic Electrophysiological Features of Interfascicular Ventricular Tachycardia

QRS is identical to sinus, particularly in the setting of RBBB and fascicular block
Activation of bundle of His precedes local ventricular activation and QRS
LB potential *precedes* bundle of His activation
H-V interval is shorter than sinus rhythm
H-H and LB-LB variation predicts VT CL changes with stable H-V and LB-V intervals

LB, *Left bundle;* RBBB, *right bundle branch block;* VT CL, *ventricular tachycardia cycle length.*

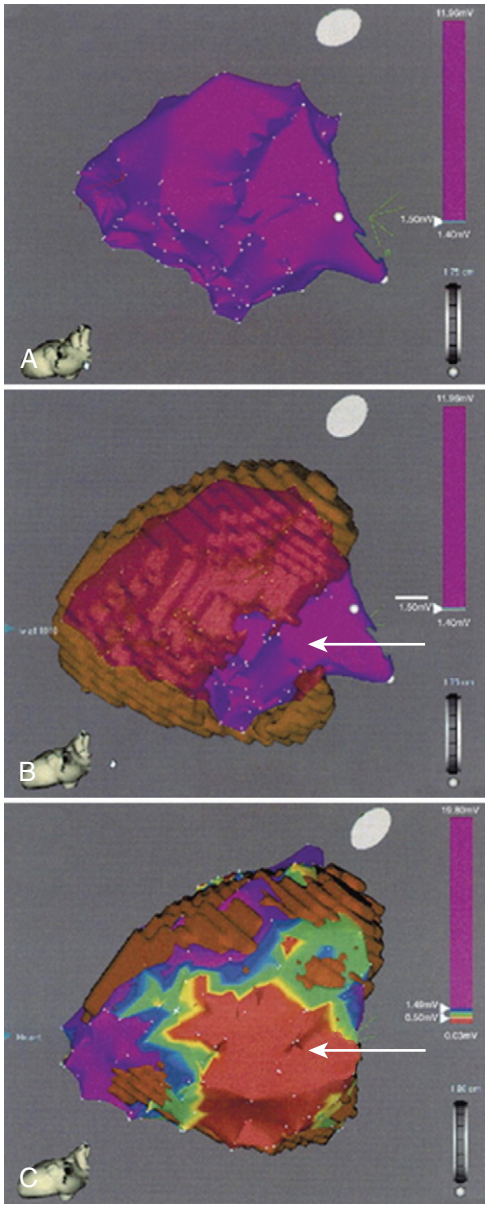

FIGURE 95-24 Integration of positron emission tomography (PET) and computed tomography (CT) with left ventricle scar maps for ventricular tachycardia (VT) ablation. The endocardial voltage map was unable to detect the myocardial scar, and all wall segments revealed >1.5 mV voltage (*left lateral view,* **A**). However, three-dimensional PET scar map (*ocher shell*) revealed a large inferobasal lateral wall defect signifying myocardial scarring, which was consistent with the exit site of the presenting VT (*white arrow,* **B**). An epicardial voltage map finally confirmed a large, nontransmural scar (*red area*, <0.5 mV) in the inferobasal lateral location (*white arrow,* **C**). Registration of the epicardial voltage map and three-dimensional PET scar map demonstrates good correlation between the epicardial voltage-defined scar and the PET-defined scar. *(From Dickfeld T, Lei P, Dilsizian V, et al: Integration of three-dimensional scar maps for ventricular tachycardia ablation with positron emission tomography-computed tomography,* J Am Coll Cardiol Imag *1:73, 2008.)*

Imaging in Procedure Planning

While substrate mapping for ablation of VT has been employed successfully, its limitations—including the impact of fixed, operator-defined thresholds to discriminate scar from healthy myocardium and intermediary tissue, the relative inability to accurately describe the three-dimensional complexities of myocardial scarring, voltage attenuation caused by poor catheter contact that overestimates scarring, poor mapping of spatial resolution, and time constraints of clinical practice in obtaining detailed maps that result in low sampling density during chamber mapping—have all encouraged preablation imaging for scar delineation and integration with electroanatomic mapping to more accurately identify border zones, isthmi, and scar exits for precise and efficient ablation.[145]

Both magnetic resonance imaging (MRI) and positron emission tomography–computed tomography (PET-CT) fusion data sets have been integrated into electroanatomic maps, affording highly accurate anatomic as well as *functional* information complementary to the electroanatomic data acquired during substrate mapping.[146,147] Preliminary work with PET-CT suggests that fluorodeoxyglucose (FDG) (metabolic) and CT (anatomic) imaging may be integrated into substrate maps (Figure 95-24) with a mean registration error less than 6 mm using the CARTOMerge platform (Biosense Webster Inc., Diamond Bar, CA), though the range of error may exceed 10 mm for individual points. By using standard voltage thresholds for healthy myocardium (>1.5 mV), and standard (<0.5 mV) and modified (<0.9 mV) voltage thresholds to define scar tissue during electroanatomic mapping and by choosing a metabolic threshold between 40% and 50% on FDG imaging, the two modalities correlate well with respect to distribution and definition of scar tissue and scar border zone. However, as both electroanatomic mapping and FDG imaging require initial definitions of scar and "partial scar" to be set by the operator, comparison of the two types of tissue introduces a bias in determining true absolute errors.

Interaction between device programming and magnetic fields has limited the use of MRI in patients with ICDs, though recent small studies involving patients with MRI-compatible ICDs have offered a glimpse into the integration of delayed-enhancement MRI to guide ablation of scar-related VT.[148] In patients with nonischemic cardiomyopathy, awareness of the spatial distribution of scar tissue (i.e., endocardial *and* epicardial distribution) identified with delayed-enhancement MRI has had a demonstrable impact on ablation success by directing a more comprehensive and therefore more effective ablation. Studies have shown that VT associated with intramural scarring can be eliminated only if it is associated with endocardial or epicardial extension and that VTs not involving epicardial or endocardial scar extensions or those arising in intramural-only scar tissue cannot be eliminated (see Figure 95-24).

Bipolar electrogram voltage less than 1.54 mV best predicted the presence of MRI-identified scar tissue in patients who have had an MI. The voltage level was significantly higher for intramural or epicardial scar tissue (1.52 ± 1.41 mV) as opposed to endocardial scar tissue (0.94 ± 1.07 mV). Using the 1.5-mV bipolar threshold, mismatch of more than 20% of infarct surface was seen in 33% of patients; 75% of these, in fact, demonstrated no MRI evidence of scar tissue and, in 25%, electroanatomic mapping underestimated scarring compared with delayed-enhancement MRI (Figure 95-25).[149] Most thought-provoking is the fact that

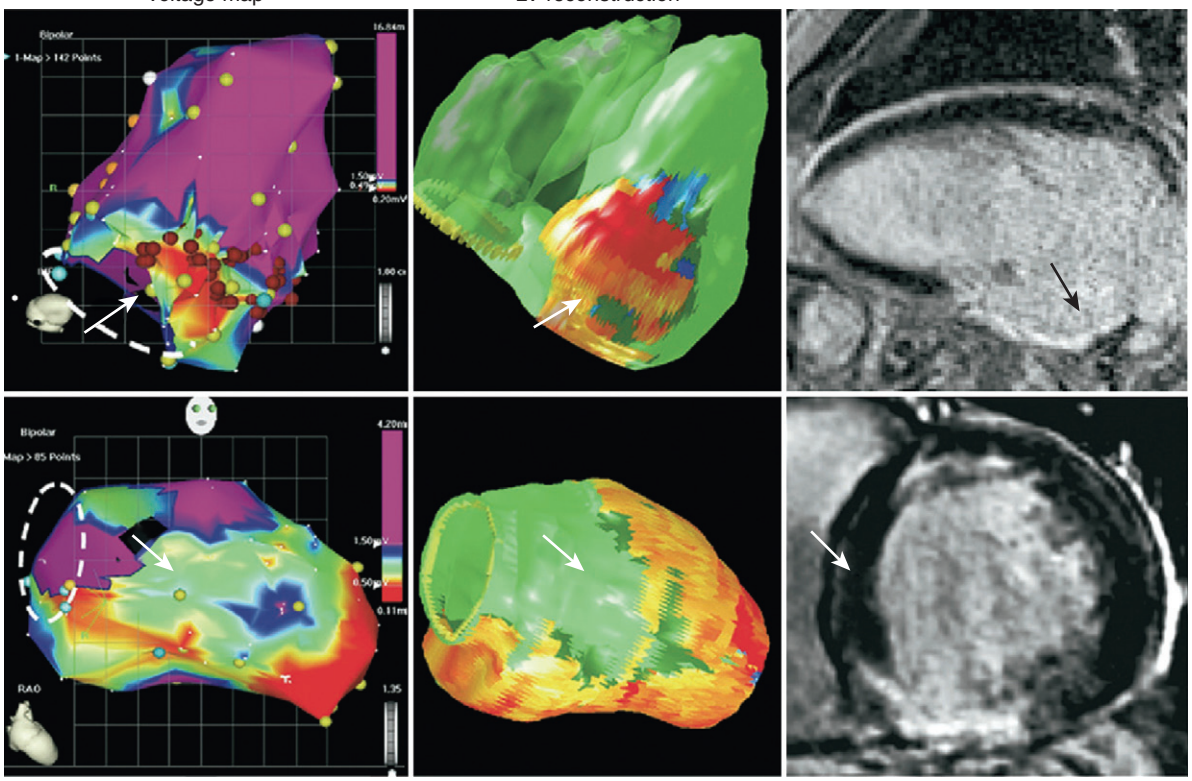

FIGURE 95-25 Mismatch in scar delineation between CARTO bipolar maps and magnetic resonance imaging (MRI) shells. *Left,* CARTO bipolar maps; (*middle*) MRI shells; (*right*) native MRI images. The top row shows the underestimated inferior wall scar on the CARTO map. The bottom row shows the left ventricular septal scar on the CARTO map not confirmed by MRI. On each panel, the arrows show the mismatch zone. The dotted lines represent the mitral annulus plane. *LV,* left ventricle. *(From Codreanu A, Odille F, Aliot E, et al: Electroanatomic characterization of post-infarct scars comparison with 3-dimensional myocardial scar reconstruction based on magnetic resonance imaging,* J Am Coll Cardiol *52:839, 2008.)*

traditional electroanatomic mapping inadequately depicts the distribution of scar.

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CHAPTER 96

Advances in Catheter Ablation of Primary Ventricular Fibrillation

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Ventricular fibrillation (VF) is a potentially lethal cardiac rhythm disorder and is the most frequent cause of sudden cardiac death (SCD). It can complicate the course of any cardiomyopathy or occur unexpectedly in patients who do not have structural heart disease. It is often initiated by ventricular premature depolarization at a critical coupling interval (primary VF) or by ventricular tachycardia (VT) that further degenerates into fibrillatory activity (secondary VF). The Purkinje-myocardium junction plays a key role in triggering ectopy and in sustaining re-entry in the early stages of VF.[1] Perpetuation of VF is thought to be mediated either by one or several periodical sources, intramyocardial and intra-Purkinje re-entry, or by multiple interacting wavelets.[2,3] Both mechanisms have been observed during VF in humans.[3]

Premature Ventricular Contractions Initiating Ventricular Fibrillation

The vulnerable period during which a premature ventricular beat can provoke VF encompasses the end of ventricular repolarization. Conditions that lengthen QT increase the risk of VF; however, in idiopathic VF, the QT interval is normal. In patients with no apparent heart disease, short-coupled premature ventricular contractions (PVCs) occurring within 20 to 40 ms of the peak of the T wave have been documented to initiate VF.[4] Although the culprit PVCs initiating VF may be monomorphic in patients with normal hearts, PVCs are often polymorphic in patients with structural heart disease (Figures 96-1 and 96-2).

The role of the Purkinje network in triggering PVCs leading to VF in humans has been evidenced by mapping PVCs in survivors from VF and SCD.[5] All patients from this initial description had normal hearts and were diagnosed as having idiopathic VF. Conventional mapping for the earliest activation during premature beats revealed that PVCs originated from the Purkinje network in 12 of 16 patients, the others having PVCs originating from the myocardial tissue.[5] Further studies confirmed this finding: In a series of 27 patients with idiopathic VF, PVCs originated from the Purkinje network in 23 and from the right ventricular outflow tract (RVOT) myocardial tissue in 4.[6] Three studies in the literature reported ablation of VF triggers in a total of 17 patients with ischemic cardiomyopathy. All mapped PVCs arose from the Purkinje system, mainly from the left ventricle.[7-9] In 4 patients with a history of VF and long QT syndrome (LQTS), 3 had PVCs triggered by Purkinje tissue and 1 from RVOT, whereas in 3 patients with Brugada syndrome, only 1 had Purkinje-initiated ectopic beats.[10] Eight patients with malignant early repolarization had a total of 26 different ectopic beat morphologies, 10 arising from Purkinje tissue and 16 from the myocardium.[11] Finally, isolated reports of Purkinje PVCs initiating VF after aortic valve repair, in the context of an acute coronary syndrome, in infiltrative cardiac amyloidosis, in coronary artery disease, and in chronic myocarditis are found in the literature.[12] In a minority of cases, the culprit PVCs originate from myocardial tissue, mostly from the RVOT area. This finding, however, seems to be more frequent in patients with Brugada syndrome.

Catheter Ablation for Ventricular Fibrillation

Indications

In patients with multiple episodes of VF occurring despite medical therapy, catheter ablation directed at VF triggers can be attempted. Current guidelines state that "ablation of Purkinje fiber potentials may be considered in patients with ventricular arrhythmia storm consistently provoked by PVCs of similar morphology" as a class IIb level of evidence C recommendation.[13]

When clusters of VF occur in a patient, investigations should initially search for secondary modifiable arrhythmogenic conditions such as myocardial ischemia, electrolyte imbalance, QT prolongation caused by medication, substance abuse or medication abuse or toxicity, hypothermia and rare conditions, for example, infiltrative cardiac disorders, or cardiac masses or tumors. In the absence of a reversible cause, a drug trial is indicated and should be tailored to the underlying pathology. In the absence of contraindications, patients with ischemic heart disease should receive β-blockers or amiodarone; patients with LQTS can be treated with β-blockers; and those with malignant early repolarization syndrome, idiopathic VF, and Brugada syndrome should be treated with quinidine.[13-15] Implantable cardioverter-defibrillators (ICDs) should be implanted in all SCD survivors if no reversible cause is found to explain the event. If these strategies fail to control VF episodes, catheter ablation should be considered.

Contraindications

Obvious contraindications to catheter ablation for VF, as to all invasive procedures, are documented thrombus in the chamber of interest, active systemic infection, and significant coagulation deficit. Moreover, catheterization is not indicated in the absence of documented PVCs or in a patient whose disease is well controlled

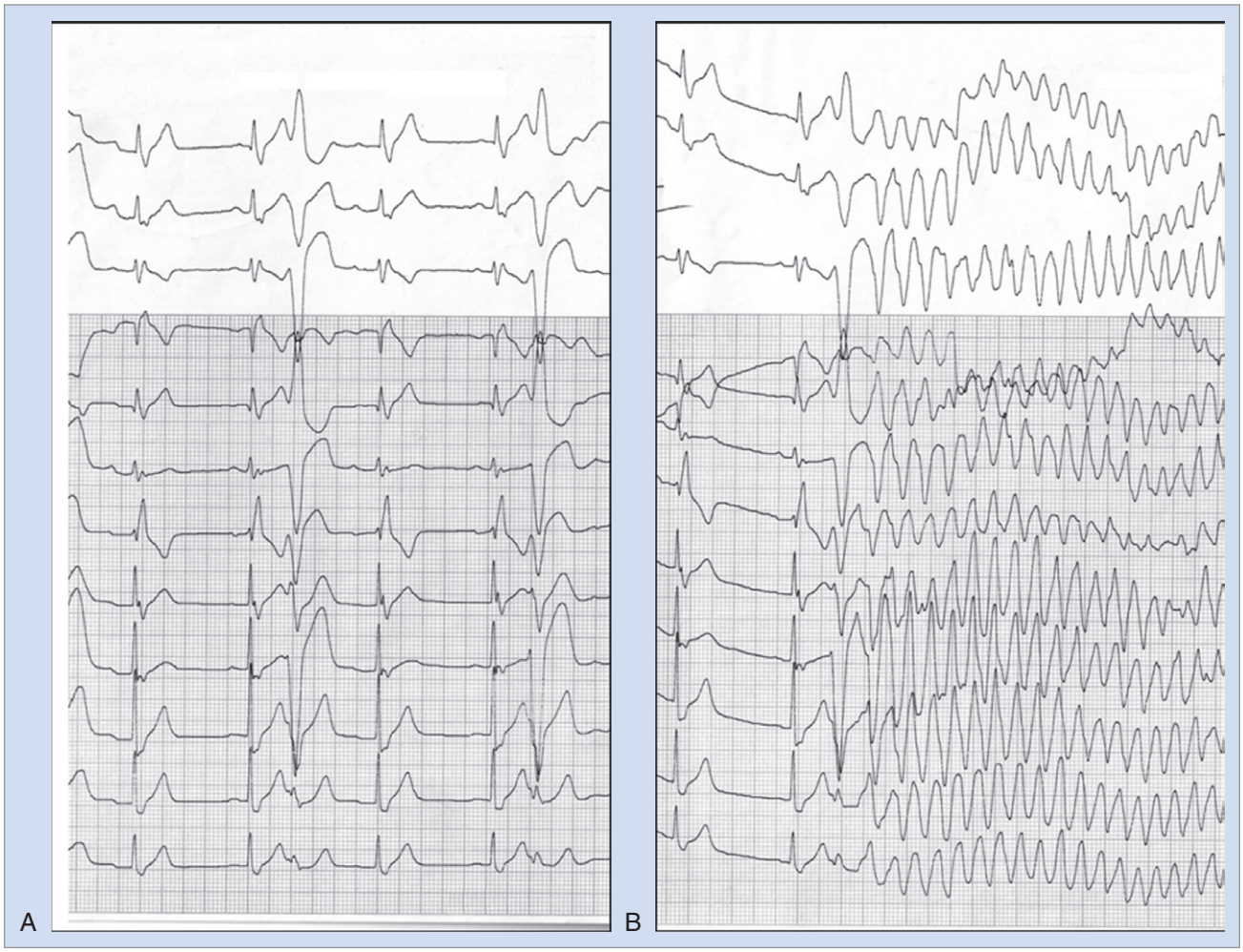

FIGURE 96-1 A, Frequent premature ventricular contractions (PVCs) from the right ventricle. **B,** The same PVCs are triggering an episode of ventricular fibrillation.

with a tolerated drug regimen and ICD protection. Finally, in rare patients with acute VF storm and multiple episodes of arrhythmia, which are sometimes refractory to defibrillation, and hemodynamic instability, extreme caution is advised as radiofrequency (RF) thermal irritability could potentially increase the arrhythmia's refractoriness to defibrillation. Such cases should be cared for in tertiary centers with available backup for circulatory assistance.

Preparation

Since catheter ablation for VF is directed at triggering PVCs, it is imperative to have recordings of the morphologies of all possible triggers. The patient should be monitored with a 12-lead electrocardiogram (ECG) over several hours to gather enough information that will help identify all ectopic foci. Another essential condition for a successful ablation is the presence of spontaneous PVCs during the procedure. In the absence of native PVCs, pacemapping can approximate the culprit zone, but ablation is not as precise. All antiarrhythmic drugs should be withdrawn prior to ablation. Pain control and sedation should be balanced against the possibility of PVC suppression caused by deep sedation or general anesthesia. In the authors' center, procedures for VF ablation are performed under conscious sedation. During the procedure, the ICD should be switched off to avoid inadvertent shocks during RF, and all staff should be ready for prompt defibrillation if sustained VF occurs.

Electrocardiogram Morphology of Premature Ventricular Contractions

Twelve-lead ECG reveals important clues for the ablation procedure. First, it documents if PVCs are monomorphic or polymorphic. PVC negativity in V1 simulating a left bundle branch block pattern indicates origination from the right ventricle and indicates origination from the left ventricle when positive in V1 with a right bundle branch block appearance. PVC polymorphism can be seen in 85% of patients. The arborization of the Purkinje network makes it possible for the influx to take different routes, and the exit point may vary from one PVC to another, causing subtle changes in the morphology of ectopic beats. These changes are dependent on the extent of the Purkinje arborization and, therefore, are more evident when PVCs originate from the left ventricle and more subtle when origination is from the right, as the right-sided Purkinje network has fewer ramifications than the left-sided Purkinje network (Figure 96-3). PVCs arising from the

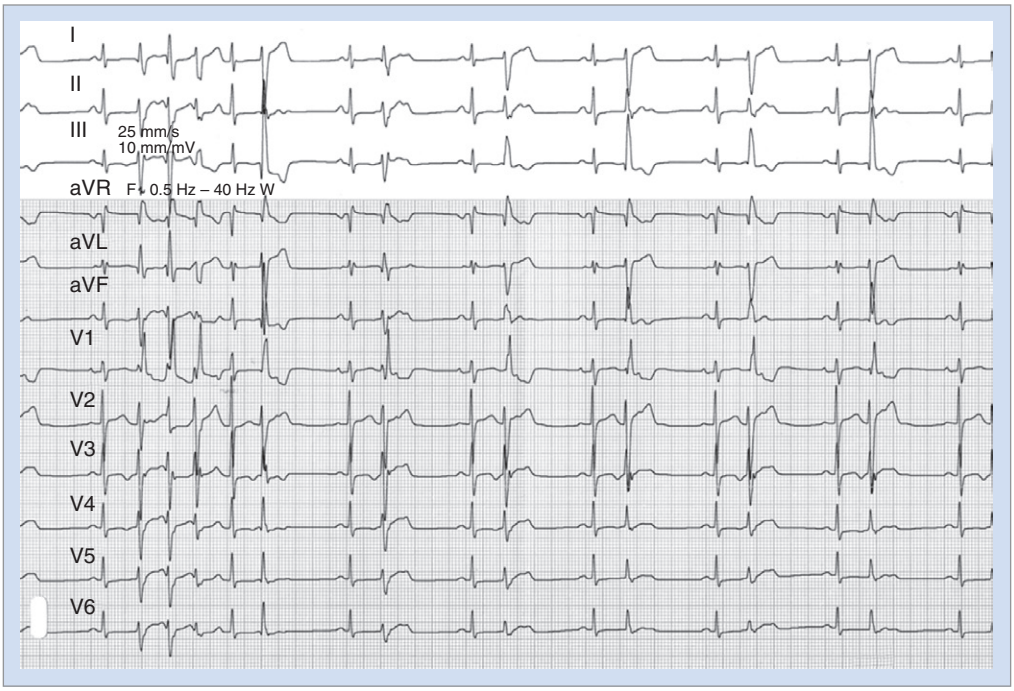

FIGURE 96-2 Premature ventricular contractions of different morphologies in a patient with a history of sudden cardiac death caused by ventricular fibrillation. In this tracing, at least three distinct morphologies are seen.

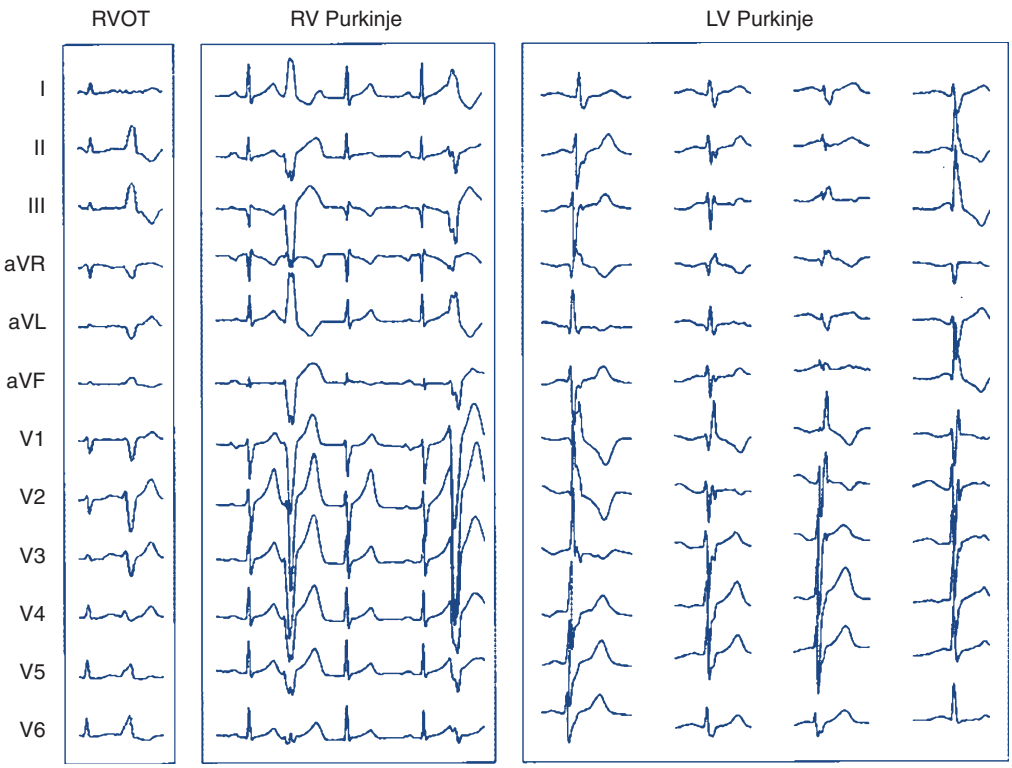

FIGURE 96-3 Twelve-lead electrocardiogram recordings of premature ventricular contractions (PVCs) originating from the right ventricular outflow tract (*RVOT*), right Purkinje network (*RV Purkinje*), and left Purkinje network (*LV Purkinje*). The PVCs arising from the left ventricle (*LV*) are from the same patient; different morphologies are seen as the influx exits at different sites from the left Purkinje arborization. *RV*, Right ventricle. *(From Haïssaguerre M, Shoda M, Jaïs P, et al: Mapping and ablation of idiopathic ventricular fibrillation,* Circulation *106:962–967, 2002.)*

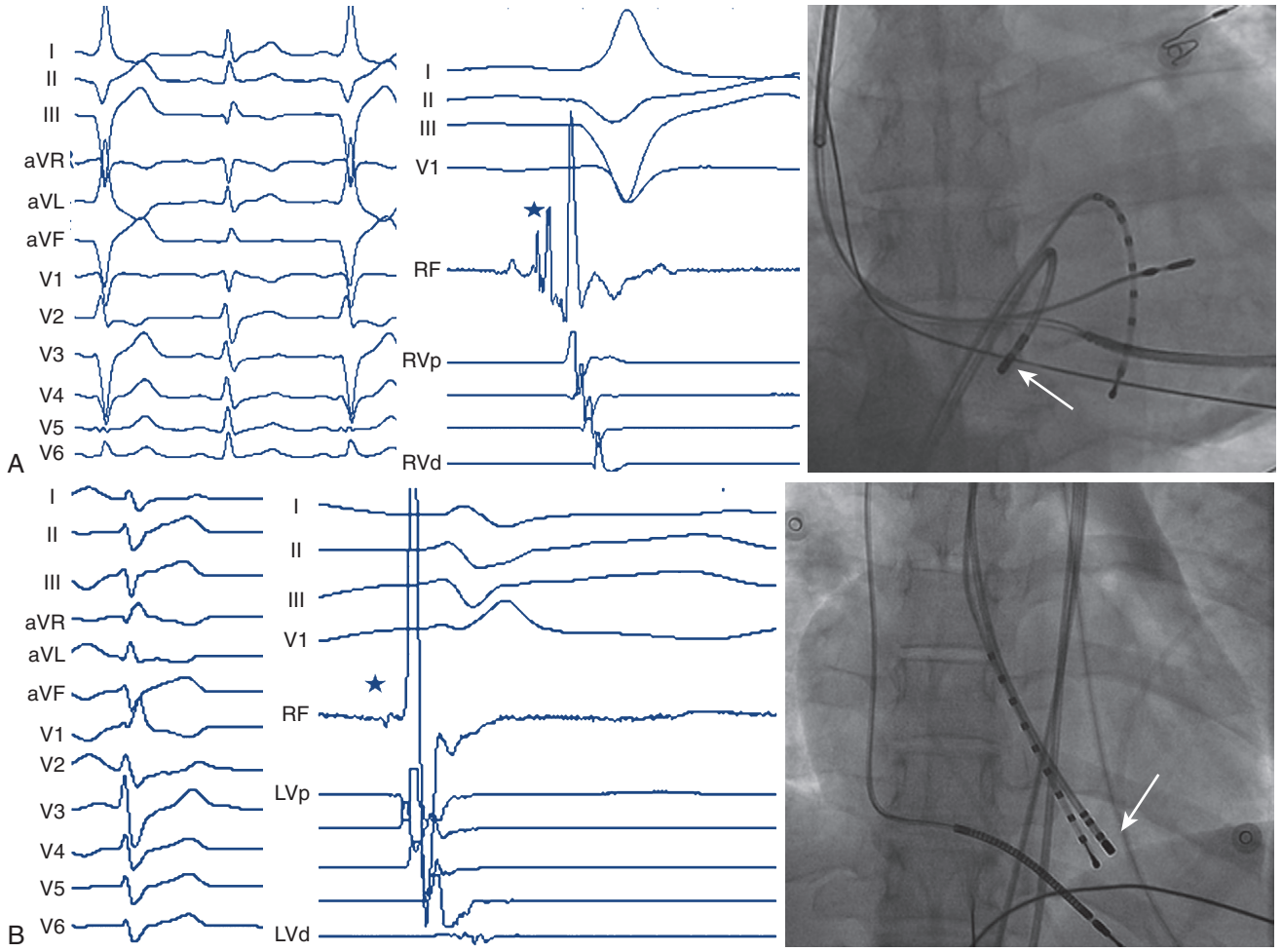

FIGURE 96-4 Premature ventricular contractions (PVCs) from the right Purkinje. **A,** Twelve-lead electrocardiogram: negativity in lead V1. **B,** Endocardial tracing showing a Purkinje potential preceding ventricular activation. PVCs originating from the left Purkinje specialized tissue have a sharp onset, and the QRS is narrower than PVCs originating from the myocardium or the right Purkinje. Moreover, PVCs from the left Purkinje are usually shorter in duration than are ectopic beats from the right Purkinje. The QRS in this example is 120 ms in duration. **C,** Fluoroscopic image in posteroanterior projection; the *arrow* points to the catheter's position.

Purkinje network typically display a relatively narrow QRS and a sharp onset, more abrupt as the PVC arises from the proximal Purkinje or fascicules and become more slurred distally. Right Purkinje ectopic beats are typically wider in duration than is left Purkinje ectopy.[5] PVCs arising from myocardial tissue display wider QRS (145 ms vs. 126 ms for Purkinje ectopies in one study, $P = .04$) and a slurred uptake (Figures 96-4 and 96-5).

Electrophysiological Study: Mapping of Premature Ventricular Contractions

Sources, which are mapped either conventionally or by using a three-dimensional mapping system, are localized at the sites of the earliest onset of electrogram relative to the QRS onset on the surface ECG. Occurrence of spontaneous PVCs greatly helps in finding the source location. A sharp potential (<10-ms duration) preceding PVCs indicates origination from Purkinje tissue, and absence of such a potential at the earliest local electrogram indicates myocardial origination. Purkinje potentials have been reported to precede the local electrogram during ectopy by 22 to 90 ms, with greater precocity for left ventricle PVCs (average delay, 46 ms) than the right ventricle PVCs (average delay, 19 ms).[6-8,10,12] In cases of short runs of multiple ectopic beats, conduction time from Purkinje to the local myocardium could be measured from 15 to 120 ms. Conduction block between the Purkinje potential and the myocardium (nonconducted Purkinje ectopy) was also observed.[6] Moreover, evidence shows that ectopic beats arising from Purkinje tissue can follow different paths before exiting, leading to different conduction times from the recorded Purkinje to the local ventricular electrogram and to differences in QRS morphologies. During sinus rhythm, the Purkinje potential preceding ventricular activation by <15 ms arises from the peripheral Purkinje network, whereas greater precession indicates origination from the proximal Purkinje system. To avoid alteration in intraventricular conduction and QRS morphology, proximal Purkinje tissue should not be targeted during ablation (Figure 96-6).

In patients without frequent ectopy, mapping can be performed in sinus rhythm, and recordings of Purkinje potentials at

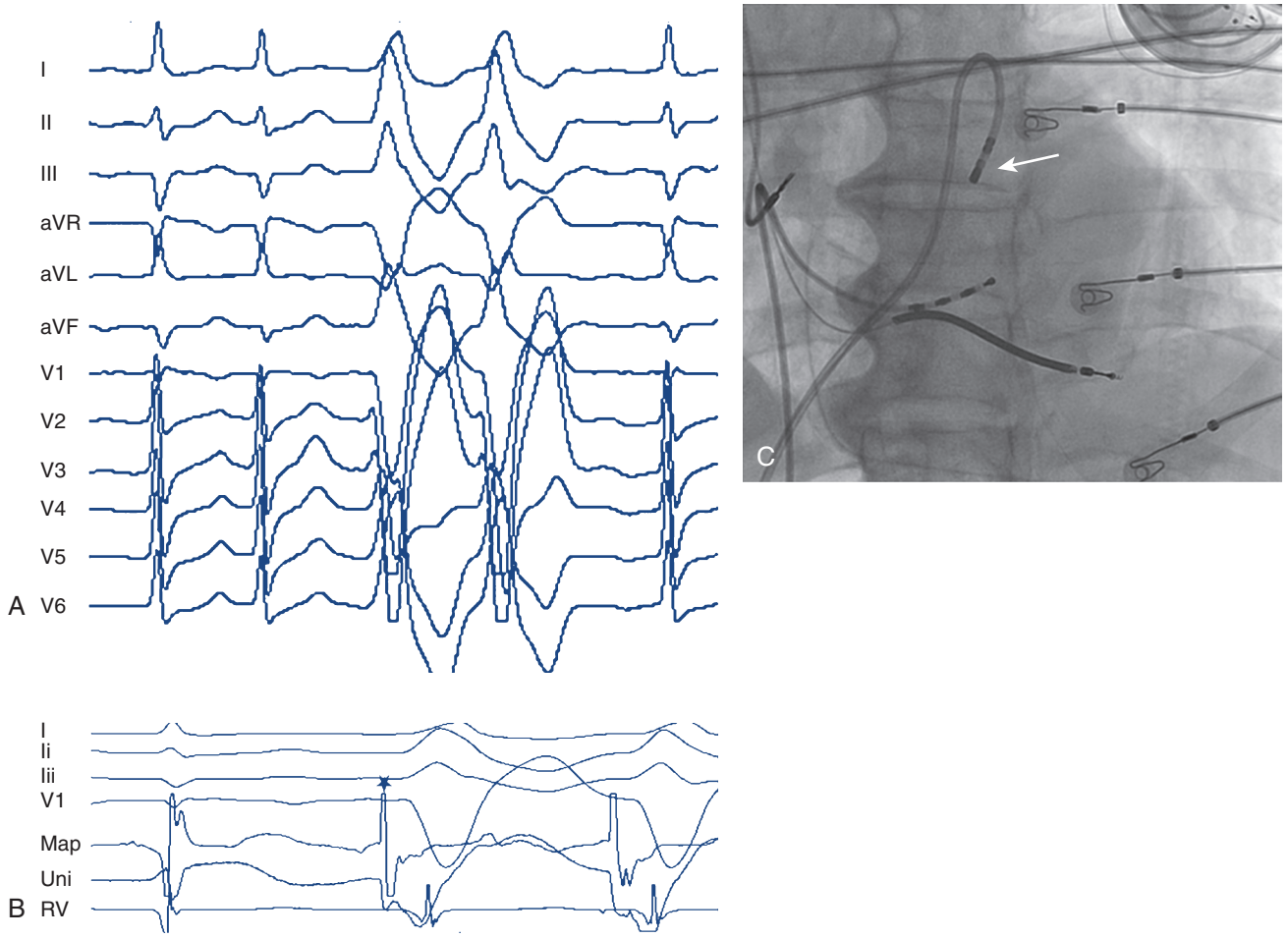

FIGURE 96-5 Premature ventricular contractions from the right ventricular outflow tract. **A,** Twelve-lead electrocardiogram: negativity in lead V1 and superior axis, duration of 160 ms. **B,** Early local electrogram present on endocardial tracing, with no potential seen before. **C,** Fluoroscopic image in posteroanterior projection; the *arrow* points to the catheter's position. *RV,* right ventricle.

sites of perfect pacemapping matches can be adequate surrogates to activation mapping. When PVCs are known to come from the RVOT region, perfect pacemapping sites (without local Purkinje) indicate the source of triggers.

To facilitate mapping and to see Purkinje potentials during sinus rhythm, it is essential to avoid mechanical bundle branch block ipsilateral to the mapped chamber (especially the right bundle). Inadvertent bundle branch block will occur. Purkinje potential in sinus rhythm, but the potential will still be seen preceding PVCs, and retrograde penetration of the Purkinje can sometimes be observed in sinus rhythm (Figure 96-7).

Radiofrequency Ablation

All reported cases of ablation of VF triggers have used RF energy, using 4-mm dry RF catheters or 3.5-mm externally irrigated cooled-tip catheters. Ablation of Purkinje tissue typically provokes initial exacerbation of PVCs, runs of polymorphic VT, and even runs of VF, which are most of the time nonsustained; but cases of RF-induced VF requiring defibrillation have been described (Figure 96-8). The endpoint of ablation should be complete elimination of all clinical PVCs known or suspected to be triggering VF. When Purkinje tissue is ablated, intraventricular conduction delay can sometimes be observed, in increments of 20 to 30 ms in QRS duration. A proximal Purkinje ablation carries a greater risk of QRS prolongation and even fascicular block (Figure 96-9).

All published cases or series report success in acute elimination of culprit PVCs in a high percentage (>90%) of patients, regardless of the underlying pathology. In one series, 2 of 27 patients had immediate recurrence of PVCs and underwent a successful second ablation within days of the first procedure.[6] In patients with multiple morphologies of ectopic beats, the acute success rate is lower.[11]

Long-Term Outcome of Ablation

The long-term outcome of ablation is excellent in all reported studies (Table 96-1). The largest available cohorts with the longest follow-up are made up of patients with idiopathic VF. Freedom from VF, sudden death, or syncope was achieved in 89% (24 of 27) at 2 years in one study.[6] In a recent publication, of 38 patients,

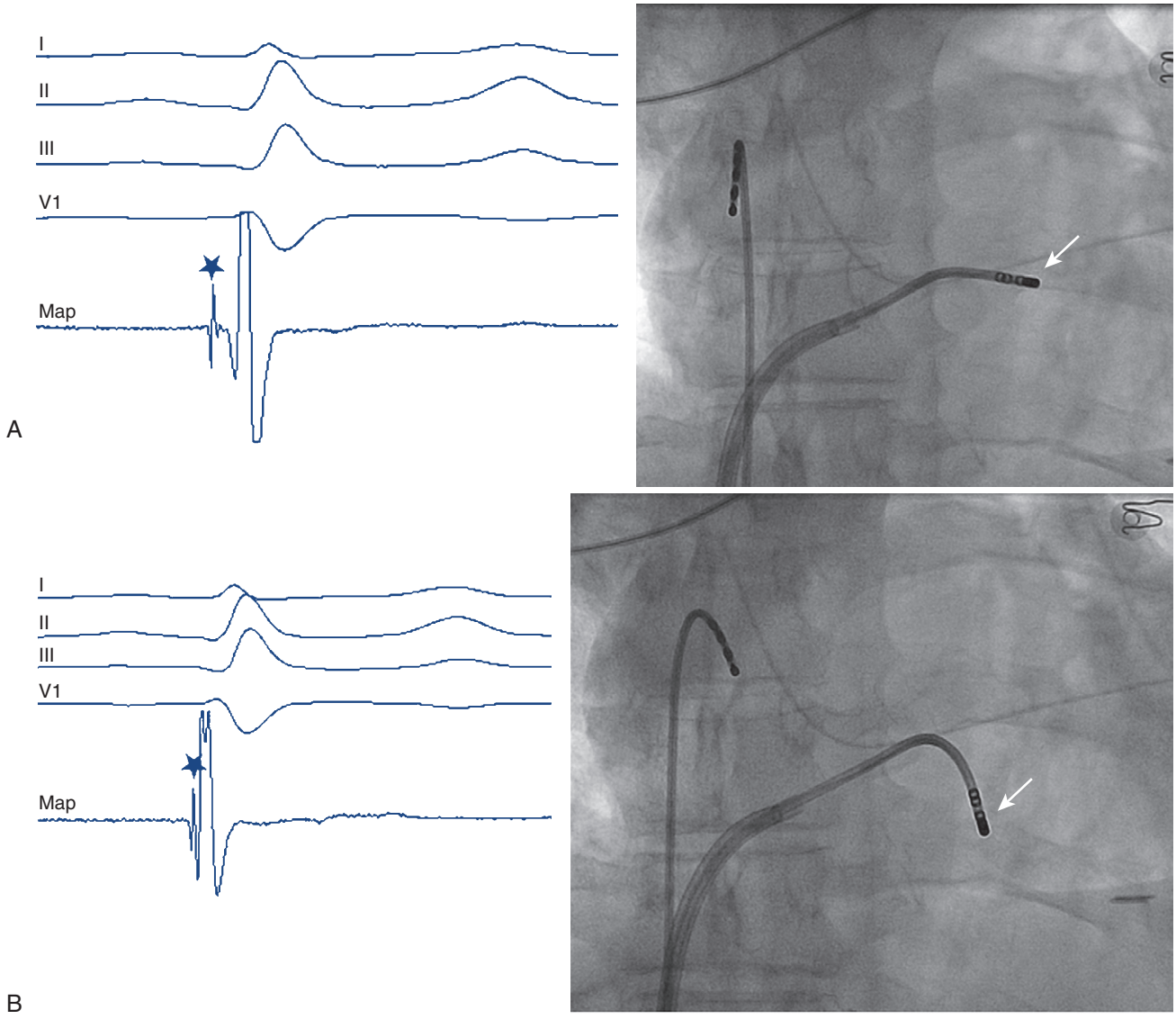

FIGURE 96-6 A, Proximal Purkinje recording in sinus rhythm. The Purkinje potential precedes the ventricular electrogram by 24 ms. The *right image* shows the catheter position in the posteroanterior projection. **B,** Peripheral Purkinje recording during sinus rhythm. The Purkinje potential precedes the ventricular electrogram by 6 ms. The *right image* shows the catheter position in the posteroanterior projection.

82% remained arrhythmia free after 5 years following ablation of VF triggers. Of the 7 patients who experienced recurrences, 5 were successfully re-ablated and had no recurrences at 28 months. Three patients had documented electrical storm at follow-up at 1, 48, and 60 months, respectively, compared with 12 patients who had it before the ablation procedure. Overall, the success rate of ablation of VF triggers reported in this study was 95% at 4.3 years after 1.3 procedures per patient.[16]

Ablation of VF triggers in ischemic heart disease also yielded encouraging results. Three studies report results for 17 patients with ischemic heart disease, both acute and chronic, and at 1 year, only one patient experienced VF recurrence. Other cases have been reported with excellent results up to 19 months of follow-up.[7-9]

VF triggers in Brugada syndrome originate mainly from the RVOT myocardium. Abolition of these PVCs can be successfully achieved, and long-term results are excellent. In one study, in patients with LQTS, ectopic beats arose from Purkinje fibers in 75%; ablation in all patients led to successful elimination of triggers and no further VF episodes. Three patients with Brugada syndrome and 4 patients with LQTS were arrhythmia free after 17 months of follow-up.[10] In malignant early repolarization syndrome, PVCs were abolished by ablation in 5 of 8 patients with no recurrences of VF at 1 year. However, in this condition, the triggering beats tend to be polymorphic and more widespread, making catheter ablation less appealing.[11]

Other articles in the literature reported isolated cases of PVCs triggering VF in patients with cardiac amyloidosis, after aortic valve repair, and in the context of catecholaminergic polymorphic VT; these patients were successfully ablated and had an uneventful follow-up.

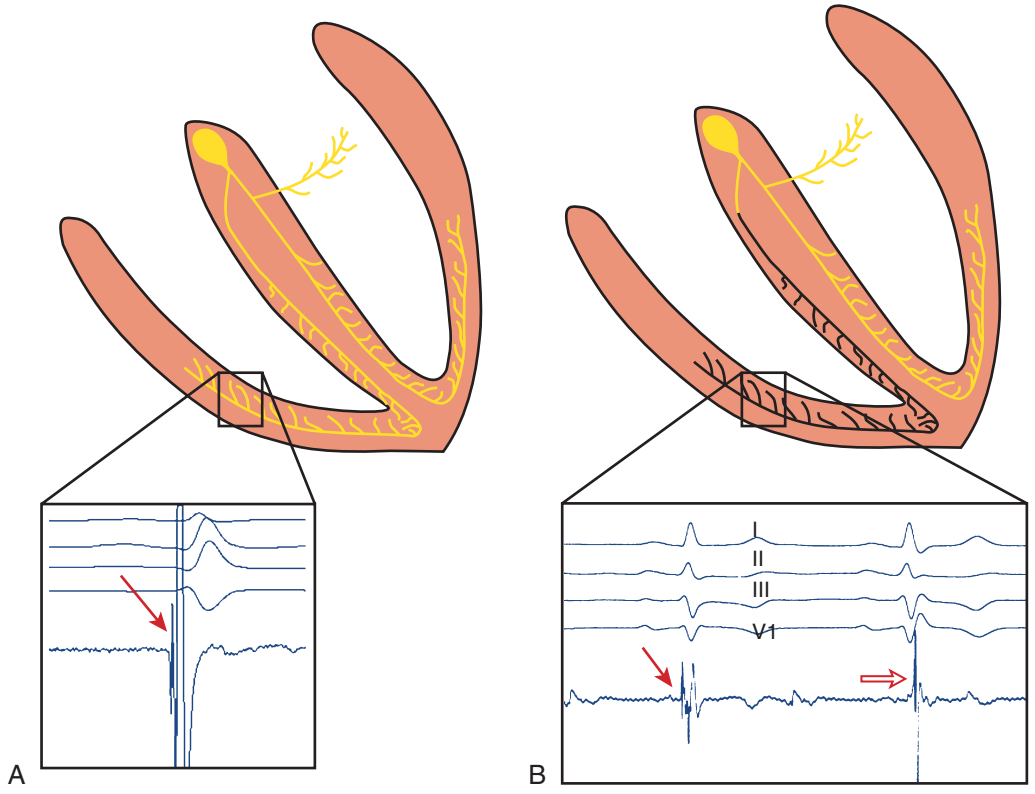

FIGURE 96-7 A, Sinus input entering the Purkinje system distally to the atrioventricular node and traveling all the way to the distal Purkinje arborization. A Purkinje potential can be recorded by a catheter placed at the Purkinje-myocardium interface (*arrow*). **B,** Right bundle branch block induced, preventing the sinus influx to travel antegradly through the right Purkinje system. It travels down the left bundles and then through the myocardial tissue to reach the right ventricle; hence it penetrates the Purkinje in a retrograde manner, and the potential can be seen buried inside the local ventriculogram (*open arrow*).

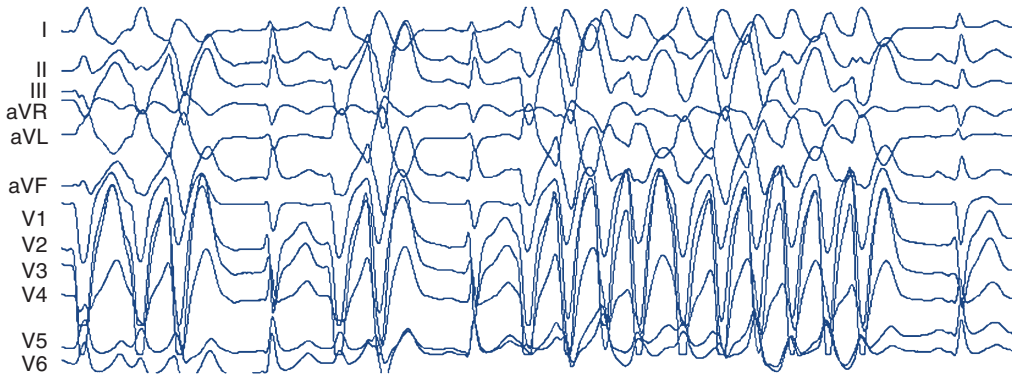

FIGURE 96-8 Nonsustained ventricular fibrillation during radiofrequency delivery.

Conclusion

Catheter ablation of VF triggers has proven efficient in a variety of cardiac disorders. Despite limited data in the literature, acute elimination of triggering PVCs and mid-term to long-term freedom from VF can be achieved in the majority of patients. Triggers dominantly arise from the Purkinje system but can also originate from ventricular myocardium, especially the RVOT region, and disease-specific patterns can be observed with regard to the type and location of ectopic foci. However, the limited number of patients treated and the limited data on long-term follow-up mandate caution. ICD implantation remains the therapeutic mainstay for secondary prevention of SCD in VF survivors.

Table 96-1 Long-Term Outcome of Ablation

	NO. PATIENTS	UNDERLYING CONDITION	MONOMORPHIC OR POLYMORPHIC PVCS
Haïssaguerre et al, *Circulation* 2002	27	IVF	RVOT: 1 polymorphic, 3 monomorphic PN: 18 polymorphic, 5 monomorphic
Kohsaka et al, *PACE* 2007	1	IVF	Monomorphic
Knecht et al, *J Am Coll Cardiol* 2009	38	IVF	1.7 ± 2.0 morphologies per patient
Marrouche et al, *J Am Coll Cardiol* 2004	8	Ischemic cardiomyopathy, chronic	Monomorphic
Szumonski et al, *J Am Coll Cardiol* 2004	5	Ischemic heart disease, 3 subacute phase of MI, 2 chronic	4 monomorphic, 1 polymorphic
Bansch et al, *Circulation* 2003	4	Acute MI after successful revascularization	Monomorphic, 1 had 2 morphologies
Enjoji et al, *PACE* 2006	1	Acute coronary syndrome, revascularized	Monomorphic
Haïssaguerre et al, *Circulation* 2003	7	3 Brugada syndrome 4 LQTS	3 Monomorphic 2 Monomorphic, 2 polymorphic
Micochova et al, *J Cardiovasc Electrophysiol* 2006	2	Cardiac amyloidosis	Monomorphic
Li et al, *J Cardiovasc Electrophysiol* 2004	1	Post aortic valve repair	2 morphologies
Bode et al, *PACE* 2008	7	4 CAD 1 after AVR 2 Myocarditis	Monomorphic

AVR, Aortic valve replacement; CAD, *coronary artery disease;* IVF, *idiopathic ventricular fibrillation;* LQTS, *long QT syndrome;* RVOT, *right ventricular outflow tract;* PN, *Purkinje network;* LP, *left ventricular Purkinje fibers;* RP, *right ventricular Purkinje fibers;* PVC, *premature ventricular contractions;* HF, *heart failure;* MI, *myocardial infarction;* MOF, *multiple organ failure;* NA, *not available; ?, unknown.*

Modified from Li YG, et al: Catheter ablation of frequently recurring ventricular fibrillation in a patient after aortic valve repair, J Cardiovasc Electrophysiol*15(1):90–93, 2004; Enjoji Y, et al: Catheter ablation for an incessant form of antiarrhythmic drug-resistant ventricular fibrillation after acute coronary syndrome,* Pacing Clin Electrophysiol *29(1): 102105, 2006; and Mlcochova H, et al: Catheter ablation of ventricular fibrillation storm in patients with infiltrative amyloidosis of the heart,* J Cardiovasc Electrophysiol *17(4): 426–430, 2006.*

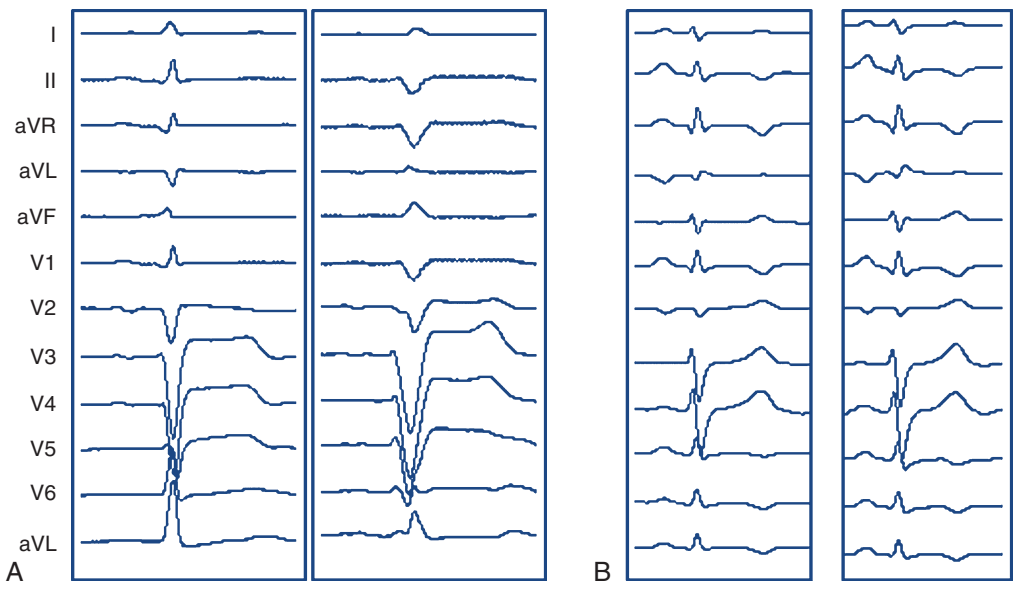

FIGURE 96-9 A, Surface electrocardiogram before and after the procedure in a patient who received Purkinje ablation near the anterior fascicule. QRS duration increased from 86 ms to 154 ms. **B,** Surface electrocardiogram before and after the procedure in a patient who received distal Purkinje ablation; no changes were seen in QRS duration and morphology.

ORIGIN OF PVCS	COUPLING INTERVAL TO INDUCE VF (ms)	ACUTE ELIMINATION OF PVCS	DURATION OF FOLLOW-UP (mo)	LONG-TERM SUCCESS
4 RVOT 23 PN: 10 LP, 9 RP, 3 LP+RP	355 ± 30 280 ± 26	2 recovered and were re-ablated	24	89%
RP	?	Yes	12	No recurrence[17]
5 Myocardium (4 from RVOT) 33 PN: 16 RP, 14 LP, 3 RP+LP	355 ± 23 276 ± 22	Yes	63	82% VF free after one procedure
5 LP 3 LP in scar border zone ablated but no PVC during mapping	195 ± 45	Yes	10	1 recurrence of VF
5 LP 1 RP	320–600	Partial	16 ± 5	No recurrence
LP	270–400	Yes	14	No recurrence
LP	?	Yes		NA[18]
2 RVOT, 1 RP 1 RVOT, 3 LP	342 ± 21 503 ± 29	Yes	17	No recurrence
LP	370 and 400	Yes	8.75	No recurrence, patient 2 died at 3 weeks from other cause[19]
LP	?	Yes	2	No recurrence[20]
LP LP 1 LP and 1 RP	230–460	Yes	19 5 1 and 15	2 no recurrence, 2 died of HF/MOF No recurrence No recurrence

Catheter ablation should be considered in patients with recurrent VF despite antiarrhythmic drugs.

Acknowledgment

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All references cited in this chapter are available online at expertconsult.com.

CHAPTER 97

Surgery for Ventricular Arrhythmias

John M. Miller and Yousuf Mahomed

Introduction

Cardiac tachyarrhythmias are a source of significant morbidity and mortality in the general population. Between 300,000 and 500,000 sudden cardiac deaths occur per year in the United States, the majority of which are caused by ventricular tachyarrhythmias (VTAs) such as ventricular tachycardia (VT) and ventricular fibrillation (VF). VTA episodes that do not result in sudden cardiac death may cause a range of symptoms, including palpitations, chest pain, dyspnea, dizziness, and syncope. In the last decade, results of several large clinical trials and refinements in implantable cardioverter-defibrillator (ICD) technology have combined to make the ICD the default therapy for patients with previous VTA episodes (secondary prevention) as well as for those who have not yet had a clinical VTA episode but have enough risk factors that an ICD is warranted (primary prevention). The original ICDs were placed via thoracotomy by surgeons, but currently almost all ICDs are implanted percutaneously by cardiologists in a subclavicular, subcutaneous pocket. Other surgical methods for controlling VTAs antedate the ICD by many years but are rarely used currently. This chapter details these other surgical methods of treating VTAs.

Pathophysiology of Ventricular Tachyarrhythmias

In most patients with sustained VTAs, significant structural heart disease (SHD) is present and forms the basis or substrate for the arrhythmia. The common denominator in most forms of SHD is replacement of myocardial cells by scar tissue. This is a heterogeneous process, resulting in strands of viable myocardial cells and often Purkinje cells insulated from other strands by electrically inert scar tissue. If one or more of these surviving muscle strands connect at both ends to the larger mass of the myocardium outside the scar zone, a potential circuit is present. Re-entrant tachycardias can occur based on this substrate; if the same path is used for repetitive cycles, the electrocardiographic result is VT of uniform morphology, in which each QRS is fundamentally identical. In VF, however, either the path changes from cycle to cycle, multiple wave fronts propagate through the myocardium at any instant, or a single rapidly spinning, relatively stationary rotor sends propagation waves in different directions during each cycle. Focal excitation from a relatively normal myocardium (i.e., no scar) is responsible for VTAs in most patients without SHD but is a rare cause in patients with SHD.

Surgical Methods for Controlling Ventricular Tachyarrhythmias

Surgical techniques for control of VTAs can be placed into two categories: *indirect* and *direct*. Indirect methods include those that do not alter the myocardial substrate for VTAs, such as simple aneurysmectomy, coronary artery bypass grafting (CABG), ventricular reconstruction surgery, and neural modulation (e.g., stellate ganglionectomy). Direct methods include those that primarily impact the myocardial substrate of VTAs, usually by excision (endocardial resection), incision (encircling ventriculotomy), or ablation (cryosurgery, laser surgery, etc.).

Indirect Methods

The first reported surgical cure of VT resulted from excision of a left ventricular aneurysm. When aneurysmectomy was used more widely as a treatment for VT, however, it became apparent that this procedure had low efficacy and high mortality rates (often because of intractable VT). CABG was also used in an attempt to control VT, with similarly poor results. These methods generally failed because although aneurysms are frequently present in patients with VT, the excised portion of the aneurysm does not contain critical portions of VT circuits, and VT episodes usually do not result from acute ischemia (which could be corrected by coronary bypass). CABG has definite application in relatively rare cases of polymorphic VT or VF that clearly occurs in the setting of acute ischemia. CABG and aneurysmectomy are both still performed in some cases of VT but only as adjunctive methods along with one of the more direct techniques discussed below. Neural modification, typically with left or bilateral stellate ganglionectomy, has benefit in selected patients with VTAs: patients with long QT syndrome (LQTS) who have recurrent syncope or cardiac arrest despite β-blocker and ICD therapies; patients with recurrent episodes of VF in the absence of SHD (idiopathic VF); and patients with catecholaminergic polymorphic VT. A variety of approaches have been used for the destruction or removal of the left or bilateral stellate ganglia (cervical, thoracotomy incisions). Thoracoscopic techniques are being more widely used for approaching the stellate ganglion, rather than open surgical exposure.[1]

Direct Methods

After the failure of CABG and aneurysmectomy to reliably affect VT recurrence, several investigators began using intraoperative electrophysiological mapping studies to understand more about

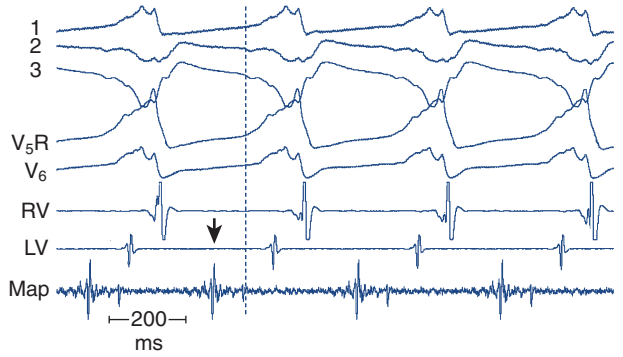

FIGURE 97-1 Surgical mapping during post-infarct ventricular tachycardia (VT). Surface electrocardiogram leads and endocardial electrograms recorded during VT. The *dashed line* shows the onset of the QRS complex in VT; the *arrow* indicates a recording in mid-diastole in a critical area of a VT circuit. Excision of the surrounding region eliminated VT. *RV*, Right ventricle; *LV*, left ventricle.

where VT was originating. The rationale was that a site in the ventricle from which VT arose, or exited from a circuit, should precede the onset of each surface QRS complex by greater than 40 ms, or even occur in mid-diastole. Epicardial mapping during VT usually did not reveal sites of activation that met this criterion; endocardial mapping, after ventriculotomy, routinely showed sites activated prior to the QRS during VT (Figure 97-1). These areas were typically near the border between the aneurysm or the dense infarct and more normal muscle. Several means of therapy targeting these regions were devised in the late 1970s, including excision (endocardial resection) an isolating incision (encircling ventriculotomy), and cryoablation. Additional modalities have been used, including intraoperative laser photoablation. Because these hearts have already suffered extensive damage from the infarction that caused the arrhythmia, a cardinal principle of surgical therapy is to remove or destroy only as much tissue as is necessary to eliminate the VT while damaging as little remaining normal myocardium as possible. Mapping tools and techniques have aided in the discrimination between normally and abnormally functioning tissue.

Ventricular Tachycardia

In the vast majority of cases, uniform morphology VT (i.e., identical QRS complexes during an episode) is caused by re-entry within damaged myocardium. The most extensive experience in surgical therapy of VT is in the setting of prior myocardial infarction (MI). In a typical case, damage from a large MI heals by replacing the necrotic myocardium with dense collagenous scar tissue. In some areas (typically at the periphery of the infarct zone), surviving myocardial strands remain, interspersed with scar tissue. If these layers connect at one or more points, they can form a potential circuit of conductive tissue, with an insulative layer of scar tissue protecting it from most outside influences. These surviving muscle bundles are most commonly situated near the endocardial surface rather than in deeper myocardial layers. In patients with VT, in the setting of dilated cardiomyopathy, the same pathophysiology is probably present, although more diffusely within the myocardium.

Preoperative Studies

Because most patients undergoing surgery for VT have prior infarction from coronary atherosclerosis, cardiac catheterization with coronary arteriography is an important part of the preoperative evaluation. Coronary stenoses that should undergo bypass grafting can thus be identified and any possible valvular lesions identified. Ventriculography (assessing overall left ventricular function) can be helpful in estimating operative risk. In the presence of coronary stenoses of uncertain flow-limiting significance, stress testing with some form of perfusion imaging can help determine whether bypass grafting of particular arteries would be beneficial. Preoperative electrophysiological study (EPS) is almost always indicated (except in cases of severe left main stenosis or three-vessel disease, in which the rapid heart rates encountered during induced VT could possibly be detrimental). This study can provide information as to how readily inducible VT is as a guide to how vigorous intraoperative stimulation will need to be. Endocardial catheter mapping can also be performed at this time to help focus attention on certain areas that need to be ablated during surgery. However, if mapping is performed in this setting, it is almost always accompanied by ablation attempts; if the ablation successfully eliminates inducibility of one or more morphologies of VT, they no longer need surgical attention. If ablation is not successful, the validity of the mapping information may be called into question. Thus preoperative mapping may have a more limited role than was once thought. Percutaneous access to the pericardial space has been used for epicardial mapping and ablation; this is more frequently necessary in cardiomyopathic cases than in post-MI VT. Recently, a hybrid procedure has been developed in which epicardial catheter mapping has been facilitated by surgical exposure of the pericardial space using a small subxiphoid incision. This is particularly helpful when prior cardiac surgery has resulted in extensive pericardial adhesions that would significantly restrict catheter mobility and access to all areas of the epicardial surface.[2]

Principles of Cardiac Mapping

If mapping is to be performed, several pieces of equipment are necessary beyond the usual requirements for open-heart surgery. These include electrodes, a mapping system (consisting of amplifiers and a recording and analysis system), and a stimulator with which to initiate VT. Several commercial mapping systems are available, capable of recording from 64 to 256 electrodes simultaneously, online analysis of activation times, and generation of isochronal maps. Most record onto magnetic or optical media for data archiving. At the time of surgery, the electrocardiogram (ECG) leads from the patient are connected to the mapping system. The heart is exposed through a median sternotomy, and a pericardial cradle is formed. Cannulae are placed for cardiopulmonary bypass, and reference electrodes are inserted and tested. The heart is inspected for regions of infarct or aneurysm, through which the ventricle may be entered without damaging the viable myocardium; sometimes, this area is only evident after the patient is on cardiopulmonary bypass and the left ventricle (LV) has been vented. Cardiopulmonary bypass is then established while maintaining a perfusate temperature of 37° C to 38° C. This is necessary because cardiac electrical activity deteriorates at cooler temperatures and arrhythmias may not be inducible or mappable. Radiant heat loss of the heart surface during mapping may necessitate even slightly higher perfusate

temperatures. Epicardial mapping during sinus rhythm or VT can be performed with the heart closed, but this is usually omitted in the interests of time unless specific circumstances suggest its usefulness. In most cases, once the heart-lung machine is running well, the LV is then opened through the previously identified infarct or aneurysm. The endocardial surface is inspected for the presence of any adherent thrombus, which is then removed. An electrode or multipolar electrode array is placed on the endocardial surface in an area of obvious scar tissue. At this time, sinus rhythm mapping can be performed to designate areas with abnormal electrograms indicating damaged myocardium; this step usually adds little and is omitted except in special situations. In most cases, VT is then initiated using previously placed electrodes, and endocardial mapping is performed during VT. Some tissue is activated at every instant during a re-entrant arrhythmia, even during the diastolic interval between discrete QRS complexes; sites from which diastolic activation is recorded during VT are of particular interest, since these regions are often in "protected" corridors that are critical for continued re-entry. Computerized mapping systems are able to quickly display these areas of diastolic activation (Figure 97-2).

Because most patients with post-infarct VT have more than one ECG morphology of VT that may arise from the same or different regions, attempts are made to initiate and map other morphologies of VT. Because of time limitations, rigorous entrainment studies (overdrive pacing during VT) to validate the activation mapping data are often not performed. Once all inducible morphologies of VT have been mapped, the electrode array is removed and the ablation portion of the procedure begins. Several different procedures have been used for this purpose (Figure 97-3), including:

1. *Endocardial resection*, in which a 1- to 2-mm thick layer of endocardial tissue is dissected from subjacent layers; this is designed to remove all or part of the region of diastolic activation required for re-entry (Figure 97-4).[3]

2. *Encircling endocardial ventriculotomy*, in which an incision is made circumscribing the regions indicated by mapping, extending about halfway through the myocardial wall; this is intended to isolate the arrhythmogenic region, or incise through critical portions of circuits.[4]

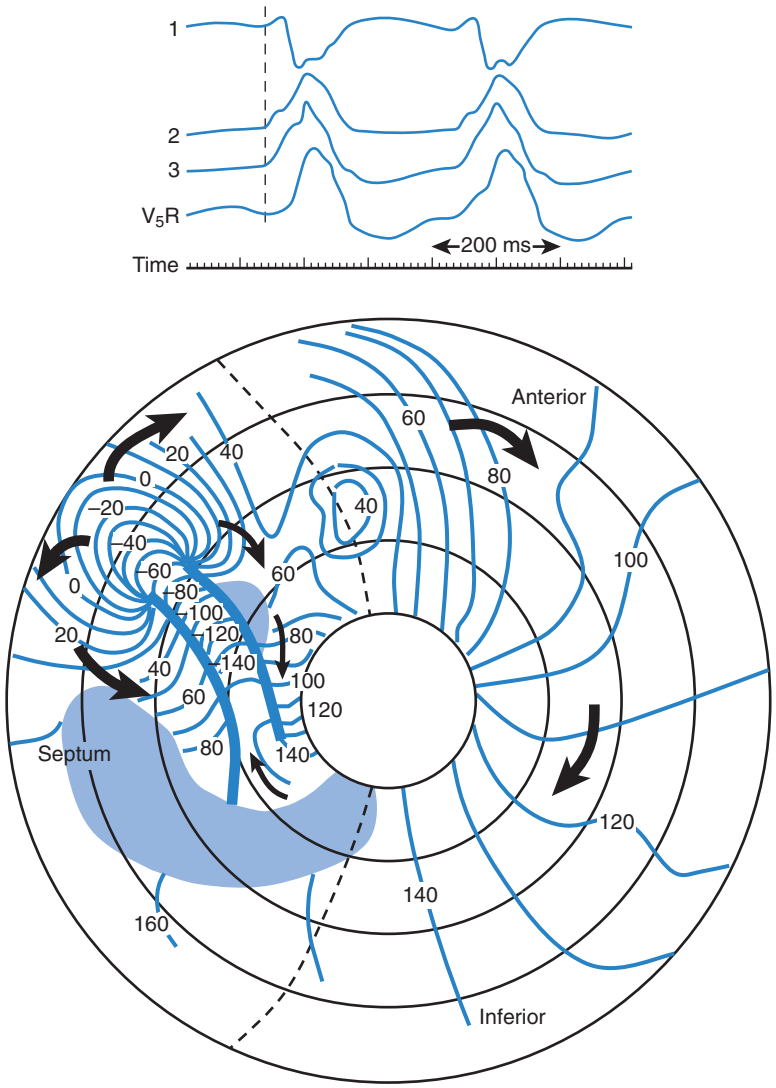

FIGURE 97-2 Isochronal maps during ventricular tachycardia (VT). The endocardial surface is shown in a polar projection with the apex at the center, septum at on the left, lateral wall on the right. Lines of isochronal activation during VT are shown at 10-ms intervals; *thick dark lines* denote arcs of block; *shaded curved arrows* denote the direction of wavefront propagation. Four electrocardiogram leads are shown above with a timeline. A nearly complete figure-of-8 re-entrant pattern is shown; mid-diastolic recordings are made from the narrow zone between the arcs of block. No electrical activity could be recorded from the shaded areas.

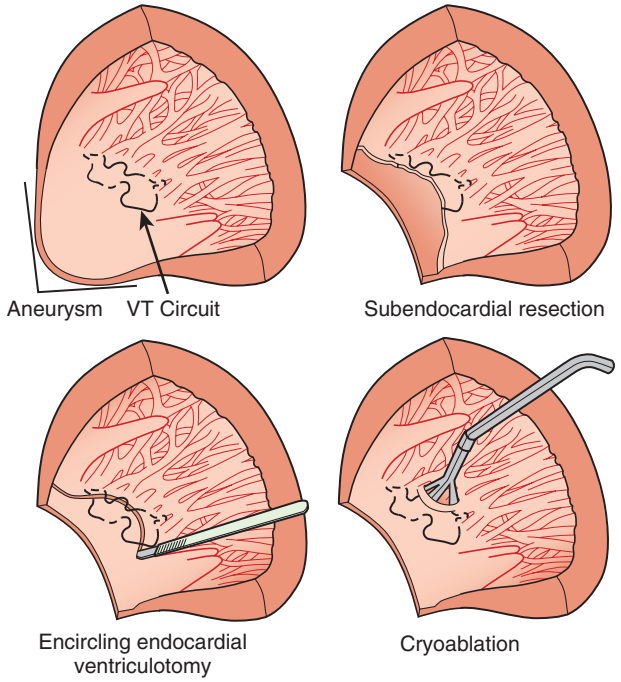

FIGURE 97-3 Surgical procedures for ventricular tachycardia (VT). In each panel, the opened left ventricle is depicted as viewing the septal endocardial surface showing papillary muscles and a thin, smooth aneurysm as opposed to the trabeculated normal endocardium. A VT circuit is shown, some of which is near the endocardial surface (*solid line*) and some in deeper layers (*dotted line*). *Lower left*, Encircling endocardial ventriculotomy incises near the perimeter of the endocardial scar and transects a portion of the circuit. *Upper right*, Subendocardial resection removes a superficial portion of the circuit, and cryoablation destroys a portion by freezing. Of note, to prevent VT, none of these procedures needs to destroy or remove the entire circuit, only a critical portion of it.

3. *Focal cryoablation*, using a 1.5-cm probe cooled to –70° C for 1 to 2 minutes; this destroys myocardial cells without removing or disrupting the fibrous stroma.[5]

4. *Encircling cryoablation*, combining focal cryoablation with encircling ventriculotomy.[6]

5. *Laser photoablation*, using Nd:YAG, argon or carbon dioxide sources; this has fundamentally the same effect as cryoablation.[7]

After the ablation portion, attempts are usually made to re-initiate VT with the same type of stimulation used during mapping. If VT can still be initiated, mapping is repeated; this usually reveals sites just outside the area ablated or deep to it (intramural). Ablation is performed again (often cryoablation of deeper sites), and cycles of stimulation, mapping and ablation are repeated until VT can no longer be induced. This technique results in postoperative noninducibility of VT approaching 90%. In inferior infarction, cryoablation of the isthmus of the ventricular myocardium between the ventriculotomy and the mitral annulus has increased surgical success rates.[8] The ventriculotomy is closed and other procedures performed, such as CABG or valve surgery. If no other procedures are needed, the patient is weaned from cardiopulmonary bypass. Recent innovations in how the ventriculotomy is closed (aneurysmorrhaphy) have led to improvements in postoperative left ventricular function. Patients typically undergo EPS 5 to 7 days after surgery to assess its antiarrhythmic efficacy.

In some cases, no obvious site for making a ventriculotomy to enter the ventricle (no infarct or aneurysm) exists. This is especially true in inferior infarctions and cases in which early reperfusion of the infarct (pharmacologic or mechanical) yielded only a partial success. In these cases, an electrode-studded inflatable latex balloon can be inserted through the mitral orifice after a purse-string left atriotomy. Once the balloon is in the

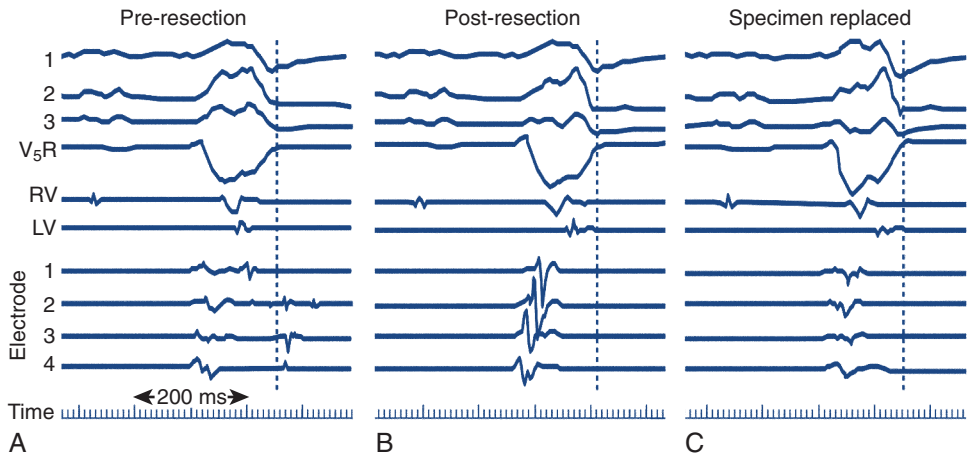

FIGURE 97-4 Effect of endocardial resection on electrograms. Electrodes 1 through 4 are closely spaced recordings from a multipolar array. All three panels show a single complex in sinus rhythm; *dashed line* is the end of QRS. **A,** Recordings before resection in an area from which diastolic activation occurred in VT show isolated potentials, some of which occur after the QRS end. **B,** Recordings made after resection show loss of delayed potentials and increase in amplitude of signals in the QRS. **C,** Recordings from same site after resection and replacement of specimen show decrease in signal amplitude similar to **A,** but no late potentials. Thus resection removes tissue from which the late potentials derive as well as attenuates amplitude of recordings from subjacent tissue.

ventricular cavity, it is inflated such that its electrodes contact the endocardial surface. Mapping can then be carried out as indicated above but without ventriculotomy, and ablation can be performed either with electrical energy (DC shock or radiofrequency energy) delivered through appropriately located electrodes, or using a cryoprobe advanced through the mitral orifice as the array had been.[9]

Because of the presence of diseased myocardium, many areas have abnormal electrograms during sinus rhythm or VT but do not actually participate in the re-entrant wavefront. This low specificity, as well as the fact that up to 15% of VTs have been mapped to regions with relatively normal electrograms during sinus rhythm, limits the use of simple ablation of areas with abnormal electrograms. Furthermore, some sites have diastolic activation during VT but represent side branches that are not in the re-entrant path. Some of these display 2:1 conduction of potentials during VT; obviously, these sites are not in the re-entrant circuit because VT continues despite their absence on alternate beats, but they are typically recorded from regions near the actual circuit.

Mapping or No Mapping?

Although early map-guided surgical series reported good results, some investigators questioned the contribution of mapping to the results, noting that mapping equipment is expensive and that electrophysiologists and surgeons skilled in these techniques are not universally available. They also argued that the same results might be obtained by ablation of regions of visible scar because these areas coincided with those designated by time-consuming mapping studies. Although this is largely true, critical circuit pathways are outside the areas of visible scar in about 15% of cases, and in VT occurring within the first few weeks after infarction, the endocardial appearance of arrhythmogenic zones has not yet become distinct from normal areas. In addition, removal of all endocardial scar would necessitate papillary muscle removal and mitral valve replacement in a large proportion of patients. Finally, evidence supports that the more thoroughly mapped a patient's VTs are, the higher are the surgical success rates.

Efficacy

The success rates for the various surgical ablation procedures vary according to the procedure as well as the definition of "success." Most data indicate that elimination of all inducible VT at postoperative EPS is the most reliable endpoint of success and that simply eliminating the inducibility of certain VT morphologies (but not all VTs) will not prevent subsequent recurrences of other VTs. Measured against the more stringent standard of eliminating all inducible VTs, most of the procedures discussed above yield success rates from 70% to 90%.[10]

Operative Risk

Because of pre-existing extensive myocardial damage, the operative mortality rates of VT surgery are higher than in other forms of elective cardiac surgery. Mortality rates range from 3% to 20% in different patient subsets. Because of this, several investigators have evaluated the risk factors for VT surgery and have identified left ventricular wall motion score, age greater than 65 years, and emergency surgery as factors that increase risk of operative mortality. A major cause of perioperative mortality is heart failure; in the early surgical experience, the aneurysm was removed (or plicated) and its cut edges sutured together. This could result in an inordinately small left ventricular cavity and compromise cardiac output. In the 1990s, a more physiological closure method, introduced by Dor and colleagues, more closely approximated the normal ventricular shape.[11] Lower operative mortality rates and better functional capacity have been reported with this method (Figure 97-5).

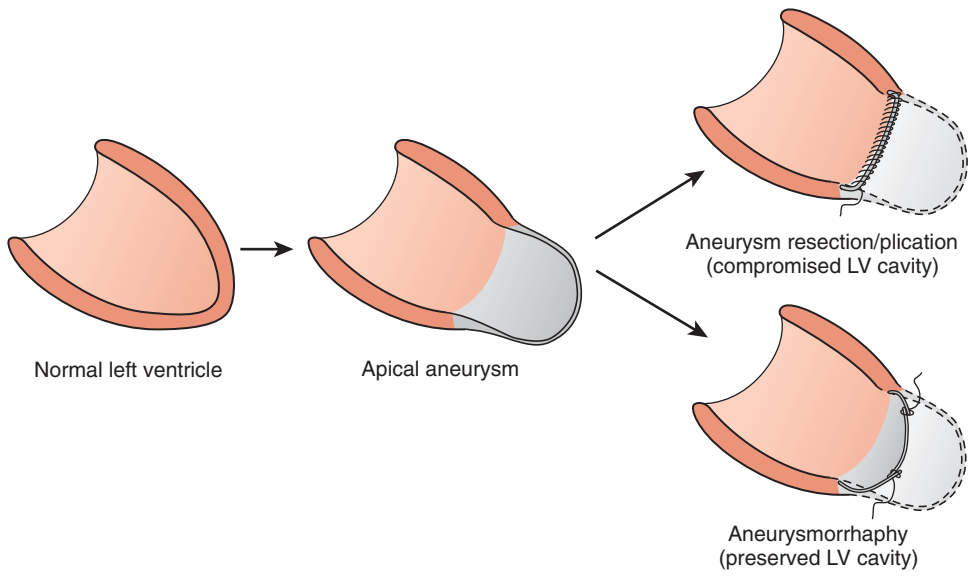

FIGURE 97-5 Ventricular remodeling after aneurysm surgery. *Left,* A normal left ventricular contour (right anterior oblique view). Infarction results in aneurysm formation (*center*). Earlier work with aneurysm resection (or plication) made a simple closure that compromised cavity size and thus stroke volume. More recent developments include repair of the aneurysm, involving partial resection and use of prosthetic patch material to restore more normal ventricular geometry. *LV*, Left ventricle.

Patient Selection

Because of the above features and the availability of lower-risk alternative therapies, surgery is rarely performed for VT. The benefits and risks of surgery, as well as the availability of the necessary mapping equipment and electrophysiological and surgical expertise, must be carefully weighed before proceeding.

Other Substrates of Ventricular Tachycardia

Re-entrant VT can occur in other settings such as idiopathic cardiomyopathy, arrhythmogenic right ventricular dysplasia (ARVD), and Chagas disease or after right ventriculotomy for repair of congenital heart disease (ventriculoseptal defect, tetralogy of Fallot). There is relatively little surgical experience with cardiomyopathic VT. The arrhythmogenic substrate appears to be located on the endocardial aspect of the LV in most cases, as in post-infarct VT. Unlike the latter, however, there is usually no readily available region of scar or aneurysm through which the ventricle can be opened to allow endocardial access. It is generally undesirable to make a large incision through normal-appearing myocardium, the closure of which could itself conceivably become a source of re-entrant arrhythmias postoperatively. Some cases of VT caused by ARVD were managed surgically in the 1970s and 1980s; the substrate in these cases was relatively thin strands of surviving normal myocardium separated by large zones of adipose and fibrous tissues that had replaced portions of the right ventricular free wall. Three major regions were identified, in which this transformation was most commonly observed: the apex, the outflow tract, and the inferolateral basal right ventricle (RV) near the tricuspid annulus. The first surgical efforts in this disorder were directed at incising visually identifiable zones of fatty replacement of the right ventricular wall. However, postoperative VT recurrences in some cases were determined to be caused by re-entry in other regions of the RV that had not been sources of arrhythmia earlier. This led to the right ventricular disarticulation procedure, in which the entire right ventricular free wall was incised from its septal attachments, and the myocardium that could not be completely incised (infundibulum, near the valve annuli) was frozen with a cryoprobe. The right ventricular free wall was then reattached with a long suture line. In this way, VT could still occur in the isolated RV, but not spread to the LV (which remained in sinus rhythm). Although conceptually elegant, the results of this procedure were disappointing; arrhythmia "cure" rates were high, but poor hemodynamic performance (with the RV as merely a passive conduit) caused significant morbidity and even death. As a result, this procedure is rarely performed now; patients with ARVD most commonly receive ICD therapy.

In cases of VT after right ventriculotomy for repair of congenital heart disease, mapping studies have usually shown a re-entrant wave front circulating around the incision that acts as a nonconducting barrier. This can be treated by continuing the incision to another nonconducting barrier such as the pulmonic valve annulus. This is usually accomplished with extensive cryoablation. In some cases, VT appears to be due to re-entry around the ventriculoseptal defect patch.

Rarely, VT occurs in the absence of structural heart disease. Several syndromes of VT in this setting have been relatively well characterized, including exercise-provoked right ventricular outflow tract (RVOT) VT of focal origin, and a re-entrant arrhythmia involving a portion of the left ventricular Purkinje system, right bundle branch block with left-axis deviation (RBBB-LAD) VT. An uncommon variant of RVOT VT arises in the LV, often near the aortic or mitral valve annulus. Although some of the earliest reports of surgical therapy of VT were for these arrhythmias, surgery is rarely needed currently because of the very high success rates of catheter ablation (>90%). Several patients underwent surgery for RVOT VT before the development of catheter ablation techniques. General anesthesia can have a profound quieting effect on these types of VT; catecholamine infusion may restore firing of the focus but can also simply increase the sinus rate over the intrinsic rate of the VT. We have had to pack the sinus node in ice to prevent this latter effect and allow the VT to become manifest so that its origin could be mapped. Recently, minimally invasive surgical therapy for epicardial foci of VT that have not responded to catheter ablation has been reported. Only rare cases of RBBB-LAD VT have undergone surgical therapy; in one fascinating case, the tachycardia terminated following incision of a left ventricular false tendon. Histologic examination revealed a large number of Purkinje cells, strengthening the association of the specialized conduction system with this unusual arrhythmia.

Current Status

Because of the high efficacy and low morbidity and mortality of ICD implantation and catheter ablation, surgical therapy for VT has largely been relegated to the second or even third tier of therapy, after these other methods have failed to effect adequate arrhythmia control. However, in some situations, surgical therapy warrants earlier consideration:

1. In patients who are undergoing other indicated cardiac surgical procedures such as CABG or valve surgery, VT surgery can be performed at the same time. This additional procedure almost surely increases operative risk to some degree, but no studies have addressed question this directly.

2. In patients with incessant or very frequent, hemodynamically poorly tolerated VT episodes, in whom medical therapy has failed to control recurrences and when percutaneous or standard ventricular assist device therapy is not available for hemodynamic support, VT surgery is often the only reasonable option. ICD therapy is contraindicated when it would result in frequent repeated shocks, and hemodynamic instability or presence of left ventricular thrombus often precludes any consideration of catheter ablation. In these emergency situations, VT surgery can be life saving.

3. In patients who simply prefer the chance of "cure" of their arrhythmia rather than rescue from episodes (such as the ICD provides), in whom catheter ablation is not possible or is not preferred, VT surgery is a reasonable option. Careful counseling of the patient and their family members is necessary for this unusual situation.

Ventricular Fibrillation

VF as the first recorded arrhythmia may be caused by severe ischemia (with or without prior myocardial damage), LQTS (congenital or acquired), idiopathic VF, Brugada syndrome, and other less common settings. Conversely, an episode of rapid VT may

have degenerated to VF that was present at the time of the first ECG recording. The patient's medical history, resting ECG, and assessment of left ventricular function can help suggest one or another of these causes. Distinguishing between a solely ischemic cause and one that has a basis in prior infarct or cardiomyopathy ("substrate") is of critical importance, since the treatments for these disorders are drastically different. If severe ischemia is the cause, revascularization alone suffices, and an antiarrhythmic drug or ICD therapy is at best unhelpful and may even be proarrhythmic. Conversely, if previously damaged myocardium provides the substrate for VT or VF, treatment of ischemia alone will not prevent arrhythmia recurrences. Although make this distinction can sometimes be made on clinical grounds, it is often not possible to make a certain diagnosis. For instance, many patients with severe coronary stenoses that may be capable of producing VF also have an area of previous infarction. Because the consequences of choosing the wrong therapy are very serious, every effort should be made to determine the correct diagnosis. Patient evaluation should include clinical history, physical examination, and standard ECG; assessment of resting left ventricular function; and assessment for the presence and extent of myocardial ischemia (functional assessment as well as coronary arteriography). The clinical history may strongly suggest severe ischemia as the provocation for VF (i.e., the patient was exercising or arguing vigorously and complained of increasing chest pain just prior to collapse), but often a detailed history of the event is not available. Exercise testing, at which severe ischemia at low workloads leads to nonsustained or sustained polymorphic VT or VF, may be diagnostic but should not be performed prior to knowing the patient's coronary anatomy.

On the basis of the results of these tests, patients may be characterized in several distinct subsets:

1. Severe coronary stenoses (typically >90%) with readily provocable ischemia, normal left ventricular function, no scar—the most likely cause is pure ischemically mediated VF.

2. Moderate to severe coronary stenoses with or without significant ischemia, reduced LV function, with myocardial scar—these patients may have post-infarct myocardial substrate for rapid VT that degenerates to VF, or ischemically mediated VF.

3. Moderate to severe coronary stenoses without significant ischemia, markedly reduced LV function, no scar—the most likely diagnosis is cardiomyopathy with an ill-defined myocardial substrate for arrhythmias (VT or VF).

4. No significant coronary stenoses, normal LV function, no scar—the most likely diagnoses are idiopathic VF, Brugada syndrome or its variants, or a form fruste of LQTS.

Patients in the first group, with very severe coronary stenoses, normal left ventricular function and wall motion, and no clinical, electrocardiographic or angiographic evidence of prior damage, appear to respond well to revascularization alone. Although a theoretical risk of recurrent VF is always present if graft occlusion or re-stenosis occurs, this has not been a reported clinical problem (with limited numbers of cases). Patients in the second group (with significant coronary stenoses, reduced left ventricular function and prior scar), for whom revascularization is planned, should undergo EPS prior to and following revascularization to determine whether ventricular arrhythmias are inducible with programmed stimulation. If VT or VF can be initiated prior to surgical revascularization but not following the procedure, the chance of arrhythmia recurrence is significantly lower than if the VT or VF can still be initiated postoperatively.[12] Although data are limited, it appears that patients in this latter group (persistent arrhythmia inducibility following revascularization) should undergo ICD therapy as well since they have evidence for the ongoing presence of substrate for these arrhythmias. Some patients in this group with myocardial scar and VF have frequent recurrences of arrhythmia in the absence of significant ischemia; some of the patients have responded well to endocardial resection or cryoablation guided by mapping of fractionated electrograms during sinus rhythm. Patients in the third group (cardiomyopathy) cannot be expected to have antiarrhythmic benefit from revascularization and should undergo ICD therapy, as should patients in the fourth group (no evidence of structural disease), who have no other reliable means of preventing arrhythmia recurrences.

Thus, patients presenting with VF comprise a very heterogeneous group with a wide variety of causes of arrhythmia for which optimal treatments vary markedly. These patients must undergo thorough evaluation, since an improper therapy based on an incorrect diagnosis can have disastrous results.

Summary

Surgical therapy for ventricular arrhythmias is much less commonly performed than a decade ago, primarily because of advances in ICD and catheter ablation technologies, but still has a role in selected cases of uniform-morphology VT and ischemic VF. Improvements in ventricular closure have increased operative survival and postoperative functional capacity. Especially in treatment of VT, the combination of a surgeon and electrophysiologist who are experienced in these techniques and the use of proper equipment for mapping and ablating the arrhythmia play a key role in the ultimate success of the procedure.

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CHAPTER 98

Surgical Ablation of Atrial Fibrillation

Anson M. Lee, Rochus K. Voeller, and Ralph J. Damiano Jr.

Although atrial fibrillation (AF) is often regarded as an innocuous arrhythmia, it is associated with significant morbidity and mortality secondary to its detrimental sequelae: (1) palpitations resulting in patient discomfort and anxiety; (2) loss of atrioventricular (AV) synchrony, which can compromise cardiac hemodynamics and result in various degrees of ventricular dysfunction or congestive heart failure; (3) stasis of blood flow in the left atrium, increasing the risk of thromboembolism and stroke.[1-10]

Because of the shortcomings of the medical treatment of AF, an interest in nonpharmacologic approaches to treat this arrhythmia has led to the development of catheter-based and surgical techniques beginning in the 1980s. Initial attempts were aimed at providing rate control but failed to address the detrimental hemodynamic and thromboembolic sequelae of AF. Early attempts at finding a surgical treatment culminated in the introduction of the Maze procedure in 1987, which became the gold standard for many years.

The following section will briefly describe the historical aspects of surgery for AF.

Historical Aspects

Left Atrial Isolation Procedure

The first procedure designed specifically to eliminate AF was first described in 1980 in the laboratory of Dr. James Cox at Duke University. The *left atrial isolation procedure*, which confined AF to the left atrium, restored the remainder of the heart to sinus rhythm (Figure 98-1).[11] This procedure was significant because it restored a regular ventricular rate without requiring a permanent pacemaker. Since the sinoatrial (SA) node, AV node, and internodal conduction pathways are located in the right atrium and the inter-atrial septum, the left atrial isolation procedure did not affect normal AV conduction. Isolating the left atrium allowed the right atrium and the right ventricle to contract in synchrony, providing a normal right-sided cardiac output. This effectively restored normal cardiac hemodynamics.

By confining AF to the left atrium, the left atrial isolation procedure eliminated two of the three detrimental sequelae of AF: (1) an irregular heartbeat and (2) compromised cardiac hemodynamics. However, it did not eliminate the thromboembolic risk, since the left atrium usually remained in fibrillation. This procedure never achieved clinical acceptance, though it was performed by Dr. Cox in a single patient.

Catheter Ablation of the Atrioventricular Node–His Bundle Complex

In 1982, Scheinman and coworkers introduced *catheter fulguration of the His bundle*, a procedure that controlled the irregular cardiac rhythm associated with AF and other refractory supraventricular arrhythmias.[12] This procedure electrically isolated the fibrillation to the atria. Unfortunately, ablating the bundle of His required permanent ventricular pacemaker implantation to restore a normal ventricular rate.

The shortcoming of this intervention was that it only eliminated the irregular heartbeat. Both atria remained in fibrillation, and the risk of thromboembolism persisted. AV contraction remained desynchronized, compromising cardiac hemodynamics. In addition, all patients required a permanent pacemaker. Nevertheless, AV node ablation has remained a common treatment for medically refractory AF.

Corridor Procedure

In 1985, Guiraudon et al developed the *corridor procedure* for the treatment of AF.[13] This operation isolated a strip of atrial septum harboring both the SA node and the AV node, allowing the SA node to drive both ventricles. This procedure effectively eliminated the irregular heartbeat associated with AF, but both atria either remained in fibrillation or developed their own asynchronous intrinsic rhythm because they were isolated from the septal "corridor" (Figure 98-2). Furthermore, the atria were isolated from their respective ventricles, thereby precluding the possibility of AV synchrony. The corridor procedure was abandoned because it had no effect on the hemodynamic compromise or the risk of thromboembolism associated with AF.

Atrial Transection Procedure

In 1985, Dr. James Cox and associates described the first procedure that attempted to terminate AF.[14] This was different from the earlier surgical procedures that only isolated or confined AF to a certain region of the atria. Using a canine model, Cox's group found that a single long incision around both atria and down into the septum could terminate AF. This *atrial transection procedure* prevented the induction and maintenance of AF or atrial flutter in every canine that underwent the operation.[15] Unfortunately, this procedure was not effective clinically and was abandoned.

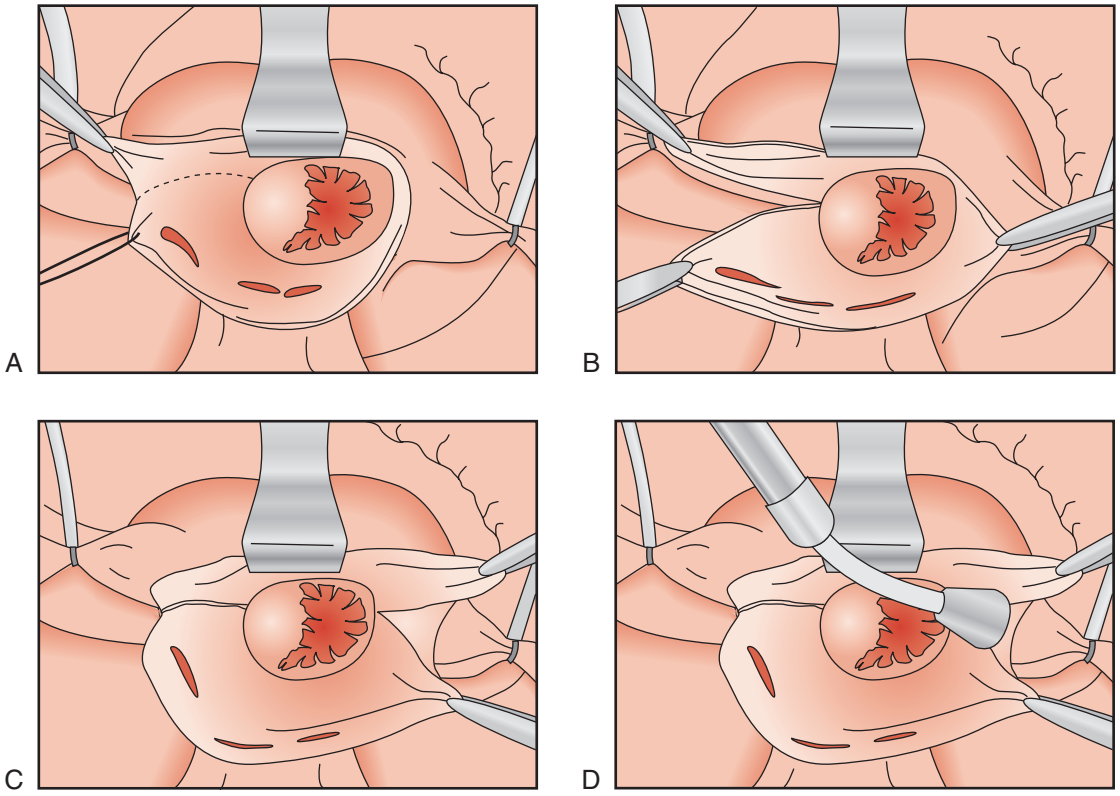

FIGURE 98-1 The surgeon's view of the left atrial isolation procedure. The superior and inferior venae cavae can be seen coursing to the left and right of each panel. The orifices of the right pulmonary veins are seen at the lower edge of the left atriotomy (**A**). This atriotomy is extended to the superior portion of the mitral valve (**B**) and then to the inferior portion (**C**). Cryoablation is used to finish the line of conduction block at the valve annuli (**D**). *(From Williams JM, Ungerleider RM, Lofland GK, Cox JL: Left atrial isolation: New technique for the treatment of supraventricular arrhythmias,* J Thorac Cardiovasc Surg *80[3]:373–380, 1980.)*

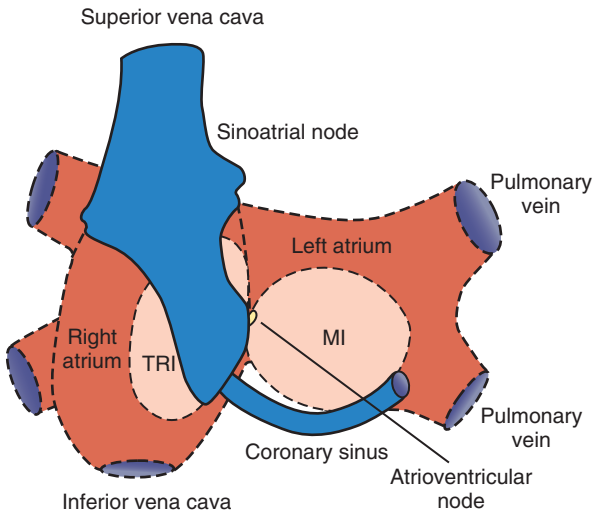

FIGURE 98-2 Schematic diagram demonstrating the isolated strip of atrial tissue containing the sinoatrial node and atrioventricular nodes created with the corridor procedure. *(From van Hemel NM, Defauw JJ, Kingma JH, et al: Long-term results of the corridor operation for atrial fibrillation,* Br Heart J *71[2]:170–176, 1994.)*

Development of the Cox-Maze Procedure

The Maze procedure was clinically introduced in 1987 by Dr. Cox after extensive animal investigation at Washington University in St. Louis.[15-17] The Cox-Maze procedure was developed to interrupt any and all macro–re-entrant circuits that were felt to potentially develop in the atria, thereby precluding the ability of the atrium to flutter or fibrillate (Figure 98-3). Unlike earlier procedures, the Cox-Maze procedure successfully restored both AV synchrony and sinus rhythm, thus potentially reducing the risk of thromboembolism and stroke.[18] The operation consisted of creating a myriad surgical incisions across both the right and left atria. These incisions were placed so that the SA could still direct the propagation of the sinus impulse throughout both atria. It allowed for most of the atrial myocardium to be activated, resulting in the preservation of atrial transport function in most patients.[19]

The original version, the Maze I procedure, was modified because of problems with late chronotropic incompetence and a high incidence of pacemaker implantations. The Maze II procedure, however, was extremely difficult to perform technically. It was soon replaced by the Maze III procedure, also known as the *Cox-Maze III procedure* today (Figure 98-4).[20,21]

The Cox-Maze III procedure—often referred to as the "cut-and-sew" Maze—became the gold standard for the surgical treatment of AF. In a long-term study of patients who underwent the

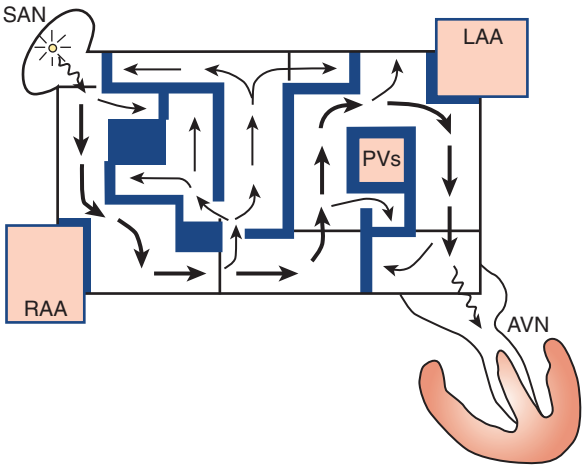

FIGURE 98-3 The Maze procedure is designed to preclude the ability of the atria to fibrillate by creating numerous surgical incisions in the atria. *AVN*, Atrioventricular node; *LAA*, left atrial appendage; *PVs*, pulmonary veins; *RAA*, right atrial appendage; *SAN*, sinoatrial node.

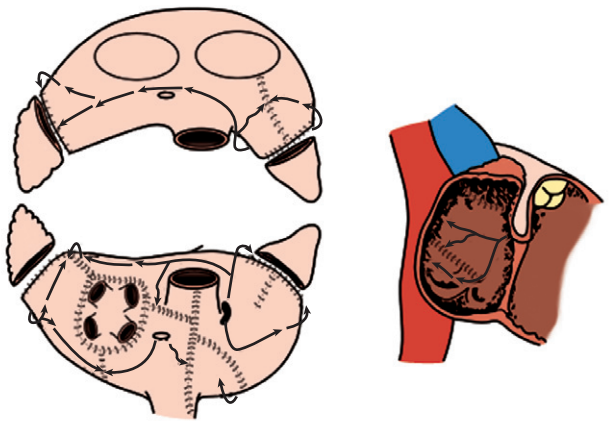

FIGURE 98-4 The traditional "cut-and-sew" Cox-Maze III procedure.

Cox-Maze III procedure at the authors' institution, 97% of the patients at late follow-up were free of symptomatic AF.[22] These excellent results have been reproduced by other groups worldwide.[23-25]

Although the Cox-Maze III procedure was effective in eliminating AF, it is presently mainly of historical interest. It was technically difficult and invasive, and only a handful of cardiac surgeons still perform this operation today. At most centers around the world, the surgical incisions have been replaced with ablations using a variety of energy sources. These ablation-assisted procedures have greatly expanded the field of AF surgery in the past decade. With the current ablation technology, surgery can be performed with low mortality and often with limited-access incisions.

The indications for surgery have been defined in a recent consensus statement.[26] These presently include (1) all symptomatic patients with documented AF undergoing other cardiac surgical procedures, (2) selected asymptomatic patients with AF undergoing cardiac surgery in which the ablation can be performed with minimal risk in experienced centers, and (3) standalone AF, which should be considered for symptomatic patients with AF who prefer a surgical approach, have failed one or more attempts at catheter ablation, or are not candidates for catheter ablation.

The referral of patients for surgery with medically refractory, symptomatic AF in lieu of catheter ablation is still being debated. The problem is that no head-to-head comparisons of outcomes with catheter and surgical ablation are available. In these instances, clinical decisions should be made on the basis of the individual institution's experience with catheter and surgical ablations, the relative outcomes and risks of each in the individual patient, and patient preference. Programs involved in the surgical treatment of AF should develop a team approach to these patients, with the team including both electrophysiologists and surgeons, to ensure appropriate selection of patients.

In the authors' opinion, relative indications for surgery were not included in the consensus statement. The first is a contraindication to long-term anticoagulation in patients with persistent AF and a high risk for stroke (CHADS score ≥2). Up to one third of patients with AF screened for participation in clinical trials of warfarin were deemed ineligible for chronic anticoagulation, mainly because of a perceived high risk of bleeding complications.[27,28] In fact, patients on warfarin have twice the rate of intracerebral hemorrhage and mortality in a dose-dependent relationship.[29] In one study, the annual rate of intracranial hemorrhage in anticoagulated patients with AF was 0.9% per year, and the overall major bleeding complications was 2.3% per year.[28] The Cox-Maze procedure not only is able to eliminate AF in most patients but also amputates the left atrial appendage. The stroke rate following the procedure off anticoagulation has been remarkably low, even in patients with a CHADS score ≥2. At the authors' institution, only 5 of 450 patients had a stroke after a mean follow-up of 6.9 ± 5.1 years. No difference in stroke rate was observed in those patients with CHADS scores above or below 2.[30] This low risk of stroke following the Cox-Maze procedure has been noted in other series as well.[18,31,32]

Surgical treatment for AF with amputation of the left atrial appendage also should be considered in patients with chronic AF who have suffered a cerebrovascular accident despite adequate anticoagulation. These patients are at high risk of recurring neurologic events. Anticoagulation with warfarin reduces the risk of ischemic and hemorrhagic strokes by over 60% in patients with AF but does not completely eliminate this serious complication.[9,33] At the authors' institution, 20% of patients who underwent the Cox-Maze III procedure had experienced at least one episode of cerebral thromboembolism that resulted in a significant temporary or permanent neurologic deficit prior to undergoing the operation.[22] No late strokes occurred in this population, with 90% of patients off anticoagulation at last follow-up.[22]

In patients undergoing concomitant valve surgery, studies have shown that adding the Cox-Maze procedure can decrease the late risk of cardiac-related and stroke-related deaths.[34,35] However, there have been no prospective or randomized studies demonstrating the survival or other benefits of adding a Cox-Maze procedure in patients with AF. The contraindication to a Cox-Maze procedure in this group would be in asymptomatic patients who have tolerated their AF well and have not had problems with anticoagulation and in whom adding the ablation would increase their surgical risk.

Surgical Ablation Technology

The development of surgical ablation technology has revolutionized the field of AF surgery. It has transformed a technically difficult and time-consuming operation that few surgeons were willing to perform into a procedure that is technically easier, less invasive, and easy to be routinely performed by most surgeons. This section will briefly summarize the various energy sources being used for surgical ablation.

For ablation technology to successfully replace incisions, it must meet several criteria. (1) It must create linear ablation lines that reliably produce bi-directional conduction block. This is the mechanism by which incisions prevent AF, by either blocking macro–re-entrant or micro–re-entrant circuits or isolating trigger foci. The authors' laboratory and others have shown that this requires a transmural lesion, as even small gaps in ablation lines can conduct both sinus and fibrillatory impulses.[36,37] (2) The ablation device must be safe. This requires a precise definition of dose-response curves to limit excessive or inadequate ablation. The surgeon must also have knowledge of the effects of a specific ablation technology on surrounding vital cardiac structures such as the coronary sinus, coronary arteries, and valvular structures. (3) The ablation device should make AF surgery simpler and require less time to perform. This would require the device to create lesions rapidly, be simple to use, and have adequate length and flexibility. (4) The device should be adaptable to a minimally invasive approach. This would include the facility to insert the device through minimal access incisions or ports, and the device should be able to create epicardial transmural lesions on the beating heart. Currently, no device has met all of these criteria. The following sections will briefly summarize the current ablation technologies and their advantages and disadvantages.

Cryoablation

Cryoablation technology is unique in that it destroys myocardial tissue by freezing rather than heating. It has the benefit of preserving the fibrous skeleton and collagen and is thus one of the safest energy sources available. The devices work by pumping a refrigerant to the electrode tip, where it undergoes transformation from a liquid state to a gaseous state, releasing energy into the tissue that is in contact with the tip. The formation of intracellular and extracellular ice crystals disrupts the cell membrane and kills the cell. Evidence that the induction of apoptosis plays a role in late lesion expansion is also available. Lesion size depends on the temperature of the probe, thermal conductivity, and the temperature of the tissue.

Currently, two commercially available sources of cryothermal energy are being used in cardiac surgery. The older technology, based on nitrous oxide, is manufactured by AtriCure (Cincinnati, OH). More recently, ATS Medical (Minneapolis, MN.) has developed a device based on argon. At 1 atmosphere of pressure, nitrous oxide is capable of cooling tissue to –89.5° C, while argon has a minimum temperature of –185.7° C. The nitrous oxide technology has a well-defined efficacy and safety profile and is generally safe except around the coronary arteries.[38,39] The potential disadvantage of cryoablation, however, is the relatively long time that is needed to create lesions (1 to 3 minutes). Creating lesions on the beating heart is also difficult because of the "heat sink" of the circulating blood volume.[40] Furthermore, if blood is frozen during epicardial ablation on the beating heart, it coagulates, creating a potential risk for thromboembolism.

Radiofrequency Energy

Radiofrequency (RF) energy, which has been used for cardiac ablation for many years in the electrophysiology laboratory, was one of the first energy sources to be applied in the operating room.[41] RF energy uses alternating current in the range of 100 to 1000 kHz. This frequency is high enough to prevent rapid myocardial depolarization and the induction of ventricular fibrillation, yet low enough to prevent tissue vaporization and perforation. Resistive RF energy can be delivered by either unipolar electrodes or bipolar electrodes, and the electrodes can be either dry or irrigated. With unipolar RF devices, the energy is dispersed between the electrode tip and an indifferent electrode, usually the grounding pad applied to the patient. In bipolar RF devices, alternating current is passed between two closely approximated electrodes embedded in the jaws of a clamp. The lesion size depends on electrode-tissue contact area, the interface temperature, the current and voltage (power), and the duration of delivery. The depth of the lesion can be limited by char formation, epicardial fat, myocardial and endocavity blood flow, and tissue thickness.

Numerous unipolar RF devices have been developed for ablation. These include both dry and irrigated devices and devices that incorporate suction. Although dry unipolar RF has been shown to create transmural lesions on the arrested heart in animals with sufficiently long ablation times, problems have occurred in humans. After 2-minute endocardial ablations during mitral valve surgery, only 20% of the in vivo lesions were transmural.[42] Epicardial ablation on the beating heart has been even more problematic. Animal studies have consistently shown that unipolar RF is incapable of creating epicardial transmural lesions on the beating heart.[43,44] Epicardial RF ablation in humans resulted in only 10% of the lesions being transmural.[45] This deficiency of unipolar RF has been felt to be caused by the heat sink of the circulating blood.[46] This has led some groups to examine the addition of both irrigation and suction to improve lesion formation. While these additions have improved the depth of penetration, a device capable of creating reliable transmural lesions on the beating heart is still not available.

To overcome this problem, bipolar RF clamps were developed. With bipolar RF, the electrodes are embedded in the jaws of a clamp to focus the delivery of energy. The electrodes are shielded from the circulating blood pool, and this allows for faster ablation times and limits collateral injury to tissue that is close to the electrodes. Bipolar ablation has been shown to be capable of creating transmural lesions on the beating heart, both in animals and humans, with short ablation times.[47-49] Three companies (AtriCure; Medtronic, Minneapolis, MN; and Estech, San Ramon, CA) currently market bipolar RF devices.

Another advantage of bipolar RF energy is its safety profile. A number of clinical complications of unipolar RF devices that have been reported include coronary artery injuries, cerebrovascular accidents, and esophageal perforation leading to atrio-esophageal fistula.[50-53] Bipolar RF technology has eliminated most of this collateral damage, and no injuries have been described with these devices despite extensive clinical use.

High-Intensity Focused Ultrasound

High-intensity focused ultrasound (HIFU) is another modality that is applied clinically for surgical ablation (St. Jude Medical, St. Paul, MN). Ultrasound effectively ablates tissue via mechanical hyperthermia. When ultrasound waves are emitted from the transducer, the resulting wave travels through the tissue causing compression, refraction, and particle movement. This translates into kinetic energy and ultimately thermal coagulative tissue necrosis. HIFU produces rapid, high-concentration energy in a focused area and is reportedly able to create transmural epicardial lesions through epicardial fat in a short time.[54]

HIFU is unique in that it is able to create noninvasive, noncontact focal ablation in three-dimensional volume without affecting intervening and surrounding tissue. It uses ultrasound beams in the frequency range of 1 to 5 MHz or higher, creating focused lesions quickly by rapidly raising the temperature of the targeted tissue to above 80° C, effectively killing the cells. By focusing the ultrasound waves, HIFU is able to create targeted thermal coagulation of tissue at a very well-defined focus without harming intervening tissue. Its ability to focus the target of ablation at specific depths is its major advantage over other energy modalities.

Another advantage of HIFU technology is its mechanism of thermal ablation. Unlike all other energy sources that heat or cool tissue by thermal conduction, HIFU ablates tissue by directly heating the tissue in the acoustic focal volume and is therefore much less affected by the heat sink of the circulating endocardial blood pool. A few clinical studies using HIFU have shown some encouraging results.[54-57] However, the efficacy of HIFU devices to reliably create transmural lesions has not been independently verified. The fixed depth of penetration of these devices may be a major problem in pathologically thickened atrial tissue. Moreover, these devices are somewhat bulky and are expensive to manufacture.

In summary, each ablation technology has its own advantages and disadvantages. In the future, it will be imperative for surgeons to develop a more compete understanding of the effects of each surgical ablation technology on atrial hemodynamics, function, and electrophysiology. This will allow for the more appropriate use of devices in the operating room. The inability to create reliable linear lesions on the beating heart remains a shortcoming of most devices and has impeded the development of minimally invasive procedures, especially for patients with longstanding AF and large left atria.

Surgical Techniques

The numerous procedures that are currently performed to surgically ablate AF can be grouped into three broad categories: (1) the Cox-Maze procedure, (2) left atrial lesion sets, and (3) PV isolation. These approaches will be described in the following section.

The Cox-Maze IV Procedure

The original cut-and-sew Cox-Maze III procedure is only rarely performed today. At most centers, the surgical incisions have been replaced with lines of ablation using a variety of energy sources. At the authors' institution, bipolar RF energy has been used successfully to replace most of the surgical incisions of the Cox-Maze III procedure. The current RF ablation–assisted procedure, termed *Cox-Maze IV*, incorporates the lesions as does Cox-Maze III (Figure 98-5).[58] The authors' clinical results have shown that this modified procedure has significantly shortened operative time while maintaining the high success rate of the original Cox-Maze III procedure.[59]

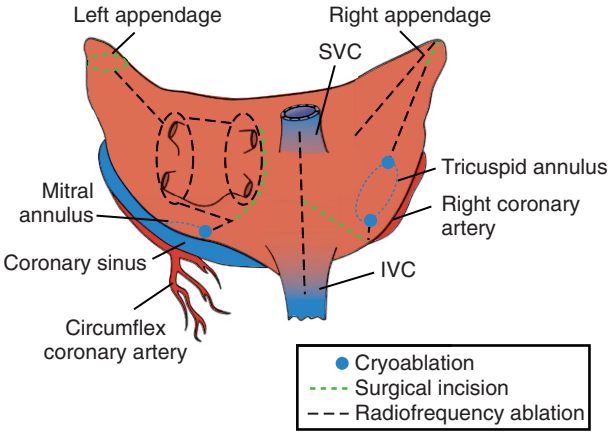

FIGURE 98-5 The Cox-Maze IV lesion sets. *IVC*, Inferior vena cava; *SVC*, superior vena cava.

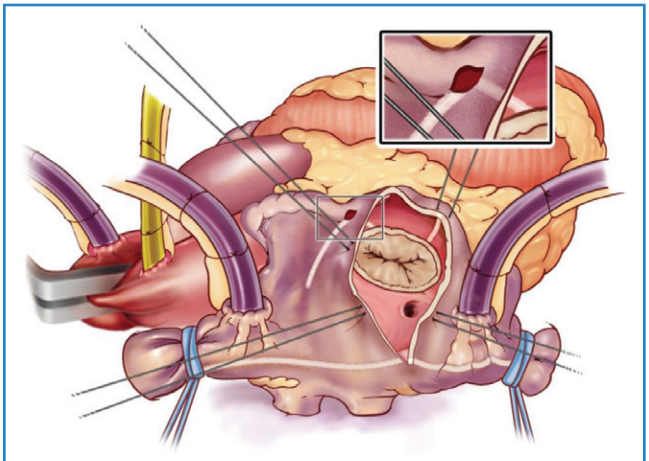

FIGURE 98-6 Illustration of the right atrial lesion set. *Lines* indicate bipolar RF ablation. Cryoablation or unipolar RF energy is used to complete the ablations line at the tricuspid valve annulus.

The Cox-Maze IV procedure is performed on cardiopulmonary bypass. The operation can be done either through a median sternotomy or a less invasive right minithoracotomy. The right and left pulmonary veins (PVs) are bluntly dissected. If the patient is in AF, amiodarone is administered, and the rhythm is electrically cardioverted. Pacing thresholds are obtained from each PV. Using a bipolar RF ablation device, the PVs are individually isolated by ablating a cuff of atrial tissue surrounding the right and left PVs. Proof of electrical isolation is confirmed after ablation by demonstrating exit block, entrance block, or both.

The right atrial lesion set is performed on the beating heart, as shown in Figure 98-6. A bipolar RF clamp is used to create most of the lesions. A unipolar device, either cryoablation or RF

energy, is used to complete the ablation lines endocardially down to the tricuspid annulus because of the difficulty of clamping in this area.

The left-sided lesion set (Figure 98-7) is performed via a standard left atriotomy on the arrested heart. The incision is extended inferiorly around the right inferior PV and superiorly onto the dome of the left atrium. Connecting lesions are made with the bipolar RF device into the left superior and inferior PVs and down toward the mitral annulus. The authors' group has shown that isolating the entire posterior left atrium with ablation lines into both left PVs resulted in a better drug-free survival from AF at 6 and 12 months.[60] A unipolar device, either cryoablation or RF, is used to connect the lesion to the mitral annulus and complete the left atrial isthmus line. The left atrial appendage is amputated, and a final ablation is performed through the amputated left atrial appendage into the one of the left PVs.

Left Atrial Procedures

Over the past decade, a number of new surgical procedures have been introduced in an attempt to cure AF. These procedures have generally involved some subset of the left atrial lesion set of the Cox-Maze procedure. The results have been variable and have ranged from 20% to 90% freedom from AF.[50,61-68] They have been dependent on the technology used, the lesion set, and the patient population.

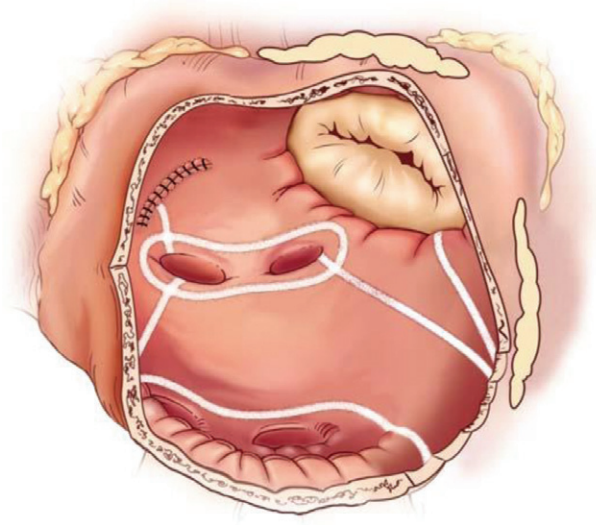

FIGURE 98-7 Illustration of the left atrial lesion set. *White lines* indicate RF bipolar ablation. Cryoablation is used to complete the ablation line at the mitral valve annulus.

Pulmonary Vein Isolation

PV isolation (PVI) is an attractive therapeutic strategy because the procedure can be done without cardiopulmonary bypass and with minimally invasive techniques, using either an endoscopic approach or small incisions. On the basis of the original report of Hassaiguerre, it has been well documented that the triggers for paroxysmal AF originate from the PVs in the majority of cases.[69] However, it is important to remember that up to 30% of triggers may originate outside the PVs.[70] To increase efficacy, some investigators have added ablation of the ganglionic plexi (GP).[71-73]

The PVs can be isolated separately or as a box (Figure 98-8). The most common technique, which will be described later, uses an endoscopic, port-based approach to minimize incisional size and pain for the patient. At the authors' center, bipolar RF clamps are favored to isolate the PVs, but unipolar RF and HIFU devices have also been used.[56,74] Patient preparation begins with double-lumen endotrachial intubation. A trans-esophageal echocardiogram is performed to confirm the absence of thrombus in the left atrial appendage. If a thrombus is found, the procedure is either aborted or converted to an open procedure, where the risk of systemic thromboembolism from left atrial clot can be minimized. External defibrillator pads are placed on the patient, and the patient is positioned with the right side turned upward 45 to 60 degrees and the right arm positioned above the head to expose the right axilla.

An initial port for the thoracoscopic camera is placed at the sixth intercostal space. Under thoracoscopic vision, a small working port can then be placed in either the third or fourth intercostal space at the midaxillary line, depending on the preference of the surgeon and the patient's anatomy. The right phrenic nerve is identified to avoid injury to this structure. An incision is made in the pericardium, anterior and parallel to the phrenic nerve, to expose the heart from the superior vena cava to the diaphragm. Through this pericardiotomy, the space above and below the right PVs is dissected to allow enough room for the insertion of a specialized thoracoscopic dissector. The dissector with a guiding sheath is introduced through a second port, either lateral or medial to the scope port, and guided into the space between the right PVs and the right pulmonary artery. After the dissector is carefully removed from the chest, the sheath remains in place as a guide for the insertion of the bipolar RF clamp. At this point, cardioversion to sinus rhythm occurs so that pacing

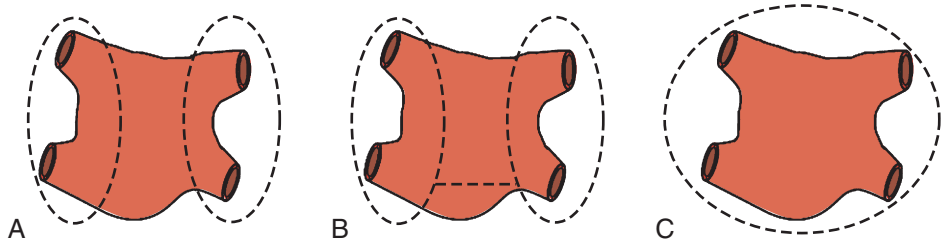

FIGURE 98-8 Diagram illustrating the methods to isolate the pulmonary veins, either separately (**A**), with a connecting lesion (**B**), or as a box isolation of the entire posterior left atrium (**C**).

thresholds can be obtained. As with the Cox-Maze IV procedure, it is critical to document the entrance block and the exit block after ablation to confirm PVI. Some surgeons also use the opportunity provided by surgical exposure to test and ablate ganglionated plexi at this time.

After the pacing maneuvers are completed, the sheath is attached to the lower jaw of a bipolar RF clamp. The clamp is introduced into the chest, and the veins are clamped and ablated. After confirmation of isolation, the instruments are removed from the right chest, and the right chest incisions are closed.

The approach to the left chest is similar to that to the right. The patient is repositioned such that the left chest is elevated 45 to 60 degrees, and the left arm is held up to expose the left axilla. A port for the thoracoscopic camera is placed in the sixth intercostal space, slightly more posterior than on the right side. With thoracoscopic visualization, a left-sided working port is created in the third or fourth intercostal space. The left phrenic nerve is identified, and the pericardium is opened posterior to the course of the nerve. The ligament of Marshall is identified and divided. The dissector is then introduced through a second port, also in the sixth intercostal space. This port site is placed to allow for a straight line introduction of the dissector around the PVs. The guiding sheath is used to position the RF clamp around the left PVs, and they are isolated. Again, exit and entrance blocks are confirmed with pacing.

The procedure is not complete until the left atrial appendage has been addressed. Traditionally, this has been done by stapling across the base of the left atrial appendage with an endoscopic stapler. This has rarely proven to be technically difficult and can result in tears and bleeding.[75] Several devices are being designed to address this difficulty. One such device with promise is a clip device, simply placed over the base of the left atrial appendage to exclude it (Figure 98-9). After ablation of the left PVs and exclusion of the left atrial appendage, the left side of the pericardium must be closed to avoid herniation of the heart.

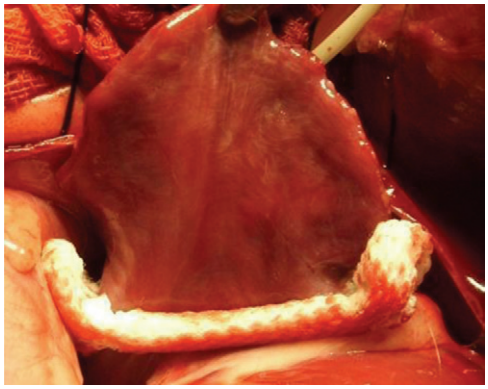

FIGURE 98-9 Example of an occluding clip device in development applied to the canine left atrial appendage. *(Courtesy AtriCure, Inc., Cincinnati, OH.)*

Surgical Results

Cox-Maze Procedure

The Cox-Maze III procedure has had excellent long-term results. In the authors' series at Washington University, 97% of 198 consecutive patients who underwent the procedure with a mean follow-up of 5.4 years were free from symptomatic AF. No difference was observed in the cure rates between patients undergoing a stand-alone Cox-Maze procedure and those undergoing concomitant procedures.[22] Similar results have been obtained from other institutions around the world with the traditional cut-and-sew method.[23,25,76]

The authors' results from patients who underwent the Cox-Maze IV procedure have been encouraging as well. In a prospective, single-center trial from their institution, 91% of patients at 6-month follow-up were free from AF.[49,59] The Cox-Maze IV procedure has significantly shortened the mean cross-clamp times for a lone Cox-Maze from 93 ± 34 minutes for the Cox-Maze III to 47 ± 26 minutes for the Cox-Maze IV ($P < .001$), and from 122 ± 37 minutes for a concomitant Cox-Maze III procedure to 92 ± 37 minutes ($P < .005$) in those undergoing the Cox-Maze IV procedure concomitantly with another cardiac operation.[49] A propensity analysis performed by the authors' group has shown that no significant difference is present in the freedom from AF at 3, 6, or 12 months between the Cox-Maze III and Cox-Maze IV groups.[77]

The Cox-Maze IV procedure also worked just as well for patients with paroxysmal AF compared with persistent or long-standing persistent AF. The 6-month freedom from AF was 91% in the paroxysmal group compared with 88% in the persistent group ($P = .53$). Success with achieving a drug-free state was also similar.[78] The authors' present series consists of 263 consecutive patients undergoing the Cox-Maze IV procedure between January 2002 and June 2009. All patients have been monitored with electrocardiograms (ECGs) or prolonged monitoring. In the authors' center, the rate of 12-month freedom from AF was 93%, with 78% of patients off all antiarrhythmic drugs. This center has had no intraoperative mortalities in 90 consecutive patients with lone AF who underwent this procedure.

Left Atrial Lesion Sets

A number of centers around the world have suggested that ablation be confined only to the left atrium to cure AF. This concept is supported by the fact that the majority of paroxysmal AF appears to originate around the PVs and the posterior left atrium. A left atrial lesion set typically involves PVI with a lesion to the mitral annulus as well as removal of the left atrial appendage. Numerous ablation technologies have been used to create these lesion sets with varying degrees of success.[50,61-68]

No randomized trials of bi-atrial ablation versus left atrial ablation only have been conducted in the surgical population. Because of this, the importance of the right atrial lesions of the traditional Cox-Maze procedure is difficult to determine. A meta-analysis of the published literature by Ad and colleagues revealed that a bi-atrial lesion set resulted in a significantly higher late freedom from AF when compared with a left atrial lesion set alone (87% vs. 73%; $P = .05$).[79] This is not surprising, considering the results of intraoperative mapping of patients with AF. The authors' group and others have shown that AF can originate from the right atrium in 10% to 50% of cases.[80-82]

Of the specific left atrial lesions of the Cox-Maze procedure, it is difficult to determine the precise importance of each particular ablation. All surgeons agree on the importance of isolating the PVs. Work from Gillinov et al also has shown the importance of the left atrial isthmus in a retrospective study.[83] In a rare

randomized trial, Gaita and coworkers examined PVI alone versus two alternative lesion sets, both of which included ablation of the left atrial isthmus. In this study, normal sinus rhythm at 2-year follow-up was only seen in 20% in the PVI group versus 57% in the other groups ($P < .006$).[66] Finally, the authors' group has shown that isolating the entire posterior left atrium significantly improved drug-free freedom from AF at 6 months (54% vs. 79%; $P = .011$) in a retrospective analysis of results.

Pulmonary Vein Isolation

The results of PVI alone have been variable and dependent on patient selection. In the first report of surgical PVI, Wolf and colleagues reported that 91% of patients undergoing video-assisted bilateral PVI and left atrial appendage exclusion were free from AF at 3-month follow-up.[84] Edgerton et al reported on 57 patients undergoing PVI with GP ablation with more thorough follow-up and found 82% of their patients with paroxysmal AF to be free from AF at 6 months, with 74% off anti-arrhythmic drugs.[85] Subsequent studies have shown encouraging results in patients with paroxysmal AF. In a study involving 21 patients with paroxysmal AF undergoing PVI with GP ablation, McClelland et al reported 88% procedural success, which was defined as freedom from AF at 1 year without antiarrhythmic drugs.[72] A larger, single-center trial recently reported 65% success with a single procedure at 1 year in a series of 45 patients undergoing PVI with GP ablation, including patients with persistent and paroxysmal AF.[86] A multiple-center trial reported 87% normal sinus rhythm in a more diverse patient population, including patients with longstanding, persistent AF; however, those patients with longstanding, persistent AF only had a 71% normal sinus rhythm rate.[87]

In patients with longstanding, persistent AF, the results have been worse. In a study from Edgerton and his group, only 56% of patients were free from AF at 6 months (35% off antiarrythmics).[88] With concomitant procedures, the success rate of PVI is even lower. Of 23 patients undergoing mitral valve surgery or coronary revascularization with concomitant PVI, only half were free from AF at a follow-up of 57 ± 37 months.[89] In the setting of mitral valve disease, Tada and colleagues reported 61% freedom from AF and only 17% freedom from antiarrythmic drugs in their series of 66 patients undergoing PVI.[90]

Ganglionated Plexus Ablation

Convincing experimental data have demonstrated that autonomic ganglia in GP play a role in the initiation and maintenance of AF.[91,92] As a result, some authors have added GP ablation to PVI in the hope of increasing procedural efficacy. Some of the initial results of these trials have been encouraging. However, no randomized trials demonstrating the efficacy of adding GP ablation in the surgical setting have been conducted. In 2005, Scherlag and colleagues reported a study of GP ablation combined with catheter PVI in 74 patients with lone AF. After a relatively short median follow-up of 5 months, 91% of patients were found to be free from AF.[92]

However, the effects of vagal denervation are not clearly defined. Experimental evidence in the authors' laboratory and others have demonstrated recovery of autonomic function as early as 4 weeks after GP ablation.[93-95] It is worrisome that the reinnervation is not homogenous and may result in a more arrhythmogenic substrate. In a more recent report, Katritsis and colleagues used left atrial GP ablation to treat 19 patients with paroxysmal AF. Fourteen of these patients had recurrent AF during 1-year follow-up.[96] The authors' practice is not to perform GP ablation to treat AF. Furthermore, long-term follow-up data on the effects of GP ablation are lacking. Thus, GP ablation should be reserved only for centers participating in clinical trials.

Future Directions in Atrial Fibrillation Surgery

Although the Cox-Maze procedure achieves high rates of success and recent technological advances have made it more accessible and easier to perform, it still remains an invasive procedure that requires cardiopulmonary bypass. Ideally, surgeons would like to develop a simple, minimally invasive operation that will not require cardiopulmonary bypass. Such a procedure should preserve normal atrial physiology, have minimal morbidity, and a success rate >90%. Achieving this goal will require significant progress in three major areas: (1) understanding the mechanism of AF in individual patients, (2) redesigning the surgical approach based on these mechanisms and a better understanding of the effect of surgical ablation on atrial electrophysiology, and (3) a better definition of the effect of surgical ablation on atrial hemodynamics and function.

It is now known that multiple different possible mechanisms of AF exist and that multiple-point mapping is necessary to describe this complex arrhythmia.[80-82,97,98] Epicardial activation sequence mapping has been the traditional gold standard for mapping of AF, but it is invasive and time consuming, which limits its clinical use.[17] A newer noninvasive technique, electrocardiographic imaging (ECGI), offers a potentially useful way to describe the atrial activation sequence and determine mechanistic information from conscious patients.[99] The technique uses body surface potentials, measured by surface electrodes, and anatomic data obtained through computed tomography (CT) scanning to indirectly calculate the surface potentials on the surface of the heart. This technique has been shown to work well for normal sinus rhythm and atrial flutter as well as for ventricular arrhythmias.[100-102] Currently, the authors' group is testing the technique in patients with persistent AF, in collaboration with Dr. Yoram Rudy, the developer of ECGI, at Washington University. The initial results are promising.[100,103]

The information acquired from ECGI can be analyzed to determine the activation sequence and frequency maps for individual patients noninvasively. Using these data, a strategy for designing patient-specific optimal lesion sets is being developed, taking into account the patient's atrial geometry, conduction velocity, and refractory period.[104] Initial lesions will be determined by a calculation of the critical area needed to maintain AF in the individual patient by using mechanistic information derived from activation data and anatomic data from the CT scan. It will also allow identification of focal sources that can then be isolated or ablated in the electrophysiological laboratory or operating room.

In instances where a specific mechanism of AF cannot be defined, the goal will be to create a lesion pattern that will prevent the atria from fibrillating. In this sense, the Cox-Maze III and IV procedures have failed to achieve this goal, with higher failure rates seen in patients with increasing left atrial size or longstanding AF.[31,105,106] A recent study performed by the authors' laboratory on a canine model found that the probability of maintaining AF is correlated with increasing atrial tissue areas, widths, and weights, as well as the length of the effective refractory period and

the conduction velocity of the tissue.[104] All of these data can be acquired noninvasively through ECGI. Using these data may allow surgeons to design operations customized for each patient on the basis of the mechanism of their arrhythmias and their specific atrial anatomy or electrophysiology.

Finally, the limitations of the current ablation devices have impeded the development of a truly minimally invasive procedure. Unfortunately, the creation of reliable transmural lines of ablation on the beating heart has been difficult. The probable reason is the heat sink of the circulating endocardial blood pool.[46] Future advances may offer devices that overcome this limitation or introduce hybrid procedures in which surgeons and electrophysiologists work together to complete the lines of block.

In conclusion, the development of ablation technologies has dramatically changed the field of AF surgery. The replacement of the surgical incisions with linear lines of ablation has transformed a complex, technically demanding procedure into one accessible to the majority of surgeons. More importantly, these new ablation technologies have introduced the possibility of minimally invasive surgery for AF, which has prompted numerous efforts to develop simpler procedures that can be performed epicardially on the beating heart. Strong evidence that PVI may be effective in a subset of patients with paroxysmal AF is already available. With extended lesion sets, it may be possible to extend the efficacy of minimally invasive procedures to patients with persistent and longstanding AF. However, surgeons must remember that the Cox-Maze procedure is efficacious in these patients and can be performed using a small thoracotomy with acceptable success and low morbidity.[32] Surgeons need to be careful in employing experimental procedures without informed consent from patients. It is also imperative that surgeons who are trying new procedures carefully follow their results and publish them in peer-reviewed journals. Surgeons performing AF ablation must adhere to the recently published guidelines for follow-up of patients and for determining success or failure after these procedures. As we learn more about the mechanisms of AF and develop improved preoperative diagnostic technologies capable of precisely locating the areas responsible for AF, it will become possible to tailor specific lesion sets and ablation modalities to individual patients, making the surgical treatment of AF more effective and available to a larger population of patients.

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CHAPTER 99

Interventional Device Therapy in Atrial Fibrillation

Heyder Omran

Thromboembolism is the most feared complication in patients with permanent atrial fibrillation (AF).[1] The risk of embolism may vary from less than 1% to 20%, depending on the underlying disease. Obviously, patients with previous strokes have the highest risk of embolism. Trans-esophageal echocardiographic (TEE) studies show that most thrombi are located in the left atrial appendage (LAA) and that only a few thrombi originate in the left atrium itself.[2,3] Although prospective and randomized studies show that oral anticoagulation (OAC) reduces the risk of thromboembolism significantly, patients often may not receive OAC because of bleeding complications, increased bleeding risk, allergies to warfarin derivates, or fear of complications.[4,5] Occluding the LAA is another way to reduce the risk of thromboembolism. Hence, the LAA is often occluded or removed in patients undergoing cardiac surgery with concomitant AF. Surgical obliteration of the LAA in patients with a high risk for thromboembolism is a well-established procedure to eliminate this predilection site for the development of thrombi.[6-8]

In 2001, an alternative procedure was introduced for patients with contraindications for OAC, that is, the interventional occlusion of the LAA.[9-11] This chapter provides information on the indication, technique, safety, results, imaging, and potential future applications of percutaneous LAA occlusion.

Indication

Oral anticoagulation is contraindicated for at least an estimated 30% of patients with AF. Furthermore, it has been shown that contraindications for OAC are particularly common in older patients.[5] Interventional occlusion of the LAA is suggested for patients with a high risk of embolism and a contraindication for OAC. Often the so-called *CHADS2 score* is used for defining the risk of embolism.

In addition to assessing the patient's individual thromboembolic risk, the following factors need to be addressed:

- Life expectancy of the patient
- Procedural risk
- Technical considerations, that is, access to the LAA and anatomy of the appendage
- Morphological features

Hence, any decision for an interventional occlusion of the LAA has to be an individualized one: It has to balance the advantages and possible disadvantages of the therapy.

Recently, the U.S. Food and Drug Administration advisory panel recommended the approval of the Watchman LAA closure device, stating that it is comparable to long-term warfarin therapy for the prevention of stroke in warfarin-eligible patients with nonvalvular AF.

Devices and Implantation Techniques

The first device for the interventional occlusion of the LAA was introduced by Lesh and co-workers (animal studies).[9] The device was called *PLAATO* (percutaneous left atrial appendage transcatheter occlusion). It consists of a self-expanding, balloon-shaped nitinol cage with an expanded polytetrafluoroethylene (ePTFE) membrane with three rows of anchors stabilizing the device in the appendage (Figure 99-1). The membrane covers the atrial surface of the device, whereas the opposite surface is not covered, which allows secondary thrombosis of the lumen by the device. The morphology of the LAA is evaluated by angiography and simultaneous TEE. The maximal diameter of the LAA orifice is determined by both methods and a mean diameter obtained. A 20% to 30% oversized occlusion device is selected. The device is introduced via a 14-F femoral vein sheath and advanced to the LAA after trans-septal puncture of the atrial septum. Then, the device is expanded and the position is controlled using both angiography and TEE (Figure 99-2). The mean size of the devices used is 29 mm. After verifying the optimal position and adequate sizing of the device, it is released and the final position assessed by repeat angiography.

A similar device, called *Watchman device*, was introduced by Atritech (Plymouth, MN) (Figure 99-3).[12] It is similar to the PLAATO device and consists of a self-expanding nickel-titanium frame structure with external fixation barbs and a permeable polyester fabric cover (sizes ranging from 21 to 33 mm). The procedure of implanting the device is similar to that of the implantation of the PLAATO device.

Meier and coworkers published a study on the successful occlusion of the LAA using an Amplatzer device, which was not designed uniquely for this purpose.[13] In December 2008, AGA Medical (Plymouth, MN) received the European Conformite Europeene mark of approval for an LAA occlusion device that is different from the previously described ones. It is called a *cardiac*

FIGURE 99-1 First left atrial appendage occlusion device (PLAATO, ev3). It consists of a self-expanding, balloon-shaped nitinol cage with an expanded ePTFE membrane with three rows of anchors.

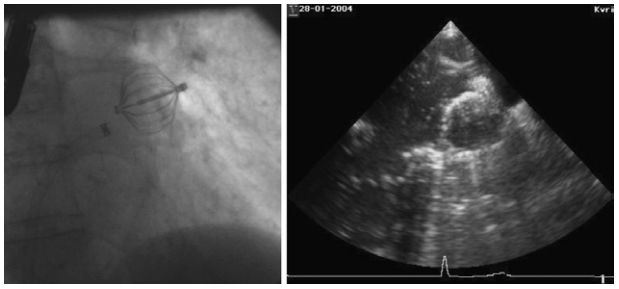

FIGURE 99-2 Left atrial appendage occlusion device as imaged by fluoroscopy and echocardiography.

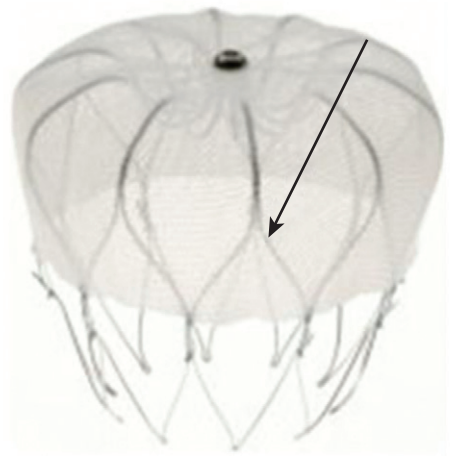

FIGURE 99-3 Watchman device (Atritech) with a self-expanding nitinol frame structure with external fixation barbs.

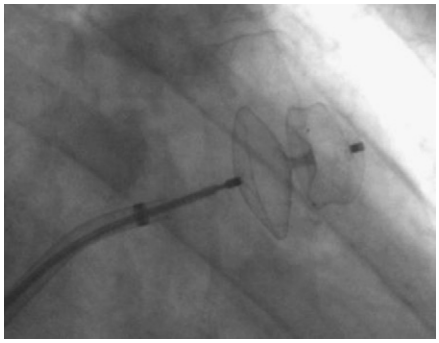

FIGURE 99-4 Cardiac plug left atrial appendage occlusion device (Atritech). It consists of a distal lobe and a disc.

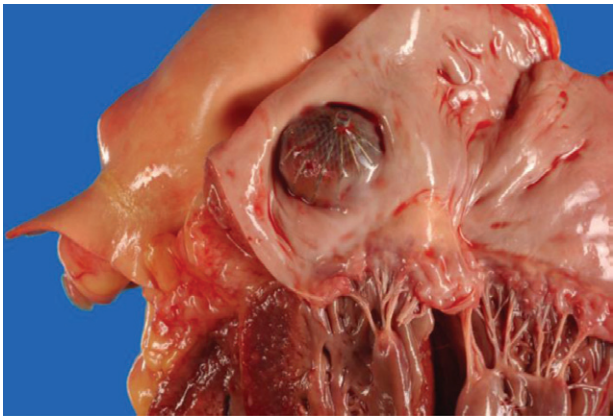

FIGURE 99-5 Postmortem image of PLAATO device in the left atrial appendage.

plug and is designed to achieve optimal occlusion of the LAA; it consists of a distal lobe and disc that is designed to cover the orifice of the LAA (Figure 99-4). The diameter of the lobe ranges from 16 to 30 mm, and the corresponding disc diameter ranges from 20 to 36 mm.

Safety and Results

In various studies, data about the safety and success of LAA occlusion were collected for both the PLAATO device (Figure 99-5) and the Watchman device.[12,14]

The researchers evaluating the PLAATO device showed that the procedure is feasible and may be performed within 2 hours.[13] Detailed results concerning 111 patients with attempted LAA occlusion were published in 2005.[13] The procedure was successful in 97% of the patients. Migration of the device or formation of mobile thrombi on the surface of the device were not observed during follow-up 10 months later. One of the patients in the study group died because of procedural complications. Pericardiocentesis was performed in three patients for cardiac tamponade. In addition, one patient developed left-sided hemothorax. Hence, relevant procedural complications were not uncommon. However,

they occurred less frequently with increasing experience of the operator.

Two patients had a stroke, and two patients experienced transient ischemic attacks during the observation period. No thrombi formed on the device in any of the patients. Another study followed up the patients closely via echocardiography and showed that the implant was covered with a neointima after 6 months and that the device did not alter pulmonary vein flow.[11] Furthermore, no significant atrial septal defects were detected after the puncture of the intra-atrial septum with an F-14 sheath.[15] Because of the high rate of complications, a randomized study comparing anticoagulation and device therapy was requested. Such a study has not been performed yet, and the company has halted distribution of the device. Long-term follow-up data have not systematically been published yet.[16-18]

Similar experiences were reported for the Watchman device from Atritech. Sick et al provided information on 75 patients who had the device implanted.[12] A failure rate of 10% was reported for implantation of the device. Two patients experienced device embolization. The devices were successfully retrieved percutaneously in both cases. Two cardiac tamponades and one air embolism were reported as well. One device had a wire fracture and needed to be explanted surgically. In four patients, flat thrombi had formed on the atrial surface of the device by the time of the 6-month echocardiographic follow-up. Two neurologic complications occurred during the follow-up period. To assess how effectively strokes and bleeding events are reduced in patients with AF by occluding the LAA with the Watchman device, the prospective Embolic Protection in Patients with Atrial Fibrillation (PROTECT-AF) study was performed in patients with nonvalvular AF and a CHADS2 score greater than 1.[19] It is a key study for evaluating the concept of LAA occlusion for the prevention of thromboembolism in patients with AF, and hence the study will be discussed in detail in this chapter.

The trial included patients aged 18 years or older with all types of nonvalvular AF and at least one risk factor on the CHADS2 risk score. Patients were excluded if they had contraindications for warfarin or had comorbidities requiring the use of long-term OAC. In addition, all patients with an LAA thrombus, a patent foramen ovale with atrial septal aneurysm and right to left shunt, mobile atheroma, and symptomatic carotid artery disease were excluded from the study. Patients were randomized to either interventional occlusion of the LAA or warfarin therapy in a 2:1 ratio. After implantation of the Watchman device, patients were treated for 45 days with warfarin. Thereafter, clopidogrel (75 mg) and aspirin (81 to 325 mg) once daily were prescribed for the remaining period up to the 6-month follow-up visit. Then clopidogrel was discontinued. The primary endpoint of the study was to show non-inferiority of the device compared with warfarin therapy by use of a composite endpoint consisting of efficacy (ischemic and hemorrhagic stroke), cardiovascular or unexplained death, or systemic embolism. The safety endpoint consisted of excessive bleeding events and procedure-related complications. Patients were followed up for an aggregate of 1065 patient-years. Successful implantation was performed in 88% of patients scheduled for intervention. An international normalized ratio range of 2 to 3 was achieved in 66% of patients in the medical treatment group. The primary efficacy event rate was 3 per 100 patient years in the intervention group and 4.9 in the control group. The probability of non-inferiority of the intervention was 99.9%. Hemorrhagic strokes occurred in 0.1% in the intervention group and in 1.6% in the control group.

Primary safety endpoints occurred at a significantly higher rate in the intervention group than in the control group (7.4 vs. 4.4) and were associated mainly with procedural complications, that is, 22 patients had serious pericardial effusions. Device embolization was observed in three patients. The rate of serious pericardial effusion declined with increasing experience of the operator.

In summary, the results of the PROTECT-AF trial demonstrated the non-inferiority of LAA occlusion compared with warfarin therapy for the primary efficacy endpoint. However, a higher initial safety event rate is observed for device implantation.

Other studies on LAA occlusion included far fewer patients. Meier et al provided information on the use of the Amplatzer device for occluding the LAA in 16 patients.[13] One patient had an embolization of the device. All other patients had no serious complications.

Other devices are currently being assessed in animal models. Fumoto et al reported on the successful implantation of a third-generation atrial exclusion device in 14 dogs.[20] Jayakar et al investigated a tissue welding technology to obliterate the LAA.[21]

Importantly, long-term data or data from randomized prospective trials are not available yet.

Imaging

Imaging of the left atrium and the LAA is very important for planning and performing LAA occlusion. In addition, potential thrombi in the LAA need to be excluded. The anatomies of the left atrium and the LAA are complex and varies considerably as shown by anatomic studies.[22,23] The LAA orifice is usually oval in shape and averages 17.4 mm.[23] Adjacent structures are the left upper PV (11 mm) and the mitral valve (10.7 mm). Histologic examination of the LAA shows that the wall is very thin in places, which explains the high risk of perforation during the procedure. Hence, visual guidance of the procedure is of extreme importance.

Multiple-plane TEE has been shown to exclude left atrial thrombi very accurately and should be performed in all patients considered for LAA occlusion.[24-27] Both TEE and intracardiac echocardiography may be used to guide the procedure for the following purposes[28,29]:

- Guidance of trans-septal puncture
- Visualization of the delivery sheath position
- Analysis of the position of the device
- Monitoring to identify potential complications

Furthermore, imaging is very important for the follow-up of patients. All patients should be assessed for thrombus formation on the device prior to discontinuation of the anticoagulants.

Computed tomography (CT) has been used for analyzing the size and morphology of the LAA. However, measurements vary considerably between TEE and CT.[30] Hence, further studies are needed to determine whether CT may be used alternatively for device sizing prior to the procedure.

SUMMARY

Multiple reports have shown that LAA occlusion is technically feasible. However, a considerable risk in employing the procedure still exists.[31] Potentially, increased operator experience, better

patient selection, and improvement of technology will lead to a decrease in the complication rate. Hence, patient selection for the procedure is very important. Importantly, the randomized PROTECT-AF study demonstrated the non-inferiority of LAA occlusion with the Watchman device in preventing stroke compared with treatment with warfarin. Nevertheless, ideal candidates for LAA occlusion have contraindications for long-term OAC, or these patients may refuse to take OAC. In any case, the risk and benefits have to be carefully weighted.

Modern anticoagulants are currently being developed and tested clinically. These medications may have fewer side effects and a lower bleeding rate than do the current oral anticoagulants, as recently shown in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RELY) study.[32] Therefore, clinicians will have to observe these developments carefully and decide accordingly.

In conclusion, LAA occlusion devices are an important alternative to OAC in patients with AF.

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