Clinical Cardiac Electrophysiology in the Young

Second Edition

Macdonald Dick, II
Editor

Springer

Clinical Cardiac Electrophysiology in the Young

Macdonald Dick, II
Editor

Clinical Cardiac Electrophysiology in the Young

Second Edition

Springer

Editor
Macdonald Dick, II, MD
Pediatric Cardiology
The University of Michigan Congenital Heart Center
Department of Pediatrics and Communicable Diseases
University of Michigan
Ann Arbor, MI, USA

ISBN 978-1-4939-2738-8 ISBN 978-1-4939-2739-5 (eBook)
DOI 10.1007/978-1-4939-2739-5

Library of Congress Control Number: 2015945964

Springer New York Heidelberg Dordrecht London

Printed on acid-free paper

Springer Science+Business Media LLC New York is part of Springer Science+Business Media (www.springer.com)

Foreword to the First Edition

The text of *Clinical Cardiac Electrophysiology in the Young* provides a systematic approach to the anatomy, pathophysiology, basic electrophysiology, diagnosis, and therapy of atrial and ventricular arrhythmias as well as conduction abnormalities in the young. It elucidates the broad spectrum of rhythm disturbances that may occur from the fetus to young adult, as an isolated abnormality, in the presence of underlying congenital heart disease, both prior to and subsequent to surgical repair. The clinical manifestations, diagnosis, and appropriate pharmacologic and interventional therapy by a trained healthcare team are fully discussed. Science is consistently used to explain the electrophysiologic diagnoses, pharmacologic, interventional, and surgical treatment. Some prior knowledge and understanding of electrophysiology and rhythm disturbances is helpful and the information provided here may be utilized as a guidebook, resource, and reference for residents, cardiology fellows, trained cardiologists, and electrophysiologists as well as other allied health professionals. The rapid advances in the field in such areas as interventional and surgical cryoablation techniques, complexity of rhythm disturbances, new monitoring devices, and pharmaceuticals make it an invaluable text.

Dr. Macdonald Dick as an author and editor of the book is an internationally recognized scholar and clinical pediatric electrophysiologist. A superb teacher and role model for trainees and faculty, his affability and diligent effort have brought about the compilation and publication of the book. The majority of the knowledgeable and experienced contributors have received their training in pediatric cardiology at the University of Michigan. The authors are indebted to their medical and surgical colleagues, fellows, family members, and respective institutions for the support and encouragement in the endeavor.

University of Michigan Medical School
Ann Arbor, MI, USA

Amnon Rosenthal, MD

Preface to the First Edition

It takes a certain hubris to come forth with a book entitled *Clinical Cardiac Electrophysiology in the Young*. There are a number of excellent texts, monographs, and reviews on cardiac arrhythmias in both adults and children—Josephson's and also Zipes and Jalife's comprehensive texts come to mind, as well as a number of others, including Deal, Wolff, and Gelband's, the several volumes from Gillette, and the recent text from Walsh, Saul, and Triedman, the latter three texts focusing on children.

Nonetheless, the past three decades have witnessed enormous advances in the understanding and management of human cardiac arrhythmias. This development represents the fruits of both basic and clinical investigations in cardiac impulse formation and propagation at the organ, tissue, and more recently, cellular and molecular levels. This information explosion may result in information overload and frustrate the student, the young physician in training, as well as the seasoned practitioner. This book focuses on the practical (and theoretical when applicable) aspects of clinical electrophysiology of cardiac arrhythmias in the young. Our intention is that the young house officer or mature physician who is faced with a child with a cardiac arrhythmia will find this book useful in increasing their understanding, sparking their interest, and perhaps leading them to a therapeutic solution.

This book emerges from the clinical practice and research of the pediatric cardiac electrophysiology group in the Division of Pediatric Cardiology at the C.S. Mott Children's Hospital, the University of Michigan in Ann Arbor, and the former pediatric electrophysiology fellows from Michigan, now established electrophysiologists in their own right. It represents a compilation of the clinical course, electrocardiograms, electrophysiologic studies, pharmacological management, and transcatheter ablation therapy in patients from infancy through young adulthood seen in Ann Arbor and at the current clinical sites of the former Michigan fellows. Thus, while the product may be idiosyncratic, it is not provincial. We are interested in "how it is done" but not to the exclusion of other approaches. This is only one (or several) way to address the clinical problem of arrhythmias in children, and surely not the only way, especially as one views the future of emerging energy sources for ablation, nonionizing radiation imaging techniques, and molecular diagnostic possibilities.

The book is divided into two parts. The first part, Background (Chapters 1–3), discusses the cardiac conduction system—development, anatomy, and physiology. Particular attention is directed to the clinical electrophysiology of the

cardiac conduction system and the techniques of electrophysiologic study that are specific to children and that have been developed and practiced at the University of Michigan and at other centers. The second part, Cardiac Electrophysiology in Infants and Children (Chapters 4–23), focuses on the clinical science of cardiac arrhythmias in infants and children.

Chapters 4–12 discuss the mechanism, the ECG characteristics, the electrophysiologic findings, the treatment, and the prognosis of tachyarrhythmias. Chapters 13–16 focus on bradyarrhythmias. Chapters 17–20 address certain specialized subjects including syncope, cardiac pacemakers, implantable cardiac defibrillators, genetic disorders of the cardiac impulse, fetal arrhythmias, and sudden cardiac death as it occurs in the young. Chapters 21–22 center on the pharmacology of antiarrhythmic agents, indications for use, doses, side effects, and toxicity, as well as on transcatheter arrhythmia ablation. Finally, what the practitioner can expect to see from the impact of cardiac arrhythmias on the life of the patient and family is discussed from the nursing point of view in Chapter 23.

The intent of the book is practical and thus the suggested readings are selected and not encyclopedic. They are meant as a starting place for the interested reader. Examples and tables are included in the anticipation that the reader will rapidly be able to match the clinical problem to the examples and the accompanying text.

A text or technical book is rarely the product of a single individual. With that in mind, any value or sense that can be made of this work is solely due to the terrific efforts of the authors; any error or fault can be correctly attributed to me. I am deeply grateful to all of the authors for their contributions, as well as their patience in bringing the project together. I want to recognize the generosity of my colleagues at Michigan in providing coverage when I would hide out (including a sabbatical) to work on the text. Thanks also to the medical electrophysiology group at Michigan for encouragement and support for the pediatric program. I also want to thank my local editor, Kathryn Clark, for all her efforts in keeping me on task, endlessly and repeatedly formatting the multiple revisions of the text, and finding and eliminating too many examples of “nonsense” to count. Finally, I want to thank Melissa Ramondetta at Springer for her great patience, great good humor, and sound advice throughout the course of the project. Carolin, my wife, graciously permitted me to weed the book of its unwanted wordage (probably missed a bit) rather than our yard of unwanted plant life on numerous weekends.

Ann Arbor, MI
August 2005

Macdonald Dick, II, MD

Preface to the Second Edition

A second edition of any text book calls for some justification. Of course, the short answer is that new technology and information have emerged, but no doubt a longer answer is required. First, a wider application of cryotherapy for arrhythmia in young patients has reduced the low but real risk of heart block (Chapter 23 and others). Second, navigation systems detecting electrode catheters within the heart and displaying their relative positions and shapes in real time in "virtual three dimensions" on a monitor screen have led to a marked reduction in radiation exposure to the young patient (Chapters 3, 23, and others). Third, classical embryogenesis has relinquished center stage to molecular biology exploring the role of a vast and sequential (and often dizzying) array of multiple genetic signals and protein products for successful cardiac development, including that of the structure and function of the cardiac conduction system (Chapters 1 and 2). Fourth, our understanding of inherited genetic mechanisms of arrhythmias has greatly enlarged. It is now clear that 10–15 % of SIDS victims have associated mutations in their cardiac ion channels, likely contributing to their demise. This rapid growth in our understanding of genetic mechanisms of disease not only has led to molecular diagnoses for inherited arrhythmias but also has unmasked the complexity of genetic mutation and phenotypic expression (Chapter 19). Fifth, best practice policies and consensus statements have given guidance to both referring physicians and electrophysiology cardiologists who take care of children with arrhythmias. Sixth, more information and discussion, if not yet firm policy, has emerged regarding sudden cardiac death in the young, particularly athletes. Conferences and symposia have been held, papers have been published, and the discussion has been thoughtful and vigorous. The role of cardiac devices and ECG screening in young patients is challenged by the infrequency of an abnormality posing risk, the low frequency of an event even in an genotype positive individual, the cost of detecting a low risk a priori and, finally, competing values (cost-effective analysis; individual versus the public interest). This discussion is importantly expanded in the chapter on sudden cardiac death in the young (Chapter 21). Finally, a new cohort of young electrophysiologists brings their energy, insight, questions, and research to the field. All of the authors are practicing clinical cardiac electrophysiologists. All, as in the first edition, are linked to the Michigan Congenital Heart Center at the University of Michigan, directly as faculty or former fellows; many have produced their own generation of independent cardiologists who have signed on as authors.

The intent of the book is to present the "thinking and style" of the authors when they manage young patients with arrhythmias. Thus, the "Suggested Reading" rather than cited references in the text. There is two exceptions—Chapters 1 and 19. Because of the complex nature of the material, the specific citations within the text are retained.

I am indebted to all of the authors for their contributions, and especially, to my wife, who graciously reviewed many of the manuscripts. I also want to thank Mr. Michal D. Sova, Springer Developmental Editor, for his generous patience in extending our deadline as needed. In addition, thanks go to Ms. Lana Emmons for securing permissions for copyrighted material, reviewing and organizing "Suggested Readings" lists, and preparing much of the manuscript. Any errors, as before, are mine.

Ann Arbor, MI
February 2015

Macdonald Dick II, MD

Contents

Contributors

Patricia L. Arscott, MS Pediatric Cardiology, The University of Michigan Congenital Heart Center, Department of Pediatrics and Communicable Diseases, University of Michigan, Ann Arbor, MI, USA

David J. Bradley, MD Pediatric Cardiology, The University of Michigan Congenital Heart Center, Department of Pediatrics and Communicable Diseases, University of Michigan, Ann Arbor, MI, USA

Burt I. Bromberg, MD Department of Pediatrics, Mercy Clinic, St. Louis, MO, USA

Craig J. Byrum, MD Pediatrics—Cardiology, Syracuse, NY, USA

Robert Campbell, MD Sibley Heart Center, Children's Healthcare of Atlanta, Department of Pediatrics, Emory University School of Medicine, Atlanta, GA, USA

Aarti Dalal, DO Sibley Heart Center, Children's Healthcare of Atlanta, Department of Pediatrics, Emory University School of Medicine, Atlanta, GA, USA

Srikant Das, MD Department of Pediatric Cardiology, Arkansas Children's Hospital, University of Arkansas for Medical Sciences, Little Rock, AR, USA

Brynn E. Dechert, MSN, CPNP Pediatric Cardiology, The University of Michigan Congenital Heart Center, Department of Pediatrics and Communicable Diseases, University of Michigan, Ann Arbor, MI, USA

Macdonald Dick II, MD Pediatric Cardiology, The University of Michigan Congenital Heart Center, Department of Pediatrics and Communicable Diseases, University of Michigan, Ann Arbor, MI, USA

Parvin Dorostkar, MD, MS, MBA Pediatric Cardiology, Department of Pediatrics, University of Minnesota, St. Paul, MN, USA

Carlen G. Fifer, MD Pediatric Cardiology, The University of Michigan Congenital Heart Center, Department of Pediatrics and Communicable Diseases, University of Michigan, Ann Arbor, MI, USA

Peter S. Fischbach, MD, MS Sibley Heart Center, Children's Healthcare of Atlanta, Department of Pediatrics, Emory University School of Medicine, Atlanta, GA, USA

Matthew Hazle, MD Pediatric Cardiology, Wake Forest Baptist Health, Wake Forest University, Winston Salem, NC, USA

Adam S. Helms, MD, MS Department of Internal Medicine, University of Michigan Health Systems, Ann Arbor, MI, USA

Anna Kamp, MD Pediatric Cardiology, Department of Pediatrics, Ohio State University, Columbus, OH, USA

Adam C. Kean, MD, MPH Section of Pediatric Cardiology, Indiana University School of Medicine, Indianapolis, IN, USA

Martin J. LaPage, MD, MS Pediatric Cardiology, The University of Michigan Congenital Heart Center, Department of Pediatrics and Communicable Diseases, University of Michigan, Ann Arbor, MI, USA

Ian H. Law, BSE, MD Division of Cardiology, Department of Pediatrics, University of Iowa Children's Hospital, University of Iowa Carver College of Medicine, Iowa City, IA, USA

Sarah S. LeRoy, RN, MSN, DNP Department of Nursing, Wayne State University College of Nursing, Detroit, MI, USA

Andrew Papez, MD Pediatric Cardiology, Arizona Pediatric Cardiology/ Phoenix Children's Hospital, Phoenix, AZ, USA

Mark W. Russell, MD Pediatric Cardiology, The University of Michigan Congenital Heart Center, Department of Pediatrics and Communicable Diseases, University of Michigan, Ann Arbor, MI, USA

Elizabeth Vickers Saarel, MD Department of Pediatrics, University of Utah, Salt Lake City, UT, USA

William A. Scott, MD Department of Pediatrics, UT Southwestern Medical Center, Dallas, TX, USA

Gerald A. Serwer, MD Pediatric Cardiology, The University of Michigan Congenital Heart Center, Department of Pediatrics and Communicable Diseases, University of Michigan, Ann Arbor, MI, USA

Ira Shetty, MD Pediatric Cardiology, Advocate Children's Hospital, Oak Lawn, IL, USA

Christopher B. Stefanelli, MD Department of Pediatric Cardiology, Hawaii Permanente Medical Group, Honolulu, HI, USA

Margaret J. Strieper, DO Sibley Heart Center, Children's Healthcare of Atlanta, Department of Pediatrics, Emory University School of Medicine, Atlanta, GA, USA

Vincent C. Thomas, MD, MHA Department of Pediatrics, University of Nevada School of Medicine, Las Vegas, NV, USA

Johannes C. von Alvensleben, MD Pediatric Cardiology, The University of Michigan Congenital Heart Center, Department of Pediatrics and Communicable Diseases, University of Michigan, Ann Arbor, MI, USA

Nicholas Von Bergen, MD Department of Pediatrics, University of Wisconsin—Madison, Madison, WI, USA

Stephanie Wechsler, MD Department of Pediatric Cardiology, DUMC, Durham, NC, USA

Part I

Background

Development and Structure of the Cardiac Conduction System

1

Parvin Dorostkar and Mark W. Russell

A major function of the heart is to propel blood, by mechanical contraction of the cardiac muscle, through the vascular (arterial and venous) system. To achieve this task, the underlying electrical conduction system generates an electrical impulse that sequentially propagates from the sinus node through the atria, the atrioventricular node, and His-Purkinje system to the ventricles. This process initiates electromechanical engagement or coupling, producing myocardial contraction.

This chapter will review the embryology and development of the conduction system, outlining known transcriptional regulators and signaling pathways that support formation and differentiation of the specialized cells the conduction system and will discuss how disorders of development lead to abnormalities of conduction and to clinical arrhythmias. In addition, the chapter will review the anatomy of the heart with focus on the structures that support the electrophysiologic properties of the conduction system as well as describe the conduction system abnormalities associated with specific congenital cardiac defects.

Part I—Development of the Conduction System

It is not a surprise that the cardiac conduction system develops in concert with the structural maturation of the heart itself (Fig. 1.1). The heart forms early in embryogenesis as cardiac cells originate in the epiblast, which is lateral to the primitive streak. From here, cardiac cells migrate in a rostrolateral direction to bilateral areas of a lateral plate mesoderm. The lateral mesoderm separates into somatic and splanchnic epithelial layers. The bilateral splanchnic mesoderm will generate cardiac precursor cells and is referred to as the primary heart field. It is a subset of these cells that migrate towards the midline and fuse to form the primary myocardial heart tube. The heart tube is lined by an outer layer of cardiac jelly which is in turn surrounded by differentiating mesoderm from the primary heart tube which will form the myocardium. During further development of the heart tube, additional cells from the splanchnic mesoderm, from the caudal portion of the secondary heart field, will continue to contribute to the dorsal (venous) pole of the heart. Progenitor cells in the pharyngeal mesoderm and the remainder of the secondary heart

P. Dorostkar, M.D., M.S., M.B.A. (✉)
Pediatric Cardiology, Department of Pediatrics, University of Minnesota, 225 North Smith Ave., Suite 504, Saint Paul, MN 55102, USA
e-mail: pcd@umn.edu

M.W. Russell, M.D.
Pediatric Cardiology, The University of Michigan Congenital Heart Center, Department of Pediatrics and Communicable Diseases, University of Michigan, Ann Arbor, MI, USA

M. Dick, II (ed.), *Clinical Cardiac Electrophysiology in the Young*,
DOI 10.1007/978-1-4939-2739-5_1

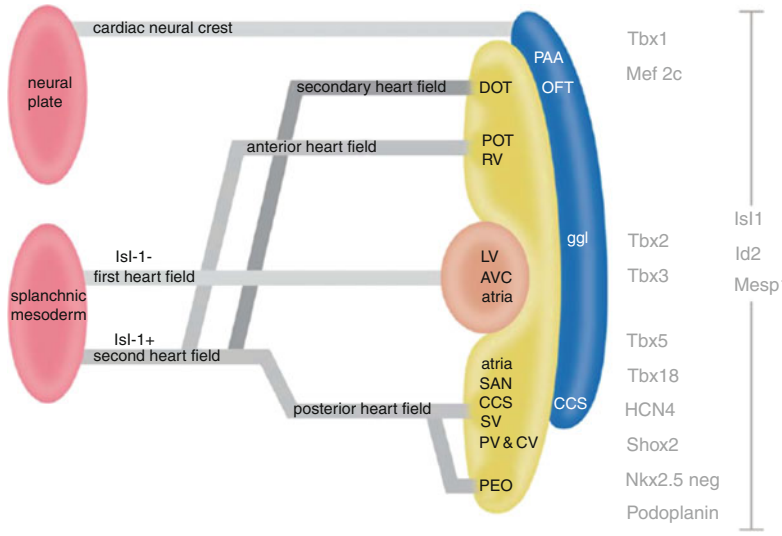


Fig. 1.1 Schematic representation of the primary heart tube (*brown*) and the secondary added myocardium derived from the second heart field (*yellow*), including differential genes and proteins expressed in the second heart field. The second heart field can be divided into an anterior heart field and a secondary heart field at the anterior pole of the heart, and a posterior heart field at the venous pole of the heart. At the venous pole of the heart, the proepicardial organ (PEO) is also derived from the posterior heart field, and is the source of the epicardium and epicardium-derived cells. Neural crest cells (depicted in *dark blue*) migrate to the heart and enter the heart at both the arterial and venous pole. *AVC* atrioventricular canal, *CV* cardinal veins, *CCS* central conduction system, *DOT* distal outflow tract, *LV* left ventricle, *OFT* outflow tract, *PAA* pharyngeal arch arteries, *POT* proximal outflow tract, *PV* pulmonary veins, *RV* right ventricle, *SAN* sinoatrial node, *SV* sinus venosus

field contribute to the arterial pole (outflow tract) and right ventricle of the heart tube (Fig. 1.2). The heart tube is associated with the embryonic dorsal mesocardium, which is thought to be disrupted during looping, only leaving contact at the arterial and venous poles. After looping, the heart tube consists of several segments: the left and right horn of the sinus venosus, the primitive atrium, the ventricular inlet segment, and the ventricular outlet segment [1].

Chamber differentiation occurs during further rightward looping of the heart tube, which results in positioning of the ventricles and the outflow tract of the heart in an anterior/ventral position, and of the atria in a dorsal/posterior position (Fig. 1.3). Transcriptional regulators (Nkx2-5, Tbx1, Tbx2, Tbx3, Tbx5, GATA4, Irx3 along with many others) and signaling pathways (including Notch, WNT, Bone Morphogenetic Protein [BMP], and Retinoic Acid) control chamber differentiation and formation of septal structures, the valves, and the great arteries [2, 3]. Electrical activity occurs early during development of the heart in conjunction with further differentiation of the simple heart tube into a four-chambered structure [4].

There has been much controversy with regard to the origin of the specialized myocardial tissue that leads to the development and expression of the conduction system. Current understanding suggests that cardiac myocytes, rather than neural crest cells, for example, are the progenitors of specialized conduction tissue. These findings were primarily supported by retroviral reporter gene transfection lineage studies [5–9]. The exact factors dictating this differentiation and development, however, remain to be elucidated, but it appears that neuregulin plays a crucial role in this differentiation process [10–16].

In a brief review in 1976, Wenink and colleagues proposed that there were four rings of specialized tissue in the embryo that could be

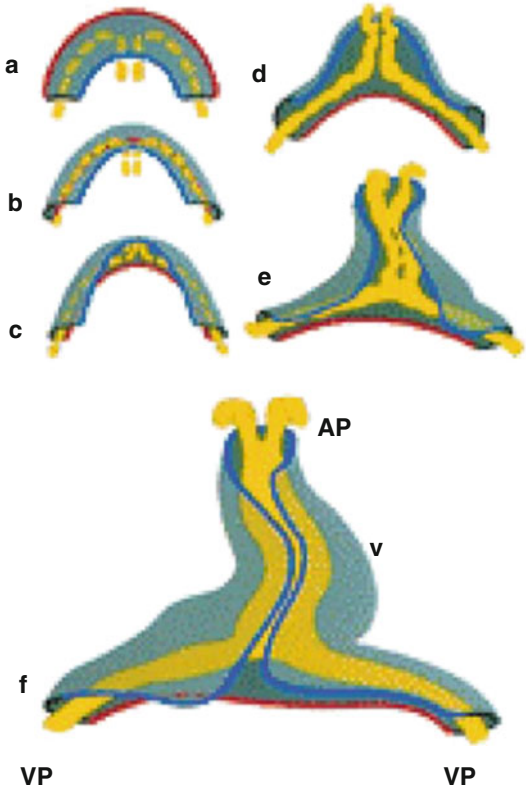


Fig. 1.2 Transformation of the flat cardiogenic crescent into a cardiac tube is displayed. During this process, the red outer contour of the myocardial crescent (*gray*) folds around the fusing endocardial vesicles (*yellow*) and passes the blue inner contour of the crescent, thereby forming the cardiac tube. *AP* anterior pole, *VP* venous pole, *V* future ventricle [Adapted from AFN Moorman et al., Development of the cardiac conduction system. Circulation Research 1998; 82:629–644. With permission from Wolters Kluwer Health]

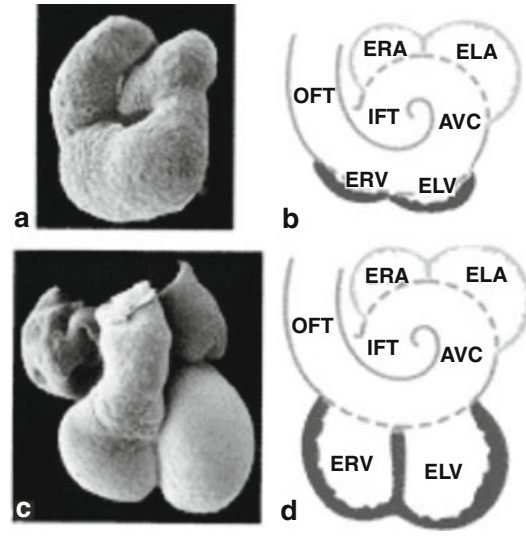


Fig. 1.3 Scanning electron photomicrographs (**a** and **c**) and schematic representations (**b** and **d**) of a 3-day embryonic chicken heart, where the first signs of the ventricles emerge (**a** and **b**), and of a 37-day embryonic human heart with clearly developed ventricles (**c** and **d**). *ERA* embryonic right atrium, *ELA* embryonic left atrium, *ELV* embryonic left ventricle, *ERV* embryonic right ventricle. The atrial segment is indicated in *blue*; the ventricular segment, in *red*; and the primary heart tube, encompassing the flanking segments, IFT, AVC, and OFT, as well as the atrial and ventricular parts, in purple [Adapted from AFN Moorman et al., Development of the cardiac conduction system. Circulation Research 1998; 82:629–644. With permission from Wolters Kluwer Health]

distinguished from the surrounding myocardium once looping of the heart had occurred [17]. These four rings (Fig. 1.4) were thought to mark transitional zones of the heart and included: the sinoatrial ring, between the sinus venosus segment and the primitive atrium; the atrioventricular ring, between the primitive atrium and primitive left ventricle; the primary ring or fold, that separates the primitive left ventricle from the primitive right ventricle; and the ventriculoarterial ring, at the junction of the primitive right ventricle and the truncus or putative outflow tract of the heart [1] (Fig. 1.3). It is thought that during completion of looping of the primitive heart tube, these four rings come together in the inner curvature of the heart and with further differentiation; part of this tissue loses its specialized character. What remain of the rings become the definitive elements of the mature conduction system. According to this theory, the sinoatrial ring contributes to the formation of the sinoatrial node; both the sinoatrial ring and the atrioventricular ring contribute to the atrioventricular node. The primary ring gives rise to the His bundle and bundle branches while the ventriculoarterial ring regresses almost entirely.

Studies in the 1990s used the expression pattern of a neurofilament-like protein as a marker for the developing conduction system. The presence of neurofilament-like protein was used to demonstrate a ring at the sinoatrial and atrioventricular junctions, and in ventricular components of the developing conduction system, which were

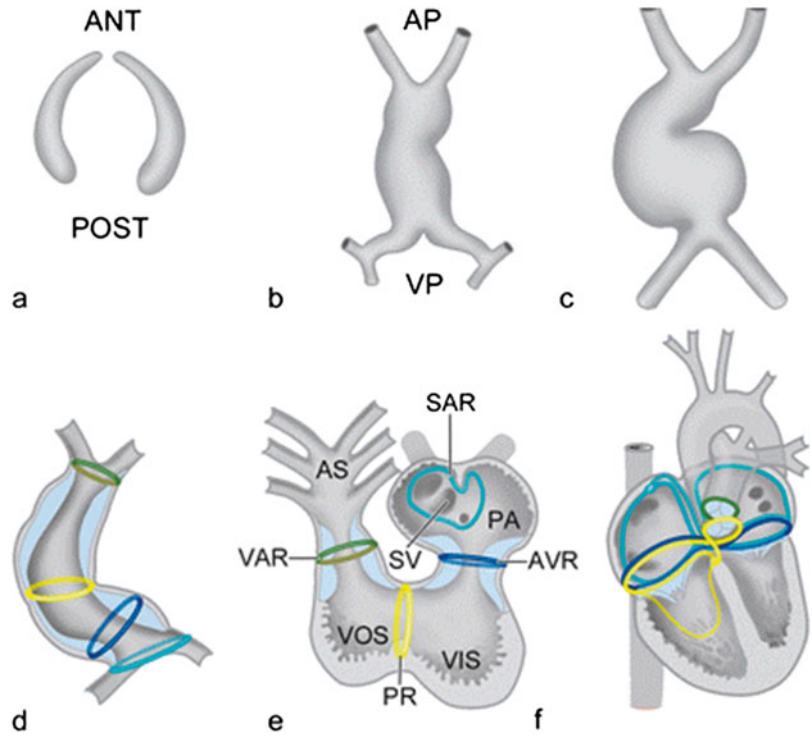


Fig. 1.4 Schematic representation of the bilateral formation of the cardiogenic plates, which are derived from the splanchnic mesoderm (**a**). The bilateral plates fuse and form an initially straight heart tube (**b**) that starts looping to the right (**c**, **d**). After looping, the so-called transitional zones or rings can be recognized in the heart that are positioned in between the putative cardiac chambers, i.e., the sinoatrial transition (SAR), the atrioventricular transition (AVR), the primary ring (PR), and the ventriculoarterial transition (VAR) (**e**). Position of these rings during further cardiac development (**f**). *Ant* anterior, *AP* arterial pole, *AS* aortic sac, *PA* primitive atrium, *post* posterior, *SV* sinus venosus, *VIS* ventricular inlet segment, *VOS* ventricular outlet segment, *VP* venous pole. **a–c** [Adapted from Gittenberger-de Groot AC, Bartelings MM, Deruiter MC, Poelmann RE. Basics of cardiac development for the understanding of congenital heart malformations. Pediatric Research 2005;57:169–176. With permission from Nature Publishing Group]

distributed in the ventricular subendocardium and connected to the atrioventricular ring [18–22]. In contrast to the theory that local cells undergo specialized differentiation, other studies suggest that conduction tissue cells (of the rabbit heart, for example) may originate from a population of neural crest-derived cells migrating from the branchial arches into the developing heart [20].

As these conflicting theories continued to be investigated, several immunohistochemical and molecular markers for cardiac conduction system development were used to support the hypothesis that conduction system cells differentiate from local cells. Even though none of the immunohistochemical markers are truly specific for labeling specialized conduction system cells, supportive evidence seemed to favor the "four ring theory." Using a monoclonal antibody to HNK1 antigen, for example, investigators demonstrated findings consistent with the notion that rings of conduction system tissue exist and undergo further differentiation (Fig. 1.5). HNK1 is predominantly expressed in the developing sinoatrial and atrioventricular junction of the conduction system, and the expression pattern seems to correspond with the rings described early on by Wenink. In human embryos, antibodies to HNK1 antigen stains the sinoatrial node, the internodal myocardium in the right atrium, the right atrioventricular ring with a future posterior and

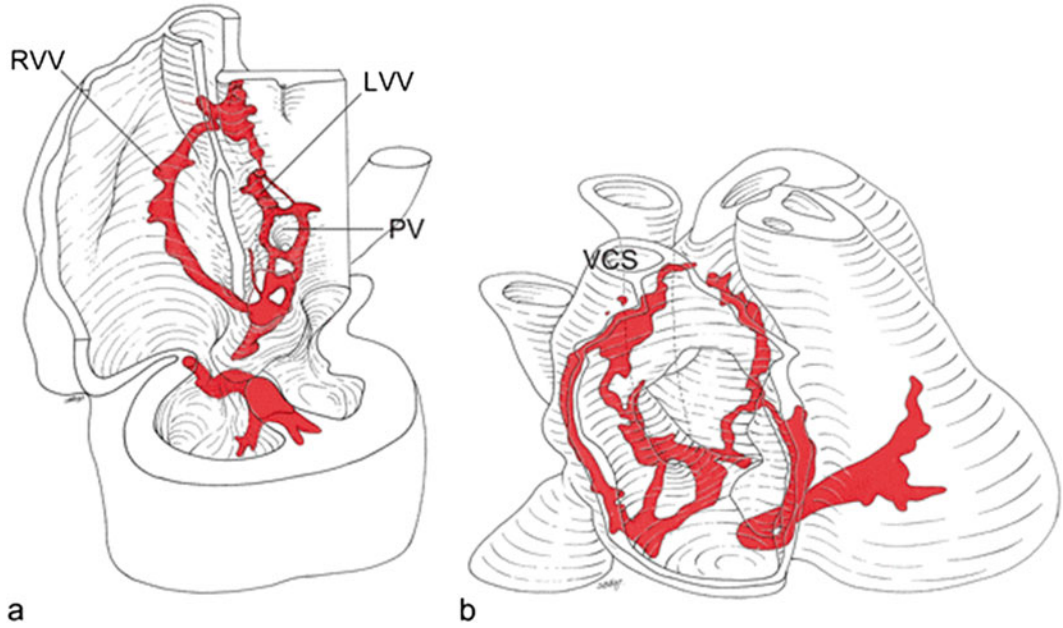


Fig. 1.5 HNK1 stains the sinoatrial node, the internodal myocardium in the right atrium, the right atrioventricular ring with the posterior and anterior atrioventricular nodes, a retroaortic ring, the His bundle, and the bundle branches in human embryos. Furthermore, the myocardium surrounding the primitive pulmonary vein demonstrates transient staining. *RVV* right venous valve, *LVV* left venous valve, *PV* pulmonary veins, *VCS* superior vena cava [Adapted from Blom NA, Gittenberger-de Groot AC, DeRuiter MC, Poelmann RE, Mentink MMT, Ottenkamp J. Development of the cardiac conduction tissue in human embryos using HNK-1 antigen expression—Possible relevance for understanding of abnormal atrial automaticity. Circulation 1999;99:800–806. With permission from Wolter Kluwers Health]

anterior atrioventricular node, a retroaortic ring, the His bundle, and the bundle branches. It appears that the myocardium surrounding the primitive pulmonary veins also demonstrates transient staining of HNK1 [23].

Podoplanin is a 43-kd, mucin-type transmembrane glycoprotein that is found outside the heart in several organs and tissues [24–32], such as osteoblasts, the nervous system, epithelia of lung, eye, esophagus, and intestine, mesothelium of the visceral peritoneum; the podocytes of the kidney; and lymphatic endothelium [33–36]. It is thought that podoplanin expression in the developing heart is a marker for the developing sinus venosus myocardium, supporting its development from the posterior heart field. Podoplanin is expressed in the areas that are in close contact with the sinoatrial nodal myocardium and in the underlying mesenchyme adjacent to the cardinal veins. It appears that podoplanin-positive mesenchyme differentiates into myocardium that stains negative for Nkx2.5. During cardiac development, podoplanin is expressed in myocardium along bilateral cardinal veins and in both the right-and left-sided sinoatrial nodes. This expression is maintained on the right as part of the right sinus node and right-sided venous valves, at the base of the atrial septum, the posterior atrioventricular canal, the atrioventricular nodal region, and the His-Purkinje system; it is opposed by the expression of Nkx2.5. Also, during later developmental stages, podoplanin is expressed in the pulmonary veins. In podoplanin negative mice, myocardial components around pulmonary veins are reduced and there is underdevelopment of the atrial septum [28, 37]. It appears that podoplanin plays a critical role in myocardial tissue associated with the sinus node and that abnormal epithelial-to-mesenchymal transformation of the coelomic epithelium due to up-regulated E-cadherin and down-regulated RhoA impose abnormalities in the formation of cells that form the sinus venosus [28].

Even though the development of anatomical structures supporting the specialized conduction system offers insight into genesis of the conduction system, functionally, the development of impulse generation and propagation remains to be fully understood. In the mature heart, the sinoatrial node is the primary pacemaker of the heart, and impulse propagation occurs through the atrioventricular node and specialized His-Purkinje system. Impulse propagation, itself, can be further divided into fast, as in the His-Purkinje system, and slow as seen in myocardial tissue, and slower yet, as seen in the atrioventricular node [6]. Different animals reveal complex variations in the organizational and functional components of the conduction system [7, 8, 38–40]. For example, the study of the chick embryo allowed understanding of a pacing generator around 25–35 h of development in the posterior most part of the tubular heart [41]. Similarly, pacing activity is noted around 7.5 days and 21 days in mice and humans, respectively [42]. At this time, the heart consists of a simple heart tube and the initial contractions are slow and rhythmic [43], but establish unidirectional flow and posterior to anterior polarity [44–48]. These peristaltic contractions can be recorded, inscribing a sinusoidal ECG [49].

Furthermore, there appear to be transient expression of key transgenic markers, timed chronologically, that determine developmental fate of myocardial cells. For example, the heart tubes in zebrafish, chicks, and mice appear to have retinoic acid-sensitive markers along the heart tube that dictate formation of atrial tissue [50]. Retinoic acid appears to control atrial-specific gene expression and exclusion of retinoic acid from ventricular tissue precursors seems essential for correct specification of the ventricular muscle development. In addition, transmembrane hyperpolarization-activated cyclic nucleotide-gated family of ion channel subunits plays a key role in impulse generation supporting pacemaker activity, both in the embryo and the adult human heart [49, 51–53]. Other genes also play a role in impulse generation as can be seen in studies that show that knock-out of the NaCa exchanger gene causes mortality due to inhibition of pacing function in the tubular heart [54]. Along with further differentiation, the developing atrial and ventricular myocardial cells acquire high conductance gap junctions that can then support rapid transmission of an electrical impulse by rapid proliferation and up-regulation of genes. These working myocardial cells have increased mitochondria and increased sarcomere components.

In contrast to rapidly proliferating myocardial tissue, cells in the atrioventricular canal area retain their slow proliferation rates, and also retain their “embryonic-like” mode of conduction, which is much slower [51, 55, 56]. In association with chamber formation, slow wave propagation producing peristaltic contractions are replaced by rapid depolarizations (and contractions) of cells of the atrium and ventricles, inscribing an ECG that resembles the one of the mature heart. These changes seem to occur in parallel with anatomical looping of the heat tube. Differential expression in conduction velocities of the conduction system components in the mature heart accompanies looping. These structural changes parallel a delay in conduction time in the mature atrioventricular node [57–59]. In fact, in the adult myocardium, the impulse proceeds from the sinus node to the crux of the heart at 0.1–1.0 m/s and is slowed at the atrioventricular node to 0.01–0.05 m/s, increasing its velocity to 2–4 m/s in the His-Purkinje system, with a decrease to 0.3–1.0 m/s in the ventricular myocardium [4]. Thus, sequential contraction of the atrial and ventricular chambers in higher species is dependent on the specific functional development of atrioventricular delay [5, 6, 16, 43, 60, 61]. This delay can be seen at 42 h of development in the chick and at 8 and 25 days in the mouse and human [6, 7], respectively. Furthermore, in the looping heart, there are two other areas of relatively slow conduction: the sinoatrial area and the outflow tract area. This slow conduction is associated with the expression of connexin 45, which is characterized by high voltage sensitivity and low permeability [62–65]. Knock-out mice of the connexin 45 gene result in death from heart block at looped, tubular stages of heart development [66, 67].

The His-Purkinje system is the last component of the conduction system to differentiate. In mammals, differentiation of the His-Purkinje system is quite advanced, resulting in markedly efficient and coordinated myocardial activation and associated myocardial contraction [5, 8, 68]. Retroviral lineage studies suggest that central and distally located components of the His-Purkinje system differentiate separately, but then link together during development [7]. In 1999 and 2000, differentiation of the His-Purkinje system in ventricular myocytes was found, in the chick embryo, to be induced by endothelin-1, secreted from adjacent coronary arterioles [69, 70]. This particular finding was not noted in the mouse, however. Similarly, some in vitro evidence suggested that neuregulin-1 played a role [15, 71, 72] in His-Purkinje development. In addition, cellular studies observed that there is a switch in activation sequence in the developing heart. The emergence of the mature His-Purkinje system in the developing chicken embryo had been studied using anti-polysialylated neural cell adhesion molecule (PSA-NCAM) and the HNK1 antibody against a sulfated carbohydrate epitope (antigen). The appearance of the mature form of the His-Purkinje system coincided with the onset of the mature electrophysiological patterns of ventricular activation. These data suggested that, at the completion of ventricular septation, the His-Purkinje system undergoes critical structural and functional transitions that impacted the global pattern of impulse conduction and contraction of the developing four-chambered heart [73, 74]. Using cardiac conduction system-lacZ line of reporter mice, several investigators tested the ability of endocardial-derived and secreted (paracrine) factors to convert contractile cardiomyocytes into conduction system cells. It appeared that neuregulin-1, a growth and differentiation factor essential for ventricular trabeculation was sufficient to induce ectopic expression of a lacZ conduction marker. In the mouse model, this inductive effect of neuregulin-1 was restricted to a window of sensitivity between 8.5 and 10.5 days fertilization. Thus, it appeared that endocardial-derived neuregulins may be responsible for inducing murine embryonic cardiomyocytes to differentiate into cells of the conduction system [15]. In a similar manner, Gassanov et al. described differentiation of atrial-derived cardiomyocytes to a pacemaker-like phenotype induced by endothelin-1, but not associated with neuregulin [72].

Cellular Development of "Nodal" Phenotype

In the mature heart, the atrioventricular nodal myocytes display a variety of embryonic characteristics. Despite these characteristics, nodal cells are poorly distinguishable from surrounding myocardium in the embryonic heart. During gestation and development, nodal cells retain organized actin and myosin filaments and a poorly developed sarcoplasmic reticulum. Nodal cells also continue to express different structural and cellular markers, which are species specific. Several classes of markers have been identified including connexins, specific contractile proteins, desmin, and neurofilaments. These specific markers provide an opportunity for the study of conduction system development. During development, unique characteristics of nodal cells include the expression of higher amounts of calcium-release channel/type-1 inositol triphosphate receptor, gamma enolase, alpha 1 and alpha 2 units of the sodium pump, G-protein alpha subunit, and angiotensin II receptor [26, 75–86]. The role of these differences is unclear at this time. Antibodies to carbohydrate markers such as the polysialylated neural cell adhesion molecule and HNK1 have been used to study the development of specific regions of the specialized conduction tissue. The role of some of these key factors is reviewed below.

The T-Box Family of Transcription Factors

The T-box transcription factors Tbx2 and Tbx3 are expressed in the cardiac inflow tract, the atrioventricular canal, the outflow tract, and inner curvature of the heart during development.

These factors are transcriptional repressors of chamber formation. Both Tbx2 and Tbx3 suppress the genes Nppa and connexin 40, present in working myocardium [55, 76, 87–89]. In general, expression of Tbx2 and Tbx3 is observed in slow-conducting areas, but also in the His bundle and the proximal part of the bundle branches. The expression of Tbx2 decreases from early fetal stages, whereas the expression of Tbx3 increases.

In the developing heart, expression of Tbx3 is observed in the sinoatrial node and atrioventricular node, but also in the internodal myocardium, in the atrioventricular cushions and in the His bundle and proximal bundle branches [88, 89]. Homozygous Tbx3-mutant mice display a syndrome known in humans as ulnarmammary syndrome and display early embryonic mortality, presumably due to severe compromise of the yolk sac [90]. The role of Tbx3 in controlling the sinoatrial node gene program has also been described [88, 89]. Tbx3 is expressed in the developing and mature sinoatrial node and is required to suppress the expression of genes regulating atrial differentiation. Furthermore, Tbx3 can induce ectopic pacemaker sites in the atria [88, 89].

The T-box transcription factor Tbx5 is expressed in the developing the atrioventricular node, His bundle, and bundle branches [85]. Mice lacking Tbx5 display a cardiac phenotype that resembles the Holt–Oram syndrome, including atrial septal defects and conduction system abnormalities [2]. Tbx5 targets atrial naturetic factor (ANF) and connexin 40 as part of the fast-conducting components of the conduction system. In mice, Tbx5 haplo-insufficiency causes a maturation failure of conduction system morphology and function [85]. Tbx5 is required for connexin 40-independent patterning of the cardiac conduction system and it is thought that the electrophysiologic defects in Holt–Oram syndrome reflect a developmental abnormality of the conduction system [82]. Tbx18 is expressed in the sinus horns and is likely essential for the formation of the sinus venosus. In mice that are deficient for Tbx18, formation of the sinus venosus is disturbed [87].

Homeodomain Transcription Factors

The homeodomain transcription factor Nkx2.5 is expressed early in development, in the cardiogenic mesoderm and is present throughout the developing heart [91]. As part of an ongoing chamber formation program, Tbx5 and Nkx2.5 stimulate a variety of cardiac genes. During development certain regions in the linear heart tube remain embryonic in nature and do not develop into working chamber myocardium due to the presence of Tbx2. Thus, it appears that Nkx2.5 and Tbx2 form a repressor complex that suppresses genes that promote a chamber differentiation program. Tbx2 is expressed in the primary myocardium of the inflow tract, atrioventricular canal, and outflow tract. It appears that Tbx2 competes with Tbx5, and when Tbx2 is expressed in conjunction with Nkx2.5, it seems to act as a repressor of further differentiation.

The expression of Nkx2.5 is elevated in the differentiating atrioventricular conduction system, compared to its expression in the adjacent working myocardium. This expression correlates with the recruitment of cells to the developing atrioventricular conduction system [92]. In Nkx2.5 haplo-insufficient mice, there is hypoplasia of the atrioventricular node and His bundle, and the number of peripheral Purkinje fibers is significantly reduced [93–95].

Cardiac phenotypes of mutations in Nkx2.5 in mouse models resemble those in humans and include conduction defects [96]. It is known that Nkx2.5 is not expressed in posterior heart field-derived myocardium, including the sinoatrial node and the sinus venosus [87]. Furthermore, Nkx2.5 interacts with the connexin 40 promoter region and mice lacking Nkx2.5 demonstrate a significant decrease in connexin 40 expressions [97]. Nkx2.5 can form a complex with the transcription factor Tbx2 that is able to suppress ANF promoter activity in the atrioventricular canal, which may be a mechanism that helps to regulate some of the sites of chamber formation in the developing heart [91]. Nkx2.5 can also bind to Tbx5. This complex is an essential component for the activation of the atrial naturetic factor gene.

The homeodomain transcription factor Msx2, a downstream target of Pax-3/splotch (which is a key player within early cardiac neural crest development), is expressed in the developing central conduction system, but not the peripheral Purkinje fibers, in the chick. However, no abnormalities in the cardiac conduction system have been observed in Msx2-mutant mice [95, 98].

The homeobox gene Hop is strongly expressed in the atrioventricular node, His bundle, and bundle branches of the adult cardiac conduction system and Hop-null mice demonstrate conduction defects below the atrioventricular node, related to decreased expression of connexin 40 [99].

The homeodomain transcription factor Shox2 is expressed in the embryo in the craniofacial region, limbs, brain, and heart [100, 101]. In the heart, Shox2 can be detected early in the posterior region of the primitive heart tube. During further development, Shox2 is expressed in the sinus venosus myocardium, which includes the sinoatrial nodal region and the venous valves; expression is also observed in the primitive left and right bundle branches. Shox2 knock-out mice die between 11.5 and 13.5 days postfertilization and show severe hypoplasia of the sinus venosus myocardium of the posterior heart field, including a decreased size of the sinoatrial node region and hypoplastic venous valves. When Shox2 is absent in knock-out mice, aberrant expression of connexin 40, connexin 43, and Nkx2.5 is observed within the sinoatrial node, indicating abnormal differentiation of the sinoatrial node as well as disturbed pacemaker function. This finding is also noted in the node in zebrafish embryos [100]. Given these findings, it appears that Shox2 is important in recruiting sinus venosus myocardium, including the sinoatrial nodal region.

The bicoid-related homeodomain transcription factor Pitx2c is involved in directing left/right identity in the heart at the venous pole [83] and is probably involved in suppression of left-sided sinus node formation, as Pitx2c-deficient fetuses form sinoatrial nodes in both the right and left atrium [102, 103].

Id Family of Transcriptional Repressors (Helix-Loop-Helix Containing Transcriptional Repressors)

Early in cardiac development, the temporal and spatial expression of Tbx5 supports specification of cells for the conduction system. Tbx5-dependent expression of connexin 40 and presumably other molecules are required for the critical electrophysiologic properties of these cells. It is thought that Tbx5 directs the expression of certain genes, such as those for connexin 40, in the mature conduction system, after the primitive atrioventricular node, left bundle branch and right bundle branch have assumed their adult structures. This observation may explain why some Holt–Oram patients, for example, or Tbx5del/+ mice show an evolution of conduction system disease with age [90, 91].

The gene Id2 has been identified by serial gene expression analysis (SAGE) as having ventricular conduction system expression and is a downstream target of Tbx5 and Nkx2.5. Id2 negative mice demonstrate ECG features of abnormal interventricular conduction, such as left bundle branch block in newborn and adult knock-out mice. Furthermore, intracardiac recordings are consistent with abnormal intraventricular conduction within the bundle branches [85]. In situ hybridization demonstrated that Id2, expressed in the conduction system in wild-type hearts, is not expressed in compound Tbx5/Nkx2.5 hearts, indicating that ventricular conduction system-specific expression of Id2 is dependent on Nkx2.5 and Tbx5. These findings support a link between a patterning abnormality of the developing conduction system and a functional abnormality of the mature conduction system [85].

Basic Helix-Loop-Helix (bHLH) Transcription Factors

Fate mapping analysis has revealed that Mesp1 is expressed in almost all of the precursors of the cardiovascular system, including the endothelium,

endocardium, myocardium, and epicardium. Mesp1-nonexpressing cells were found to be restricted to the outflow tract cushion and along the interventricular septum. When the interventricular cells were examined by using the pattern of beta-galactosidase activity, approximately 20 % of the ventricular conduction cells within the intraventricular septum correspond to Mesp1-nonexpressing cells. These data suggested that the ventricular conduction system is of heterocellular origin [104].

The GATA Family of Transcription Factors/Zinc Finger Subfamilies

The GATA family is a relatively small family of transcription factors. For three of the six known vertebrate GATA transcription factors, a role in cardiogenesis has been identified: these include GATA4, GATA5, and GATA6 [105]. Expression of GATA4 is present in both the adult and embryonic heart, and its disruption results in cardiac dysmorphogenesis with early embryonic mortality [87]. A significant interaction among the different transcription factors was shown in a study that demonstrated that, next to Tbx3 and Nkx2.5, the connexin 40 promoter is also modulated by the cardiac transcription factor GATA4 [97]. In addition, GATA4 is expressed in Purkinje fibers of the adult chick heart [106]. GATA5 mRNA is observed in the pre-cardiac mesoderm of the primitive streak embryo. In the embryonic heart, there is expression of the GATA5 gene in the atrial and ventricular chambers that, during further development, becomes restricted to the atrial endocardium [107]. Furthermore, GATA5 is expressed in the endocardial cushions and in the cardiac conduction system, in the sinoatrial node, atrioventricular node, bundle of His, and left and right bundle branches [84]. Interestingly, the GATA5 gene is expressed in a dynamic fashion over time in the septum transversum and in the epicardial organ of the mouse and avian heart, giving rise to the (GATA5-expressing) epicardium [84]. The cGATA6 gene enhancer specifically marks components of the developing cardiac conduction system and atrioventricular node [78, 108], but not the more distal components of the cardiac conduction system. Expression of cGATA6 remains visible in the mature cardiac conduction system.

MinK/lacZ Knock-In/Knock-Out

The minK gene (also known as IsK and KCNE1) encodes a 129-amino-acid protein that modifies transmembrane electrical currents in the heart resulting from expression of the genes HERG and KvLQT1 [109]. Mutations in both HERG and especially KvLQT1 that encode the structural subunits for the channels involved in the cardiac delayed rectifier currents IKr and IKs, respectively, are the most common causes of congenital long-QT syndrome (LQTS) [109]. Disruption of the minK gene and integration of the lacZ gene results in β-galactosidase expression under the control of endogenous minK regulatory elements, which has been used to study the expression pattern of minK in mice. Disruption of the minK gene causes inner ear defects and QT interval prolongation in bradycardic conditions, the combination of which is known in the human as the Jervell and Lange-Nielsen syndrome [110]. MinK–/– myocytes lack the delayed rectifier current IKs and demonstrate significantly reduced IKr, which indicates a role of minK in modulating both rectifier currents [109]. The spatial expression of minK-lacZ in the adult mouse heart has been shown to be coincident and closely related to the conduction tissue. The expression of minK-lacZ has been used to trace the embryonic development of the conduction system. Expression of minK-lacZ was first seen on the eighth embryonic day in the mouse. Subsequently, discrete rings were found at the sinoatrial, atrioventricular, interventricular, and ventricular–arterial junctions, and with time, the expression became restricted to boundary regions of the heart, such as the hinges of the leaflets of the pulmonary and aortic valves, the atrioventricular rings, and the venous valves, but was also noted in the definitive conduction tissue. In the postnatal mouse heart, areas retaining minK-lacZ positivity outside of the definitive conduction

tissues were thought to designate sites of origin of abnormal cardiac rhythms, suggesting that ectopic foci may derive from tissues that share a common developmental pathway with the definitive conduction system [111]. These observations suggest that the boundary regions between compartments, along with the atrioventricular conduction axis, share common developmental pathways and may support a certain arrhythmia expression later in life. Expression of minK-lacZ was not present at the site of the pulmonary veins [111].

Cardiac Conduction System lacZ Insertional Mutation

In 2000, it was noted that the random insertion of a lacZ gene into the murine genome unexpectedly resulted in a mouse line (named Cardiac Conduction System-LacZ [CCS-LacZ]) with expression of lacZ in the (developing) conduction system of the heart. Genetic mapping demonstrated that the transgene inserted into a regulatory region on mouse chromosome 7, altering transcription of several nearby genes including Slco3A1 [10–15, 47].

Regulatory elements from the gene Slco3A1 influenced cardiac conduction system-restricted reporter gene expression [112]. Members of the Slco family encode for organic anion-transporting polypeptides that mediate transport of natural substances (such as prostaglandins, bile salts, thyroid, and steroid hormones) as well as exogenous drugs (including digoxin, angiotensin-converting enzyme inhibitors, HMG-coenzyme A reductase inhibitors, methotrexate, and rifampin) across the cell membrane [113]. Considering the extent of the recombination observed in the CCS-LacZ model, it was thought that it would be likely that regulatory elements from more than one gene are involved [112]. In the CCS-LacZ mouse LacZ is expressed in all components of the developing cardiac conduction system, including the right and left venous valves and septum spurium of the sinus venosus and the putative sinoatrial node, the left and right atrioventricular ring, His bundle, bundle branches, and Purkinje fibers. CCS-LacZ is also expressed in the moderator band of the right ventricle, Bachmann's bundle, the retroaortic root bundle, and in the myocardial sleeve that develops around the pulmonary vein, areas related to arrhythmias in adults. Findings in several models support the hypothesis that the occurrence of cardiac arrhythmias in the heart, especially on the left atrial side, may be related to persistent or reactivated areas of developing cardiac conduction system [114–116].

CCS-LacZ expression was also noted in intraluminal endothelial cells, which are thought to be linked to the secretion of endothelial-derived factors involved in induction of cardiomyocytes to acquire a conduction system phenotype. Indeed, the endothelial paracrine factor neuregulin-1 has been demonstrated to induce ectopic expression of CCS-LacZ and, therefore, may play a critical role in recruitment of cells to the cardiac conduction system [15]. Timing of exposure to the endothelial factors may be crucial, as the inductive effect of neuregulin in the CCS-LacZ mouse was restricted to a window of sensitivity between E8.5 and E10.5 [15]. In the adult mouse heart, using serial sections of CCS-LacZ hearts, connexin 40 immunostaining (marking ventricular cardiac conduction system cells) could be co-localized with CCS-LacZ transgene expression in the atrioventricular node, His bundle, bundle branches, and subendocardial Purkinje fibers along the interventricular septum. In contrast to the developing heart and neonatal heart, cardiac CCS-LacZ expression was no longer present within the sinoatrial node in the adult mouse heart [117].

The Hyperpolarization-Activated Cyclic Nucleotide-Gated Cation (HCN) Channel Family

Four genes that encode HCN channels have been identified: HCN1, HCN2, HCN3, and HCN4. HCN channels carry an inward current, which is the depolarizing Na/K current if, that underlies cardiac pacemaker activity. In the adult heart, both HCN2 and HCN4 are expressed. During development, HCN4 is expressed as early as

E7.5 in the cardiac crescent [118, 119]. Interestingly, in the early heart tube, using optical mapping studies in the chick [120, 121], expression is observed bilaterally in the sinus venosus. Later in development, expression of HCN becomes asymmetrical and restricted to the right atrium, at the site of the developing sinoatrial node [118]. In the postnatal and adult heart, HCN4 is highly expressed in the sinoatrial node [118, 119]. HCN4 knock-out mice die between E9.5 and E11.5. These knock-out mice do not display mature pacemaker potentials, and thus, it is thought that HCN4 channels are required for proper pacemaker function of the sinoatrial node [119]. The expression pattern of HCN4 overlaps with the expression of markers of the posterior heart field, such as podoplanin and Shox2. The expression of HCN4 reflects the sinus venosus myocardium of the posterior heart field and becomes restricted to the sinoatrial node [118]. HCN2 is expressed in a broader distribution pattern than HCN4 and includes the ventricular myocardium, but is also moderately expressed in the sinoatrial node [118].

Connexins

The transmission of the electrical action potential is thought to occur primarily through gap junctions. Gap junctions are aggregates of membrane channels, composed of protein subunits named connexins that are encoded by a multi-gene family. Connexins hexamers make up connexons that then form the gap junction. Four different connexins are expressed in the mammalian heart including connexin 30.2, 40, 43, and 45. In the early myocardium, both number and size of gap junctions are small but they increase during development. The number of gap junctions remains scarce in the developing sinoatrial node and the atrioventricular node. The low abundance of connexin expression in the two nodes corresponds to their slow conduction velocities. This difference in connexin concentration has been an important marker for nodal-specific tissue. An abrupt rather than gradual increase in the number of gap junctions is found at the transition zone of nodal tissue to working myocardium. This boundary is thought to be due to a decrease in the number of nodal cells towards the atrial working myocardium rather than a gradient due to a change in molecular phenotype. Fast-conducting cardiac tissues in the atria express connexin 40 [122, 123] and slower conducting working myocardium express connexin 43 [124]. Connexin 45 seems to play a crucial role in delineating the conduction system during development and is seen in slow-conducting pathways, including the sinoatrial node and atrioventricular node during development [62–65, 124]. The expression of the different connexins varies among species but does provide an insight into the interplay and non-static nature of gap junction expression during development. For example, connexin 40 can be detected early in the mouse heart, where it is present first in the primitive atria and primitive left ventricle, and also in the primitive right ventricle, but not in the AV canal and interventricular septum. During development, together with the development of the specialized conduction system tissue, expression of connexin 40 becomes restricted to atrial myocytes and the ventricular conduction system [123]. Connexin 40 knock-out mice display an increased incidence of inducible atrial arrhythmias, and significant conduction delay in the infra-His and distal atrioventricular nodal conduction [62, 63, 122, 123, 125–129].

Connexin 43, in contrast, is first detected in the primitive ventricle and, some, in the atria and its expression increases and is present in the adult ventricular (working) myocytes [122, 123, 128]. Connexin 43 knock-out mice die at birth because of developmental defects in the pulmonary outflow tract, presumably resulting from defective migration of cardiac neural crest cells to this region [129]. In addition, cardiac-specific deletion of connexin 43 results in sudden cardiac death from spontaneous ventricular arrhythmias at 2 months postnatally, which suggests an important role for connexin 43 with regard to maintenance of electrical stability in the heart [130].

Connexin 45 is expressed in all compartments of the linear heart tube, including the inflow tract, atrioventricular canal, and outflow tract. Expression of connexin 45 decreases throughout

development and in the adult mouse heart, but remains present in the atrioventricular node, His bundle, and surrounding Purkinje fibers [62–65]. Connexin 45 knock-out mice demonstrate conduction block and die of heart failure [130].

Finally, connexin 30.2 slows impulse propagation through the atrioventricular node, which is important in preventing rapid conduction of an impulse into the ventricles [131–133]. In mice, in which the coding region of connexin 30.2 has been replaced by a lacZ reporter gene, a shortening of the QT interval by 25 % is seen [131].

Cytoskeletal Proteins

Nodal-specific developmental expression of contractile proteins such as myosin heavy chain and its isoforms, desmin and neurofilament, has been used to delineate the sinoatrial and atrioventricular nodes. However, inter-species variability in the staining of these markers does not produce sufficiently consistent data to draw definitive conclusions with relation to development or morphologic changes that are specific to the conduction system or its development and differentiation.

Atrioventricular Junction: Accessory Pathways/Mahaim Fibers

The atrial and ventricular myocardium including the atrioventricular canal is a continuous structure during embryogenesis of the heart tube and development of the four-chambered heart [134]. As demonstrated in the chick, accessory atrioventricular myocardial continuities may persist in the embryo until later stages, causing premature activation of the ventricles even after septation has occurred [135]. In normal adult cardiac conduction, the atrioventricular node-His bundle is the only functional atrioventricular conduction tract between the atria and ventricles. Rarely, accessory myocardial bundles or pathways connecting atrial and ventricular myocardial tissue persist, thus bypassing the insulating function of the atrioventricular groove [134] resulting in the well known in Wolff–Parkinson–White syndrome in humans [134]. A rare form of an accessory pathway is a right-sided accessory bundle with atrioventricular node-like conduction properties, at one time thought to be Mahaim fibers, but more correctly are atriofasicular fibers [116, 134, 135]. Data derived from the CCS-LacZ mouse demonstrate that the occurrence of these rare fibers may be related to the embryonic development of the right ventricular inflow tract. The development of the right atrial/right ventricular connection and concomitant outgrowth of the right ventricle results in a division of the primitive left and right ventricles. This division results in the development of the right ventricular moderator band that forms a right-sided atrioventricular continuity, similar to a Mahaim fiber. Electrophysiological experiments supported the presence of a slowly conducting right-sided atrioventricular pathway [116]. Other rare anomalous fibers that bypass the normal atrioventricular node-His-Purkinje axis are nodoventricular fibers atrioventricular node-ventricular connection) and fasciculo-ventricular (His bundle or right bundle connection) fibers that can cause pre-excitation and, rarely, reentry tachycardia. They are known as Mahaim fibers. These forms of pre-excitation can result in atrioventricular reentrant tachycardia (Chap. 4).

To date, there are two mouse models of Wolff–Parkinson–White syndrome. Mutations in the gene PRKAG2 (that encodes the γ-2 subunit of the AMP-activated protein kinase) seem to be associated with the expression of Wolff–Parkinson–White syndrome [136, 137] in humans. Mice that carry a mutation in the PRKAG2 gene display ventricular pre-excitation and a phenotype identical to humans with the familial form of ventricular pre-excitation [138]. Another form of pre-excitation has been demonstrated where the postnatal development of myocardial connections through the annulus fibrosus of the atrioventricular valves in mice overexpressing the PRKAG2 mutation occurs [139]. In this type of pre-excitation, there seems to be accumulation of excessive amounts of cardiac glycogen, and disruption of the annulus fibrosus by glycogen-filled cardiomyocytes [140, 141]. This form of pre-excitation is associated with myocardial hypertrophy.

A specific deletion of the gene ALK3 in the atrioventricular canal, coding for the type 1a receptor for bone morphogenetic proteins in the atrioventricular canal during development, causes ventricular pre-excitation, also, supporting the notion that this gene is important for normal atrioventricular junction development [80].

Epicardial inhibition studies demonstrate that reduced periostin expression at the atrioventricular junction, results in disturbed development of fibrous tissue at the atrioventricular junction, persistent atrioventricular myocardial connections with resulting ventricular pre-excitation, which may be another mechanism explaining Wolff–Parkinson–White syndrome [135].

In contrast to arrhythmias associated with accessory pathways, several other arrhythmias have been described that originate from the tricuspid and mitral valve junctions [142, 143] or around the atrioventricular annuli. Atrioventri cular cells surrounding both the tricuspid and mitral annuli have been shown to resemble nodal cells in their cellular electrophysiology [144], and thus, could support arrhythmias similar to those intrinsic to the atrioventricular node.

In summary, evidence suggests that the specialized conduction system develops from further differentiation of local myocytes. The molecular signals for this differentiation are multiple, variable, interactive, and dose- and timing dependent. The exact stimulants for differentiation, selective cellular potency, and variable cell protein and channel expression and their roles in differentiation deserve further study.

Part II—Anatomy of the Mature Cardiac Conduction System

The specialized conduction system of the mature human heart consists of a single sinoatrial node, atrial and intranodal pathways, the AV node, and the His-Purkinje system, the latter includes the right and left bundle branches of the His-Purkinje system, and the peripheral His-Purkinje system. This section focuses on the anatomy of the conduction system and its relationship with the luminal working myocardium as both are developed, in parallel and in conjunction with each other.

All cells in the heart are capable of conducting an electrical impulse, but a special subpopulation of myocytes differentiates to support both generation and propagation of the cardiac impulse. Even though microscopic inspection provides considerable insight into the structure of the conduction system [145], this method is incomplete and does not fully define and delineate specialized tissue behavior with regard to intramyocardial behavior and interaction [146, 147].

In the mature heart, the sinoatrial (SA) node is the dominant pacemaker of the heart and lies in the right atrium at the superior vena cava/right atrial junction, one millimeter below the epicardium of the sulcus terminalis [148–150]. It was first described in the early 1900s [151]. The sinoatrial node has the shape of an inverted comma, descriptively containing a head, body, and tail [145, 152–155]; rarely, the sinoatrial node has a horseshoe-shaped structure [156]. It tapers both medially and laterally and bends backward towards the left and then downward [157]. Several authors document a paranodal area, where cells are of the node intermingle with atrial cells [158–160]. The sinoatrial node is supplied by a relatively large artery, which courses through and gives off branches to the sinus node and adjacent atrial myocardium. It originates from the right coronary artery about 55 % of the time and from the left circumflex artery in about 45 % of cases [156].

With regard to the atrial body itself, it is controversial whether preferential intranodal pathways exist [161, 162] because conclusive anatomic data is missing.

Even though evidence for preferential intraatrial pathways is missing, there appears to be preferential conduction or impulse propagation that may be associated with the underlying anatomic differences in muscle density, muscle fiber orientation, and/or the thickness of the right atrial wall and its pectinate muscles. Some authors argue that “specialized pathways” consisting of aggregations and or concentrations of myocardial muscle fibers, bridge the SA and atrioventricular nodes or the right atrium to the left atrium.

These authors propose three internodal tracts: the anterior, middle, and posterior internodal fibers. The anterior intermodal fibers are thought to have two components: Bachman's Bundle, which bridges right and left atrium and "descending branches," which descend in the intra-atrial septum. The middle internodal tracts also known as Wenchebach's bundle are thought to arise from the posterior portion of the sinus node and then descend within the intra-atrial septum, anterior to the fossa ovale. And the posterior internodal tracts, also known as Thorel's pathway, are thought to exit the sinus node posteriorly and then descend within the crista terminalis, traversing through the Eustachian ridge, entering the AV node, posteriorly, in the mouth of the coronary sinus [161, 162]. An alternate hypothesis is that intra-arterial conduction depends on gap junction density at the cellular level.

Because it was difficult to differentiate electrical myocardium from working myocardium, anatomically, in 1910, the German Pathological Society defined myocytes that were responsible for conduction to be associated with: 1—histologically discrete from adjacent contracting myocardium, 2—traceable from pathologic section to section, and 3—insulated to some degree from adjacent tissue by a fibrous sheath. These criteria, established in 1910 have remained intact, although the specified distinctions can now be evaluated with more detailed histochemical staining techniques [146]. These staining methods, subsequently, led to the study of electromechanical coupling [146, 159].

The atrioventricular node is located in the posteroseptal area, primarily on the right atrial side, at the apex of the region known as the triangle of Koch. This triangle is defined by a fibrous structure known as the Tendon of Todaro, the edge of the septal leaflet of the tricuspid valve and the edge of the mouth of the coronary sinus, which marks the base of the triangle. A second isthmus is present between the mouth of the coronary sinus and the septal leaflet of the tricuspid valve that is thought to support slow pathway contributions to the atrioventricular node. In the adult, the triangle measures 14–20 mm in its longest apex-to-base dimension. In children, as expected, the dimensions vary based on height, weight, body surface area age, and heart weight [163]. The atrioventricular node abuts the mitral valve annulus and tricuspid valve annulus with its posterior margin abutting the coronary sinus. Unlike the bundle of His, the atrioventricular node cannot be seen visually, nor does it generate a distinct, recordable signal during clinical electrophysiologic testing. The knowledge of its location is inferred during electrophysiologic testing in association with mapping techniques. The anterior portion or distal ends of the atrioventricular node blend with the bundle of His, which penetrates the central fibrous body. The atrioventricular node is thought to be a flattened, oblong structure with multiple extensions, some extending to the left atrium. The atrioventricular node is also thought to have extensions with a compact portion of the node existing more closely associated with the perimembranous portion of the ventricular septum. The atrioventricular node is usually supplied by an atrioventricular nodal artery, which arises from the right coronary artery in 90 % of cases and from the left circumflex artery in 10 % of the cases.

The bundle of His consists as an extension of the atrioventricular node. These extensions occur distal to the compact atrioventricular node. The bundle of His is characterized by fibers, which are organized in parallel channels or strands. These fibers are surrounded by a fibrous sheath more proximally and are, therefore, well insulated. The bundle of His penetrates the fibrous body and proceeds anteriorly descending towards the atrioventricular septum where it divides into the right and left bundle branches [164–166]. The compact atrioventricular node is thought to be buried inside the central fibrous body insulated by fibrous tissue continuing with extensions to the bundle of His and the bundle branches.

The right bundle is a relatively well defined and easily dissectible structure situated beneath the epicardium on the right side of the intraventricular septum. The right bundle branch proceeds along the free edge of the moderator band to the base of the anterior papillary muscles in the

right ventricle and along the septal band to the apex of the right ventricle and to the "breakout point" on the anterior surface of the right ventricle [167].

The left bundle passes down the left side of the intraventricular septum and emerges below the posterior cusp of the aortic valve. In contrast to the right bundle, the left bundle breaks up almost immediately into a number of small fan-shaped branches, which proceed down the smooth aspect of the left side of the intraventricular septum. The bundle contains two major branches including an anterosuperior division and a posteroinferior division. The anterosuperior division is relatively long and thin whereas the posteroinferior division is relatively short and thick. The anterosuperior division is closer to the aortic valve whereas the posteroinferior division supplies the posterior and inferior aspect of the left ventricle [146].

Using histochemical techniques, researchers have been able to identify tissue that supports slow conduction in the posteroseptal area and also at the base of the aortic valve. Further staining studies confirmed a "figure of eight" configuration of these areas as the aorta moved closer to the left ventricle during development. Remnants of this slowly conducting tissue are thought to play a role in patients in congenitally corrected transposition of the great arteries or other abnormal muscular connections between the atrioventricular junction [43]. Transcription factor, Tbx3, is thought to play a crucial role during development, preventing such cells from conversion to working myocardial cells [160].

The nervous system serves a regulatory role by way of an integrated balance of sympathetic, parasympathetic, and sensory nervous system signaling supporting the heart in its development. The mature heart is extensively innervated. The sympathetic nervous system releases endorphins to increase heart rate, conduction velocity, myocardial contraction, and relaxation. Regional differences in sympathetic innervation of the heart have been noted during development and also during diseased states and vary with regard to patterning, signaling, and relevance. It appears that neural crest cells migrate during the middle of gestation and give rise to sympathetic neurons. Thus, sympathetic neurons extend from the stellate ganglion to the heart and into the myocardium. Specialized conduction tissue is more abundantly innervated compared to working myocardium [168–171]. Quantitative immunohistochemical and histochemical techniques confirm that regions of the conduction system possess a significantly higher relative density of total neural population immunoreactivity for the general neuronal marker proteins. Initial sympathetic dominance in the neural supply to the human cardiac conduction system in infancy and its gradual transition into a sympathetic and parasympathetic co-dominance in adulthood correlate well with the physiologic alterations known to occur in cardiac rate during postnatal development. The finding of reduction in density of innervation of the conduction tissue with ageing is also in agreement with clinical and electrophysiological findings such as age-associated reduction in cardiac response to parasympathetic stimulation [172].

Ganglia are located at the base of both atria and ventricles with a higher nerve density on the endocardium and greater nerve thickness on the epicardium. Parasympathetic supply to the myocardium arises from branches from the right and left vagus nerves. The right vagus nerve supplies primarily the sinoatrial node, given that the sinoatrial node originates from the right horn of the sinus venosus. The left vagus nerve supplies primarily the atrioventricular node due to its origin from the left horn of the sinus venosus. The parasympathetic nervous system mainly releases acetylcholine to decrease heart rate, cardiac output, atrial contractility, and conduction through the atrioventricular node. Finally, sensory signals from the myocardium are transmitted via thinly myelinated A-fibers and unmyelinated C-fibers to the upper thoracic dorsal horn via the dorsal root ganglia; the role of these fibers has not been fully elucidated.

The growth, migration, and behavior of cardiac neurons are orchestrated by a complex interaction and modulation between neural chemo-attractants and chemo-repellants. A set of neurotrophic factors act as chemo-attractants

both in the peripheral organs and in the central nervous system. There are two basic groups: (1) the neurotroponin family which include nerve growth factor, brain-derived neurotrophic factor, neurotroponin-3, and neurotroponin 4/5; (2) the glial cell line-derived neurotrophic factor family, which include glial cell line-derived neurotrophic factor, neurturin and atremin which bind to glial cell line-derived neurotrophic factor receptors. Glial cell line-derived neurotrophic factor and receptor signaling are required for normal parasympathetic innervation.

Because it is important to have a sound understanding of the atrioventricular junction for successful diagnosis and management of many cardiac arrhythmias, the Cardiac Nomenclature Study Group has divided the atrioventricular junction into anatomically distinct and separate regions for description of accessory pathway location and better health care professional communication. In addition, it is important to appreciate developmental changes as these have important implications for the study of the electrophysiologic structures in the pediatric age group and in patients with congenital heart disease and assist in an approach to ablation of the underlying abnormal substrate.

Part III—Anatomy of the Conduction System in Congenital Heart Disease

Development of the AV node and His-Purkinje system depends on appropriate atrial and ventricular orientation and proper alignment of the atrial and ventricular septum with appropriate closure of septal defects. A number of congenital cardiac malformations can impact this development and lead to anatomic substrates that give rise to cardiac arrhythmias.

Atrioventricular Septal Defects

Atrioventricular septal defects (also known as atrioventricular canal defects or endocardial cushion defects) involving abnormal development of the endocardial cushions may be associated abnormalities in atrioventricular conduction [173, 174]. Because the crux of the heart is abnormally formed in these defects, the atrioventricular node is inferiorly and posteriorly displaced [175], situated anterior to the mouth of the coronary sinus at a site just below where the base of the triangle of Koch would have occurred if the crux of the heart were properly formed. A common His bundle extends along the lower rim of the inlet portion of the ventricular septal defect resulting in a posterior course of the intraventricular conduction network. Therefore, due to the extent of the defect; the classic ECG pattern inscribes a superior leftward axis (vector). In addition, if the patient has a coexisting right posterior accessory pathway and supraventricular tachycardia, the accessory pathway might lie very close to the posteriorly placed atrioventricular node. Application of radiofrequency ablation could jeopardize the integrity of the atrioventricular node-His-Purkinje system and may result in complete heart block. Cryoablative therapy would be an advisable alternative in that situation.

Atrial Septal Defects

Even though the conduction system forms normally with regard to its anatomical location and its relative position to the crux of the heart, atrial septal defects can be associated with conduction system disease. Patients with mutations of Tbx5 or Nkx2-5 can present with both defects in atrial septation and progressive central cardiac conduction disorder which can result in complete atrioventricular block. That Tbx5 and Nkx2-5 mutations can also lead to complete heart block in the absence of structural heart disease suggest that this transcriptional pathway is directly involved in conduction system formation and maintenance [93–95].

For Tbx5, several lines of evidence support this assertion. First, despite an intact ventricular septum, all Tbx5del/+ mice had malformations in the ventricular conduction system, usually affecting both the right and left bundle branches.

Second, there was no relationship between the specific type of atrial septal defect in Tbx5del/+ mice and conduction system abnormalities. The presence of a secundum or primum atrial septal defect did not correlate with the severity of morphologic defects in the central conduction system, and no statistically significant differential effect was observed on the PQ interval, QRS interval, or likelihood of right-bundle-branch block. Thus, Tbx5 appears to have a direct role in conduction system development independent of its role in structural heart development. Furthermore, the finding that Tbx5 is expressed at high levels in conduction system cells suggests that its conduction system requirement may be cell-autonomous. Connexin 40, a transcriptional target of Tbx5 that encodes a gap junction protein required for normal electrophysiologic function of the heart, was considered a potential cause for the patterning defects evident in the central conduction system of Tbx5del/+ mice. Similar to Tbx5del/+ mice, Cx40–/– mice demonstrate prolonged PQ intervals, prolonged QRS intervals, and in some cases right-bundle-branch block [126, 127, 175]. The degree to which the decrement in Cx40 transcription in Tbx5del/+ mice accounts for the functional conduction system abnormalities in Tbx5del/+ mice remains unclear. Recent findings demonstrate the critical importance of even limited Cx40 expression in Tbx5del/+ mice: whereas Tbx5del/+ mice usually live to adulthood, Tbx5del/+ /Cx40–/– mice die in utero.

Cx40 deficiency does not, however, explain the morphologic abnormalities of the central conduction system found in Tbx5del/+ mice. Normal morphology of the atrioventricular node, atrioventricular bundle, and bundle branches was present in all adult Cx40–/– mice, indicating that this gap junction protein is not required for the morphologic maturation or patterning of the central conduction system. These findings implicate yet unidentified genes downstream of Tbx5 in the patterning of the conduction system [176].

Likewise, animal models have determined that Nkx2.5 has a direct effect on conduction system formation and maintenance. It has been noted to interact with Tbx5 to cooperatively regulate expression of a number of genes including Cx40 [97]. Haplo-insufficiency of either Tbx5 (Tbx5del/+) or Nkx2.5 (Nkx2.5del/+) results in slowing of conduction in the His-Purkinje system and which is further impaired in mice that are haplo-sufficient for both [177]. Further studies have demonstrated that the role of Nkx2.5 is not limited to early conduction system development. Perinatal loss of Nkx2.5 results in contractile and severe conduction system deficits shortly after the gene is experimentally deleted [178] even if that occurs after completion of the structural development of the heart. The requirement for Nkx2.5 in the maintenance of a healthy conduction system was determined using a mouse model in which Nkx2.5 was deleted 2 weeks after birth [179].

Ventricular Septal Defects, Including the Tetralogy of Fallot

In patients with ventricular septal defects, the AV node is usually in its anatomically correct position [168, 171]. The penetrating His bundle and the His-Purkinje system run posteriorly along the rim of the ventricular septal defect and then penetrate and depolarize the myocardium normally.

The exceptions include ventricular septal defects that are inlet in type and, therefore, support a more inferior and posterior propagation of initial ventricular activation, similar to those seen in atrioventricular septal defects. The course of the common bundle or its branches relatively to the ventricular septal defect may exhibit a longer common bundle. In patients with either inlet, perimembranous, or outlet ventricular septal defects, the His bundle and its branches will typically be found on the lower crest of the defect, and will tend to deviate slightly towards the left side of the defect. Therefore, in postoperative patients, a ventricular septal patch may overlie the region of interest where a His bundle could be recorded. In these patients, the amplitude and frequency of a His signal may be variable and perhaps diminished.

Atrioventricular Discordance

Other abnormalities of the conduction system are associated with AV discordance either in biventricular hearts or in hearts with single ventricle physiology [180–192].

In these patients, the atrioventricular node may be duplicated, situated outside the triangle of Koch or elongated in morphology. Remnants of slowly conducting tissue are thought to play a role in patients with congenitally corrected transposition of the great arteries (CCTGA) or other abnormal muscular connections between the atrioventricular junctions [43] where anatomical malformations support expression of unusual locations of the atrioventricular node.

Usually, in CCTGA, the conduction system extends medially and runs along the right-sided mitral valve and pulmonary valve. If there is a ventricular septal defect, conduction usually occurs along the upper border of the septal defect. As such patients with CCTGA or ventriculoarterial discordance may have more than one atrioventricular node that penetrated the atrioventricular groove that could support sinus rhythm and, in some patients, reentrant tachycardia [189–192]. It is well known that the atrioventricular conduction system can be tenuous in these patients and may lead to the development of spontaneous complete atrioventricular block [193–196]. Approximately 3–5 % of patients with L-transposition, especially those with associated single ventricle are born with complete heart block with an overall risk of development of spontaneous heart block, thereafter of approximately 2 % per year.

Another type of AV discordance occurs in atrial situs inversus with D-loop ventricles. Although there is evidence to suggest embryologic development of more than one atrioventricular node in this malformation, the posterior atrioventricular node tends to persist. These patients will, therefore, have a left-sided triangle of Koch, but will usually have an associated atrioventricular node displaced posteriorly and inferiorly. If there is the presence of a ventricular septal defect, the conduction system will run along the inferior border of the septal defect [197–201]. These findings suggest that the atrioventricular node is associated primarily with the morphologic right atrium.

Atrioventricular Discordance or Transposition of the Great Arteries

Abnormalities of outflow, and other conotruncal abnormalities and septal defects remote from the crux of the heart, usually do not affect the position and the location of the conduction system. In complete or dextro-transposition of the great arteries without a ventricular septal defect, the location of the conduction system is undisturbed. The atrioventricular anatomy is normal and there is normal atrioventricular concordance, therefore, allowing for normal atrioventricular conduction system development. However, these patients, if repaired by an atrial switch operation (Senning or Mustard operations) are subject to postoperative rhythm complications (Chap. 8).

Tricuspid Atresia

In tricuspid atresia, the atrioventricular node is typically associated with the atretic tricuspid valve in the right atrium. Studies confirm that the compact atrioventricular node in tricuspid atresia is situated in the right atrium inside the underdeveloped and diminutive triangle of Koch. The orifice of the coronary sinus can still be identified as the base of the triangle, but the tricuspid valve may be small and difficult to identify. A very short common bundle is described running towards the central fiber body, which then descends along the septum. Should a ventricular septal defect be present, the conduction system tends to travel along the lower margin of the ventricular septal defect on the side of the septum between the rudimentary right ventricle and left ventricle. Because of the diminutive right ventricle, left ventricular activation is predominant, resulting in a left superior frontal plane QRS axis (vector).

Ebstein's Anomaly

Ebstein's Anomaly is associated with a normal atrioventricular node and triangle of Koch. However, because of anatomic distortions associated with displacement of the septal and posterior leaflets of the tricuspid valve in association with right atrial and right ventricular enlargement, identification of the normal anatomy may be difficult. In these cases, the coronary sinus may serve as an especially useful marker for the delineation of the triangle of Koch. Because the anatomic and electrophysiologic atrioventricular groove are not anatomically the same in patients with Epstein's anomaly, it is often helpful to perform a right coronary artery angiogram to define the anatomic atrioventricular groove that can then be used to, more accurately, deduce abnormalities of electrical conduction in association with underlying anatomic structures. Simultaneous intracardiac electrophysiologic and pressure recording can demonstrate electrophysiologic-hemodynamic dissociation (see Chap. 23, Fig. 23.14). This cardiac abnormality is often associated with one or more accessory pathways and carries with it a higher incidence of atrial arrhythmias as well. An understanding of the anatomy and an effort to delineate present distortions can be critical for successful ablation at the time of the electrophysiologic study.

Heterotaxy Syndromes

These syndromes encompass a complex set of defects associated with "sidedness" confusion of organs in the thorax and/or abdomen. Two general subgroups exist: those with right atrial isomerism or "bilateral right sidedness" (also known as the Asplenia syndrome) and those with left atrial isomerism or "bilateral left sidedness" (also known as the Polysplenia syndrome). Typical cardiac features of bilateral right sidedness include an intact inferior vena cava, unroofed coronary sinus, total anomalous pulmonary venous return, complete atrioventricular septal defect, ventricular inversion and/or transposition of the great arteries, or double outlet right ventricle with pulmonary stenosis/atresia. Features of bilateral left sidedness include interrupted inferior vena cava, total or partial anomalous pulmonary venous return common atrium, complete or partial atrioventricular septal defects, normally related great vessels and/or double outlet right ventricle with or without pulmonary stenosis. The mode of inheritance of heterotaxy syndromes remains uncertain. There is some suggestion that there may be autosomal dominant and recessive forms; the majority of cases appear to be due to mutations in genes that encode sidedness in association with environmental insults. In a large study of the electrocardiograms of 126 patients with atrial isomerism, 67 with left atrial isomerism and 59 with right atrial isomerism, the cardiac rhythm in patients with left atrial isomerism, with supposed "absence" of normal sinus nodal tissue, tends to exhibit a wide range of P-wave axes suggesting a variety of atrial pacemaker locations. In addition, patients with left-sidedness exhibit sinus node dysfunction (80 % at 10-year follow-up). Furthermore, there are some instances of atrioventricular nodal abnormalities (15 %), while there were no atrioventricular node abnormalities in patients with bilateral right-sidedness. In contrast, patients with right atrial isomerism, with supposed "bilateral" sinus nodes, tended to exhibit P-wave axes predictive of either a high right-sided (between 0° and 89°) or high left-sided (between 90° and 179°) atrial pacemaker location. In patients with Asplenia syndrome (bilateral right-sidedness), ventricular inversion is more common and, thus, these patients are subject to expression of complete heart block. The reported cases of atrioventricular block were spontaneous, but heart surgery places the conduction system at additional risk.

These anatomic variants can be associated with two compact atrioventricular nodes where both anterior and posterior nodal structures are present. Conduction can occur through both atrioventricular nodes with interaction between the nodes to support reentrant tachycardia (Mönckeberg sling). In these cases, the posterior node seems to be a more developed structure and ultimately forms the connection to the His bundle

[197, 198]. Catheter ablation can successfully treat these patients [190–192, 198–201]. This entity seems to be more common in patients with right atrial isomerism.

Conclusion

Multiple congenital and acquired abnormalities of the conduction system can occur, driven primarily by a broad array of multiple genetic signals. The complex interaction of many of these factors and elements, driven by genetics and its interplay with the environment, remains incomplete, and offers stimulating areas for further investigation.

References

1. Gittenberger-de Groot AC, Bartelings MM, Deruiter MC, Poelmann RE. Basics of cardiac development for the understanding of congenital heart malformations. Pediatr Res. 2005;57:169–76.
2. Bruneau BG. Transcriptional regulation of vertebrate cardiac morphogenesis. Circ Res. 2002;90:509–19.
3. Srivastava D, Olson EN. A genetic blueprint for cardiac development. Nature. 2000;407:221–6.
4. Kirby ML, Waldo K. Cardiac development. New York: Oxford University Press; 2007.
5. Gourdie RG, Harris BS, Bond J, et al. His-Purkinje lineages and development. Novartis Found Symp. 2003;250:110–22; discussion 122–4, 276–9.
6. Gourdie RG, Harris BS, Bond J, et al. Development of the cardiac pacemaking and conduction system. Birth Defects Res C Embryo Today. 2003;69:46–57.
7. Gourdie RG, Kubalak S, Mikawa T. Conducting the embryonic heart: orchestrating development of specialized cardiac tissues. Trends Cardiovasc Med. 1999;9:18–26.
8. Gourdie RG, Mima T, Thompson RP, Mikawa T. Terminal diversification of the myocyte lineage generates Purkinje fibers of the cardiac conduction system. Development. 1995;121:1423–31.
9. Gourdie RG, Severs NJ, Green CR, Rothery S, Germroth P, Thompson RP. The spatial distribution and relative abundance of gap-junctional connexin40 and connexin43 correlate to functional properties of components of the cardiac atrioventricular conduction system. J Cell Sci. 1993;105:985–91.
10. Rentschler S, Morley GE, Fishman GI. Molecular and functional maturation of the murine cardiac conduction system. Cold Spring Harb Symp Quant Biol. 2002;67:353–61.
11. Rentschler S, Morley GE, Fishman GI. Patterning of the mouse conduction system. Novartis Found Symp. 2003;250:194–205; discussion 205–9, 276–9.
12. Rentschler S, Harris BS, Kuznekoff L, et al. Notch signaling regulates murine atrioventricular conduction and the formation of accessory pathways. J Clin Invest. 2011;121:525–33.
13. Rentschler S, Vaidya DM, Tamaddon H, et al. Visualization and functional characterization of the developing murine cardiac conduction system. Development. 2001;128:1785–92.
14. Rentschler S, Yen AH, Lu J, et al. Myocardial Notch signaling reprograms cardiomyocytes to a conduction-like phenotype. Circulation. 2012;126:1058–66.
15. Rentschler S, Zander J, Meyers K, et al. Neuregulin-1 promotes formation of the murine cardiac conduction system. Proc Natl Acad Sci U S A. 2002;99:10464–9.
16. Pennisi DJ, Rentschler S, Gourdie RG, Fishman GI, Mikawa T. Induction and patterning of the cardiac conduction system. Int J Dev Biol. 2002;46:765–75.
17. Wenink A. Development of the human cardiac conducting system. J Anat. 1976;121:617.
18. Gorza L, Gundersen K, Lomo T, Schiaffino S, Westgaard RH. Slow-to-fast transformation of denervated soleus muscles by chronic high-frequency stimulation in the rat. J Physiol. 1988;402:627–49.
19. Gorza L, Saggin L, Sartore S, Ausoni S. An embryonic-like myosin heavy chain is transiently expressed in nodal conduction tissue of the rat heart. J Mol Cell Cardiol. 1988;20:931–41.
20. Gorza L, Schiaffino S, Vitadello M. Heart conduction system: a neural crest derivative? Brain Res. 1988;457:360–6.
21. Gorza L, Thornell LE, Schiaffino S. Nodal myosin distribution in the bovine heart during prenatal development: an immunohistochemical study. Circ Res. 1988;62:1182–90.
22. Maier A, Gorza L, Schiaffino S, Pette D. A combined histochemical and immunohistochemical study on the dynamics of fast-to-slow fiber transformation in chronically stimulated rabbit muscle. Cell Tissue Res. 1988;254:59–68.
23. Blom NA, Gittenberger-de Groot AC, DeRuiter MC, Poelmann RE, Mentink MMT, Ottenkamp J. Development of the cardiac conduction tissue in human embryos using HNK-1 antigen expression—possible relevance for understanding of abnormal atrial automaticity. Circulation. 1999;99:800–6.
24. DeRuiter MC, Hahurij N, Mahtab EA, Douglas YL, Poelmann RE, Gittenberger-de Groot AC. The influence of immigrating extracardiac cells during embryonic development. Wien Klin Wochenschr. 2007;119:13–5.
25. Douglas YL, Mahtab EA, Jongbloed MR, et al. Pulmonary vein, dorsal atrial wall and atrial septum abnormalities in podoplanin knockout mice with disturbed posterior heart field contribution. Pediatr Res. 2009;65:27–32.
26. Jongbloed MR, Vicente-Steijn R, Douglas YL, et al. Expression of Id2 in the second heart field and cardiac defects in Id2 knock-out mice. Dev Dyn. 2011;240:2561–77.

27. Mahtab EA, Gittenberger-de Groot AC, Vicente-Steijn R, et al. Disturbed myocardial connexin 43 and N-cadherin expressions in hypoplastic left heart syndrome and borderline left ventricle. J Thorac Cardiovasc Surg. 2012;144:1315–22.
28. Mahtab EA, Vicente-Steijn R, Hahurij ND, et al. Podoplanin deficient mice show a RhoA-related hypoplasia of the sinus venosus myocardium including the sinoatrial node. Dev Dyn. 2009;238:183–93.
29. Mahtab EA, Wijffels MC, Van Den Akker NM, et al. Cardiac malformations and myocardial abnormalities in podoplanin knockout mouse embryos: Correlation with abnormal epicardial development. Dev Dyn. 2008;237:847–57.
30. van Loo PF, Mahtab EA, Wisse LJ, et al. Transcription factor Sp3 knockout mice display serious cardiac malformations. Mol Cell Biol. 2007;27:8571–82.
31. Vicente-Steijn R, Kolditz DP, Mahtab EA, et al. Electrical activation of sinus venosus myocardium and expression patterns of RhoA and Isl-1 in the chick embryo. J Cardiovasc Electrophysiol. 2010;21:1284–92.
32. Weeke-Klimp A, Bax NA, Bellu AR, et al. Epicardium-derived cells enhance proliferation, cellular maturation and alignment of cardiomyocytes. J Mol Cell Cardiol. 2010;49:606–16.
33. Breiteneder-Geleff S, Matsui K, Soleiman A, et al. Podoplanin, novel 43-kd membrane protein of glomerular epithelial cells, is down-regulated in puromycin nephrosis. Am J Pathol. 1997;151: 1141–52.
34. Schacht V, Ramirez MI, Hong Y-K, et al. T1alpha/podoplanin deficiency disrupts normal lymphatic vasculature formation and causes lymphedema. EMBO J. 2003;22:3546–56.
35. Wetterwald A, Hoffstetter W, Cecchini MG, et al. Characterization and cloning of the E11 antigen, a marker expressed by rat osteoblasts and osteocytes. Bone. 1996;18:125–32.
36. Williams MC, Cao Y, Hinds A, Rishi AK, Wetterwald A. T1 alpha protein is developmentally regulated and expressed by alveolar type I cells, choroid plexus, and ciliary epithelia of adult rats. Am J Respir Cell Mol Biol. 1996;14:577–85.
37. Astarita JL, Acton SE, Turley SJ. Podoplanin: emerging functions in development, the immune system, and cancer. Front Immunol. 2012;3:283.
38. Davies MJ, Anderson RH. The conduction system of the heart. London: Butterworth-Heinemann; 1983.
39. Oosthoek P, Virágh S, Mayen A, Van Kempen M, Lamers W, Moorman A. Immunohistochemical delineation of the conduction system. I: The sinoatrial node. Circ Res. 1993;73:473–81.
40. Wessels A, Vermeulen J, Verbeek F, et al. Spatial distribution of "tissue-specific" antigens in the developing human heart and skeletal muscle III. An immunohistochemical analysis of the distribution of the neural tissue antigen G1N2 in the embryonic heart; implications for the development of the atrioventricular conduction system. Anat Rec. 1992;232:97–111.
41. Kamino K. Optical approaches to ontogeny of electrical activity and related functional organization during early heart development. Physiol Rev. 1991;71:53–91.
42. van den Hoff MJ, Kruithof BP, Moorman AF, Markwald RR, Wessels A. Formation of myocardium after the initial development of the linear heart tube. Dev Biol. 2001;240:61–76.
43. de Jong F, Opthof T, Wilde AA, et al. Persisting zones of slow impulse conduction in developing chicken hearts. Circ Res. 1992;71:240–50.
44. Manasek FJ, Burnside B, Stroman J. The sensitivity of developing cardiac myofibrils to cytochalasin-B (electron microscopy-polarized light-Z-bands-heartbeat). Proc Natl Acad Sci U S A. 1972;69:308–12.
45. Manasek FJ, Burnside MB, Waterman RE. Myocardial cell shape change as a mechanism of embryonic heart looping. Dev Biol. 1972;29:349–71.
46. Manasek FJ, Monroe RG. Early cardiac morphogenesis is independent of function. Dev Biol. 1972;27:584–8.
47. Fishman MC, Chien KR. Fashioning the vertebrate heart: earliest embryonic decisions. Development. 1997;124:2099–117.
48. Wessels A, Markman MW, Vermeulen JL, Anderson RH, Moorman AF, Lamers WH. The development of the atrioventricular junction in the human heart. Circ Res. 1996;78:110–7.
49. Biel M, Schneider A, Wahl C. Cardiac HCN channels: structure, function, and modulation. Trends Cardiovasc Med. 2002;12:206–12.
50. Xavier-Neto J, Neville CM, Shapiro MD, et al. A retinoic acid-inducible transgenic marker of sino-atrial development in the mouse heart. Development. 1999;126:2677–87.
51. Christoffels VM, Smits GJ, Kispert A, Moorman AF. Development of the pacemaker tissues of the heart. Circ Res. 2010;106:240–54.
52. Dobrzynski H, Boyett MR, Anderson RH. New insights into pacemaker activity: promoting understanding of sick sinus syndrome. Circulation. 2007;115:1921–32.
53. Mangoni ME, Nargeot J. Genesis and regulation of the heart automaticity. Physiol Rev. 2008;88: 919–82.
54. Koushik SV, Wang J, Rogers R, et al. Targeted inactivation of the sodium-calcium exchanger (Ncx1) results in the lack of a heartbeat and abnormal myofibrillar organization. FASEB J. 2001;15:1209–11.
55. Christoffels VM, Habets PE, Franco D, et al. Chamber formation and morphogenesis in the developing mammalian heart. Dev Biol. 2000;223:266–78.
56. Christoffels VM, Moorman AF. Development of the cardiac conduction system: why are some regions of the heart more arrhythmogenic than others? Circ Arrhythm Electrophysiol. 2009;2:195–207.
57. Fozzard HA. Cardiac sodium and calcium channels: a history of excitatory currents. Cardiovasc Res. 2002;55:1–8.
58. Fozzard HA, Kyle JW. Do defects in ion channel glycosylation set the stage for lethal cardiac arrhythmias? Sci STKE. 2002;2002:pe19.

59. Hilber K, Sandtner W, Kudlacek O, et al. Interaction between fast and ultra-slow inactivation in the voltage-gated sodium channel. Does the inactivation gate stabilize the channel structure? J Biol Chem. 2002;277:37105–15.
60. Mikawa T, Hurtado R. Development of the cardiac conduction system. Semin Cell Dev Biol. 2007; 18:90–100.
61. Virágh S, Challice C. The development of the conduction system in the mouse embryo heart: I. The first embryonic AV conduction pathway. Dev Biol. 1977;56:382–96.
62. Alcolea S, Jarry-Guichard T, de Bakker J, et al. Replacement of connexin40 by connexin45 in the mouse: impact on cardiac electrical conduction. Circ Res. 2004;94:100–9.
63. Alcolea S, Theveniau-Ruissy M, Jarry-Guichard T, et al. Downregulation of connexin 45 gene products during mouse heart development. Circ Res. 1999;84:1365–79.
64. Coppen SR, Kodama I, Boyett MR, et al. Connexin45, a major connexin of the rabbit sinoatrial node, is co-expressed with connexin43 in a restricted zone at the nodal-crista terminalis border. J Histochem Cytochem. 1999;47:907–18.
65. Coppen SR, Severs NJ, Gourdie RG. Connexin45 (α6) expression delineates an extended conduction system in the embryonic and mature rodent heart. Dev Genet. 1999;24:82–90.
66. Nishii K, Kumai M, Shibata Y. Regulation of the epithelial-mesenchymal transformation through gap junction channels in heart development. Trends Cardiovasc Med. 2001;11:213–8.
67. Shibata Y, Kumai M, Nishii K, Nakamura K. Diversity and molecular anatomy of gap junctions. Med Electron Microsc. 2001;34:153–9.
68. Abramson DI, Margolin S. A Purkinje conduction network in the myocardium of the mammalian ventricles. J Anat. 1936;70:250.
69. Hyer J, Johansen M, Prasad A, et al. Induction of Purkinje fiber differentiation by coronary arterialization. Proc Natl Acad Sci U S A. 1999;96: 13214–8.
70. Takebayashi-Suzuki K, Yanagisawa M, Gourdie RG, Kanzawa N, Mikawa T. In vivo induction of cardiac Purkinje fiber differentiation by coexpression of preproendothelin-1 and endothelin converting enzyme-1. Development. 2000;127:3523–32.
71. Patel R, Kos L. Endothelin-1 and Neuregulin-1 convert embryonic cardiomyocytes into cells of the conduction system in the mouse. Dev Dyn. 2005; 233:20–8.
72. Gassanov N, Er F, Zagidullin N, Hoppe UC. Endothelin induces differentiation of ANP-EGFP expressing embryonic stem cells towards a pacemaker phenotype. FASEB J. 2004;18:1710–2.
73. Watanabe M, Chuck ET, Rothenberg F, Rosenbaum DS. Developmental transitions in cardiac conduction. Novartis Found Symp. 2003;250:68–75; discussion 76–9, 276–9.
74. Watanabe M, Timm M, Fallah-Najmabadi H. Cardiac expression of polysialylated NCAM in the chicken embryo: correlation with the ventricular conduction system. Dev Dyn. 1992;194:128–41.
75. Cai C-L, Liang X, Shi Y, et al. Isl1 identifies a cardiac progenitor population that proliferates prior to differentiation and contributes a majority of cells to the heart. Dev Cell. 2003;5:877–89.
76. Christoffels VM, Hoogaars WMH, Tessari A, Clout DEW, Moorman AFM, Campione M. T-box transcription factor Tbx2 represses differentiation and formation of the cardiac chambers. Dev Dyn. 2004;229:763–70.
77. Chuck ET, Watanabe M. Differential expression of PSA-NCAM and HNK-1 epitopes in the developing cardiac conduction system of the chick. Dev Dyn. 1997;209:182–95.
78. Davis DL, Edwards AV, Juraszek AL, Phelps A, Wessels A, Burch JB. A GATA-6 gene heart-region-specific enhancer provides a novel means to mark and probe a discrete component of the mouse cardiac conduction system. Mech Dev. 2001;108: 105–19.
79. Franco D, Campione M. The role of Pitx2 during cardiac development. Linking left-right signaling and congenital heart diseases. Trends Cardiovasc Med. 2003;13:157–63.
80. Gaussin V, Morley GE, Cox L, et al. Alk3/Bmpr1a receptor is required for development of the atrioventricular canal into valves and annulus fibrosus. Circ Res. 2005;97:219–26.
81. Ji X, Chen D, Xu C, Harris SE, Mundy GR, Yoneda T. Patterns of gene expression associated with BMP-2-induced osteoblast and adipocyte differentiation of mesenchymal progenitor cell 3T3-F442A. J Bone Miner Metab. 2000;18:132–9.
82. Kuo CT, Morrisey EE, Anandappa R, et al. GATA4 transcription factor is required for ventral morphogenesis and heart tube formation. Genes Dev. 1997;11:1048–60.
83. Liu C, Liu W, Palie J, Lu MF, Brown NA, Martin JF. Pitx2c patterns anterior myocardium and aortic arch vessels and is required for local cell movement into atrioventricular cushions. Development. 2002;129:5081–91.
84. MacNeill C, French R, Evans T, Wessels A, Burch JB. Modular regulation of cGATA-5 gene expression in the developing heart and gut. Dev Biol. 2000;217: 62–76.
85. Moskowitz IPG, Pizard A, Patel VV, et al. The T-Box transcription factor Tbx5 is required for the patterning and maturation of the murine cardiac conduction system. Development. 2004;131:4107–16.
86. Munshi NV. Gene regulatory networks in cardiac conduction system development. Circ Res. 2012;110: 1525–37.
87. Christoffels VM, Mommersteeg MTM, Trowe M-O, et al. Formation of the venous pole of the heart from an Nkx2-5-negative precursor population requires Tbx18. Circ Res. 2006;98:1555–63.

88. Hoogaars WMH, Engel A, Brons JF, et al. Tbx3 controls the sinoatrial node gene program and imposes pacemaker function on the atria. Genes Dev. 2007;21:1098–112.
89. Hoogaars WMH, Tessari A, Moorman AFM, et al. The transcriptional repressor Tbx3 delineates the developing central conduction system of the heart. Cardiovasc Res. 2004;62:489–99.
90. Davenport TG, Jerome-Majewska LA, Papaioannou VE. Mammary gland, limb and yolk sac defects in mice lacking Tbx3, the gene mutated in human ulnar mammary syndrome. Development. 2003;130: 2263–73.
91. Habets PEMH, Moorman AFM, Clout DEW, et al. Cooperative action of Tbx2 and Nkx2.5 inhibits ANF expression in the atrioventricular canal: implications for cardiac chamber formation. Genes Dev. 2002;16:1234–46.
92. Thomas PS, Kasahara H, Edmonson AM, et al. Elevated expression of Nkx-2.5 in developing myocardial conduction cells. Anat Rec. 2001;263: 307–13.
93. Jay PY. Genetic wiring diagram of the cardiac conduction system. Circulation. 2007;116:2520–2.
94. Jay PY, Harris BS, Maguire CT, et al. Nkx2-5 mutation causes anatomic hypoplasia of the cardiac conduction system. J Clin Invest. 2004;113:1130–7.
95. Jay PY, Maguire CT, Wakimoto H, Izumo S, Berul CI. Absence of Msx2 does not affect cardiac conduction or rescue conduction defects associated with Nkx2-5 mutation. J Cardiovasc Electrophysiol. 2005;16:82–5.
96. Kasahara H, Wakimoto H, Liu M, et al. Progressive atrioventricular conduction defects and heart failure in mice expressing a mutant Csx/Nkx2.5 homeoprotein. J Clin Invest. 2001;108:189–201.
97. Linhares VLF, Almeida NAS, Menezes DC, et al. Transcriptional regulation of the murine Connexin40 promoter by cardiac factors Nkx2-5, GATA4 and Tbx5. Cardiovasc Res. 2004;64:402–11.
98. Satokata I, Ma L, Ohshima H, et al. Msx2 deficiency in mice causes pleiotropic defects in bone growth and ectodermal organ formation. Nat Genet. 2000;24:391–5.
99. Ismat FA, Zhang M, Kook H, et al. Homeobox protein Hop functions in the adult cardiac conduction system. Circ Res. 2005;96:898–903.
100. Blaschke RJ, Hahurij ND, Kuijper S, et al. Targeted mutation reveals essential functions of the homeodomain transcription factor Shox2 in sinoatrial and pacemaking development. Circulation. 2007;115:1830–8.
101. Blaschke RJ, Monaghan AP, Schiller S, et al. SHOT, a SHOX-related homeobox gene, is implicated in craniofacial, brain, heart, and limb development. Proc Natl Acad Sci U S A. 1998;95:2406–11.
102. Mommersteeg MTM, Brown NA, Prall OWJ, et al. Pitx2c and Nkx2-5 are required for the formation and identity of the pulmonary myocardium. Circ Res. 2007;101:902–9.
103. Mommersteeg MTM, Hoogaars WMH, Prall OWJ, et al. Molecular pathway for the localized formation of the sinoatrial node. Circ Res. 2007;100:354–62.
104. Kitajima S, Miyagawa-Tomita S, Inoue T, Kanno J, Saga Y. Mesp1-nonexpressing cells contribute to the ventricular cardiac conduction system. Dev Dyn. 2006;235:395–402.
105. Molkentin JD. The zinc finger-containing transcription factors GATA-4, -5, and -6. Ubiquitously expressed regulators of tissue-specific gene expression. J Biol Chem. 2000;275:38949–52.
106. Takebayashi-Suzuki K, Pauliks LB, Eltsefon Y, Mikawa T. Purkinje fibers of the avian heart express a myogenic transcription factor program distinct from cardiac and skeletal muscle. Dev Biol. 2001;234:390–401.
107. Morrisey EE, Ip HS, Tang Z, Lu MM, Parmacek MS. GATA-5: a transcriptional activator expressed in a novel temporally and spatially-restricted pattern during embryonic development. Dev Biol. 1997;183:21–36.
108. Edwards AV, Davis DL, Juraszek AL, Wessels A, Burch JBE. Transcriptional regulation in the mouse atrioventricular conduction system. Novartis Found Symp. 2003;250:177–89.
109. Kupershmidt S, Yang T, Anderson ME, et al. Replacement by homologous recombination of the minK gene with lacZ reveals restriction of minK expression to the mouse cardiac conduction system. Circ Res. 1999;84:146–52.
110. Drici MD, Arrighi I, Chouabe C, et al. Involvement of IsK-associated K+ channel in heart rate control of repolarization in a murine engineered model of Jervell and Lange-Nielsen syndrome. Circ Res. 1998;83:95–9102.
111. Kondo RP, Anderson RH, Kupershmidt S, Roden DM, Evans SM. Development of the cardiac conduction system as delineated by minK-lacZ. J Cardiovasc Electrophysiol. 2003;14:383–91.
112. Stroud DM, Darrow BJ, Kim SD, et al. Complex genomic rearrangement in CCS-LacZ transgenic mice. Genesis. 2007;45:76–82.
113. Hagenbuch B, Meier PJ. The superfamily of organic anion transporting polypeptides. Biochim Biophys Acta. 2003;1609:1–18.
114. Gonzalez MD, Contreras LJ, Jongbloed MRM, et al. Left atrial tachycardia originating from the mitral annulus–aorta junction. Circulation. 2004;110:3187–92.
115. Jongbloed MRM, Schalij MJ, Poelmann RE, et al. Embryonic conduction tissue: a spatial correlation with adult arrhythmogenic areas. J Cardiovasc Electrophysiol. 2004;15:349–55.
116. Jongbloed MRM, Wijffels MCEF, Schalij MJ, et al. Development of the right ventricular inflow tract and moderator band: a possible morphological and functional explanation for Mahaim tachycardia. Circ Res. 2005;96:776–83.
117. Viswanathan S, Burch JBE, Fishman GI, Moskowitz IP, Benson DW. Characterization of sinoatrial node

in four conduction system marker mice. J Mol Cell Cardiol. 2007;42:946–53.
118. Garcia-Frigola C, Shi Y, Evans SM. Expression of the hyperpolarization-activated cyclic nucleotide-gated cation channel HCN4 during mouse heart development. Gene Expr Patterns. 2003;3:777–83.
119. Stieber J, Herrmann S, Feil S, et al. The hyperpolarization-activated channel HCN4 is required for the generation of pacemaker action potentials in the embryonic heart. Proc Natl Acad Sci U S A. 2003;100:15235–40.
120. Kamino K, Hirota A, Fujii S. Localization of pacemaking activity in early embryonic heart monitored using voltage-sensitive dye. Nature. 1981;290:595–7.
121. Van Mierop LH. Location of pacemaker in chick embryo heart at the time of initiation of heartbeat. Am J Physiol. 1967;212:407–15.
122. Delorme B, Dahl E, Jarry-Guichard T, et al. Expression pattern of connexin gene products at the early developmental stages of the mouse cardiovascular system. Circ Res. 1997;81:423–37.
123. Delorme B, Dahl E, Jarry-guichard T, et al. Developmental regulation of connexin 40 gene expression in mouse heart correlates with the differentiation of the conduction system. Dev Dyn. 1995;204:358–71.
124. Yeager M. Structure of cardiac gap junction intercellular channels. J Struct Biol. 1998;121:231–45.
125. Bevilacqua LM, Simon AM, Maguire CT, et al. A targeted disruption in connexin40 leads to distinct atrioventricular conduction defects. J Interv Card Electrophysiol. 2000;4:459–67.
126. Simon AM, Goodenough DA, Paul DL. Mice lacking connexin40 have cardiac conduction abnormalities characteristic of atrioventricular block and bundle branch block. Curr Biol. 1998;8:295–8.
127. Tamaddon HS, Vaidya D, Simon AM, Paul DL, Jalife J, Morley GE. High-resolution optical mapping of the right bundle branch in connexin40 knockout mice reveals slow conduction in the specialized conduction system. Circ Res. 2000;87:929–36.
128. Fromaget C, el Aoumari A, Dupont E, Briand JP, Gros D. Changes in the expression of connexin 43, a cardiac gap junctional protein, during mouse heart development. J Mol Cell Cardiol. 1990;22:1245–58.
129. Reaume AG, de Sousa PA, Kulkarni S, et al. Cardiac malformation in neonatal mice lacking connexin43. Science. 1995;267:1831–4.
130. Nishii K, Kumai M, Egashira K, et al. Mice lacking connexin45 conditionally in cardiac myocytes display embryonic lethality similar to that of germline knockout mice without endocardial cushion defect. Cell Commun Adhes. 2003;10:365–9.
131. Kreuzberg MM, Schrickel JW, Ghanem A, et al. Connexin30.2 containing gap junction channels decelerate impulse propagation through the atrioventricular node. Proc Natl Acad Sci U S A. 2006;103:5959–64.
132. Kreuzberg MM, Sohl G, Kim J-S, Verselis VK, Willecke K, Bukauskas FF. Functional properties of mouse connexin30.2 expressed in the conduction system of the heart. Circ Res. 2005;96:1169–77.
133. Kreuzberg MM, Willecke K, Bukauskas FF. Connexin-mediated cardiac impulse propagation: connexin 30.2 slows atrioventricular conduction in mouse heart. Trends Cardiovasc Med. 2006;16:266–72.
134. Anderson RH, Becker AE, Tranum-Jensen J, Janse MJ. Anatomico-electrophysiological correlations in the conduction system—a review. Br Heart J. 1981;45:67–82.
135. Kolditz DP, Wijffels MCEF, Blom NA, et al. Persistence of functional atrioventricular accessory pathways in postseptated embryonic avian hearts: implications for morphogenesis and functional maturation of the cardiac conduction system. Circulation. 2007;115:17–26.
136. Gollob MH, Green MS, Tang AS, et al. Identification of a gene responsible for familial Wolff-Parkinson-White syndrome. N Engl J Med. 2001;344:1823–31.
137. Gollob MH, Green MS, Tang AS, Roberts R. PRKAG2 cardiac syndrome: familial ventricular preexcitation, conduction system disease, and cardiac hypertrophy. Curr Opin Cardiol. 2002; 17:229–34.
138. Sidhu JS, Rajawat YS, Rami TG, et al. Transgenic mouse model of ventricular preexcitation and atrioventricular reentrant tachycardia induced by an AMP-activated protein kinase loss-of-function mutation responsible for Wolff-Parkinson-White syndrome. Circulation. 2005;111:21–9.
139. Patel VV, Arad M, Moskowitz IPG, et al. Electrophysiologic characterization and postnatal development of ventricular pre-excitation in a mouse model of cardiac hypertrophy and Wolff-Parkinson-White syndrome. J Am Coll Cardiol. 2003;42: 942–51.
140. Arad M, Moskowitz IP, Patel VV, et al. Transgenic mice overexpressing mutant PRKAG2 define the cause of Wolff-Parkinson-White syndrome in glycogen storage cardiomyopathy. Circulation. 2003;107: 2850–6.
141. Arad M, Seidman CE, Seidman JG. AMP-activated protein kinase in the heart: role during health and disease. Circ Res. 2007;100:474–88.
142. Kistler PM, Sanders P, Hussin A, et al. Focal atrial tachycardia arising from the mitral annulus: electrocardiographic and electrophysiologic characterization. J Am Coll Cardiol. 2003;41:2212–9.
143. Morton JB, Sanders P, Das A, Vohra JK, Sparks PB, Kalman JM. Focal atrial tachycardia arising from the tricuspid annulus: electrophysiologic and electrocardiographic characteristics. J Cardiovasc Electrophysiol. 2001;12:653–9.
144. McGuire MA, de Bakker JM, Vermeulen JT, et al. Atrioventricular junctional tissue. Discrepancy between histological and electrophysiological characteristics. Circulation. 1996;94:571–7.
145. Lev M. The normal anatomy of the conduction system in man and its pathlogy in atriventricular block. Ann N Y Acad Sci. 1964;111:817–29.

146. Moorman AF, Christoffels VM, Anderson RH. Anatomic substrates for cardiac conduction. Heart Rhythm. 2005;2:875–86.
147. Anderson RH, Yanni J, Boyett MR, Chandler NJ, Dobrzynski H. The anatomy of the cardiac conduction system. Clin Anat. 2009;22:99–113.
148. Anderson RH, Ho SY. Anatomy of the atrioventricular junctions with regard to ventricular preexcitation. Pacing Clin Electrophysiol. 1997;20:2072–6.
149. Anderson RH, Ho SY. The architecture of the sinus node, the atrioventricular conduction axis, and the internodal atrial myocardium. J Cardiovasc Electrophysiol. 1998;9:1233–48.
150. Gulino SP. Examination of the cardiac conduction system: forensic application in cases of sudden cardiac death. Am J Forensic Med Pathol. 2003;24: 227–38.
151. Keith A, Flack M. The form and nature of the muscular connections between the primary divisions of the vertebrate heart. J Anat Physiol. 1907;41: 172–89.
152. Titus JL. Normal anatomy of the human cardiac conduction system. Anesth Analg. 1973;52:508–14.
153. Titus JL, Daugherty GW, Edwards JE. Anatomy of the atrioventricular conduction system in ventricular septal defect. Circulation. 1963;28:72–81.
154. Truex RC. Comparative anatomy and functional considerations of the cardiac conduction system. In: The specialized tissues of the heart. Amsterdam: Elsevier; 1961. p. 22–43.
155. James TN. Anatomy of the human sinus node. Anat Rec. 1961;141:109–39.
156. Anderson KR, Ho SY, Anderson RH. Location and vascular supply of sinus node in human heart. Br Heart J. 1979;41:28–32.
157. Saremi F, Krishnan S. Cardiac conduction system: anatomic landmarks relevant to interventional electrophysiologic techniques demonstrated with 64-detector CT. Radiographics. 2007;27:1539–65; discussion 1566–7.
158. Hoogaars WM, Barnett P, Moorman AF, Christoffels VM. T-box factors determine cardiac design. Cell Mol Life Sci. 2007;64:646–60.
159. Moorman AF, Soufan AT, Hagoort J, de Boer PA, Christoffels VM. Development of the building plan of the heart. Ann N Y Acad Sci. 2004;1015:171–81.
160. Soufan AT, van den Hoff MJ, Ruijter JM, et al. Reconstruction of the patterns of gene expression in the developing mouse heart reveals an architectural arrangement that facilitates the understanding of atrial malformations and arrhythmias. Circ Res. 2004;95:1207–15.
161. Corradi D, Maestri R, Macchi E, Callegari S. The atria: from morphology to function. J Cardiovasc Electrophysiol. 2011;22:223–35.
162. Ho SY, Anderson RH, Sanchez-Quintana D. Atrial structure and fibres: morphologic bases of atrial conduction. Cardiovasc Res. 2002;54:325–36.
163. Goldberg CS, Caplan MJ, Heidelberger KP, Dick M. The dimensions of the triangle of Koch in children. Am J Cardiol. 1999;83:117–20, A9.
164. Becker DL, Cook JE, Davies CS, Evans WH, Gourdie RG. Expression of major gap junction connexin types in the working myocardium of eight chordates. Cell Biol Int. 1998;22:527–43.
165. Inoue S, Becker AE. Posterior extensions of the human compact atrioventricular node: a neglected anatomic feature of potential clinical significance. Circulation. 1998;97:188–93.
166. Medkour D, Becker AE, Khalife K, Billette J. Anatomic and functional characteristics of a slow posterior AV nodal pathway: role in dual-pathway physiology and reentry. Circulation. 1998;98:164–74.
167. Massing GK, James TN. Anatomical configuration of the His bundle and bundle branches in the human heart. Circulation. 1976;53:609–21.
168. Gittenberger-de Groot AC, Blom NM, Aoyama N, Sucov H, Wenink AC, Poelmann RE. The role of neural crest and epicardium-derived cells in conduction system formation. Novartis Found Symp. 2003;250:125–34; discussion 134–41, 276–9.
169. Crick S, Sheppard M, Anderson R, Polak J, Wharton J. A quantitative study of nerve distribution in the conduction system of the guinea pig heart. J Anat. 1996;188:403.
170. Crick SJ, Sheppard MN, Ho SY, Anderson RH. Localisation and quantitation of autonomic innervation in the porcine heart I: conduction system. J Anat. 1999;195:341–57.
171. Tomita Y, Matsumura K, Wakamatsu Y, et al. Cardiac neural crest cells contribute to the dormant multipotent stem cell in the mammalian heart. J Cell Biol. 2005;170:1135–46.
172. Chow LT, Chow SS, Anderson RH, Gosling JA. Autonomic innervation of the human cardiac conduction system: changes from infancy to senility—an immunohistochemical and histochemical analysis. Anat Rec. 2001;264(2):169–82.
173. Anderson RH, Brown NA, Mohun TJ, Moorman AF. Insights from cardiac development relevant to congenital defects and adult clinical anatomy. J Cardiovasc Transl Res. 2013;6:107–17.
174. Feldt RE, Puga WD, Seward FJ, Adams FE. Atrial septal defects and atrioventricular canal. In: Adams FE, editor. Heart disease in infants, children and adolescents. Baltimore: Williams & Wilkins; 1983.
175. Adachi I, Uemura H, McCarthy KP, Ho SY. Surgical anatomy of atrioventricular septal defect. Asian Cardiovasc Thorac Ann. 2008;16:497–502.
176. Kirchhoff S, Nelles E, Hagendorff A, Kruger O, Traub O, Willecke K. Reduced cardiac conduction velocity and predisposition to arrhythmias in connexin40-deficient mice. Curr Biol. 1998;8:299–302.
177. Moskowitz IP, Kim JB, Moore ML, Wolf CM, Peterson MA, Shendure J, Nobrega MA, Yokota Y, Berul C, Izumo S, Seidman JG, Seidman CE. A molecular pathway including Id2, Tbx5, and Nkx2-5 required for cardiac conduction system development. Cell. 2007;129(7):1365–76.
178. Briggs LE, Takeda M, Cuadra AE, Wakimoto H, Marks MH, Walker AJ, Seki T, Oh SP, Lu JT, Sumners C, Raizada MK, Horikoshi N, Weinberg

EO, Yasui K, Ikeda Y, Chien KR, Kasahara H. Perinatal loss of Nkx2-5 results in rapid conduction and contraction defects. Circ Res. 2008;103(6):580–90.
179. Takeda M, Briggs LE, Wakimoto H, Marks MH, Warren SA, Lu JT, Weinberg EO, Robertson KD, Chien KR, Kasahara H. Slow progressive conduction and contraction defects in loss of Nkx2-5 mice after cardiomyocyte terminal differentiation. Lab Invest. 2009;89(9):983–93.
180. Allwork SP, Bentall HH, Becker AE, et al. Congenitally corrected transposition of the great arteries: morphologic study of 32 cases. Am J Cardiol. 1976;38:910–23.
181. Anderson RH, Danielson GK, Maloney JD, Becker AE. Atrioventricular bundle in corrected transposition. Ann Thorac Surg. 1978;26:95–7.
182. Anderson RH, Arnold R, Wilkinson JL. The conducting system in congenitally corrected transposition. Lancet. 1973;1:1286–8.
183. Anderson RH, Becker AE, Arnold R, Wilkinson JL. The conducting tissues in congenitally corrected transposition. Circulation. 1974;50:911–23.
184. Hausen WJ. AV-conduction disorders in corrected transposition of the great vessels. Z Kreislaufforsch. 1968;57:334–44.
185. Attie F, Iturralde P, Zabal C, et al. Congenitally corrected transposition with atrioventricular septal defect. Cardiol Young. 1998;8:472–8.
186. Daliento L, Corrado D, Buja G, John N, Nava A, Thiene G. Rhythm and conduction disturbances in isolated, congenitally corrected transposition of the great arteries. Am J Cardiol. 1986;58:314–8.
187. Wilkinson JL, Anderson RH. Anatomy of discordant atrioventricular connections. World J Pediatr Congenit Heart Surg. 2011;2:43–53.
188. Dick M, Norwood WI, Chipman C, Castaneda AR. Intraoperative recording of specialized atrioventricular conduction tissue electrograms in 47 patients. Circulation. 1979;59:150–60.
189. Liao Z, Chang Y, Ma J, et al. Atrioventricular node reentrant tachycardia in patients with congenitally corrected transposition of the great arteries and results of radiofrequency catheter ablation. Circ Arrhythm Electrophysiol. 2012;5:1143–8.
190. Epstein MR, Saul JP, Weindling SN, Triedman JK, Walsh EP. Atrioventricular reciprocating tachycardia involving twin atrioventricular nodes in patients with complex congenital heart disease. J Cardiovasc Electrophysiol. 2001;12:671–9.
191. Miyazaki A, Sakaguchi H, Uchiyama T, Kurita T, Ohuchi H, Yamada O. Accessory pathway reciprocating tachycardia involving twin AV nodes in a patient with atrioventricular discordance and mitral atresia. Pacing Clin Electrophysiol. 2010;33:637–40.
192. Takahashi K, Kurosawa H, Nakanishi T. Twin atrioventricular nodes connecting to sling of conduction tissue in congenitally corrected transposition associated with straddling tricuspid valve. World J Pediatr Congen Heart Surg. 2011;2:312–5.
193. Amikam S, Lemer J, Kishon Y, Riss E, Neufeld HN. Complete heart block in an adult with corrected transposition of the great arteries treated with permanent pacemaker. Thorax. 1979;34:547–9.
194. Anderson RH. The conduction tissues in congenitally corrected transposition. Ann Thorac Surg. 2004;77:1881–2.
195. Okamoto Y, Yamada K, Nozaki A, Watanabe Y. Disturbance of conduction system in corrected transposition of the great vessels. Nihon Geka Hokan. 1980;49:680–8.
196. Thiene G, Nava A, Rossi L. The conduction system in corrected transposition with situs inversus. Eur J Cardiol. 1977;6:57–70.
197. Miyazaki A, Kagisaki K, Kurita T, Yamada O. Corrected transposition of the great arteries involving situs inversus {I, D, D} and mild pulmonary stenosis: conduction system identified during preoperative investigations for a double-switch operation. Pediatr Cardiol. 2009;30:516–9.
198. Bae EJ, Noh CI, Choi JY, et al. Twin AV node and induced supraventricular tachycardia in Fontan palliation patients. Pacing Clin Electrophysiol. 2005;28:126–34.
199. Solomon MH, Winn KJ, White RD, et al. Kartagener's syndrome with corrected transposition. Conducting system studies and coronary arterial occlusion complicating valvular replacement. Chest. 1976;69:677–80.
200. Cheung YF, Cheng VY, Yung TC, Chau AK. Cardiac rhythm and symptomatic arrhythmia in right atrial isomerism. Am Heart J. 2002;144:159–64.
201. Stroud DM, Gaussin V, Burch JB, et al. Abnormal conduction and morphology in the atrioventricular node of mice with atrioventricular canal targeted deletion of Alk3/Bmpr1a receptor. Circulation. 2007;116:2535–43.

Physiology of the Cardiac Conduction System

2

Adam C. Kean and Peter S. Fischbach

The orderly spread of electrical activity through the myocardium is a well-choreographed process involving the coordinated actions of multiple intracellular and membrane proteins. Abnormalities in the physical structure as well as the native cellular heterogeneity of the heart may alter the function of these cellular proteins and thus serve as the substrate for arrhythmias. Cardiac myocytes, like other excitable cells, maintain an electrical gradient across the cell membrane (sarcolemma) via an energy-dependent process. Various proteins including ion channels, ion pumps, and ion exchangers span the sarcolemma membrane contributing to the voltage difference between the inside and outside of the cell. Because these integral membrane proteins, along with membrane receptors, regulatory proteins, and channels within the intracellular sarcoplasmic reticulum, form the basis of the electrophysiologic properties of the heart, a knowledge of their structure and function is necessary to understand fully cardiac arrhythmias, as well as for the appropriate use of antiarrhythmic pharmacological agents.

A.C. Kean, M.D., M.P.H. (✉)
Section of Pediatric Cardiology, Indiana University School of Medicine, 705 Riley Hospital Drive, Riley Research Room 127, Indianapolis, IN 46202, USA
e-mail: akean@iu.edu; ackean@gmail.com

P.S. Fischbach, M.D., M.S.
Sibley Heart Center, Children's Healthcare of Atlanta, Department of Pediatrics, Emory University School of Medicine, Atlanta, GA, USA

Resting Membrane Potential

The sarcolemma is a lipid bilayer that prevents the free exchange of intracellular contents with the extracellular space. The unequal distribution of charged ions across the sarcolemma leads to both an electrical and a chemical force causing the ions to move into or out of the cell down their electrochemical gradient, producing the transmembrane potential. The point at which there is no net driving force acting on any single ion across the sarcolemma is the equilibrium potential for that ion. The equilibrium potential may be calculated if the ionic concentrations on both sides of the membrane are known using the Nernst equation:

$$E_x = RT/F \ln[X]_o / [X]_i .$$

In this equation, R = the universal gas constant, T = absolute temperature, F = the Faraday constant, and X is the ion in question. As an example, the usual intracellular and extracellular concentration of potassium is 4.0 mM and 140 mM,

M. Dick, II (ed.), *Clinical Cardiac Electrophysiology in the Young*,
DOI 10.1007/978-1-4939-2739-5_2

respectively. Substituting these values into the Nernst equation gives the following values:

$$E_k = 61 \ln[4]/[140] = -94 \text{ mV}.$$

Ions can only move across the sarcolemma through selective ion channels, ion pumps, and ion exchangers. The sarcolemma has a dynamic permeability to various ions caused largely by opening and closing of these structures as well as their variable concentration with a resultant change in the membrane potential. If the cellular membrane were permeable only to potassium, then the Nernst equation would suffice to describe the membrane potential for all circumstances. As the membrane becomes permeable to various ions at different moments during the action potential, the Nernst equation is insufficient to fully describe the changes in the alteration of the membrane potential.

The membrane potential at any given moment may be calculated if the corresponding instantaneous intra- and extracellular concentrations of the ions and the permeability of the respective ion channels are known. The Goldman–Hodgkin–Katz equation describes the membrane potential for any given set of ion concentrations [X] and permeability's (P). For potassium [K], sodium [Na], and chloride [Cl], the equation is:

$$V_m = RT/F \ln\left\{P_K\left[K^+\right]_o + P_{Na}\left[Na^+\right]_o + P_{Cl}\left[Cl^+\right]_i\right\}/\left\{P_K\left[K^+\right]_i + P_{Na}\left[Na^+\right]_i + P_{Cl}\left[Cl^+\right]_o\right\}.$$

(The chloride ion concentration is inverted to account for its negative charge.) The Goldman–Hodgkin–Katz equation more closely approximates the cellular potential than the Nernst equation because it accounts for the permeability of the membrane for all active ions. This equation is used to calculate ion channel permeability from single channel experiments and then apply to computer models of single cells and cellular syncytia.

The transmembrane potential for the cardiac myocyte at baseline is defined as the resting membrane potential. The sarcolemma is nearly impermeable (highly resistant) to sodium and calcium ions while the conductance (conductance = 1/resistance) for potassium ions is high. As such, the resting membrane potential of most cardiac myocytes approaches the equilibrium potential for potassium, generally ranging from –80 to –90 mV.

The maintenance of the resting membrane potential is an active, energy-dependent process. The most important membrane proteins for establishing the resting membrane potential are the Na^+/K^+-ATPase (ion exchanger) and the potassium channel responsible for the inward rectifying potassium current (I_K). The Na^+/K^+-ATPase is an electrogenic pump that exchanges three sodium ions from the inside of the cell for two potassium ions in the extracellular space, resulting in a net outward flow of positive charge.

Ion Channels

Ion channels are macromolecular proteins that span the sarcolemma and provide a low resistance pathway for ions to enter or exit the cell. The ion channels are selective for specific ions to pass down their electrochemical gradient. The ion channels have three general properties: (1) a central water-filled pore through which the ions pass; (2) a selectivity filter; and (3) a gating mechanism to open and close the channel. The channels may be classified not only by their selectivity for specific ions, but also by the stimulus that causes the channel to open. Channels may open in response to changes in the transmembrane potential (voltage gated), in response to activation with various ligands (messenger gated), in response to mechanical forces (stretch activated), and in response to changes in the metabolic state of the cell (ATP gated).

Sodium Channels

The sodium channels provide the pathway for the sodium current, the principal current responsible for cellular depolarization in atrial, ventricular, and Purkinje fibers. They are also present in skeletal muscle and neuronal cells which can be differentiated from cardiac sodium channels by their greater sensitivity to tetrodotoxin. The cardiac sodium channels are proteins composed of a large pore-forming α-subunit and two smaller regulatory β-subunits. The α-subunit consists of four homologous domains, each of which consists of six transmembrane segments, S1–S6 (Fig. 2.1), a motif that is consistent across the voltage-gated ion channels. The transmembrane segments are hydrophobic and have an alpha-helical conformation. The fourth transmembrane segment (S4) in each domain is highly charged with arginine and lysine residues located at every third position. The S4 segment acts as the voltage sensor for the channel with membrane depolarization causing an outward movement of all of the S4 domains leading to an opening of the transmembrane pore. The channel pore is formed by the S5 and S6 segments of each of the four domains in addition to the extracellular linker between S5 and S6. The transmembrane segments are linked by short loops, which alternate between intra- and extracellular. The extracellular linker loop between S5 and S6 is particularly long and curves back into the lipid bilayer to line the pore through which the ions pass. The four extracellular S5–S6 linker loops contribute to the selectivity of the channel.

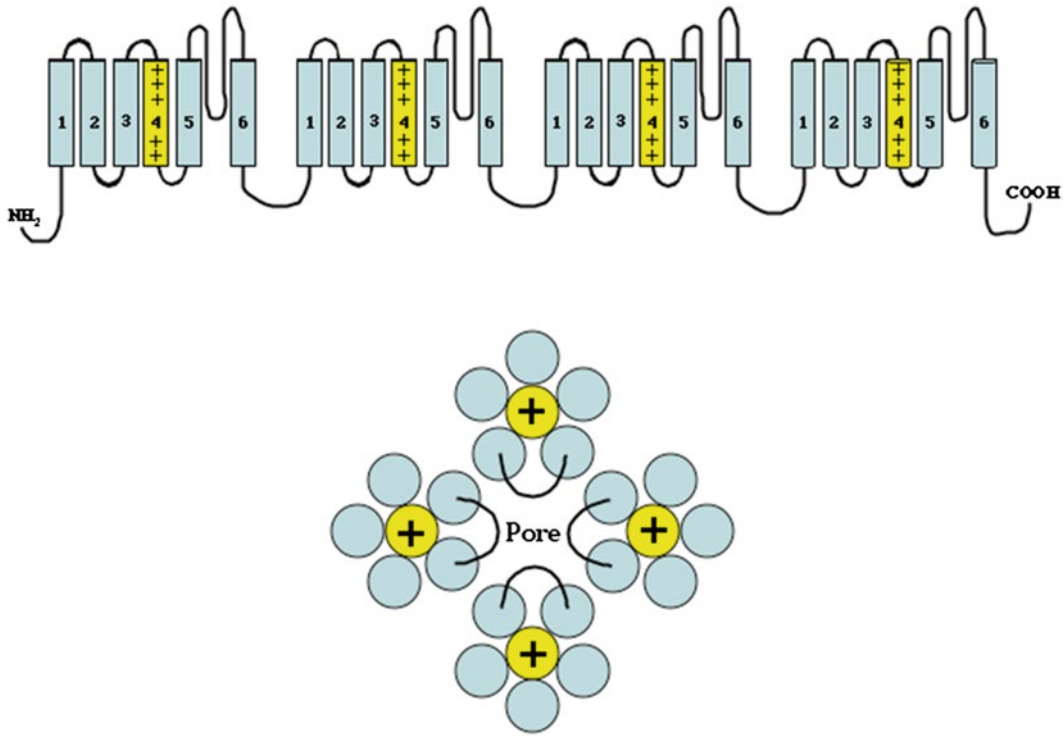


Fig. 2.1 *Top*: Drawing of a voltage-gated sodium channel. The channel is composed of four domains, each of which has six membrane-spanning hydrophobic helical segments. The fourth transmembrane segment is highly charged and acts as the voltage sensor for the channel. The linker segment between the fifth and sixth transmembrane segment in each domain bends back into the channel pore and is important in channel selectivity and gating. *Bottom*: This idealized drawing viewed from the extracellular surface demonstrates how the four domains organize to form a single pore with the S5–S6 linker segment of each domain contributing to the pore

The function of the β-subunit continues to be investigated. In addition to modulating channel-gating properties, the subunit serves as a cell adhesion molecule that interacts with the extracellular matrix serving an anchoring function. The β-subunits also regulate both the level of channel expression and the trafficking of the completed protein to the plasma membrane. In the last few years, genetic mutations leading to errors in ion channel trafficking have been linked to arrhythmogenesis. A mutation in the Nav1.5 gene (gene encoding the sodium channel) associated with Brugada Syndrome has been demonstrated to result from poor subunit trafficking. Interestingly, the class Ia antiarrhythmic drug quinidine's efficacy has been linked, in part, to increased Na-channel endocytosis (the energy-using process by which cells absorb molecules by engulfing them).

The sodium channel opens rapidly in response to a depolarization in the membrane potential above a threshold value, reaching its maximal conductance within half a millisecond. After opening, the sodium current then rapidly dissipates, falling to almost zero within a few milliseconds. The inactivation of the sodium channel is the result of two separate processes, which may be differentiated based on their time constants. An initial rapid inactivation has a fast recovery constant and is, in part, caused by a conformational change in the intracellular linker between S3 and S4 that acts like a ball valve swinging into and occluding the pore-forming region. Rapid inactivation may occur without the channel opening, a process known as "closed state inactivation." A slower, more stable inactivated state also exists and may last from hundreds of milliseconds to several seconds. The mechanism(s) underlying slow inactivation are not well understood but likely result from the linker sequences between S5 and S6 in each domain bending back into the pore of the channel and occluding it (Fig. 2.1).

The *SCN5A* gene located on chromosome 3 encodes the cardiac sodium channel, Nav 1.5. Several genetically mediated arrhythmias in humans resulting from cardiac sodium channel gene mutations have been identified (Chap. 18).

Potassium Channels

Potassium channels are major components in the establishment of the resting membrane potential (see above) and, as will be discussed, cardiac myocyte automaticity. These channels are more numerous and diverse than any other type of ion channel in the heart. In mammals, over 75 genes have been identified that code for potassium channels. The channels may be categorized by their (1) voltage, (2) time, and (3) molecular structure, dependent properties, as well as their response to pharmacological agents. Within the heart a tremendous amount of heterogeneity exists in the density and expression of the potassium channels. The varied expression level of potassium channels contributes to the variability of the action potential morphology in different regions of the heart including transmural differences within the ventricular myocardium. In addition to the natural variability in the expression of potassium channels, many disease processes such as congestive heart failure and persistent tachyarrhythmias, such as chronic atrial fibrillation, alter the density of these channels, as well as their functional properties, thereby leading to disruption of the normal electrical stability of the heart. This alteration in the density and function of these channels has been termed "electrical remodeling."

Voltage-Gated Channels

Voltage-gated potassium channels are structurally very similar to the voltage-gated sodium channels. One major difference is that instead of the channels being composed of a single large α-subunit containing four domains, they are heteromultimeric complexes consisting of four α-subunits that form the channel pore and covalently attached regulatory β-subunits. The α-subunits are the equivalents of the separate domains of the sodium channel and are composed of six membrane-spanning segments (Fig. 2.2). The voltage sensor is contained in the S4 transmembrane segments that possess the same highly charged construct as in the sodium channel with alternating arginine and lysine in every third position. The mechanism supporting channel activation has not been as clearly delin-

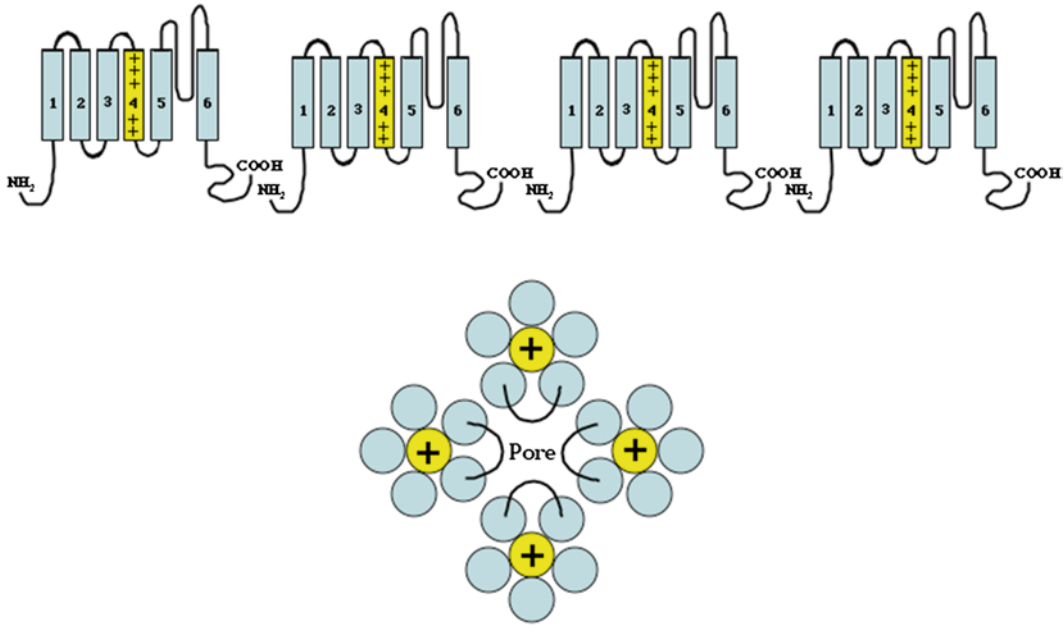


Fig. 2.2 Similar to the voltage-gated sodium channels, the voltage-gated potassium channels are composed of four domains (α-subunits) composed of six membrane-spanning segments. Unlike the sodium channels, the potassium channel domains are separate subunits that co-assemble to form a functional channel (compared with the sodium channel, which is a single large α-subunit composed of four domains. These four α-subunits assemble to form a single pore (structurally similar to the sodium channel, Fig. 2.1) with the S5–S6 linker from all α-subunits contributing to the pore. Similar to the voltage-gated sodium channel, the S4 subunit is also highly charged and serves as the voltage sensor leading to channel opening and closing

eated in potassium channels as in sodium channels. Identical to the sodium channel, the fifth and sixth transmembrane segments and the extracellular linker loop between S5 and S6 form the pore. While multiple subfamilies of potassium channel α-subunits exist, only closely related subfamilies of α-subunits are capable of co-assembling to form functioning channels.

Inwardly Rectifying Channels

The inwardly rectifying channels are structurally distinct from the voltage-gated channels. As opposed to the four membrane-spanning subunits in voltage-gated channels, the inwardly rectifying channels have two membrane-spanning subunits (M1 and M2). The association of four subunits forms a pore (Fig. 2.3). The ATP-gated channel ($I_{K\text{-}ATP}$) is more complex with the four pore-forming subunits co-assembling with four sulfonylurea receptors to form a functional channel. Inward rectification occurs via gating of the channels by magnesium and polyamines (spermine, spermidine, etc.) that block the inner opening of the pore.

I_{K1} is the dominant resting conductance current in the heart, setting the resting membrane potential in atrial, ventricular, and Purkinje cells. The heterogeneous density of channel distribution is greater in the ventricles relative to the atrium, but relatively sparse in nodal cells. I_{K1} has been demonstrated to inactivate at sustained depolarized potentials, such as during the plateau phase of the action potential.

Acetylcholine, which is released from the cardiac parasympathetic nerves, acts on type 2 muscarinic receptors to open $I_{K\text{-}Ach}$ channels via a G-protein-dependent mechanism. The channels are localized primarily in nodal cells and atrial myocytes. The presence of $I_{K\text{-}Ach}$ channels in the ventricle has been identified, although the sensitivity to ACh is less than in the nodal cells and atrial myocytes. Activation of the channels

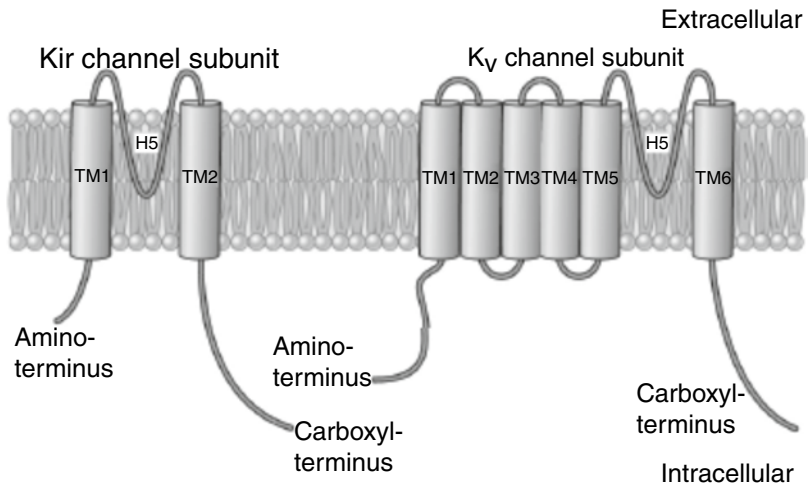


Fig. 2.3 Basic structure and Kir channel phylogenetic tree. A: primary structure of the Kir channel subunit (*left*). Each Kir subunit contains two transmembrane (TM1 and TM2) regions, a pore-forming (H5) loop, and cytosolic NH_2 and COOH termini. As a comparison, the structure of voltage-gated K^+ (K_v) channel subunit, which possesses six transmembrane (TM1–TM6) regions, is shown on the *right*

causes hyperpolarization of nodal cells and a slowing of the rate of spontaneous depolarization and shortening of the action potential in atrial and ventricular myocytes.

Molecularly Active Channels

$I_{K\text{-}ATP}$ is tonically inhibited by physiological concentrations of intracellular ATP. During periods of metabolic stress, when the ATP level decreases and the ATP/ADP ratio is altered, the inhibition on the channel is lost and the channel opens, providing a large conductance repolarizing current (outward movement of K^+). Two molecularly distinct populations of $I_{K\text{-}ATP}$ have been described in the heart: one existing in the sarcolemma and the other in the inner mitochondrial membrane. *IK-ATP*, and in particular, the mitochondrial channel, has been demonstrated to be important in ischemic preconditioning.

Calcium Channels

Calcium channels share the same basic structural motif as the voltage-gated potassium channels and the voltage-gated sodium channels. The channels are composed of a single large pore-forming α-subunit, with two regulatory subunits (β, α_2/δ). The α-subunit is similar in structure to that of the sodium channel, consisting of a single large protein with four domains composed of six membrane-spanning segments (Fig. 2.4). The voltage sensor is also localized on S4 and the pore is composed of S5, S6, and the S5–S6 linker of each of the four domains. However, the pore-forming loop between S5 and S6 is significantly different between calcium and sodium channels. The calcium channel has several calcium-binding sites on the pore-forming loop and the presence of calcium at these sites blocks sodium from entering the channel pore. When these sites are devoid of calcium, the channel passes sodium ions freely.

There are two main types of calcium channels embedded in the sarcolemma which are differentiated by their conductance, activation/inactivation, and their response to pharmacological agents. The L-type calcium channel ($I_{Ca,L}$—long acting) compared with the T-type channel ($I_{Ca,T}$—transient channel) activates at more positive membrane potentials, inactivates more slowly, and has a larger single channel conductance. L-type calcium channel blocker drugs are used as cardiac antiarrhythmics or antihypertensives, depending on whether the drugs have higher affinity for the

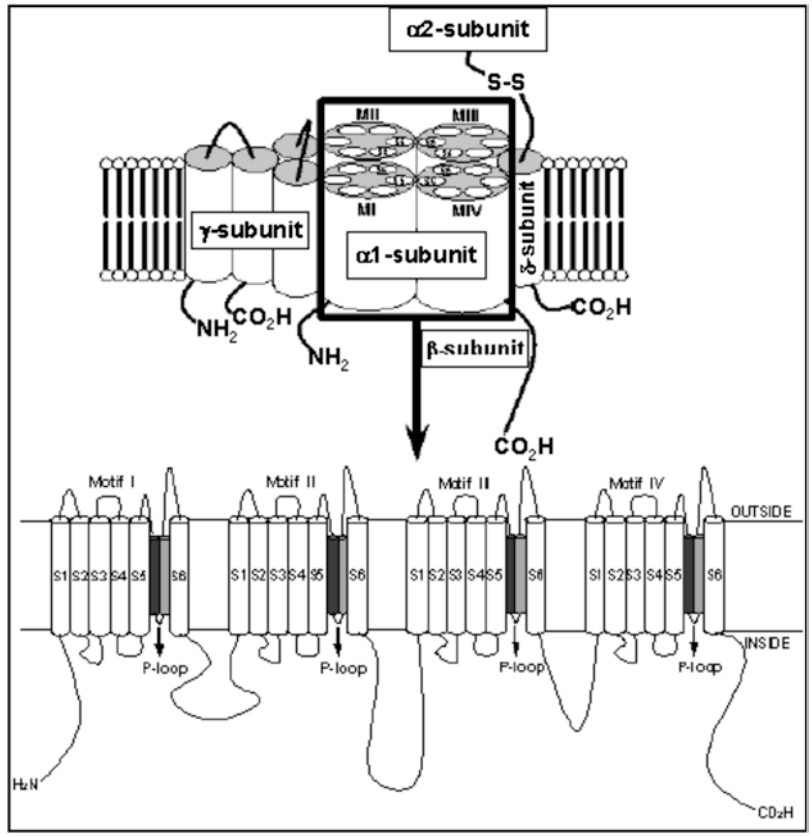


Fig. 2.4 L (transient) type calcium channel (voltage-gated). Molecular structure of the VGCC complex with zoom of the proposed transmembrane arrangement of the VGCC α 1-subunit. The dark and light gray cylinders are the SS1 and SS2 segments, respectively

heart (the phenylalkylamines, like verapamil), or for the vessels (the dihydropyridines, like nifedipine). $I_{Ca,L}$ is expressed abundantly in all myocytes responsible for bringing calcium into working myocytes and leading to calcium-dependent calcium release from the sarcoplasmic reticulum. The expression of $I_{Ca,T}$ is more heterogeneous, being most prominent in nodal cells.

Chloride Channels

Far less is known about the structure and function of cardiac channels that carry anions. There are at least three distinct chloride channels in the heart. The first is the cardiac isoform of the cystic fibrosis transmembrane conductance regulator (CFTR), which is regulated by cAMP and protein kinase A. The second is a calcium-activated channel that participates in early repolarization, and the third is a swelling activated channel. To date, no role for abnormal function of chloride channels has been found for arrhythmia formation, and the channels are not targeted by any of the currently available antiarrhythmic drugs despite having a clear effect on action potential duration.

Gap Junctions

Gap junctions are tightly packed protein channels that provide a low resistance connection between adjacent cells, allowing the intercellular passage of ions and small molecules. These

channels allow the rapid spread of the electrical signal from cell to cell. They are produced by the non-covalent interaction of two hemichannels (connexins) that are embedded in the plasma membranes of adjacent cells. A connexin is formed by the association of six connexin subunits, each of which has four transmembrane-spanning domains and two extracellular loops. There are greater than 12 types of connexins expressed in myocardium. The transmembrane domains and extracellular loops in all of the connexins are highly preserved while the intracellular loop between the second and third domain and the carboxy-terminus are highly variable. The differences in the intracellular portions of the connexins account for the difference in molecular weight and physiological properties such as the junction conductance, pH dependence, voltage dependence, and selectivity.

The connexins are named by their molecular weight, e.g., Cx40 weighs 40 kDa. The distribution of connexins within the heart is variable and changes between embryonic development and the adult heart. Connexins 40 and 43 predominate in the atria, 43 in the ventricle, and 40 and 45 in the specialized conduction tissue of the sinus node and His/Purkinje system. Heterogeneous placement in the heart as well as its location along the axis of the cardiomyocyte at the desmosome also facilitates sequential depolarization of the cell and propagation of the action potential. The embryologic differential expression of the connexins has been implicated as a possible etiology for some forms of congenital heart disease.

The Action Potential

The action potential is a time-dependent transcription of the change in voltage across the sarcolemma (cell membrane). It is divided into five phases, delineated by the dominant membrane conductance (Fig. 2.6). The action potential of fast response and slow response cells differ and will be addressed separately below:

Phase 0

The sodium current is the principal current responsible for cellular depolarization in atrial, ventricular, and Purkinje fibers. The rapid flow of ions through the sodium channel permits rapid depolarization of the sarcolemma as well as rapid conduction of the electrical signal between cells. Sodium channels are closed at normal hyperpolarized resting membrane potentials. When stimulated by membrane depolarization, they open allowing the rapid influx of sodium ions, which changes the membrane potential from −90 mV towards the equilibrium potential for sodium of +40 mV. The channel then inactivates rapidly over a few milliseconds in a time-dependent fashion—that is, even in the face of a sustained depolarized membrane potential, the channel will close after a short time.

This phase includes the rapid depolarization of the membrane. At rest, as discussed earlier, the membrane of a fast response cell is permeable almost exclusively to potassium. This drives the resting membrane potential towards the equilibrium potential of potassium (−94 mV). If the membrane potential is depolarized beyond a set threshold value, the voltage-gated sodium channels open and the membrane's dominant conductance changes to sodium. The membrane potential therefore moves towards the equilibrium potential of sodium (I_{Na} ~ +40 mV). The stimulus that generates the action potential elicits an all-or-nothing response. If the stimulus is subthreshold, the membrane is partially depolarized and then quickly returns to the resting potential. If the stimulus is of sufficient intensity to raise the membrane potential above the threshold level, a maximal response is elicited and an action potential is generated. If the threshold potential is reached, phase 0 of the action potential is not altered by the greater intensity of the stimulus (i.e., a stimulus of greater intensity does not result in an increase in V_{max}). The number of available sodium channels is dependent on the resting membrane potential of the cell and determines the V_{max}. If the resting membrane potential is depolarized (less negative) relative to the normal value

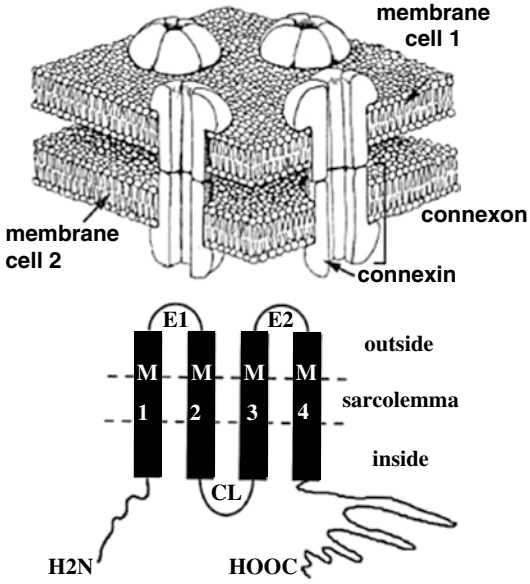


Fig. 2.5 Schematic representation of part of a gap junction. The individual gap junction channels consist of two connexins that are non-covalently attached. Each connexin is composed of six connexins. The individual connexins has four membrane-spanning regions (M1–M4), two extracellular loops (E1 and E2), and one cytoplasmic loop (CL) [Reprinted from van der Velden et al. Cardiac gap junctions and connexins: their role in atrial fibrillation and potential as therapeutic targets. Cardiovasc Res 2002;54: 270–279. With permission from Oxford University Press]

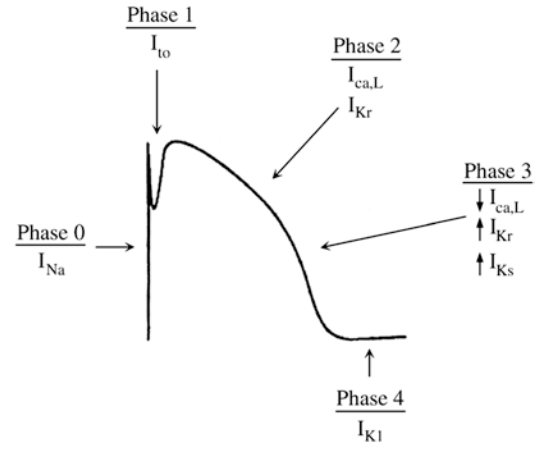


Fig. 2.6 Shown is a typical action potential recorded from an epicardial ventricular myocyte. Phase 0 is the rapid depolarization of the membrane driven by opening of the voltage-gated sodium channel. Phase 1 is rapid initial repolarization resulting from closing of the sodium channel and opening of the transient outward current carried primarily by potassium. Phase 2, the plateau phase of the action potential, is notable for a balanced flow of inward (calcium) and outward (potassium) currents resulting in no significant change in the membrane potential. Phase 3 of the action potential, rapid repolarization, results from time-dependent inactivation of the calcium channel in leaving the outward potassium current relatively unopposed. Phase 4 of the action potential is the resting membrane potential for myocytes without automaticity

(i.e., ~−90 mV), fewer sodium channels are available to be recruited to participate in the action potential due to a greater number of sodium channels in inactivated states and the V_{max} *is lower*. Clinically, this may occur during myocardial ischemia or other instances of stress. Sodium channel blocking antiarrhythmic drugs produce a decrease in dV/dt_{max} (upstroke velocity of phase 0, Fig. 2.5) and result in a prolonged phase 0.

Phase 1

The maximal depolarized membrane potential reaches approximately +20 mV, which is below the equilibrium potential for sodium. The failure to reach the equilibrium potential of sodium is due to the rapid time-dependent inactivation of sodium channels, changing to a non-conducting conformation, as well as the opening of hyperpolarizing currents, most significantly I_{to}. The transient outward current is responsible for the early repolarization of the myocytes, creating the "spike and dome" configuration of the action potential noted in epicardial ventricular myocytes (Fig. 2.6). The current may be divided into two components: a Ca independent and 4-aminopyridine-sensitive current that is carried by K, and a Ca-dependent and 4-aminopyridine-insensitive current carried by the Cl ion. There is further evidence to suggest that the portion of I_{to} carried by potassium may be further subdivided into fast and slow components. The level of expression of I_{to} is highly variable, with greater density in the atrium than the ventricles, greater density in the right ventricle than the left ventricle, and greater density in the epicardium than in the endocardium (Fig. 2.7). The heterogeneous expression of I_{to} throughout the myocardium explains the variability in the morphology of the early portion of the action potential. Those myocytes expressing relatively more I_{to} have a profound spike and dome conformation,

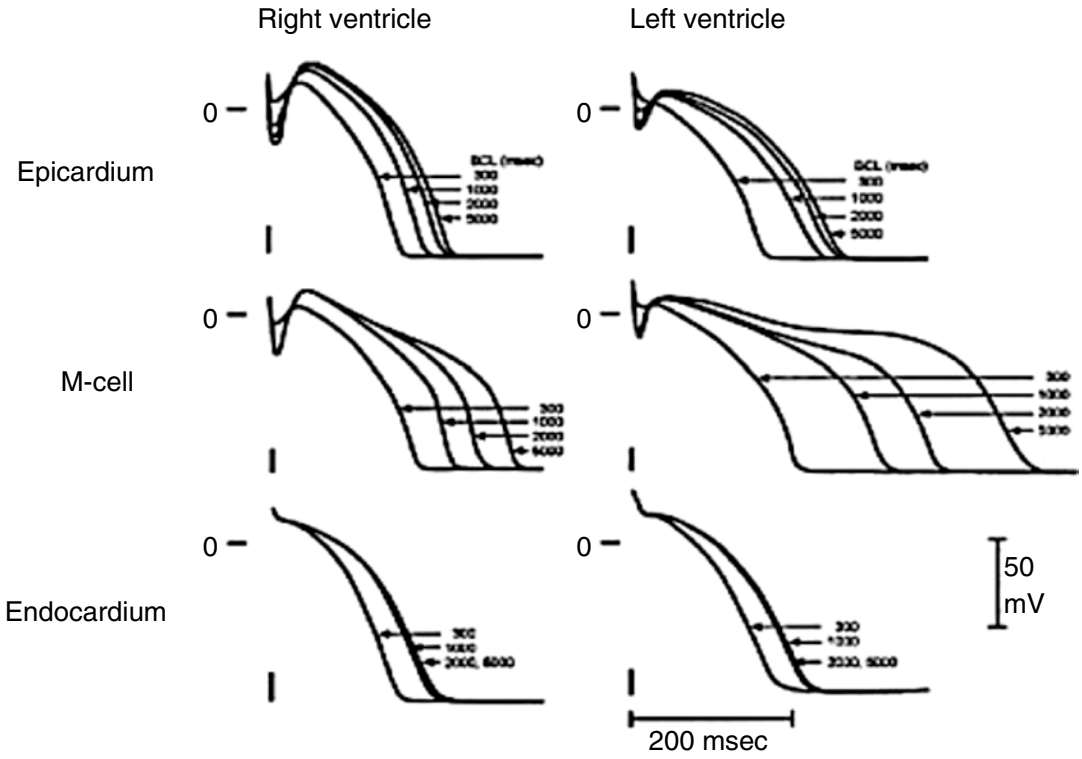


Fig. 2.7 Action potential heterogeneity. The action potentials in this figure were recorded from strips of ventricular myocardium isolated from canine right and left ventricle. The difference in the morphology of the action potentials across the ventricular wall is obvious with a longer action potential found in the M-cells, which are located in the mid-myocardium. Additionally, the spike and dome configuration of the action potential generated by the activity of the transient outward current is prominent in the epicardial cells and nearly absent in the endocardium. Differences between the action potential morphology are also evident between the right and left ventricles. Finally, the action potentials were recorded at various paced cycle lengths. The rate adaptation of the cells from the different regions of the ventricle is strikingly different [Reprinted from Antzelevitch C, Fish J. Electrical heterogeneity within the ventricular wall. Basic Res Cardiol 2001;96(6):517–527. With permission from Springer Science + Business Media, Inc.]

such as epicardial ventricular myocytes. The inactivation of I_{to} is also rapid, and so it does not contribute significantly to the plateau phase, or later repolarization of the myocyte.

Phase 2

The plateau phase of the action potential represents a balance of inward depolarizing current carried primarily by calcium with a small contribution from a background sodium window current, and outward hyperpolarizing potassium current. The calcium and potassium currents are activated by depolarization, and both are inactivated in a time-dependent fashion. $I_{Ca,L}$ serves to bring calcium into working myocytes throughout the plateau phase of the action potential and leading to calcium-dependent calcium release from the sarcoplasmic reticulum. $I_{Ca,T}$ is more important for depolarization of nodal cells.

Phase 3

At the completion of phase 2, the calcium channels close, leaving the effects of the potassium conductance unopposed. As noted above, the

potassium channels are major components in the establishment of the resting membrane potential, the plateau phase of the action potential, the repolarization (phase 3, Fig. 2.6) as well as automaticity. The membrane potential moves once again towards the equilibrium potential of potassium.

I_K (Delayed Rectifier)

The delayed rectifier current is the ionic current primarily responsible for repolarization (phase 3) of the myocytes. It opens slowly relative to the sodium channel in response to membrane depolarization near the plateau potential of the myocytes (+10 to +20 mV). Following the initial description of the delayed rectifier current, two distinct components of the current were identified: a rapidly activating (I_{Kr}) and a slowly activating (I_{Ks}) portion. Both the I_{Kr} and I_{Ks} close during phase 3 and I_{K1} becomes the dominant conductance at the conclusion of phase 3. Recently, a third component has been isolated. The different subsets may be differentiated based on their activation/inactivation kinetics, pharmacological sensitivity and conductance. The rapidly activating component (I_{Kr}) has a large single channel conductance, demonstrates marked inward rectification, activates rapidly, and is selectively blocked by several pharmacological agents including sotalol and dofetilide. Noncardiovascular drugs associated with heart rate corrected QT interval prolongation almost exclusively interact with I_{Kr} to produce their action potential prolonging effects. I_{Kr} is the product of the *KCNH2* (*HERG*) gene located on chromosome 7 and abnormalities of this channel result in LQTS type 2 (Chap. 20). The slowly activating portion of the current (I_{Ks}) has a smaller single channel conductance and is selectively inhibited by chromanol 293b. I_{Ks} inactivates more slowly than I_{Kr} and becomes the dominant repolarizing current at more rapid heart rates. I_{Ks} is the product of the *KCNQ1* (*KvLQT1*) gene on chromosome 11 and abnormalities of this channel result in LQTS type 1 (Chap. 20). The third subset of delayed rectifier current (I_{Kur}, the ultra-rapid delayed rectifier) has very rapid activation kinetics and slow inactivation kinetics with a single channel conductance that is close to that of I_{Kr}. I_{Kur} is significantly more sensitive to the potassium channel blockers 4-aminopyridine and TEA (tetraethyammonium) than either I_{Kr} or I_{Ks} and the channel may be selectively inhibited by the experimental compound S9947. I_{Kur} is the product of the *KCNA5* gene on chromosome 12.

Phase 4

Atrial and ventricular myocytes maintain a constant resting membrane potential awaiting the next depolarizing stimulus. The resting membrane potential is established by I_{K1}. The resting membrane potential remains slightly depolarized relative to the equilibrium potential of potassium due to an inward depolarizing leak current likely carried by sodium. During the terminal portions of phase 3 and all of phase 4, the voltage-gated sodium channels are recovering from the inactivated state into the resting state and preparing to participate in the ensuing action potential. The expression of the subtypes of the delayed rectifier channel is heterogeneous. The expression of all three subtypes is greater in the atrium than in the ventricle, in part explaining the shorter action potential in atrial compared to ventricular myocytes. I_{Kur} is exclusively expressed in the atrium and has not been isolated from ventricular tissue. Within the ventricle, I_{Ks} density is low in the midmyocardium, the so-called M-cells, compared with cells in the epi- and endocardium. The transmural difference in the distribution of potassium channels across the ventricular wall accounts for the longer duration of the action potential in Purkinje fibers as compared to the action potential in the epicardium and underlies the configuration of the T-wave in the surface electrocardiogram.

Chloride channels do appear to play an important role in maintaining the normal action potential. While chloride conductance does not play a role in establishing the resting membrane potential, experiments in which the extracellular chloride was replaced with an impermeant anion resulted in markedly prolonged action potentials.

Cardiac Excitation Characteristics

Myocytes may be broadly divided into two distinct cell types; fast response cells (atrial, ventricular, and Purkinje cells) and slow response cells [sinoatrial (SA) and atrioventricular (AV) nodal cells] (Fig. 2.8). The action potentials of fast response cells are notable for having a rapid upstroke (large sharp V_{max}) generated by the large conductance voltage-gated sodium channel and the hyperpolarized resting membrane potentials (as just described above in detail). The action potentials of slow response cells do not have a fixed resting membrane potential and have a slower upstroke driven by activation of L-type calcium channels. The rate at which the membrane is depolarized (V_{max}) determines how rapidly the electrical signal is conducted through tissue.

Slow Response Cells

The action potential of slow response cells is morphologically distinct from fast response cells (Fig. 2.8). Initial rapid depolarization (phase 0) in slow response cells is the result of current passing through voltage-gated calcium channels that activate at relatively depolarized potentials (−35 mV). The resultant V_{max} during phase 0 is considerably slower (slower upstroke) than that measured in fast response cells. Activation of phase 0 depolarization in slow response myocytes, similar to fast response myocytes, relies on the membrane potential surpassing a threshold potential with an all or none response in the depolarizing calcium current. Unlike the fast response myocytes, which require an external stimulus to raise the membrane potential past the threshold potential, the slow response myocytes generate their own depolarizing current. The slow response myocytes do not have a fixed resting membrane potential but rather hyperpolarize to a maximal diastolic potential (−50 to −65 mV for SA node cells) and then slowly depolarize towards the threshold potential of the calcium channels ("funny" current, I_f). Repolarization of slow response cells is the result of the time-dependent inactivation of the calcium channel in combination with the hyperpolarizing currents carried by the delayed rectifier potassium current.

Refractory Period

Following activation, all excitable cells enter a period in which repeat activation is impossible. This is referred to as the refractory period. The refractory period is longer in myocytes than in other excitable cells such as neurons or skeletal

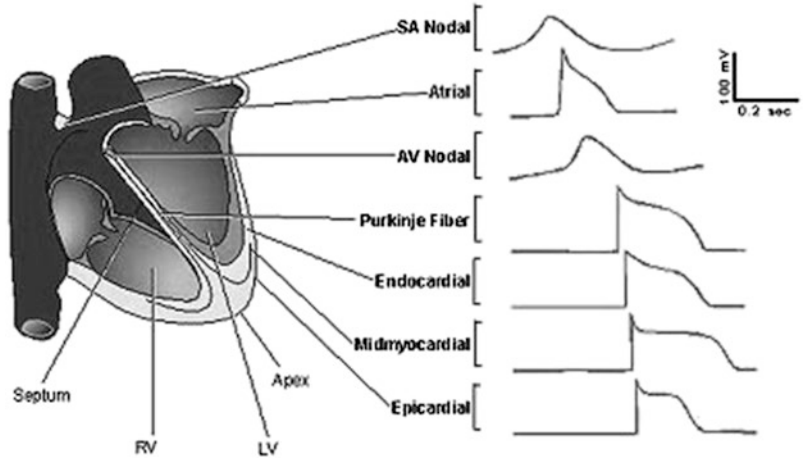


Fig. 2.8 Family of action potentials relative to tissue site in the heart

muscle. Physiologically, the refractory period allows for relaxation of the myocardium and filling of the cardiac chambers. Due to the long refractory period in cardiac muscle, tetanic contraction is not possible as it is in skeletal muscle. The refractory period may be divided into the absolute refractory period, during which time no action potential may be generated regardless of the stimulus, and the relative refractory period, in which an action potential may be induced only following a supernormal stimulus. The refractory period is the result of the slow recovery from the inactivated state of the depolarizing current (I_{Na}) combined with the slow inactivation of the repolarizing currents.

Automaticity

Automaticity is the ability of cells to spontaneously depolarize and raise the resting membrane potential past the threshold potential for triggering an action potential (phase 4 depolarization). Automaticity normally is a property of cells localized within the SA and AV nodes, as well as Purkinje fibers. There is a hierarchical pattern to the rate of spontaneous depolarization, with the most rapid depolarization occurring in the SA node followed by the AV node with the Purkinje fibers being the slowest. Both the so-called funny current (I_f) and calcium clock, described below, are involved in forming the intrinsic cardiac pacemaker. The precise mechanism of sinoatrial (intrinsic pacemaker) activity and the centrality of one mechanism compared with the other remains a topic of spirited debate among electrophysiology researchers and clinicians.

Spontaneous depolarization results from a net inward current resulting from the combination of several currents. The currents involved appear to include activation of several inward cation channels including (1) I_f, which is activated by hyperpolarization and closes shortly after the activation potential for the inward calcium channel is passed; (2) $I_{Ca\text{-}T}$, $I_{Ca\text{-}L}$ (mostly at the end of phase 4 depolarization as the activation potential is –40 mV for this current); and (3) I_b, an inward time-independent background current carried by sodium. The decay of the inward hyperpolarizing I_K also contributes to the net depolarizing current.

Additionally, the Na^+/K^+ and Na^+/Ca^{2+} exchangers, which are electrogenic, provide inward current as K^+ and Na^+ are extruded from the cell. It is important to note that I_{K1} is not expressed in nodal cells and hence the hyperpolarizing effects do not influence phase 4 depolarization. The mechanism of phase 4 depolarization in Purkinje cells appears to be somewhat different compared to nodal cells, with I_f playing a far more prominent role. The maximal diastolic potential is approximately –85 mV in Purkinje cells rather than –60 mV in nodal cells, so the contribution of calcium current is thought to be less.

There is evidence to support the central role of both mechanisms. The I_f current inhibitor ivabradine is a medication used to treat heart failure and inappropriate sinus tachycardia. Its mechanism of action has made it a good investigational drug for this question. It is effective in reducing pacemaker automaticity though does not terminate SA node activity. Definitive multicellular human cell experiments demonstrating Ca clock centrality, however, are lacking. Mechanistic interplay of the two has been suggested.

The rate of automatic discharge is under tight autonomic control. Vagal input into the heart via release of acetylcholine activates the muscarinic receptor-gated potassium channel ($I_{K\text{-}Ach}$), which leads to hyperpolarization of the nodal cells. The hyperpolarization of the nodal cells creates a greater difference between the maximal diastolic potential and the threshold potential that is unchanged by the vagal stimulation. If the slope of diastolic depolarization remains unchanged, the time it takes to reach the threshold potential will increase and the rate of depolarization will decrease. Vagal stimulation, however, also inhibits I_f and $I_{Ca\text{-}L}$ leading to a decrease in the slope of phase 4 depolarization, and further slowing the rate of spontaneous depolarization. Sympathetic stimulation conversely, via cAMP-dependent pathways, enhances I_f and $I_{Ca\text{-}L}$, increasing the slope of phase 4 depolarization and increasing the rate of spontaneous depolarization.

Signal Propagation

Electrical conduction through the myocardium may be considered on the level of the signal traversing a single myocyte, to cell-to-cell conduction, and finally conduction through the whole organ. The electrical signal passes along a myocyte by incrementally depolarizing the sarcolemma. At rest, an electrical gradient is maintained across the sarcolemma. When the local membrane potential is depolarized, sodium and calcium channels open (phase 0 of the action potential), establishing a small region of positive charge on the inner surface of the membrane and leaving a small zone of negative charge on the outer surface. This depolarizes the membrane in the immediately adjacent regions and leads to initiation of the depolarizing currents in the bordering regions. This forms a self-perpetuating reaction with the spread of depolarization. The more rapidly the local region of the membrane is able to change its potential, the more rapid is conduction down the length of the myocyte. Therefore, cells that depend on the rapid sodium current for the upstroke of phase 0 of the action potential conduct the signals rapidly, while cells that are dependent on the slower calcium current for phase 0 conduct signals more slowly. This concept is underscored by comparing the conduction velocity in the AV node (calcium-dependent action potentials) with atrial and ventricular tissue (sodium channel dependent).

The myocardium is not a perfect syncytium, and conduction is discontinuous. As noted previously, gap junctions form a low resistance passageway to allow for the rapid spread of excitation from cell to cell. It has also been noted that the tissue passes electrical current more rapidly along the long axis (length) of the myocytes than its short axis (width). The difference that exists between the conduction velocities axially versus transversely is referred to as anisotropy. The degree of anisotropic conduction varies throughout the myocardium. In the ventricle, the ratio of conduction velocity parallel as opposed to perpendicular to the long axis of the cell is approximately 3:1, while along the crista terminalis in the atrium the same ratio is 10:1.

On a macroscopic level, once the electrical signal escapes from the SA node, it rapidly spreads throughout the atrium. A debate remains as to whether or not there exist anatomically distinct internodal tracts that connect the SA and AV nodes. Histologic studies have failed to demonstrate the presence of these tracts. The SA node is located high in the right atrium adjacent to the orifice of the superior vena cava. In this location, it is susceptible to injury at the time of cannulation for cardiopulmonary bypass. Additionally, the blood supply to the SA node may be damaged during surgery that involves extensive atrial manipulation such as the Mustard operation or the hemi-Fontan procedure (see Chap. 8). The electrical signal activates the right atrium initially with conduction spread into the left atrium preferentially via Bachmann's bundle and along the coronary sinus. The atria and ventricles are electrically isolated from one another by the fibrous AV ring, with electrical continuity provided by the AV node. The compact AV node is located in the atrial septum at the apex of the triangle of Koch. The AV node is composed of three regions: the atrionodal (AN), nodal (N), and nodal-His (NH). The cells in these three regions differ in the shape of their respective action potentials and their conduction velocities. The cells in the AN region have action potentials that are intermediate between atrial and SA nodal cells with a more depolarized maximal diastolic potential, slower phase 0 depolarization, and the presence of phase 4 depolarization. The N cells are similar to the SA nodal cells. The NH cells transition between the N cells and the His bundle with action potentials that reflect this transition. Conduction through the entirety of the AV node is slower than that through the atria or ventricles and does not elicit a separate deflection on routine surface ECG. The AV node is richly innervated by the autonomic nervous system and receives its blood supply from the posterior descending coronary artery. Atrioventricular block may result from interruption of the blood supply, which may result from atherosclerotic disease, as well as due to vasospasm following the delivery of radiofrequency energy in the postero-septal region on the tricuspid valve annulus.

After passing through the AV node, the signal passes through the His bundle and enters the Purkinje fibers that divide into the bundle branches. The Purkinje cells have large diameters and preferential end-to-end connections rather than side-to-side connections, both of which lead to accelerated conduction velocities (200 cm/s compared with 5 cm/s in the SA node). The right bundle branch is cord-like and passes to the apex of the right ventricle prior to ramifying into the ventricular mass initially along the moderator band. The left bundle branch is fan-like and initially activates the ventricular septum from the left ventricular side progressing towards the right. This accounts for the Q-waves inscribed in the left lateral precordial leads in D-looped hearts, and the Q-waves in the right precordium in L-looped hearts. Indeed, the macroscopic conduction system may be duplicated in L-looped hearts (Chap. 1).

Mechanism of Arrhythmia Formation

Arrhythmias occur when the orderly initiation and conduction of the electrical signal is altered. This may result in abnormally fast or abnormally slow heart rates.

Bradycardia may result from either a failure of initiation of impulse formation such as that occurs in sick sinus syndrome, or failure of the signal to be conducted or propagated (SA node exit block, AV node block). Bradycardia is not amenable to chronic pharmacological therapy and when symptomatic requires an implantable pacemaker (Chaps. 14, 15, and 17).

Tachycardias arise from one of three general mechanisms: abnormal automaticity, triggered activity, or reentry.

Abnormal Automaticity

Abnormal automaticity implies either abnormally fast activation in cells that normally possess automatic function (enhanced automaticity) or the development of spontaneous depolarization in cells that normally do not have this ability. Abnormally enhanced automaticity may result from hyperactivity of the autonomic nervous system (junctional tachycardia), fever, thyrotoxicosis, or the exogenous administration of sympathomimetic agents.

Under normal physiological conditions, atrial and ventricular cells do not demonstrate phase 4 spontaneous depolarization. If the resting membrane potential is decreased (made less negative) to less than −60 mV, as may occur with ischemia, cells may develop spontaneous depolarization. Clinical examples of arrhythmias supported by abnormal automaticity include atrial ectopic tachycardia, junctional ectopic tachycardia (Chap. 10), accelerated idioventricular rhythm, and some ischemic ventricular tachycardias (Chap. 13).

Triggered Activity

Triggered activity arises from oscillations in the membrane potential, which if large enough, may reach threshold potentials and lead to additional action potentials. Triggered activity by definition is dependent on a preceding action potential or electrical stimulus to generate the oscillations in the membrane potential. An action potential generated via a triggered complex may serve as the stimulus for an ensuing action potential leading to a sustained arrhythmia. Triggered activity may result from oscillations in the membrane potential that occur either during phase 2 or 3 of the action potential (early after depolarization or EAD) or following full repolarization of the action potential (delayed after depolarization or DAD). Mutations in the Ryanodine receptor (RyR2) and Calsequestrin (Casq2) have been identified as the cause of Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT). Calcium dysregulation in the sarcoplasmic reticulum has been implicated as the mechanism for DAD activity and sustained VT during catecholamine stress.

EADs

These oscillations occur during the plateau phase or late repolarization of the action potential. EADs may result from a decrease in outward current, an

increase in inward current, or a combination of the two. During the plateau phase of the action potential, the absolute ionic flow across the membrane is small; hence a small change in either the inward or outward current may result in a large change in the membrane potential.

DADs

DADs occur after the cell has fully repolarized and returned to the resting membrane potential. The depolarization of the membrane resulting in DADs is caused by activation of the transient inward current (I_{ti}), which is a nonspecific cation channel activated by intracellular calcium overload.

Reentry

Reentry is far and away the most frequent mechanism supporting arrhythmias. First described by George Mines in 1914, reentry describes the circulation of an electrical impulse around an electrical barrier leading to repetitive excitation of the heart. To initiate re-entry, three conditions are required: (1) a continuous circuit, (2) unidirectional conduction block in part or limb of the circuit, and (3) conduction delay in the site of origin allowing tissue previously activated to regain its excitability by the time the advancing wave front returns. These conditions allow for a sustained circuit to be established.

Critical to the maintenance of reentrant arrhythmias are the (1) impulse conduction velocity and (2) the refractory period of the myocardium in the circuit. The interaction of these two properties of the myocardium determine whether the leading edge of electrical excitation will encounter myocardium capable of generating an action potential, or whether refractory tissue will block the circuit and cause the reentrant loop to extinguish. These two measurable quantities may be combined to calculate the "wavelength" of the arrhythmia.

$$\text{Conduction velocity (m/s)} \times \text{Refractory period } (s) = \text{Wavelength (m)}.$$

If the calculated wavelength of the arrhythmia exceeds the path length of the circuit, then reentry cannot occur. If the wavelength is less than the path length, then reentry may be sustained. This concept is the basis for the use of class III antiarrhythmic agents, which work by increasing the duration of the refractory period of the tissue by delaying repolarization. In reentrant arrhythmias with a fixed path length, an *excitable gap* exists, which is the time interval between the return of full excitability of the tissue following depolarization and the arrival of the returning electrical wave front traversing the circuit. The presence of an excitable gap allows for external stimuli to enter the reentrant circuit and either advance (speed up), delay, or terminate the tachycardia.

Many forms of tachycardia result from reentry with fixed anatomic pathways. Examples include accessory pathway-mediated tachycardia (Chap. 3), AV node reentrant tachycardia (Chap. 4), atrial flutter (intra-atrial reentrant tachycardia scar-mediated atrial flutter—Chap. 8), and ischemic ventricular tachycardia. Reentry has also been demonstrated to occur in tissue in which there are no fixed physical barriers. Reentry may be supported in this case by the development of functional barriers to conduction that serve as a focal point for the circuit to rotate around. These functional centers are not fixed and continually change and move with time. This principle referred to as "leading circle reentry and rotor reentry" is thought to underlie atrial and ventricular fibrillation. These reentrant circuits do not have an excitable gap with tissue becoming activated as soon as it is no longer refractory. The cycle length in arrhythmias supported by leading circle reentry is determined by the refractory period of the tissue that determines the circuit length.

Conclusion

Research into physiologic mechanisms of the cardiac conduction system continues to expand. Vigilance towards incorporating advances in the knowledge of the electrophysiologic mechanisms is crucial as this research paves the way for progress in arrhythmia management of the young.

Suggested Reading

Allessie MA, Bonke FI, Schopman FJ. Circus movement in rabbit atrial muscle as a mechanism of tachycardia. III. The "leading circle" concept: a new model of circus movement in cardiac tissue without the involvement of an anatomical obstacle. Circ Res. 1977;41:9–18.

Allessie M, Ausma J, Schotten U. Electrical, contractile and structural remodeling during atrial fibrillation. Cardiovasc Res. 2002;54:230–46.

Anderson ME, Al-Khatib SM, Roden DM, Califf RM, Duke Clinical Research Institute/American Heart Journal Expert Meeting on Repolarization Changes. Cardiac repolarization: current knowledge, critical gaps, and new approaches to drug development and patient management. Am Heart J. 2002;144: 769–81.

Antzelevitch C, Fish J. Electrical heterogeneity within the ventricular wall. Basic Res Cardiol. 2001;96: 517–27.

Antzelevitch C, Shimizu W, Yan GX, et al. The M cell: its contribution to the ECG and to normal and abnormal electrical function of the heart. J Cardiovasc Electrophysiol. 1999;10:1124–52.

Armoundas AA, Wu R, Juang G, et al. Electrical and structural remodeling of the failing ventricle. Pharmacol Ther. 2001;92:213–30.

Barry DM, Nerbonne JM. Myocardial potassium channels: electrophysiological and molecular diversity. Annu Rev Physiol. 1996;58:363–94.

Davis LM, Rodefeld ME, Green K, et al. Gap junction protein phenotypes of the human heart and conduction system. J Cardiovasc Electrophysiol. 1995;6: 813–22.

Dhein S, Rothe S, Busch A, et al. Effects of metoprolol therapy on cardiac gap junction remodelling and conduction in human chronic atrial fibrillation. Br J Pharmacol. 2011;164:607–16.

DiFrancesco D, Noble D. The funny current has a major pacemaking role in the sinus node. Heart Rhythm. 2011;9:457–8.

Hibino H, Inanobe A, Furutani K, Murakami S, Findlay I, Kurachi Y. Inwardly rectifying potassium channels: their structure, function, and physiological roles. Physiol Rev. 2010;90(1):291–366.

Hille B. Ion channels of excitable membranes. Sinauer: Sunderland; 2001.

Liu DW, Gintant GA, Antzelevitch C. Ionic bases for electrophysiological distinctions among epicardial, midmyocardial, and endocardial myocytes from the free wall of the canine left ventricle. Circ Res. 1993;72:671–87.

Members of the Sicilian Gambit. New approaches to antiarrhythmic therapy: emerging therapeutic applications of the cell biology of cardiac arrhythmias. Eur Heart J. 2001;22:2148–63.

Pandit SV, Jalife J. Rotors and the dynamics of cardiac fibrillation. Circ Res. 2013;112:849–62.

Priori SG, Chen SR. Inherited dysfunction of sarcoplasmic retriculum Ca^{2+} handling and arrhythmogenesis. Circ Res. 2011;108:871–83.

Roden DM, George AL. Structure and function of cardiac sodium and potassium channels. Am J Physiol. 1997;273:H511–25.

Roden DM, Balser JR, Geroge AL, Anderson ME. Cardiac ion channels. Annu Rev Physiol. 2002;64:431–75.

Salameh A, Blanke K, Daehnert I. Role of connexins in human congenital heart disease: the chicken and egg problem. Front Pharmacol. 2013;4:70.

Schram G, Pourrier M, Melnyk P, Nattel S. Differential distribution of cardiac ion channel expression as a basis for regional specialization in electrical function. Circ Res. 2002;90:939–50.

Schumacher SM, McEwen DP, Zhang L, et al. Antiarrhythmic drug-induced internalization of the atrial-specific k+channel kv1.5. Circ Res. 2009;104:1390–8.

Singh BN, Sarma JS. Mechanisms of action of antiarrhythmic drugs relative to the origin and perpetuation of cardiac arrhythmias. J Cardiovasc Pharmacol Ther. 2001;6:69–87.

Smythe JW, Shaw RW. Forward trafficking of ion channels: what the clinician needs to know. Heart Rhythm. 2010;7:1135–40.

Snyders DJ. Structure and function of cardiac potassium channels. Cardiovasc Res. 1999;42:377–90.

Sosunov EA, Anyukhovsky EP, Rosen MR. Differential effects of ivabradine and ryanodine on automaticity of canine sinoatrial node and Purkinje fibers. J Cardiovasc Electrophysiol. 2012;23:650–5.

Tamargo J, Caballero R, Gómez R, Valenzuela C, Delpón E. Pharmacology of cardiac potassium channels. Cardiovasc Res. 2004;62:9–33.

Wantanabe H, Koopmann TT, Le SS, et al. Sodium channel beta 1 subunit mutations associated with Brugada syndrome and cardiac conduction disease in humans. J Clin Invest. 2008;118:2260–8.

Williams J. The functions of two species of calcium channel in cardiac muscle excitation-contraction coupling. Eur Heart J. 1997;18(suppl A):A27–35.

Yaniv Y, Maltsev VA, Escobar AL, et al. Beat-to-beat Ca(2+)-dependent regulation of sinoatrial nodal pacemaker cell rate and rhythm. J Mol Cell Cardiol. 2011;51:902–5.

Zipes DP, Jalife J, editors. Cardiac electrophysiology: from cell to bedside. Philadelphia, PA; Saunders, 2000.

Clinical Electrophysiology of the Cardiac Conduction System

3

Martin J. LaPage, Ian H. Law, and Macdonald Dick II

Cardiac Electrophysiology in the Young

The electrophysiologic properties of the heart consist of impulse formation, conduction velocity, and refractoriness. These properties are evaluated in several components of the conduction system, including the sinoatrial (SA) node, atria, inter-nodal tracts, atrioventricular (AV) node, His bundle, bundle branches, Purkinje network, and ventricle by clinical electrophysiologic study.

The SA node, AV node, and His-Purkinje system exhibit automaticity—spontaneous depolarization dependent upon phase 4 depolarizing outward potassium current. Atrial and ventricular tissues typically develop automaticity only during pathological conditions such as ischemia. This activity is rate variable, relative to the site of origin; the SA node has the fastest spontaneous discharge rate (140–160 bpm at birth, decreasing with age), and thus is the dominant pacemaker in the normal heart. A progressive decrease in spontaneous impulse formation distinguishes different cardiac excitable tissues as the pacemaker moves from atrium to AV node to His-Purkinje system, and lastly to ventricular myocardium. When diastolic depolarization of the dominant pacemaker reaches threshold, it initiates cell-to-cell propagation (conduction), generating an excitation wave front through ordinary atrial and ventricular myocardium and the specialized conduction tissue of the AV node and His-Purkinje system. The rate of normal automaticity is a complex process modulated by circulating catecholamines, the autonomic nervous system, and pathophysiologic state of the myocardium. Autonomic tone varies with age. The newborn and infant are highly susceptible to excessive parasympathetic input that can be aggravated by analgesia, anesthetics, or manipulation of the airway, resulting in a deleterious slowing of the heart rate. Beyond the first several months of life, until adolescence, autonomic tone is fairly stable and well balanced.

The intra-atrial conduction time is a function of the size and state (fibrosis, scars, suture lines, electrical remodeling) of the atria. The AV node displays decremental conduction: conduction

M.J. LaPage, M.D., M.S. (✉) • M. Dick II, M.D.
Pediatric Cardiology, The University of Michigan Congenital Heart Center, Department of Pediatrics and Communicable Diseases, University of Michigan, Ann Arbor, MI, USA
e-mail: mlapage@med.umich.edu

I.H. Law, B.S.E., M.D.
Division of Cardiology, Department of Pediatrics, University of Iowa Children's Hospital, University of Iowa Carver College of Medicine, Iowa City, IA, USA

M. Dick, II (ed.), *Clinical Cardiac Electrophysiology in the Young*,
DOI 10.1007/978-1-4939-2739-5_3

through the AV node prolongs as the input stimulus interval shortens. AV node conduction time is highly influenced by the basic metabolic state, vagal tone, circulating catecholamines, and drug administration. Conduction through the His-Purkinje system is age dependent.

The natural history of arrhythmias is, in large part, dependent on the underlying structural and functional changes in the developing child. Accessory pathway (AP)-mediated tachycardia is the most common tachyarrhythmia occurring in infants and young children. Atrial fibrillation (AFib) and atrial flutter (AFL) are rare in the infant and small child due to insufficient cardiac mass to support the microreentry or macroreentry circuits which sustain this tachyarrhythmia, respectively. On the other hand, when anatomic conditions exist, such as dilated atria providing a circuit of sufficient length, AFib or AFL may appear, even in infants. By approximately 5 years of age, increased heart size and longer refractory periods increase the potential for reentry tachyarrhythmias. During adolescence, the predominate tachyarrhythmia shifts to AV nodal reentry tachycardia, likely reflecting developmental changes in AV node physiology and the autonomic nervous system. Automatic and triggered arrhythmias are less clearly age dependent, though multifocal atrial tachycardia and junctional ectopic tachycardia are, in general, arrhythmias of infants. Ventricular tachycardias unrelated to surgery span all age groups.

The Electrophysiology Study

Myocardial electrical activity can be recorded using electrodes on catheters placed within the heart (Fig. 3.1), and displayed as unipolar or bipolar electrograms (Fig. 3.2) which provide information on the timing of local electrical activation.

Unipolar electrograms display the electrical activation relative to a single electrode using a distant "indifferent" electrode (Wilson's central terminal or a remote electrode) as the opposite pole. The unipolar electrogram provides information on the local activation based on signal polarity, but is disadvantaged because they contain additional far-field signal. Bipolar electrograms are more commonly used. They are recorded between two adjacent electrodes (interelectrode distance is 1–5 mm), thereby minimizing much of the far-field signal and providing more precise information on the timing of local activation. Thus, by virtue of this proximity

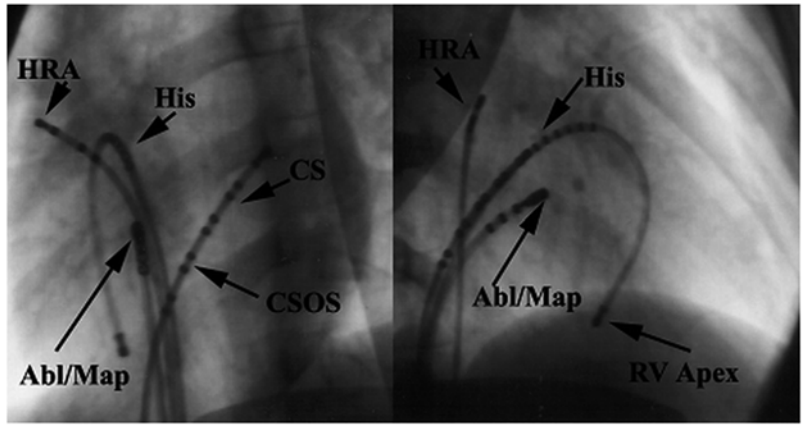


Fig. 3.1 Chest radiographs in two projections (*left panel*: left anterior oblique; *right panel*: right anterior oblique) demonstrating placement of four bipolar electrode pair electrodes; one each in the high right atrium (HRA), coronary sinus (CS), His bundle region (His), and right ventricular apex (RV apex); the last two sites are recorded through a single catheter. The mapping catheter (Abl/Map) is in the mid septal region in the triangle of Koch. The CS catheter in the right anterior oblique projection is superimposed on and obscured by the His catheter

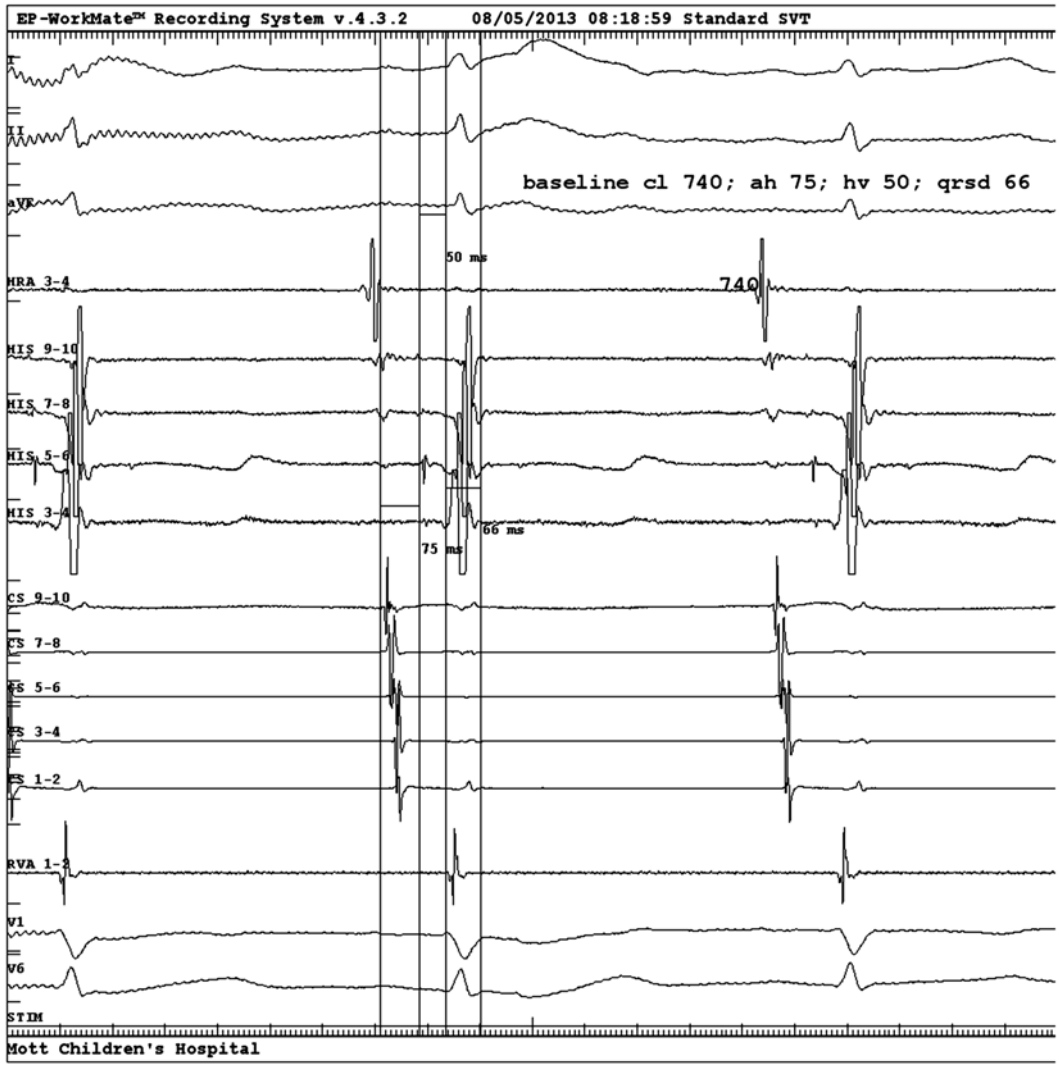


Fig. 3.2 Baseline electrograms from EPS. From *top* to *bottom*: surface ECG Leads I, II, aVF; HRA, His electrograms proximal (9–10) to distal (3, 4), CS proximal (9, 10) to distal (1, 2), RV apex, surface V1 and V6. Measured intervals as displayed are sinus cycle length 740 ms, AH interval 75 ms, HV interval 50 ms, QRS duration 66 ms. *HRA* high right atrium, *CS* coronary sinus, *RV* right ventricle

effect, the electrical activity of localized areas of the atrial and ventricular myocardium, and the His bundle potential can be recorded with intracardiac electrode pairs.

Sedation/Anesthesia

Pediatric patients and most adult patients will require sedation or general anesthesia for a typical catheter ablation procedure due to case duration. The preference for general anesthesia or moderate to deep sedation tends to be center or substrate dependent. We utilize general anesthesia almost exclusively except for substrates which may be repressed by general anesthesia. Modifications in the procedural regulations over the past decade have dictated at many centers that a dedicated physician be in charge of patient sedation. For our own center, this has been the

pediatric anesthesia service. General anesthesia allows for complete control of patient movements during ablation but requires intubation and may result in post-procedure nausea and longer recovery. General anesthesia may also act to suppress certain arrhythmia substrates—focal atrial tachycardia and atrioventricular reentrant tachycardia AVNRT due to effects of gas anesthesia on electrophysiology. For these reasons, moderate sedation may be preferable in some circumstances.

Access

The Electrophysiology Study (EPS) begins with access to the intravascular space. The chosen sites of access are operator dependent. Access is obtained using modified Seldinger technique to place valved sheaths into the vein allowing easy catheter exchange. In our laboratory, with rare exception, all access is via the femoral veins; typically, two sites on each side to accommodate three diagnostic and one ablation catheter. Many labs, however, routinely utilize jugular venous access typically for coronary sinus catheter placement. For those patients with limited femoral access, not uncommon in congenital heart disease patients, an alternative access point is a transhepatic sheath (Fig. 3.3). This typically will require interventional cardiologist involvement as coil closure of the transhepatic tract is recommended to decrease the risk of bleeding complications.

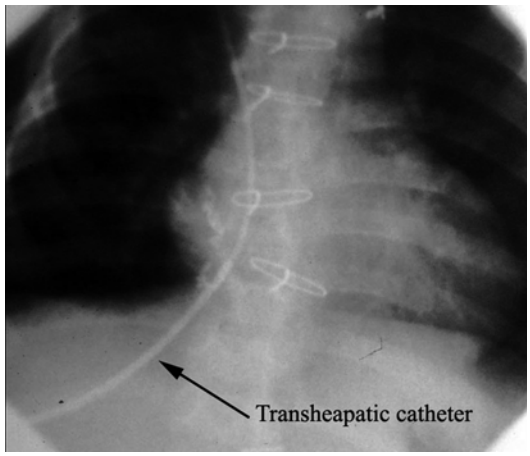


Fig. 3.3 Passage of transhepatic sheath and catheter through the liver and into the right atrium and superior vena cava in an 8-kg infant

Arterial cannulation for monitoring of systemic blood pressure can be used selectively. For most patients with supraventricular tachycardia, monitoring of the blood pressure by sphygmomanometer is sufficient, avoiding the need for an intra-arterial cannula. In patients with poor ventricular function, suspected ventricular arrhythmias, infants (≤15 kg), or patients with adult congenital heart disease, the use of direct intra-arterial blood pressure monitoring may be desirable.

Diagnostic Catheters and Placement

A variety of specially designed diagnostic catheters exist to record electrograms from varied or specific locations within the heart (Fig. 3.4). Positions are strategically chosen to allow for differentiation of the electrical activation in the heart in order to identify the origin and direction of electrical propagation. The routine sites for a typical EPS include the right atrium (RA), right ventricle (RV), coronary sinus (CS), and bundle of His (Fig. 3.2). A bipolar or quadripolar catheter suffices for the RA and RV sites. The CS catheter is usually an octapolar or decapolar catheter which allows for differentiation of the timing of left atrial activation from the CS os (proximal) to the distal CS along the lateral rim of the mitral valve annulus. The His bundle potential can be recorded by placing a catheter across the tricuspid valve annulus at the superior septum. Specially formed catheters (Josephson curve or St. Jude CRd2) may improve stability and quality of the recorded His potential. In our own lab, a combined His/RV catheter (Fig. 3.4) is preferred to decrease the number of access sites. This catheter has two distal electrodes placed in the RV and an array of proximal electrodes which sit at the His bundle. We primarily use deflectable His/RV catheters with a 30 mm His–RV separation or a 50 mm His–RV separation.

Additionally, a quadripolar or pentapolar esophageal catheter (Fig. 3.4) may be added

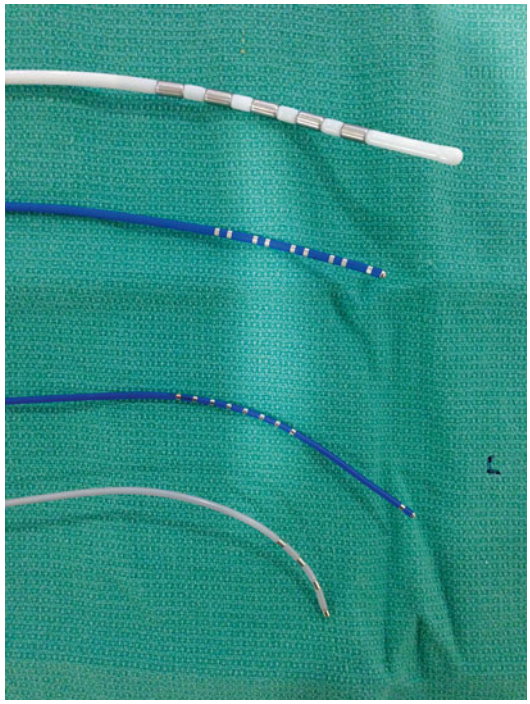


Fig. 3.4 Diagnostic catheters: Several types of diagnostic catheters used in an electrophysiology study. From *top to bottom*: Pentapolar esophageal catheter (*top catheter*). Decapolar deflectable catheter with 2–5–2 mm spacing (6Fr, *second catheter*). Deflectable decapolar His/RV combination catheter with distal bipolar pair of electrodes and a proximal array for His recording (*third catheter*). Josephson curve quadripolar catheter for multipurpose use (*bottom catheter*)

to provide an atrial pacing and recording site while potentially decreased the need for additional venous access. The esophageal catheter also functions well as a reference site for activation mapping as its position tends to be stable and easily confirmable with fluoroscopy if needed; in the infant, it can serve to deliver atrial extrastimulation.

Catheter Navigation

Visualization of the diagnostic and ablation catheters has traditionally been with fluoroscopy. Evolution of computerized 3D electro-anatomic mapping systems over the past decade has led to its nearly exclusive method for catheter navigation in our own and many pediatric laboratories across the country (also see Chap. 23).

The most commonly used systems are Ensite (St. Jude Inc., St. Paul, MN) (Fig. 3.5) and CARTO (Biosense-Webster, Diamond-Bar, CA) (Fig. 3.6). We currently use both Ensite Velocity and CARTO3 with approximately equal use between the two systems. Choice of system is primarily by attending preference and secondarily by arrhythmia substrate or patient characteristics. The Ensite system allows for visualization and placement of all diagnostic catheters prior to choosing an ablation catheter. Any radiofrequency or cryocatheter is compatible with the Ensite system. The CARTO system requires a proprietary catheter to create an endocardial geometry prior to additional catheter placement. Proprietary radiofrequency catheters must be used for ablation, though cryocatheters can be used with minor connection adjustments.

Specific Considerations for Pediatrics and Congenital Heart Disease

The EPS the infant or small child requires special considerations. First, the operator should be experienced in advancing and navigating an electrode catheter through the cardiac chambers of young patients. The operator should be fully informed regarding the clinical course and structural features of concomitant cardiac malformations. Structural congenital heart lesions affect the location of the SA and AV nodes and specialized conduction tissue. Operations for these congenital heart lesions can further alter the electrical properties of the atrial and ventricular myocardium, resulting in complex rhythm disturbances.

The risk of catheter ablation in pediatric patients was shown to carry increased, though not prohibitive, risk in children less than 5 years old or less than 15 kg. The enhanced risk includes difficulty of vascular and intracardiac access, alterations in hemodynamic state, potential perforation and pericardial effusion with tamponade, potential for excessive lesion size (and possible expansion), and injury to the AV node. Between

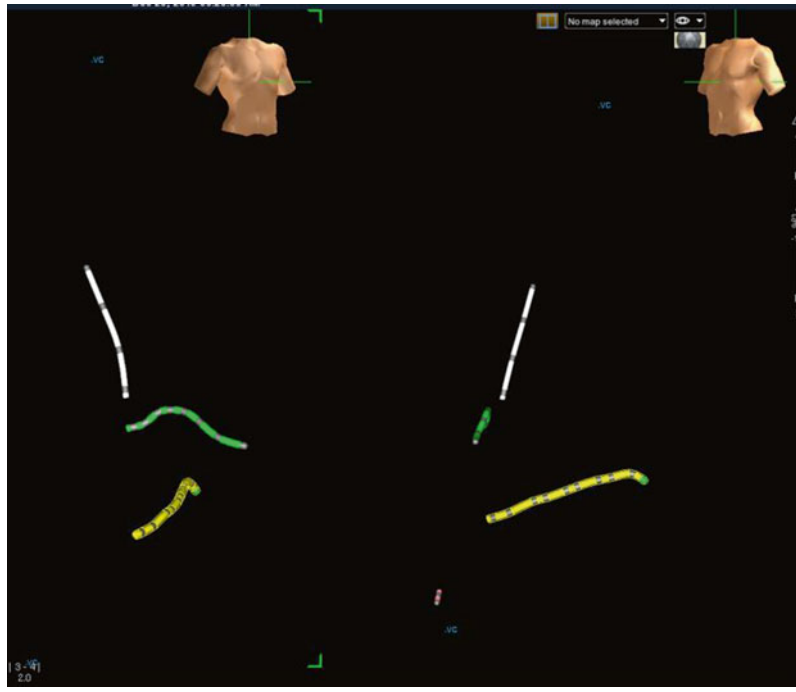


Fig. 3.5 Monitor image of Ensite Velocity electroanatomic mapping system as used for catheter navigation in routine electrophysiology study. *Left-side* is an RAO view as demonstrated by torso in upper screen. *Right side* is LAO view. *Yellow catheter* is a decapolar catheter placed in the coronary sinus. *Green catheter* is the His array of a His/RV combo catheter. RV apex electrodes are in *red* in the LAO view only. *White* catheter is a quadripolar high right atrial catheter

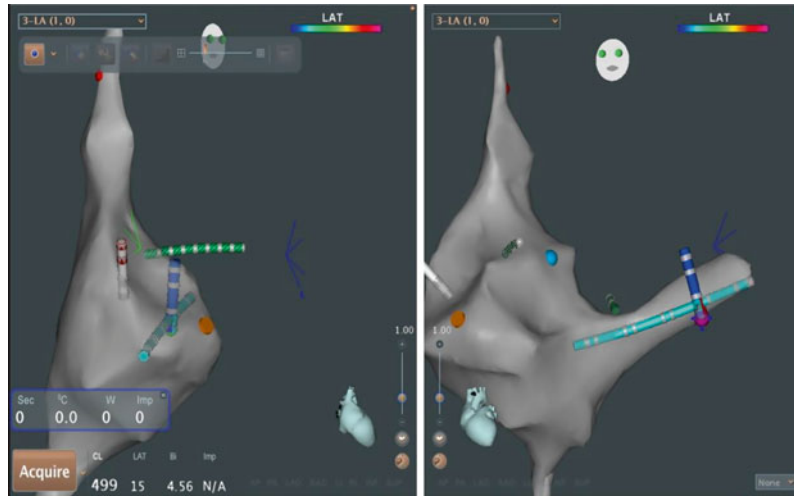


Fig. 3.6 Monitor image from CARTO3 electroanatomic mapping system as used for catheter navigation during electrophysiology study. *Left-hand panel* is RAO view as indicated by "face" position at top of screen. *Right-hand panel* is LAO view. *Aqua catheter* is decapolar catheter placed in the coronary sinus. *Green catheter* in the RAO view is the His array of a His/RV combo catheter. The *blue dot* in the LAO view was the location of a His potential. The *dark blue catheter* with *purple tip* in the LAO view is a radiofrequency catheter positioned to ablate a left lateral accessory pathway

15 and 35 kg, the risks are diminished and beyond 35–50 kg, the risk of electrophysiologic study is essentially equivalent to that in adult patients.

When considering electrophysiologic study in the small infant or child, the number of catheters, the size of the catheters, and the stiffness of the catheters should be minimized. Because of the variable dimension of the cardiac chambers in different size children, steerable catheters with different shapes and different sized curves are necessary to appropriately accommodate each patient. Adolescents are usually of sufficient size to allow use of catheters and sheaths of the length and caliber of those used in adults. However, smaller children require smaller catheters and sheaths, especially in the diameter of the operator-controlled curve. Typically, for a child 20 kg or less, diagnostic catheters should not exceed 6 French; though 7Fr ablation catheters may occasionally be necessary. For an infant under 10 kg, 4 and 5 French catheters are used including the mapping/ablation catheter; although, again 7Fr RF and cryocatheters may be required for effective ablation. Additionally, the esophageal catheter can be a useful addition to the EPS in a small patient.

Due to the vigorous contractile state and the faster heart rates in small children compared to adults, both during sinus rhythm and tachycardia, catheter stability is at risk. There is always a trade-off between catheter size (and stiffness) and catheter stability. The combined His-RV catheter adds stability to the His catheter since it is, in part, secured by the placement of the catheter tip in the RV apex. Multiple catheters produce artifacts when the electrodes from different catheters strike one another, a confounder increased in the smaller volume of a child's heart ($\leq$20 kg).

Intracardiac Electrophysiology

The purpose of the electrophysiology study is to assess the basic electrophysiologic properties of the patient's cardiac conduction system and to determine the mechanisms of the suspected or clinically demonstrated cardiac arrhythmia. The study begins with the measurement of baseline intervals (Table 3.1). The P-A interval denotes the intra-atrial conduction time. The A-H interval assesses the conduction time through the AV node. The H-V interval marks the conduction time through the His-Purkinje system. This interval is fairly constant but does increase slightly from approximately 25 ± 10 to 45 ± 10 ms from infancy to adulthood. An H-V interval greater then 60 ms in the young is abnormal and suggests an abnormality in the His-Purkinje system. It is unusual in the child, even following surgery for congenital heart disease, to have a prolonged H-V interval. Top normal H-V intervals are not uncommon, however, in patients with AV septal defects (AV canal defects) and older postoperative tetralogy of Fallot and ventricular septal defect patients.

Table 3.1 Conduction intervals

Interval	Measurement (normal values)
P-A	Atrial conduction time—beginning from the earliest P-wave on the ECG to the earliest fast atrial deflection on the low septal right atrial electrogram
A-H	AV nodal conduction time—from earliest fast atrial deflection on the annular septal right atrial electrogram to the beginning of the His bundle potential recorded on the His bundle electrogram. Varies with heart rate and autonomic tone
H-V	His-Purkinje conduction time—from beginning of the His bundle potential recorded on the His bundle electrogram to the onset of the surface QRS or earlier ventricular electrogram

In the past, evaluation of the SA node was a routine part of the EPS, though is now seldom performed. SA node function is tested by measuring the SA node recovery time (SNRT) and corrected SA node recovery time (CSNRT). A fixed train (usually 30 s) of external stimuli is delivered to the atrium. When atrial pacing is terminated, the recovery interval of the SA node is measured (i.e., time from the last pacing stimulus to the first spontaneous signal emerging from the SA node recorded as an atrial electrogram in the catheter that delivered the pacing stimuli). This procedure is performed at a pacing rate of 90,

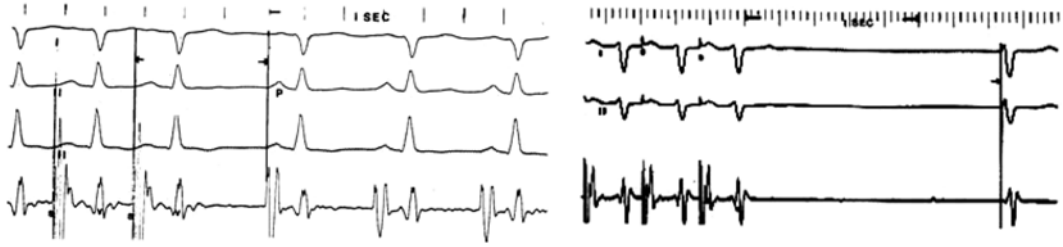


Fig. 3.7 Measurement of sinus node recovery time: *Left panel*: Atrial pacing at 400 ms (150 bpm). Upon termination of pacing, the normal recovery time of the SA node (P-wave) is 620 ms. Subtracting that interval from the basic sinus interval of this patient of 500 ms, yields a normal Maximal Corrected Sinus Node Recovery Time (MCSNRT) of 120 ms. *Right panel*: In contrast, cessation of pacing in a 15-year-old patient following the Mustard operation for transposition of the great arteries yields a junctional escape beat with an escape interval of 1,450 ms. Both the escape mechanism and the escape interval are abnormal

120, 150, 180, and 286 bpm. The maximal SA node recovery time (SNRT) is that maximal escape interval that follows termination of pacing at any pacing rate. The SNRT can be corrected for the normal spontaneous discharge rate by subtracting the basic cycle length (Fig. 3.7). To truly isolate the intrinsic automaticity of the SA node the autonomic nervous system must be attenuated using atropine and beta-blocker. Its clinical purpose was to evaluate an individual with suspected sick sinus syndrome (Chap. 13); this condition is effectively evaluated by surface ECG recordings such as the Holter 24 h dynamic ECG tracing.

Refractory periods are measured using programmed extrastimulation. A drive of 8–10 pacing stimuli are delivered at a constant interval (S1S1) followed by a premature stimulus delivered at a shorter interval (S1S2). This process is reiterated, sequentially shortening the premature beat (S2) until it fails to capture or propagate to the target tissue. This process yields the relative, functional, and effective refractory periods of the tissue in question (Tables 3.2 and 3.3). Because the AV node displays decremental conduction, several specific refractory periods can be measured (Table 3.3, displayed graphically in Fig. 3.8 and with intracardiac tracings in Fig. 3.9).

Following assessment of the electrophysiologic properties of the cardiac conduction system, induction of tachycardia and delineation of its mechanism(s) are performed. The arrhythmia classification is displayed in Fig. 3.10; all will be discussed in detail in the accompanying appropriate chapters. The great majority of tachyarrhythmias in children are due to a reentry mechanism (AVNRT, accessory pathway-mediated tachycardia). Induction of these arrhythmias typically requires a premature beat which is provided by the S1S2 programmed extrastimulation protocol described above. This produces unidirectional block in 1 limb of the circuit and delays conduction in the second limb, thereby initiating reentry. Tachycardia induction may not be as simple as a single premature atrial extrastimulus however; and other maneuvers may be required to induce tachycardia including burst atrial pacing, double or triple premature extrastimuli, alternate site for extrastimulus pacing and isoproterenol administration.

Diagnostic Electrophysiology

Whether or not the tachycardia can be initiated, diagnostic assessment and/or maneuvers are performed to identify the tachycardia mechanism. While there are numerous published techniques, the most commonly used by our laboratory will be outlined. The maneuvers are divided into those that are performed in the baseline state or during pacing and those that are performed during tachycardia. Because most pediatric arrhythmias have a reentry mechanism—AVNRT or AP mediated—most diagnostic pacing maneuvers are based on the concept of entrainment.

Table 3.2 Electrophysiologic data in children

	Group	<0.5 year	*N*	0.05–1 year	*N*	1–5 year	*N*	5–10 year	*N*	>10 year	*N*
Age		0.28	19	0.66	18	3.1	37	6.9	17	16.2	21
Range		0.01–0.18		0.52–0.98		1.0–4.9		5.1–9.9		10–25	
SCL ($x \pm SD$)	(ms)	456±50	19	471±66	18	547±37	37	610±83	17	814±132	21
Panel A: Conduction intervals ($x \pm SD$) (ms)											
	PA	24±7	10	22±14	12	29±15	30	29±12	11	29±14	13
	AH	72±14	11	75±14	14	71±20	30	75±18	12	91±21	14
	HV	33±9	11	35±4	14	36±8	30	34±6	13	41±8	17
	RVA	24±8	5	23±11	11	26±5	22	23±7	10	29±10	18
	RVO	31±5	4	41±11	8	41±10	14	52±7	5	47±14	7
	RVI	33±5	4	41±11	9	47±16	16	48±9	3	47±5	5
Panel B: Refractory periods ($x \pm SD$) (ms)											
	AT. ERP	166±25	17	163±29	12	203±26	22	239±28	7	269±39	4
	AT. FRP	205±35	17	212±18	12	243±29	22	264±24	7	301±45	4
	AVCERP	231±24	15	238±40	4	244±44	8	375	1	–	
	AVCFRP	284±30	15	305±39	11	329±35	18	381±32	6	454±85	4
	VENT ER			226	1	228	2	250	1	225	1
Panel C: Sinus node ($x \pm SD$) (ms)											
	TSACT	111±28	17	107±23	10	123±36	17	153±38	6	120±62	2
	MCSNRT	123±44	18	104±39	10	127±50	23	163±47	7	<250	

Notes: Adapted from Campbell RM, Dick M, Rosenthal A. Cardiac arrhythmias in children. Ann Rev Med 1984; 35:397–410

Abbreviations: *AT. ERP* atrial effective refractory period, *AT. FRP* atrial functional refractory period, *AH* atrial-His bundle interval, *AVCERP* atrioventricular conduction system effective refractory period, *AVCFRP* atrioventricular conduction functional refractory period, *HV* His bundle-ventricle interval, *MCSNRT* maximal corrected sinus node recovery time, *PA* high right atrial to low right atrial interval, *RVA* right ventricular apical activation time, *RVI* right ventricular inflow activation time, *RVO* right ventricular outflow activation time, *TSACT* total sinoatrial conduction time, *VERP* ventricular effective refractory period

Table 3.3 Refractory periods

Refractory period	Definition
Effective refractory period (ERP)	The longest input interval (S1-S2) that fails to depolarize (propagate to) the tissue in question
Functional refractory period (FRP)	The shortest output interval (e.g., H1-H2 or V1-V2) that propagates to the tissue in question
Relative refractory period (RRP)	The shortest output interval (e.g., H1-H2 or V1-V2) equal to the input interval (e.g., A1-A)

Diagnostic Evidence and Maneuvers Performed While Not in Tachycardia

The surface QRS morphology during sinus rhythm should be assessed for evidence of ventricular preexcitation confirmed by measurement of a short H-V interval (Fig. 3.11; also see Chap. 4, Figs. 3.2 and 3.3)).

Dual AV node physiology (DAVNP) is characterized by a "jump" in the AH interval when delivering incrementally shorter premature atrial extrastimuli (S2) (Fig. 3.12; Chap. 5). DAVNP is defined as an increase in the AH interval of at least 50 ms after a decrease in the S2 interval of 10 ms. Alternatively, a second method of diagnosing DAVNP has been identified in pediatric patients exclusively—rapid atrial pacing at progressively shorter pacing intervals which produces 1:1 conduction to the ventricle with the paced PR interval>paced RR interval. While DAVNP is typically associated with AVNRT, the finding itself is not particularly sensitive or specific. Approximately 30 % of pediatric patients

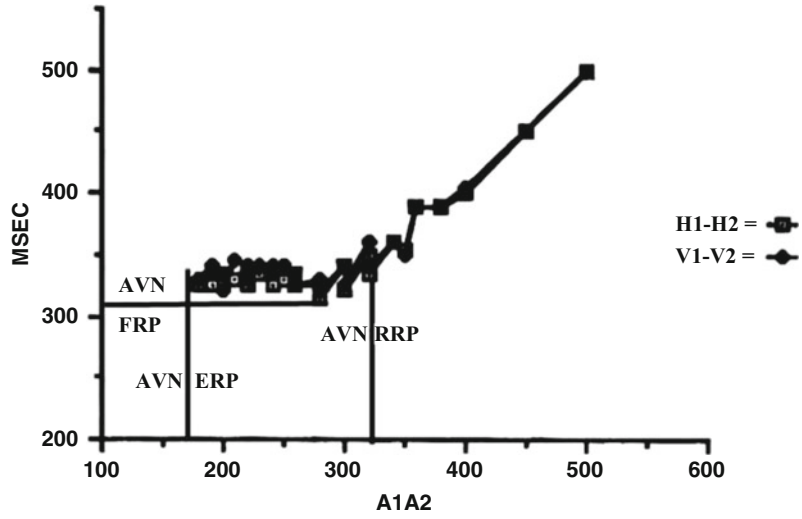


Fig. 3.8 Plot of the H1H2 and V1V2 intervals (*y*-axis) as the atrial premature interval (A1A2) is incrementally shortened (*x*-axis). Shown are the atrioventricular node relative refractory period AVRRP, the atrioventricular node effective refractory period (AVNERP) and the atrioventricular node functional refractory period (AVNFRP). The refractory periods are defined in Table 3.3

will have DAVNP without AVNRT. Retrograde DAVNP may also be demonstrated but appears to be much less specific for identifying patients with AVNRT.

A*trial activation pattern* is assessed during ventricular pacing and determined to be concentric (originating from the atrial septum) or eccentric (not originating from the septum) (Fig. 3.13). Normal retrograde conduction through the AV node produces concentric atrial activation. Left inferior or lateral APs will show eccentric activation early in the mid-distal CS electrograms. Right lateral APs will be early on the lateral tricuspid valve annulus provided the mapping catheter or the HRA catheter has been placed near this location; if the HRA catheter is high in the atrium in the absence of a mapping catheter, the earliest atrial activation for a right lateral AP will appear at the His or proximal CS and may mimic concentric activation. Concentric atrial activation should be further assessed with premature ventricular extrastimuli in order to identify decremental retrograde conduction which would suggest the conduction is via the AV node as opposed to a septal AP.

Base-apex pacing also can help in differentiating AP versus AVN conduction and is performed by delivering extrastimuli at a constant rate to the ventricle near the annulus (base) and measuring the stimulus-A interval, then pacing from the apex at the same rate and measuring the stimulus-A interval (Fig. 3.14). Because the His-Purkinje system terminates near the apex, an apically delivered extrastimuli is expected to enter the His-Purkinje system and conduct retrograde to the atria via the AV node. If there is not an AP, the stimulus-A time from the base should be longer than that from the apex, as the activation must travel through the ventricular muscle to the apex first and then enter the HPS. In the presence of a septal AP, the activation needs only to conduct through the AP to the atria, hence the stimulus-A time should be shorter. Cautious interpretation is necessary if a decremental AP is present or there is retrograde dual AV node pathway (DAVNP).

ParaHisian pacing is performed by pacing from the His catheter with the goal of capturing the His bundle—indicated by producing a relatively narrow QRS (Fig. 3.15). High output pacing is delivered from the His catheter (assuring there

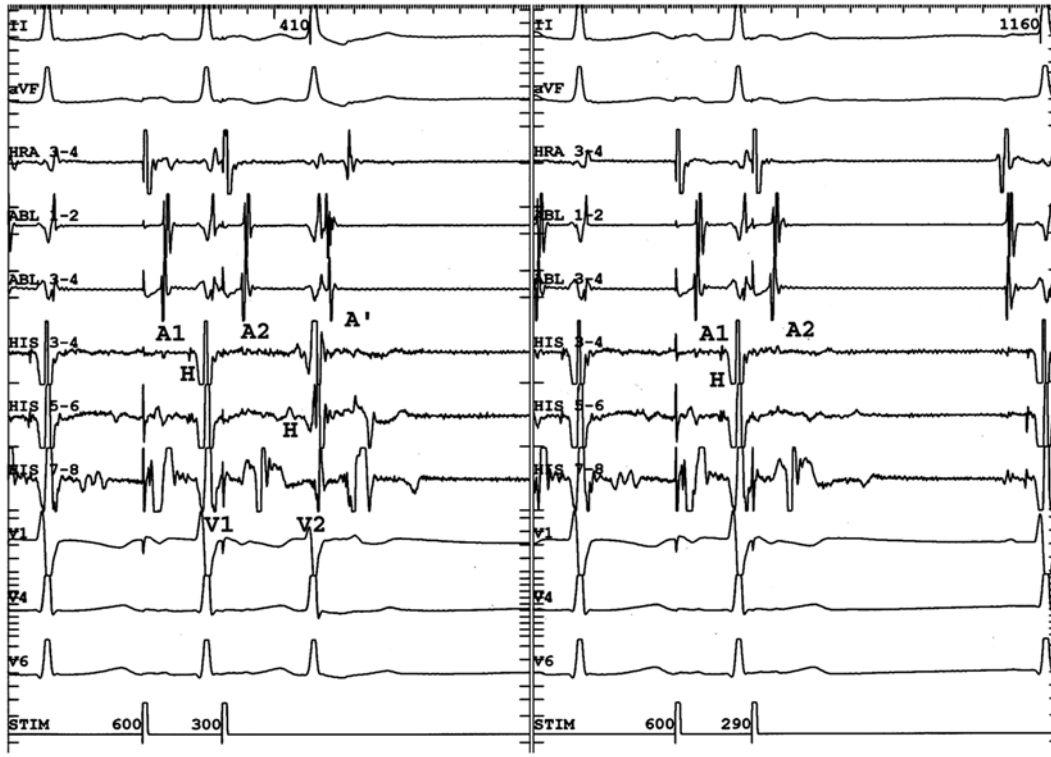


Fig. 3.9 AV node effective refractory period: Displayed from top to bottom: surface lead II, aVF, high right atrium, Ablation distal (1–2) to proximal (3–4), His distal (3–4) to proximal (7–8), surface leads V1, V4, and V6. Atrial extrastimulation yielding the effective refractory period of the AV node. *Left panel*: A premature atria stimulus (A2) is delivered at a coupling interval of 300 ms at a basic drive of 600 ms. Conduction through the AV node to the His bundle and the ventricle is intact. In addition, there is an echo beat (A′) earliest in the Abl 1–2 located in the coronary sinus. This last observation indicates a left-sided AP. *Right panel*: The coupling interval of the premature impulse (A2) was shortened to 290 ms with capture of atrial tissue and conduction block in the AV node (i.e., no His electrogram following the atrial electrogram), indicating the effective refractory period of the AV node

is no atrial capture) at a constant rate. The output is decreased gradually until a distinct increase in the surface QRS duration is noted—indicating that the His bundle is no longer being captured and ventricular activation is via local myocardial capture only. In the presence of a septal AP the stimulus-A interval is expected to be the same during both His capture and His non-capture. Without a septal AP the His captured stimulus-A interval will be shorter than the His non-captured stimulus-A as the latter must traverse the ventricle to the apex before entering the HPS and conducting retrograde via the AV node. Again, cautious interpretation is necessary in the presence of a decremental retrograde AP or retrograde DAVNP.

Adenosine may be delivered during sinus rhythm to produce AV node block and illicit ventricular activation down a manifest or latent AP. It may also be delivered during ventricular pacing for several purposes. Retrograde AV nodal conduction is expected to block and may uncover retrograde AP conduction (Fig. 3.16, also see Chap. 4, Fig. 3.12). Lack of retrograde AV block during adenosine administration is not absolutely indicative of the presence of an AP however, some patients with AVNRT may be resistant to the effects of adenosine on retrograde AV node conduction. For these patients, giving a higher dose of adenosine may produce retrograde AV node block. Additionally, rare APs

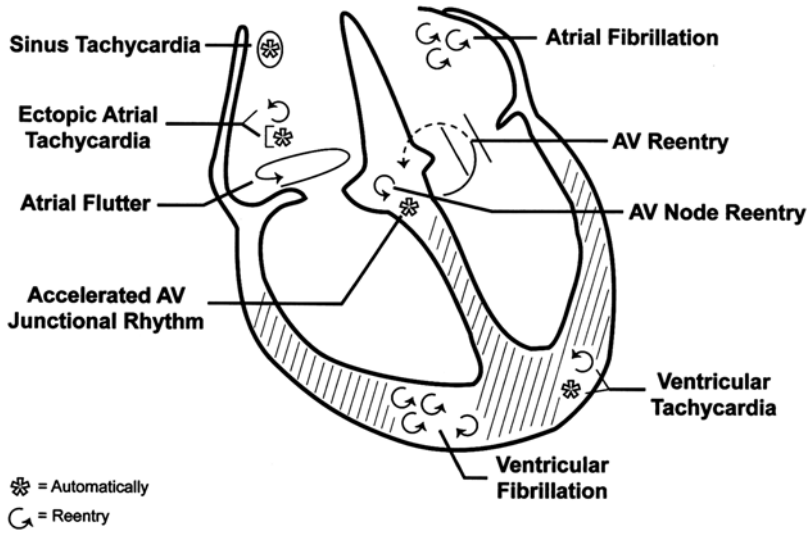


Fig. 3.10 Drawing of cardiac arrhythmias: their origin and their mechanism. Reentry arrhythmias include AP-mediated tachycardias (AV reentry) AV node reentry, atrial flutter, and some forms of ventricular tachycardia. Automatic arrhythmias consist of ectopic atrial tachycardia, accelerated AV junctional rhythm, and some forms of ventricular tachycardia (VT)

may be sensitive to adenosine, especially those displaying retrograde decremental or slow conduction. As a result of these caveats, the results of adenosine administration on retrograde AV node conduction should be interpreted along with other diagnostic evidence.

Diagnostic Evidence and Maneuvers During Tachyarrhythmia

The *surface QRS morphology* should be assessed for normality. Pediatric tachycardias tend to be narrow (or normal) complex or orthodromic tachycardias. However, preexcited tachycardias such as antidromic AP-mediated tachycardia or atrio-fascicular-mediated tachycardias are also possible and will demonstrate wide QRS morphology. Tachycardias may demonstrate rate-dependent bundle branch block (Ashman's phenomenon, aberrancy; see Chap. 13, Fig. 13.6).

The *atrial activation pattern* is assessed during 1:1 atrioventricular tachycardias. The site of earliest atrial activation should be noted and compared to atrial activation during ventricular pacing. Again, eccentric activation is differentiated from concentric activation to indicate AP-mediated tachycardia vs. AVNRT (see Chaps. 4 and 5).

A*tria to ventricular conduction* is 1:1 for all AP-mediated tachycardias and usually 1:1 for AVNRT (both block to the atrium and block to the ventricle is possible usually in a 1:2 or 2:1 pattern). Atrial tachycardia may be 1:1 or >1:1 if AV node block develops as in typical atrial flutter (Chap. 8); AV block essentially confirms atrial tachycardia except in the case of AVNRT with 2:1 block. Reciprocally, A-V conduction <1:1 should confirm ventricular tachycardia in the presence of wide complex tachycardia or junctional tachycardia if the QRS complex is narrow. Again, however, AVNRT with variable conduction to the atrium with or without bundle branch block may produce this pattern as well but is very rare.

The *ventricle to atria conduction time (VA time)* is an important clue to the tachycardia substrate and should be measured from the earliest onset of the surface QRS to the earliest intracardiac atrial electrogram. A VA interval <70 ms

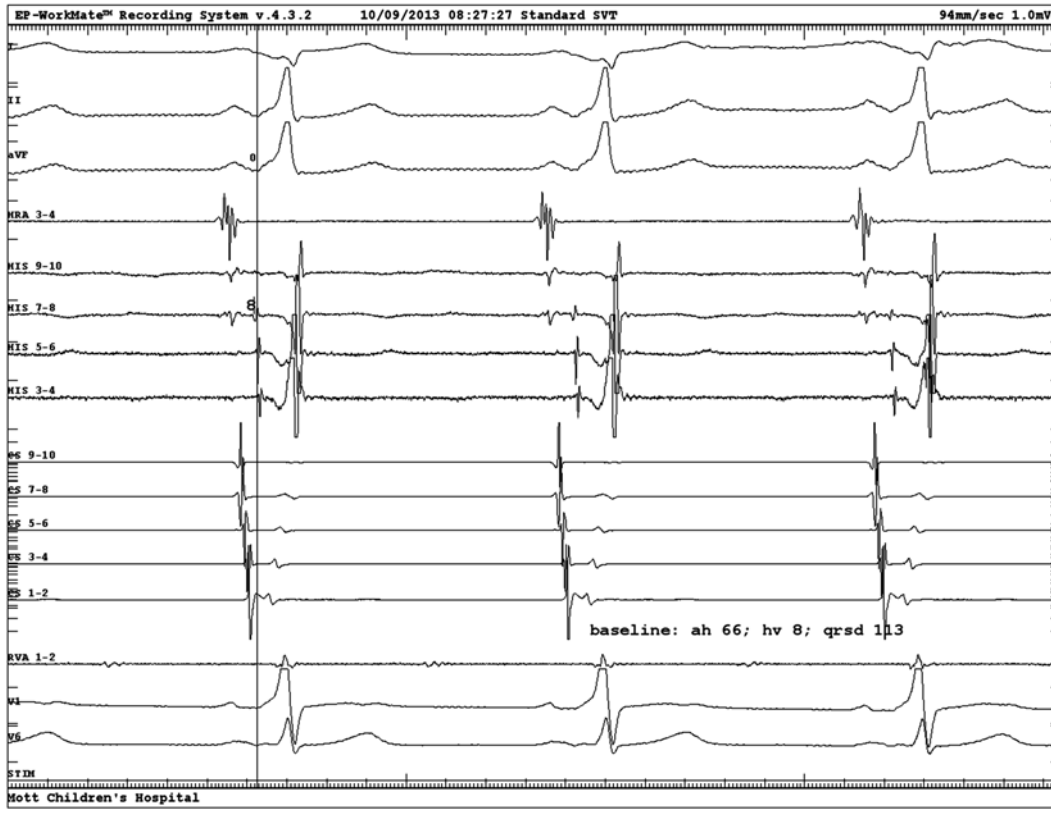


Fig. 3.11 Ventricular preexcitation: Intracardiac electrograms displayed from top to bottom as: surface leads I, II, aVF, HRA, His proximal (9–10) to distal (3–4), CS proximal (9–10) to distal (1–2), RV apex, surface leads V1 and V6. Baseline measures are shown with HV 8 ms. Horizontal line at first beat marks beginning of delta wave onset occurring simultaneous with His deflection. *HRA* high right atrium, *CS* coronary sinus, *RV* right ventricle

is diagnostic of typical AVNRT in adults and older adolescents (Fig. 3.17; Chap. 5). Younger patients, however, may have AP-mediated tachycardias with a VA time of 65 ms (Fig. 3.13, right panel). A VA time of less than 60 ms during inducible tachycardia is essentially diagnostic of typical AVNRT, though the less common junctional tachycardia may have a similar VA relationship. During AP-mediated tachycardia a change in the VA time associated with a rate-dependent bundle branch block may help localize the AP—a bundle branch block will increase the VA time through an ipsilateral AP (Coumel's phenomenon; Fig. 3.18, Chap. 4)

Entrainment is an important and useful concept and diagnostic maneuver that supports reentry as the mechanism of a tachycardia. Three criteria must be present to sustain a reentry: (1) a central obstacle for the circuit to navigate and (2) a zone of slow conduction which allows the rest of the circuit to repolarize on the return (reentry) of the impulse to the site of origin. A third criterion must occur in order to initiate a reentry tachycardia—unidirectional block in one limb of the circuit which allows for the circuit to progress in one direction. The central obstacle varies depending on the tachycardia type: the tricuspid valve annulus in typical atrial flutter, the fibrous annulus in AP-mediated tachycardias, scar in intra-atrial reentry tachycardia, and portions of the AV node and atrial septum in AVNRT. The slow zone varies as well: the cavo-tricuspid isthmus in typical atrial

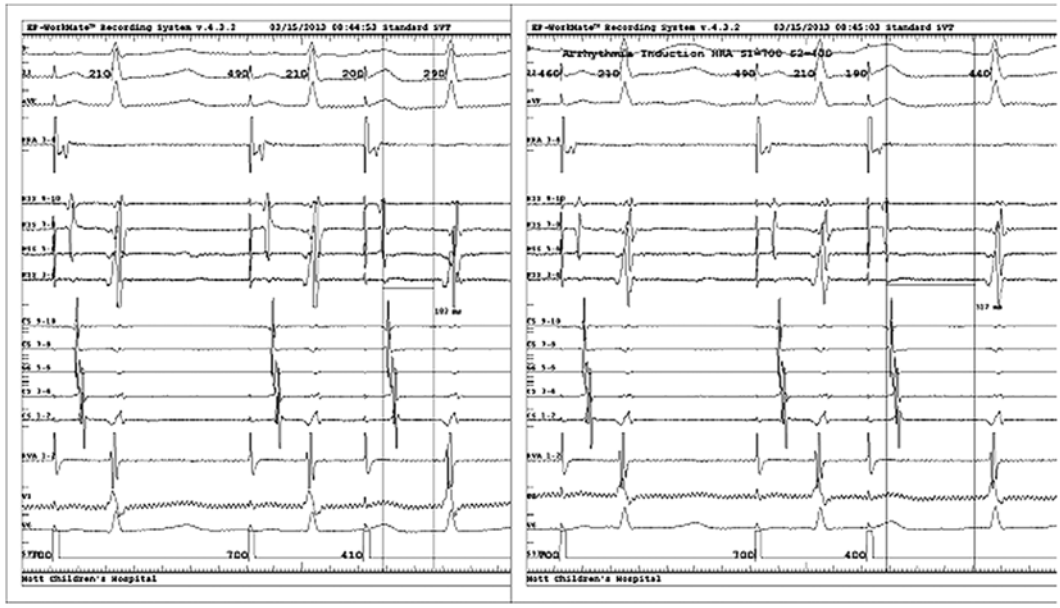


Fig. 3.12 Dual AV node physiology: Intracardiac electrograms displayed as: surface lead I, II, aVF, high right atrium, His proximal (9–10) to distal (3–4), CS proximal (9–10) to distal (1–2), RV apex, surface leads V1 and V6. *Left panel* shows premature atrial extrastimulus with S1S2 700/410 paced from the HRA. The AH interval following the premature extrastimulus is 183 ms. *Right panel* shows a premature atrial extrastimulus of S1S2 700/400 from the HRA. The AH interval has now "jumped" out to 317 ms. Important to the documentation of dual AV node physiology is that the AV node must continue to conduct with the longer AH as the premature extrastimulus shortens—700/390, 700/380, etc. *HRA* high right atrium, *CS* coronary sinus, *RV* right ventricle

flutter, the AV node its right and left extensions in AP-mediated tachycardias and AVNRT and scars in reentrant ventricular tachycardia.

Entrainment has been defined to mean: to adjust (an internal rhythm of an organism) so that it synchronizes with an external cycle, such as that of light and dark; in our case, the internal rhythm is the tachycardia and the external cycle is the pacing rate. Thus, entrainment is the delivery of programmed extrastimuli at a constant rate that is slightly faster than the tachycardia cycle length thereby transiently capturing the tachycardia mechanism by advancing the tachycardia to the paced cycle length Fig. 3.19) The delivered extrastimuli enter the tachycardia circuit in both the retrograde and antegrade directions—the retrograde activation collides with the prior wave front blocking it while the antegrade activation propagates and continues the tachycardia. As a practical example, an orthodromic AP-mediated tachycardia can be entrained from the RV. Assume a tachycardia cycle length of 300 ms. Pacing is delivered from the RV apical catheter at a cycle length of 280 ms. The paced wave front enters the HPS and propagates retrograde where it collides with the antegrade wave front of the tachycardia and blocks in the HPS. The paced wave front also activates the ventricle and traverses the AP thereby activating the atrium 20 ms earlier than the tachycardia (300 ms − 280 ms = 20 ms). With continued pacing at 280 ms, the atrial activation sequence would remain constant (IE: activated via retrograde conduction through the AP) but would occur every 280 ms instead of every 300 ms. Hence, the tachycardia would be entrained.

The post-pacing interval (PPI) is an important measure to determine whether or not the tip of the pacing catheter is positioned at a location

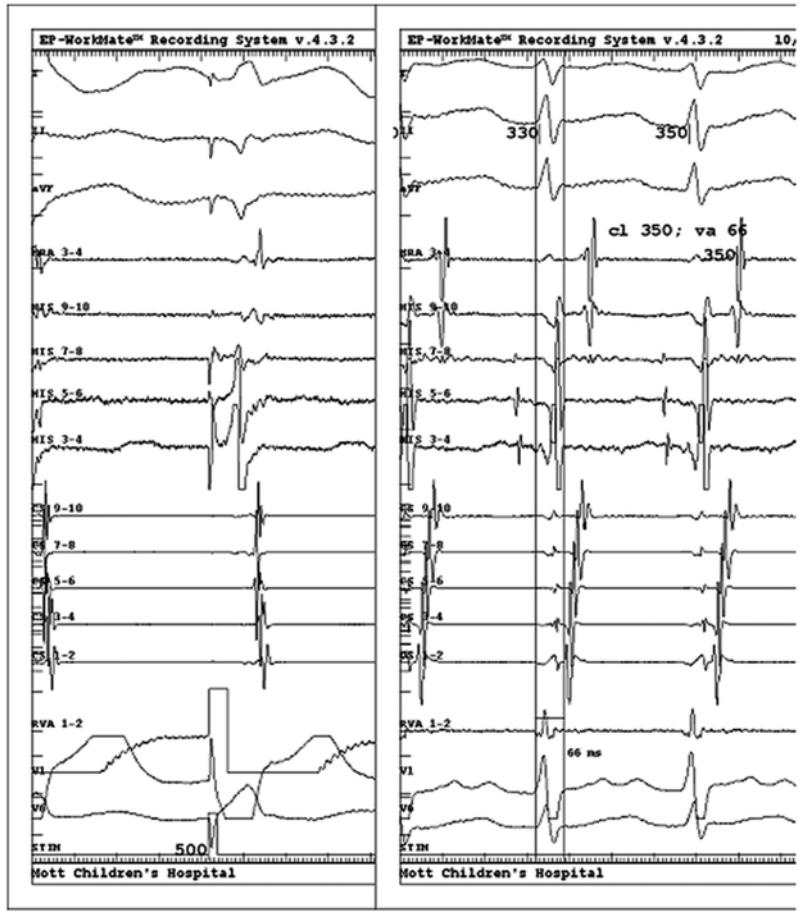


Fig. 3.13 Concentric vs. eccentric atrial activation: Intracardiac electrograms displayed as surface leads I, II, aVF, HRA, His proximal (9–10) to distal (3–4), CS proximal (9–10) to distal (1–2), RV apex, surface leads V1 and V6. *Left panel* shows ventricular extrastimulation from the RV apex. Concentric atrial activation is earliest in the His catheter and proceeds from proximal to distal in the CS catheter—consistent with retrograde atrial activation via a septal accessory pathway or the AV node. *Right panel* shows accessory pathway-mediated orthodromic tachycardia with VA time measured at 66 ms. There is eccentric atrial activation proceeding from distal CS to proximal CS consistent with retrograde activation via a left lateral accessory pathway. *HRA* high right atrium, *CS* coronary sinus, *RV* right ventricle

within the reentry circuit itself or is positioned outside the circuit in "passively" activated myocardium. The PPI is the interval from the last pacing stimulus during entrainment to the first sensed electrogram at the same pacing catheter. Using the above AP example, the final paced beat should enter the circuit in the antegrade direction and take 300 ms to traverse the entire circuit. If the pacing catheter is positioned in this 300 ms circuit, the PPI is expected to be around 300 ms. However, if the pacing catheter is outside the circuit, then the PPI will be the 300 ms circuit time plus the travel time from the catheter to the circuit and the travel time from circuit back to catheter. The tachycardia cycle length (TCL) is subtracted from the PPI to determine the difference. PPI-TCL of <|30ms| is typically considered within the circuit. These maneuvers are important when determining where to ablate an intra-atrial or ventricular reentry circuit.

Documentation of entrainment technically requires three criteria as described by Waldo.

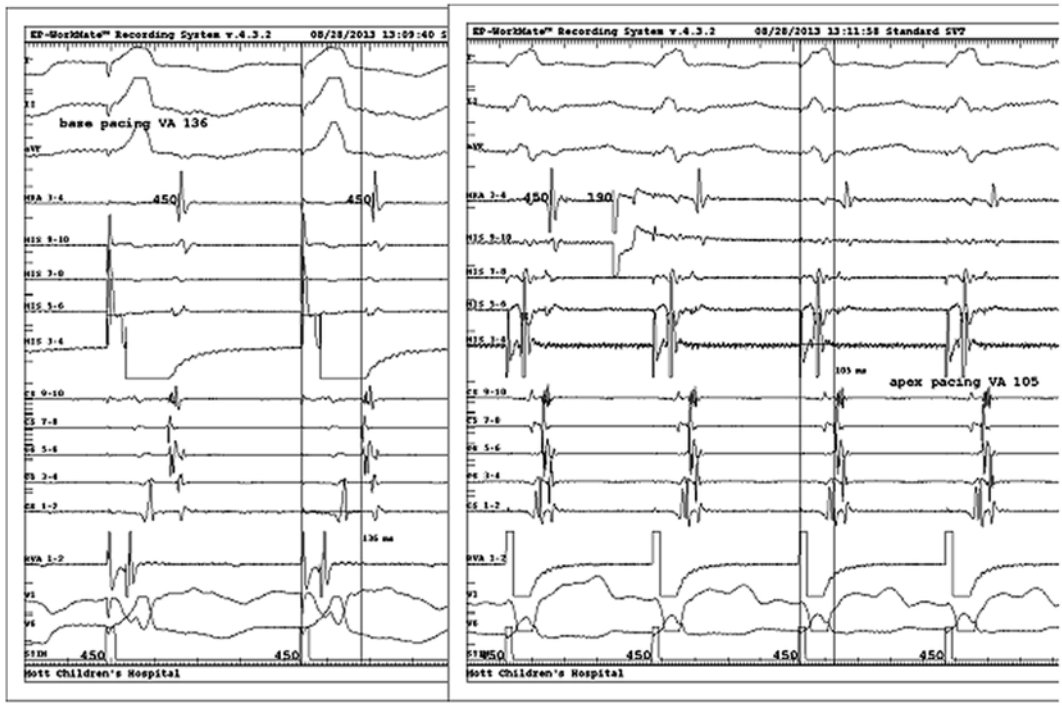


Fig. 3.14 Base/apex pacing: Intracardiac electrograms displayed as surface leads I, II, aVF, HRA, His proximal (9–10) to distal (3–4), CS proximal (9–10) to distal (1–2), RV apex, surface leads V1 and V6. *Left panel* shows RV pacing from the base with a measured stimulus to A interval of 136 ms. *Right panel* shows RV pacing from more distal toward the apex with a stimulus to A interval of 105 ms. Difference in base/apex pacing is consistent with retrograde activation via the AV node; see text. (Note: sweep speeds of tracings are slightly different.) *HRA* high right atrium, *CS* coronary sinus, *RV* right ventricle

(1) When pacing at a constant rate that is slightly faster than the rate of the tachycardia (but not terminating 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 2 or more constant rates faster than the tachycardia rate (but not terminating it), there is demonstration of different degrees of constant fusion on the ECG between the different pacing rates. (3) When pacing at a constant rate that is faster than and interrupts the tachycardia, local conduction block to a site can be demonstrated for 1 beat followed by activation of that site by the next paced beat with a shorter conduction time (Waldo 2004).

RV entrainment has been shown to distinguish septal AP-mediated tachycardias from AVNRT in children specifically when focusing on the post-pacing interval (PPI). Following tachycardia entrainment from the RV apex the corrected PPI minus the tachycardia cycle length (cPPI-TCL = (PPI-TCL) – (post-pacing AH – pre-pacing AH)) was measured and found to differentiate AVNRT (cPPI-TCL > 95 ms) from ORT (cPPI-TCL < 95 ms). Further, entrainment pacing from the RV during 1:1 narrow complex tachycardia by the same mechanism is diagnostic of an AP-mediated tachycardia if the first fully paced beat advances the atrial activation and consistent with AVNRT if the atrial activation is not advanced until after the third fully paced beat.

His-refractory Ventricular Extrastimulation (VES). During narrow complex 1:1 tachycardia, a single ventricular premature extrastimulus is

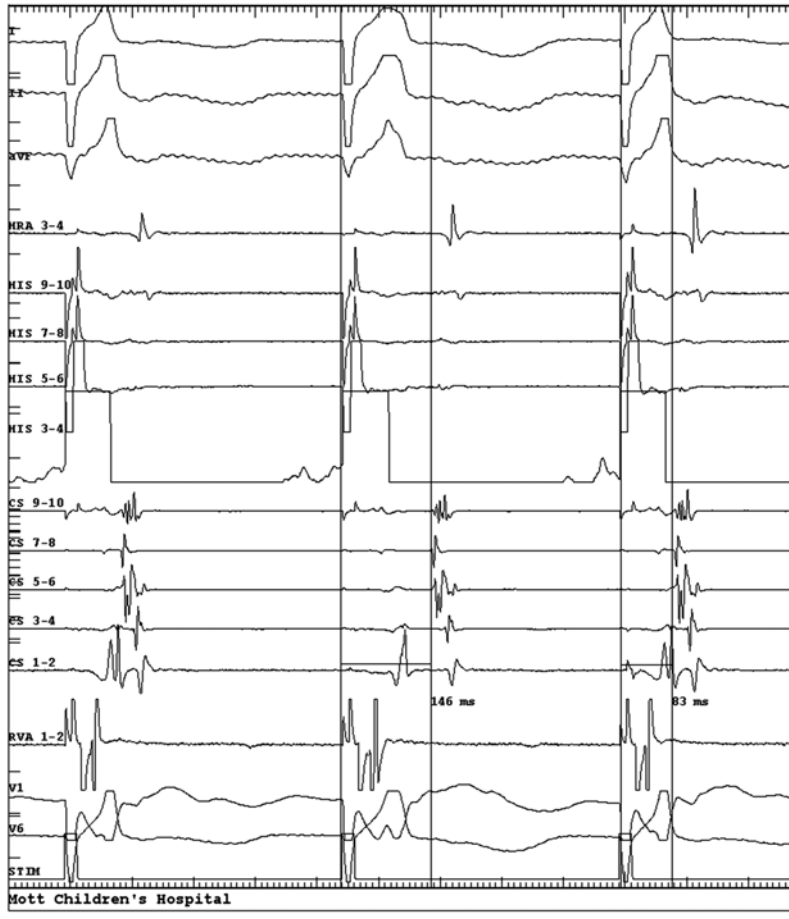


Fig. 3.15 ParaHisian pacing: Intracardiac electrograms displayed as surface leads I, II, aVF, HRA, His proximal (9–10) to distal (3–4), CS proximal (9–10) to distal (1–2), RV apex, surface leads V1 and V6. Pacing is from the distal His catheter. The second beat displays a wide QRS indicating the absence of His bundle capture—with a measured stimulus to A interval of 146 ms. The third beat displays a narrow QRS indicating capture of the His bundle with a stimulus to A interval of 83 ms. The shorter stimulus to A interval with His capture is consistent with retrograde conduction via the AV node and the absence of a septal accessory pathway. See text for details. *HRA* high right atrium, *CS* coronary sinus, *RV* right ventricle

delivered when the His is refractory (Fig. 3.20). If this *His-refractory VES* advances the subsequent atrial activation, it is 100 % diagnostic of the presence of an AP. Absence of the response, however, does not rule out an AP. Entrainment pacing from the RV during 1:1 narrow complex tachycardia by the same mechanism is diagnostic of an AP-mediated tachycardia if the first fully paced beat advances the atrial activation and consistent with AVNRT if the atrial activation is not advanced until after the third fully paced beat.

Ventricular pacing during narrow complex 1:1 tachycardias may also reveal the diagnosis of atrial tachycardia. If the ventricular activation, while pacing faster than the tachycardia rate, can be dissociated from the atrial activation without affecting the timing of atrial activation, then atrial tachycardia is diagnosed. Alternatively, if at the termination of ventricular pacing there is demonstrated a stimulus-V-A-A-V interval followed by continuation of the tachycardia, this too is diagnostic of an atrial tachycardia. In this

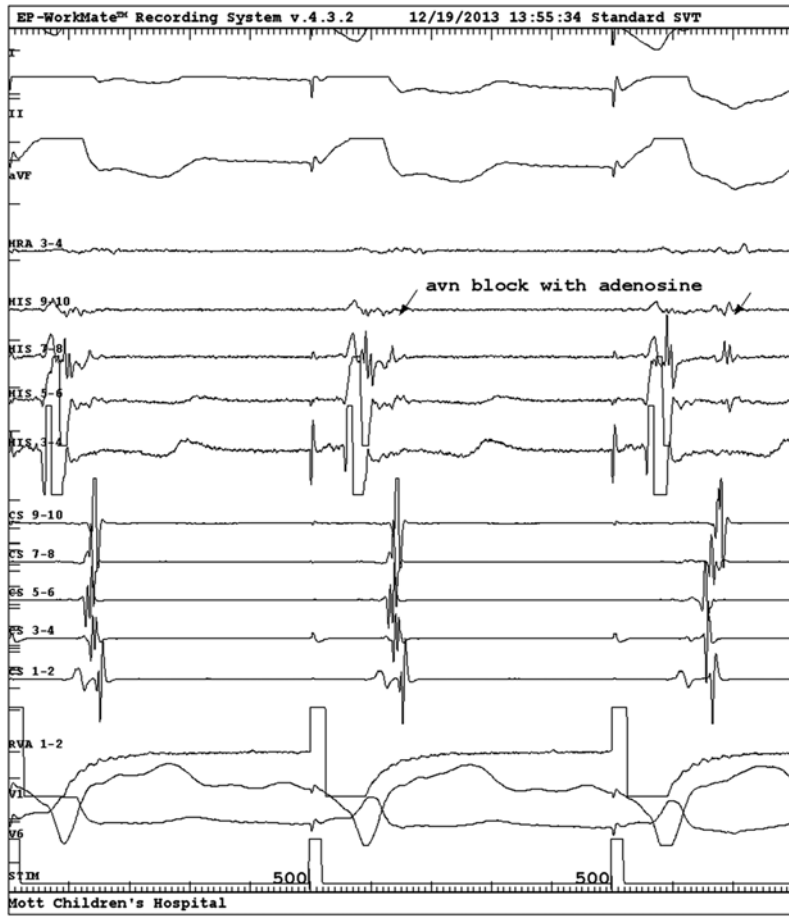


Fig. 3.16 Adenosine reveals AP conduction: Intracardiac electrograms displayed as surface leads I, II, aVF, HRA, His proximal (9–10) to distal (3–4), CS proximal (9–10) to distal (1–2), RV apex, surface leads V1 and V6. Pacing is from the RV catheter at 500 ms cycle length during adenosine administration. The first and second beats display retrograde activation via the AV node with earliest atrial activation at the His catheter. The third beat shows the effect of adenosine with a change in atrial activation. The atrial activation at the His is delayed and retrograde activation proceeds through a left inferior accessory pathway earliest in CS 5–6. *HRA* high right atrium, *CS* coronary sinus, *RV* right ventricle

circumstance, a pseudo V-A-A-V response must be ruled out which would occur during atypical AVNRT (Fig. 3.21).

Late coupled premature atrial extrastimulus: A narrow complex 1:1 tachycardia with a very short VA time <70 ms may be consistent with either typical AVNRT or a junctional tachycardia. While AVNRT should be able to be pace induced and pace terminated, sometimes additional evidence is necessary to fully determine the tachycardia mechanism. A *late coupled premature atrial extrastimulus* during the tachycardia can serve to aid this differentiation (Fig. 3.22). The AES delivered during junctional tachycardia is expected to advance the immediately following ventricular activation. On the other hand, in typical AVNRT the AES would enter the antegrade slow pathway and alter the timing of not the immediate V, but the subsequent V activation (Padanilam et al. 2008).

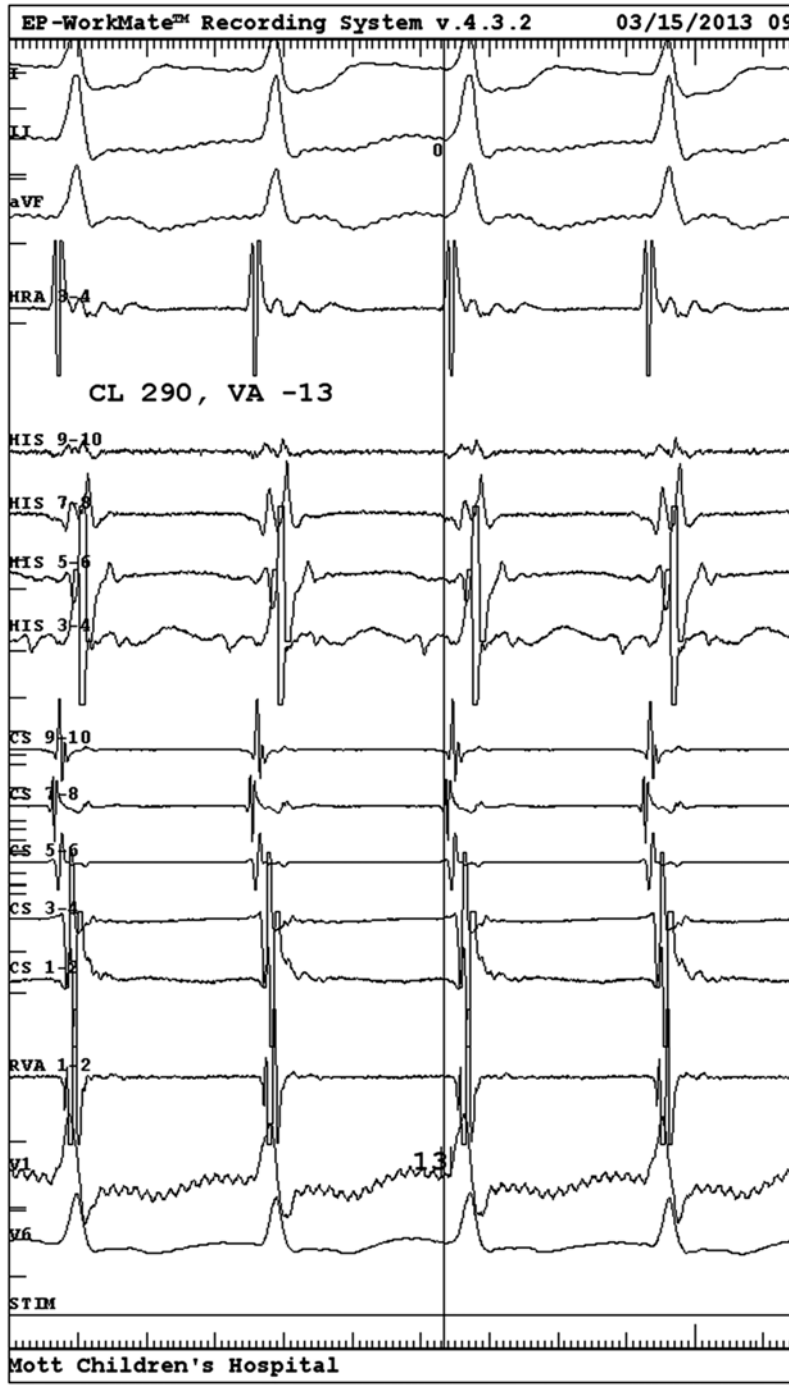


Fig. 3.17 AVNRT: Intracardiac electrograms displayed as surface leads I, II, aVF, HRA, His proximal (9–10) to distal (3–4), CS proximal (9–10) to distal (1–2), RV apex, surface leads V1 and V6. The rhythm is AVNRT. The atrial and ventricular activation is simultaneous. Measured cycle length is 290 with VA interval—13 ms. *HRA* high right atrium, *CS* coronary sinus, *RV* right ventricle

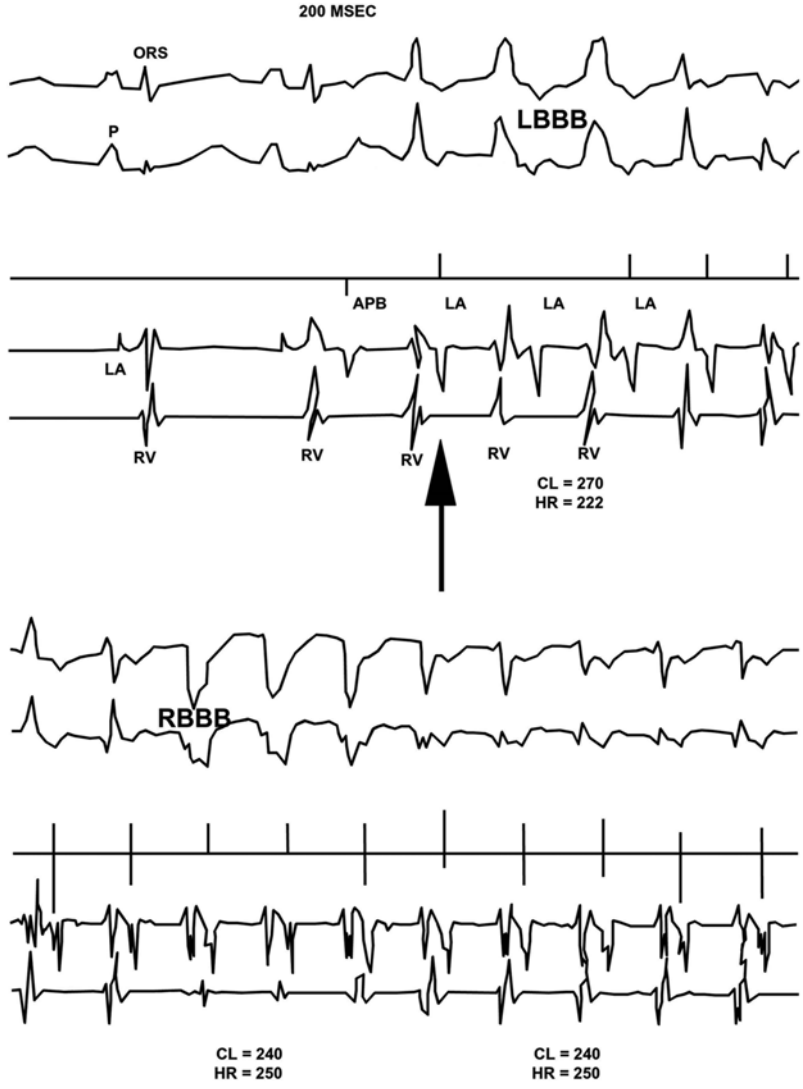


Fig. 3.18 Electrocardiographic tracings (Lead I and II, *top* 2 tracings) and cardiac electrograms form the left atrium (LA) and the right ventricular (RV) during supraventricular tachycardia. *Arrow* indicates spontaneous premature atrial beat initiating tachycardia. Note left bundle branch block configuration (3–5 beats) with increased retrograde conduction interval between the RV and the LA. In contrast as the QRS normalizes the RV-LA interval shortens; then, (*bottom tracings*) right bundle branch block develops, but the RV to LA interval stay short and persists even when the QRS totally normalizes, indicating a left-sided accessory pathway supporting the tachycardia

A multitude of alternative diagnostic maneuvers are documented in the literature. These generally serve to differentiate AVNRT from accessory pathway-mediated tachycardia or atrial tachycardia. Long RP tachycardias especially tend to require diagnostic maneuvers to prove the diagnosis. The majority of diagnostic maneuvers are variations on the concept of entrainment.

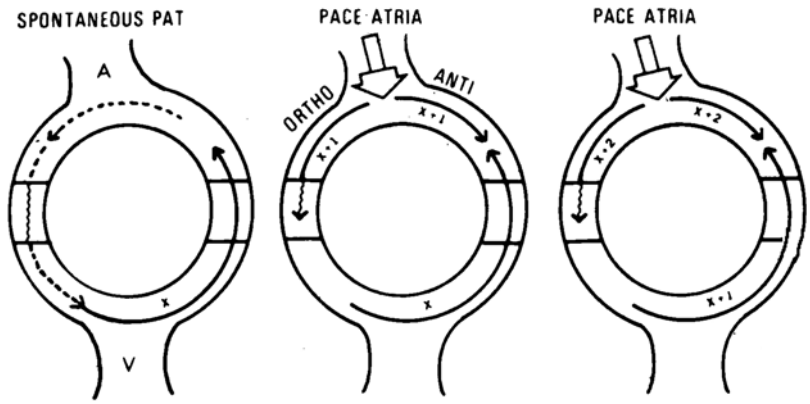


Fig. 3.19 Cartoon displaying *Entrainment*. See text. [Reprinted from Waldo AL, et al., Transient entrainment and interruption of the atrioventricular bypass tract type of paroxysmal atrial tachycardia. A model for understanding and identifying reentrant arrhythmias. Circulation 1983; 67(1): 73–83. With permission from Wolters Kluwer Health]

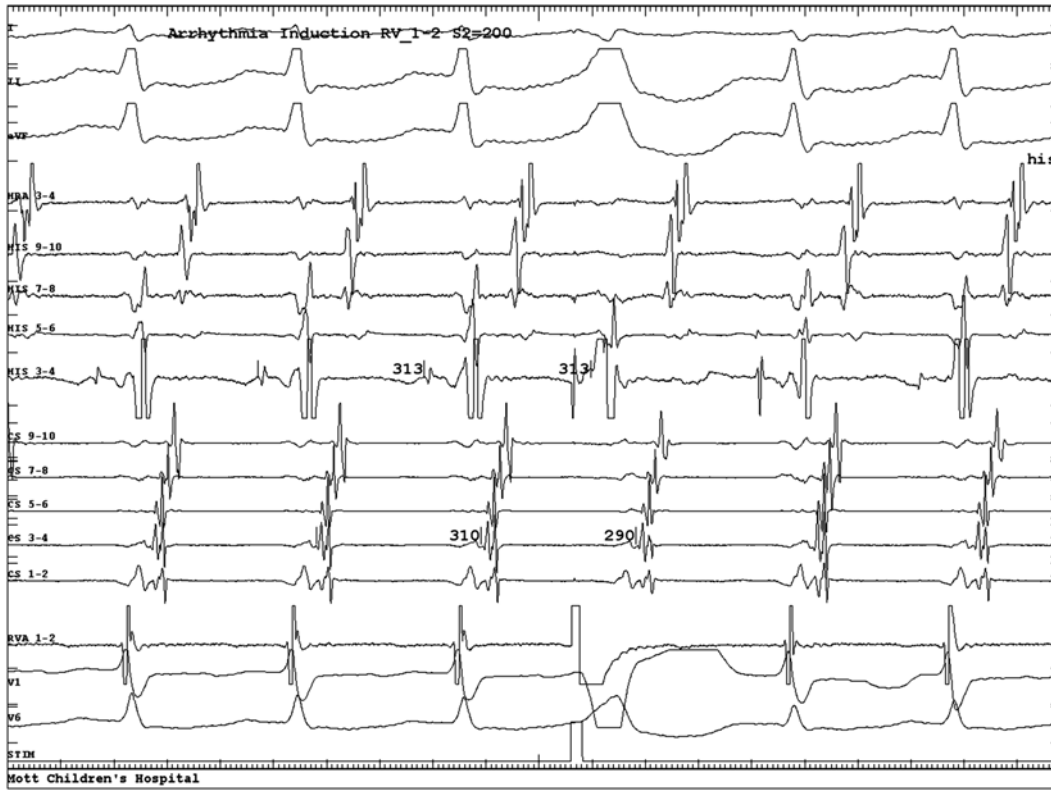


Fig. 3.20 His refractory PVC: Intracardiac electrograms displayed as surface leads I, II, aVF, HRA, His proximal (9–10) to distal (3–4), CS proximal (9–10) to distal (1–2), RV apex, surface leads V1 and V6. The rhythm is an orthodromic reentry tachycardia via a left lateral accessory pathway. The His bundle interval and tachycardia CL is measured in His 3–4. A premature ventricular extrastimulus delivered to time with His refractoriness. The subsequent atrial activation is early—measured at 290 ms confirming the presence of a retrograde accessory pathway. *HRA* high right atrium, *CS* coronary sinus, *RV* right ventricle

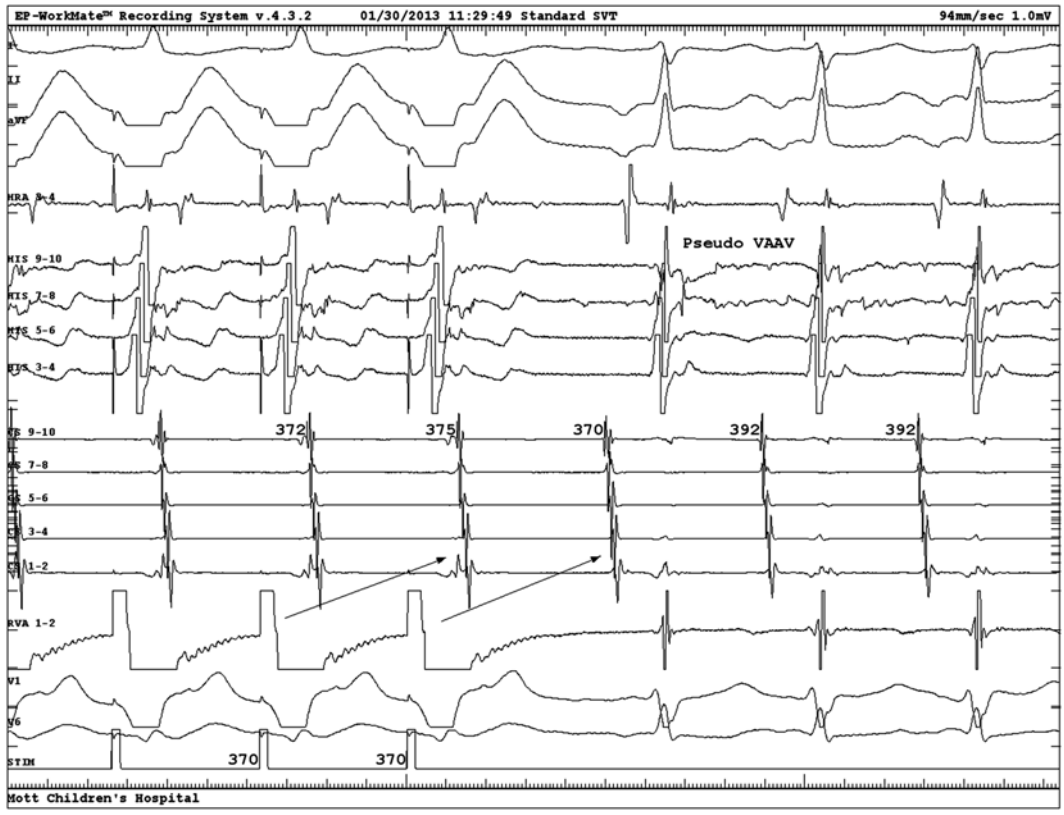


Fig. 3.21 Pseudo VAAV response during atypical AVNRT: Intracardiac electrograms displayed as surface leads I, II, aVF, HRA, His proximal (9–10) to distal (3–4), CS proximal (9–10) to distal (1–2), RV apex, surface leads V1 and V6. The rhythm is a long RP tachycardia with negative P-waves in the inferior leads. The tachycardia cycle length is 392 ms. Ventricular pacing at 370 ms conducts to the atrium at the same rate and with the same activation pattern. The response after termination of pacing is V-A-A-V which would typically indicate atrial tachycardia as the mechanism. However, this is a pseudo V-A-A-V response. The second A of the V-A-A-V response is entrained to the pacing rate of 370 ms indicating that this A is conducted from the last pacing beat. The ventricular pacing is conducting to the atrium via the slow pathway of the AV node. *HRA* high right atrium, *CS* coronary sinus, *RV* right ventricle

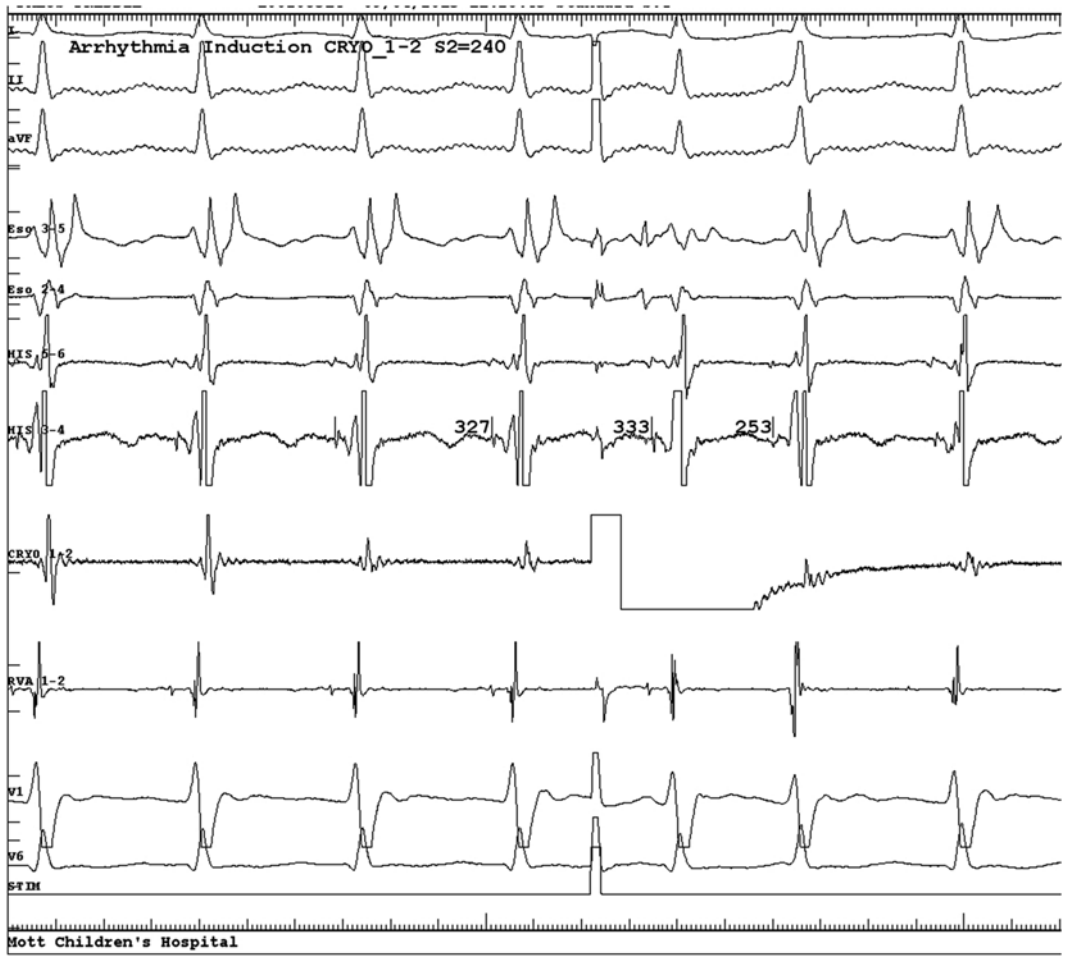


Fig. 3.22 Premature AES confirming AVNRT: Intracardiac electrograms displayed as surface leads I, II, aVF, esophageal, His proximal to distal, cryoablation distal, RV apex, surface leads V1 and V6. The rhythm is a narrow complex 1:1 tachycardia with near simultaneous VA activation at 330 ms, consistent with either AVNRT or junctional tachycardia. A premature atrial extrastimulus is delivered. The subsequent His signal is on time (333 ms), but the next His is early at 253 ms. This is consistent with AVNRT. The premature atrial extrastimulus entered the slow pathway of the AV node and conducted down to the ventricle bringing in the $n+1$ His. The His immediately following the premature atrial extrastimulus was activated from the beat prior to the premature extrastimulus. If this had been a junctional tachycardia, the first His after the premature extrastimulus would have been early. *HRA* high right atrium, *CS* coronary sinus, *RV* right ventricle

Conclusion

The EPS is the first step toward successful catheter ablation of tachyarrhythmias in pediatric and congenital heart disease patients. In-depth knowledge of clinical electrophysiology and a diagnostic armamentarium are important for procedure success. The ultimate goal of the EPS is to identify the target for ablation which will be addressed in the subsequent chapter.

Suggested Reading

Cohen MI, Wieand TS, Rhodes LA, Vetter VL. Electrophysiologic properties of the atrioventricular node in pediatric patients. J Am Coll Cardiol. 1997;29(2):403–7.

Dick II M, Law IH, Dorostkar PC, Armstrong B. Use of the His/RVA catheter in children. J Electrocardiol. 1996;29(suppl):227–33.

Josephson ME. Clinical cardiac electrophysiology: techniques and interpretations. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2008.

Kannankeril PJ, Bonney WJ, Dzurik MV, Fish FA. Entrainment to distinguish orthodromic reciprocating tachycardia from atrioventricular nodal reentry tachycardia in children. Pacing Clin Electrophysiol. 2010; 33:469–74.

Knight BP, Ebinger M, Oral H, Kim MH, Sticherling C, Pelosi F, Michaud GF, Strickberger SA, Morady F. Diagnostic value of tachycardia features and pacing maneuvers during paroxysmal supraventricular tachycardia. J Am Coll Cardiol. 2000;36:574–82.

Murgatroyd F, Krahn AD, Yee R, Skanes A, Klein GJ. Handbook of cardiac electrophysiology: a practical guide to invasive EP studies and catheter ablation. London: Remedica; 2002.

Padanilam BJ, Manfredi JA, Steinberg LA, et al. Differentiating junctional tachycardia and atrioventricular node re-entry tachycardia based on response to atrial extrastimulus pacing. Am Coll Cardiol. 2008;52:1711–7.

Saul JP, Hulse JE, De W, et al. Catheter ablation of accessory atrioventricular pathways in young patients: use of long vascular sheaths, the transseptal approach and a retrograde left posterior parallel approach. J Am Coll Cardiol. 1993;21(3):571–83.

Stevenson WG, Soejima K. Recording techniques for clinical electrophysiology. J Cardiovasc Electrophysiol. 2005;16:1017–22.

Veenhuyzen GD, Quinn FR, Wilton SB, Clegg R, Mitchell LB. Diagnostic Pacing Maneuvers for Supraventricular Tachycardias: Part 1. Pacing Clin Electrophysiol. 2011;34:767–82.

Veenhuyzen GD, Quinn FR, Wilton SB, Clegg R, Mitchell LB. Diagnostic pacing maneuvers for supraventricular tachycardias: Part 2. Pacing Clin Electrophysiol. 2012; 35:757–69.

Waldo AL. From bedside to bench: entrainment and other stories. Heart Rhythm. 2004;1:94–106.

Part II

Clinical Electrophysiology in Infants and Children

Atrioventricular Reentry Tachycardia

4

Vincent C. Thomas, Nicholas Von Bergen, and Ian H. Law

Accessory Pathways

An anomalous strand of working myocardium, called an accessory pathway, bridges the electrically isolated gap between the atria and ventricle (i.e., the AV groove) and supports atrioventricular reentrant tachycardia (AVRT, Fig. 4.1). These pathways are likely formed as a result of incomplete senescence (apoptosis) and differentiation during the first trimester of gestation. During embryologic development, the fetal muscle fibers are oriented longitudinally in the straight heart tube which loops and differentiates into the four chamber heart. Some of the fibers of the straight heart tube undergo senescence (apoptosis—programmed cell death) leaving only the atrioventricular node and His-Purkinje system (AVN-HPS) electrically connecting the atria and ventricles. However, in some cases there is failure of apoptosis and anomalous connections—the accessory pathways—may persist beyond birth (see Chap. 1).

V.C. Thomas, M.D., M.H.A. (✉)
Department of Pediatrics,
University of Nevada School of Medicine,
3006 S. Maryland Parkway, Suite 690,
Las Vegas, NV 89109, USA
e-mail: vthomas@childrensheartcenter.com

N. Von Bergen, M.D.
Department of Pediatrics, University of Wisconsin—Madison, Madison, WI, USA

I.H. Law, B.S.E., M.D.
Division of Cardiology, Department of Pediatrics,
University of Iowa Children's Hospital, University of Iowa Carver College of Medicine,
Iowa City, IA, USA

Manifest Accessory Pathways

Accessory pathways may be manifest or concealed. Manifest accessory pathways comprise antegrade activation of the ventricular myocardium through the accessory pathway and can "manifest" as preexcitation on an electrocardiogram during sinus rhythm (Figs. 4.1, 4.2, 4.3). This pattern is called the Wolff–Parkinson–White syndrome for the three physicians who described the syndrome in 1930—short PR interval, preexcitation (delta wave), paroxysmal tachycardia, usually first appearing in young persons. Even when ventricular preexcitation is present on the surface ECG during sinus rhythm, the mechanism of the tachycardia is usually orthodromic AVRT.

Concealed Accessory Pathways

Concealed accessory pathways are those that do not have antegrade conduction, but only

M. Dick, II (ed.), *Clinical Cardiac Electrophysiology in the Young*,
DOI 10.1007/978-1-4939-2739-5_4

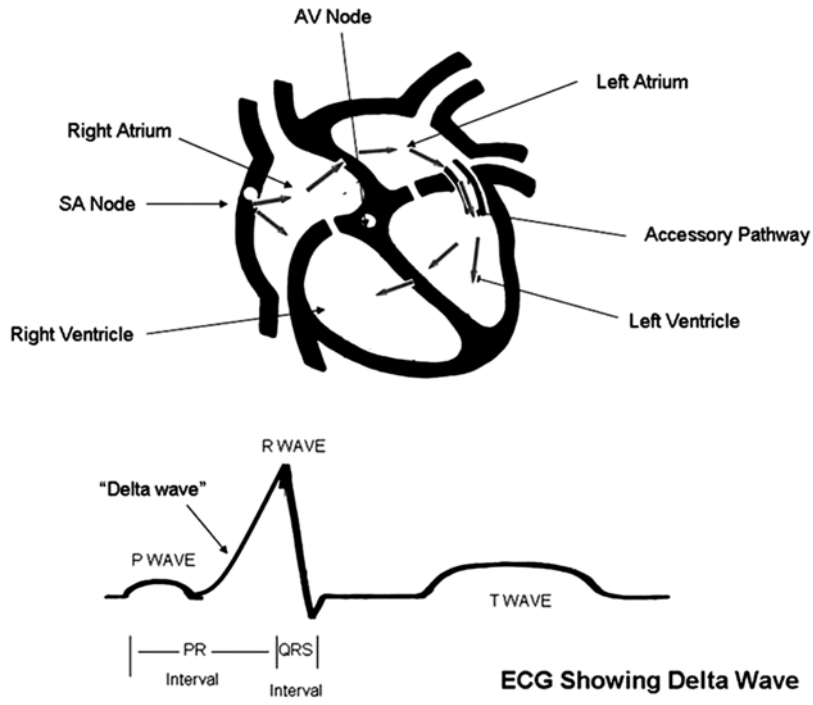


Fig. 4.1 Cartoon of the heart demonstrating the atrioventricular conduction system with a left accessory connection. The P-wave and QRS complex are show short the indicating the impulse PR interval bypassing the AV node; also shown is the "delta wave" transcribing the slow anomalous ventricular activation and resulting in the early arrival (preexcitation of the ventricle) of the impulse through the accessory pathway. [Reprinted Kuilig J, et al. Wolff-Parkinson White syndrome and accessory pathways. Circulation 2010;122(15): e480–e483. With permission from Wolters Kluwer Health]

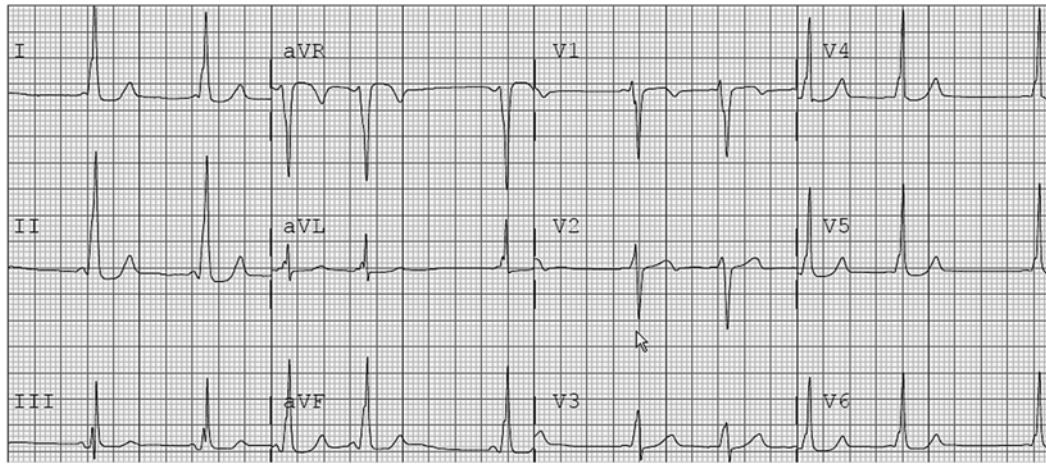


Fig. 4.2 12-Lead ECG demonstrating preexcitation with a right-sided pathway in an 8-year-old female. This was mapped to the right anterior septal area as suggested with the R/S transition between V2 and V3 (suggesting a possible septal pathway) and the positive preexcitation noted in II, III, aVF

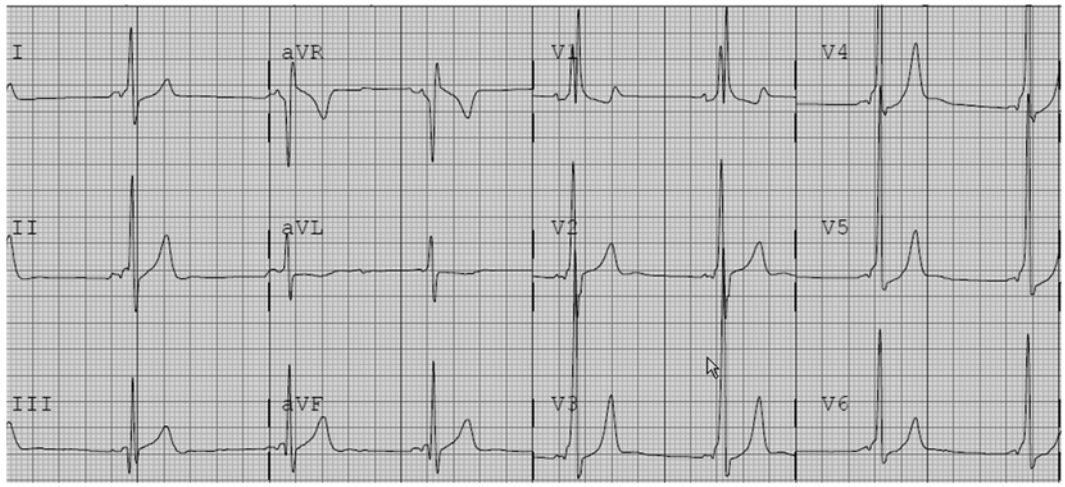


Fig. 4.3 12-Lead ECG of patient with Wolff–Parkinson–White syndrome with a left posterior accessory pathway. The PR interval is short and delta waves are easily visualized. The R/S transition is before V1 suggesting a left-sided pathway

Definitions:

Orthodromic is used to describe accessory pathway (AP)-mediated tachycardias in which there is normal conduction from the atria to the ventricle via the AVS-HPS.

Antidromic is used to describe AP-mediated tachycardias which traverse the AP from atrium to ventricle and proceed backwards up the HPS.

Antegrade indicates conduction from atria to ventricle.

Retrograde indicates conduction from ventricle to atrium.

Concealed pathways only conduct in the retrograde direction.

Manifest pathways conduct in the antegrade direction with or without retrograde conduction as well.

Mechanism of Atrioventricular Reentrant Tachycardia

Atrioventricular reentrant tachycardia can be either orthodromic or antidromic. Orthodromic AVRT (Fig. 4.4), comprising approximately 90 % of AVRT, denotes antegrade conduction through the AVN-HPS and retrograde conduction through the accessory pathway, producing a narrow QRS tachycardia. This pattern can be seen in all patients with concealed and the great majority of patients with manifest pathways. If a patient has a manifest accessory pathway (WPW), ventricular preexcitation is no longer present during orthodromic AVRT as the antegrade ventricular activation occurs through the His-Purkinje system, no longer passing from the atrium to the ventricle across the accessory pathway.

In contrast, antidromic AVRT is characterized by antegrade conduction through a manifest accessory pathway (and not a concealed one) and retrograde conduction through the His-Purkinje-AV nodal system, resulting in a wide QRS complex tachycardia, mimicking ventricular tachycardia (Figs. 4.5a and 4.6). Activation of the ventricular myocardium via the accessory pathway results in a wide QRS complex secondary to working myocardial cell-to-cell conduction rather than conduction through the His-Purkinje system.

ECG Diagnosis

For those patients with manifest pathways, the ventricular preexcitation pattern in sinus rhythm can be helpful in determining the location of the

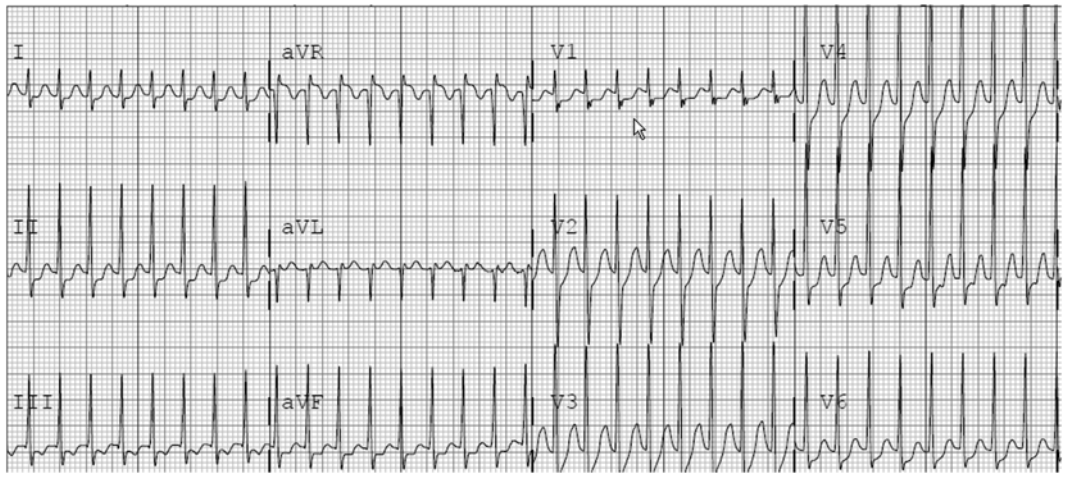


Fig. 4.4 12-Lead ECG with narrow QRS tachycardia in a 10-year-old female

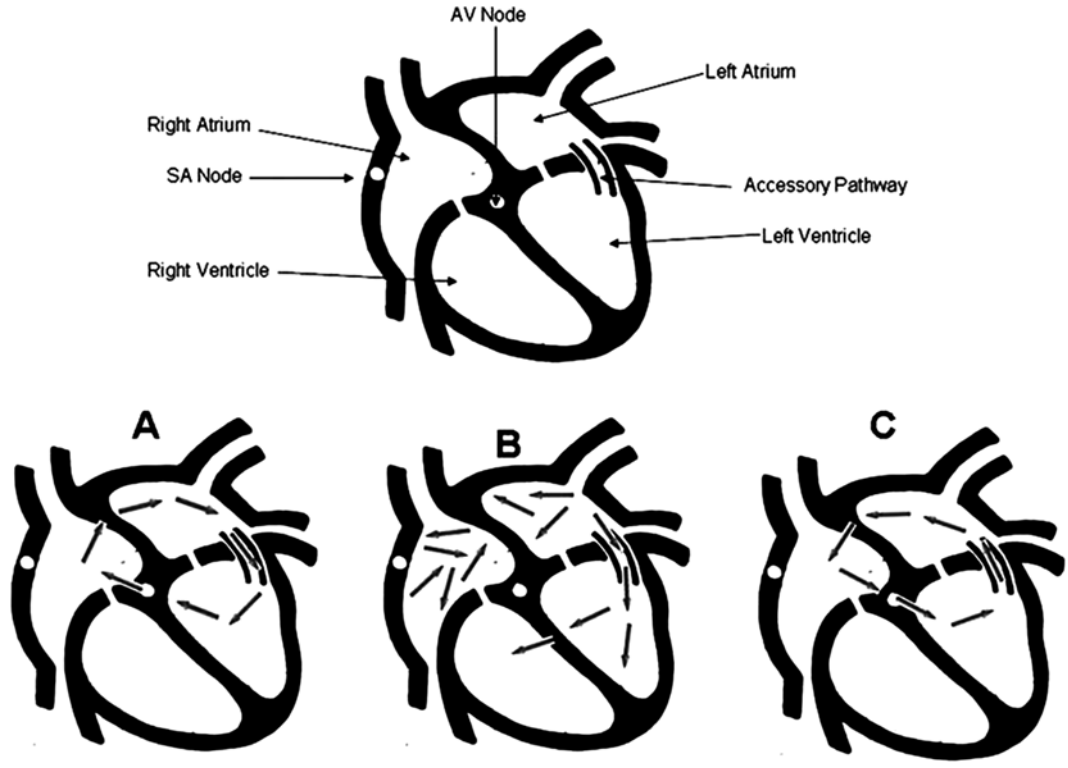


Fig. 4.5 Cartoon demonstrating typical orthodromic AVRT (*C*), rare antidromic AVRT (*A*), and antidromic AVRT during atrial fibrillation (*B*). (see text). [Reprinted Kuilig J, et al. Wolff–Parkinson–White syndrome and accessory pathways. Circulation 2010;122(15): e480–e483. With permission from Wolters Kluwer Health]

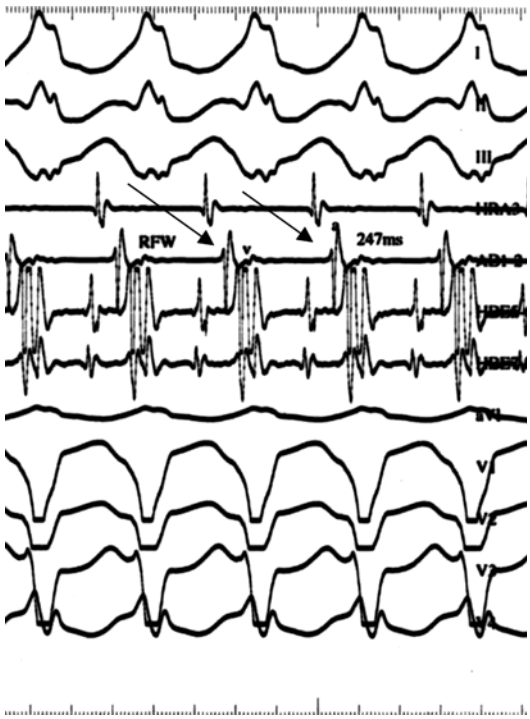


Fig. 4.6 An 8-Lead ECG demonstrating antidromic tachycardia in a 5-year-old boy. The *top* three tracings are recorded through the limb leads I, II, III; the *bottom* four tracings are aVL, V1, V2, V3, V4. The tracing fourth from the top is recorded through the high right atrial catheter. The tracing fifth from the top is recorded through the mapping catheter located in the right atrial free wall near the tricuspid valve. The sixth and seventh tracings are recorded through the His bundle catheter located at the low right atrial-septal area. Note the wide QRS tachycardia with maximal preexcitation of a left bundle branch configuration, compatible with a right-sided pathway. Note the tight AV relationship between the right atrial free wall electrogram (*arrows*) and the surface QRS complex (and intracardiac ventricular electrogram) indicating antidromic conduction down the right lateral accessory conduction to the ventricle. Retrograde conduction (not shown) supporting the tachycardia was through a left-sided concealed accessory pathway. Ablation of both pathways was successful

accessory pathway. A number of algorithms have been developed to aid in pathway location with variable accuracy depending on the accessory pathway location. Briefly, if the QRS transition (R greater than S-wave) is after V3 in the precordial leads, the pathway is most likely on the right side; if it is at or between V2 to V3, it is most likely a septal pathway. If the transition is before V2, it is most likely on the left side. Using published algorithms, further analysis of the delta wave polarity in the ECG leads can identify the location of the accessory pathway even more precisely. In patients with a concealed accessory pathway, the resting ECG is of no diagnostic value to determine accessory pathway location.

An ECG obtained during SVT can be very helpful to indicate AVRT (vs. AVNRT) and occasionally to evaluate the location of the accessory pathway, especially when compared to an ECG obtained in sinus rhythm. Retrograde P-waves are typically present (typically with an R-P retrograde interval greater than 65–70 ms) in the ST segment or T-wave during AVRT, especially in Lead I, and suggests the diagnosis. This contrasts with a retrograde P-wave less than 40–60 ms in typical AVNRT. Table 4.1 summarizes the findings for manifest and concealed pathways characteristically seen on the surface electrocardiogram during either sinus rhythm or SVT.

Manifest Accessory Pathways

Wolff–Parkinson–White Syndrome

The preexcitation is the result of a congenital accessory pathway that conducts antegrade reaching the ventricles in advance of activation through the AVN-HPS (Figs. 4.1, 4.2, 4.3). The incidence of Wolff–Parkinson–White syndrome in children has been estimated around one in every 1,000 individuals. Ventricular preexcitation can be quite subtle, occasionally apparent only as a lack of a q-wave in the lateral precordial leads due to slow conduction in the accessory pathway; accelerated conduction through the AV node (as is common in children); or in later accessory pathway activation of a left-sided pathway (the most frequent site of a pathway).

While both manifest and concealed pathways can mediate reentrant tachycardia, patients with Wolff–Parkinson–White syndrome have a greater rate of recurrent SVT than those without preexcitation. The clinical course of AVRT is age related. If diagnosed as an infant, the preexcitation may resolve to complete disappearance as a child

Table 4.1 Summary of the findings for manifest and concealed pathways

	Sinus			SVT				
							Mahaim	
	Concealed	Manifest WPW	Mahaim (Manifest)	Concealed	WPW Orthodromic	WPW Antidromic	Atriofascicular	Nodo-or fasciculoventricular
Rate—beats/min	Within normal limits for age	Within normal limits for age	Within normal limits for age	Infants: 200–300; children: 160–250	Infants: 200–300; children: 160–250	Infants: 200–300; children: 160–250	Infants: 200–300; children: 160–250	Infants :200–300; children: 160–250
Rhythm	Regular	Regular	Regular	Regular	Regular	Regular	Regular	Regular
P-wave	Normal	Normal	Normal	Absent or negative, within T-wave of lead II, aVF	Absent or negative, within T-wave of lead II, aVF	Absent	Absent	Absent or negative, buried within T-wave of lead II
PR interval and QRS complex	Normal	Pre-excited (delta-wave, short PR interval)	Pre-excited (delta-wave, short PR interval)	Normal or wide when aberrantly conducted	Normal or wide when aberrantly conducted	Wide with QRS pattern similar to or wider than sinus rhythm	Wide (ART-AVRT) with LBBB QRS pattern	Wide (ORT-AVRT) with QRS pattern

Comparison of concealed and manifest accessory pathways, and Mahaim fibers during sinus rhythm and SVT. *WPW* Wolff–Parkinson–White syndrome, *ART* antidromic reentrant tachycardia, *ORT* orthodromic reentrant tachycardia, *AVRT* atrioventricular reentrant tachycardia, *LBB* left bundle branch

grows, usually by 18–24 months of age (30 % recurrence if diagnosed less than 1 year of age). However, if preexcitation or documented SVT is seen after this age, AVRT is unlikely to self-resolve (94 % recurrence rate).

Furthermore, patients with WPW are noted to have a very small, albeit increased, risk for a sudden cardiac arrest. During atrial fibrillation, a conduction of the fibrillatory impulses may preferentially cross a fast conducting manifest accessory pathway, bypassing the more slowly conducting AV node resulting in a rapid life-threatening ventricular response (>250–300 bpm) (Fig. 4.5b; Chap. 20, Fig. 20.2). The incidence of sudden cardiac arrest in WPW patients has been estimated between one and 4.5 per 1,000 patient years, reflecting a higher incidence of atrial fibrillation in WPW patients. The highest prevalence of sudden cardiac arrest appears to be between the ages of 15 and 35 years. Patients with WPW syndrome who experience sudden cardiac death may have no history of a tachyarrhythmia. On the other hand, they may have had previous syncopal episodes. Potential risk factors for a sudden cardiac event with WPW include a younger age (<30 years), prior syncope or atrial fibrillation, male gender, familial WPW, or other heart disease.

The majority of accessory pathways are seen in patients with structurally normal hearts; however, approximately 10–15 % of patients with Wolff–Parkinson–White syndrome has congenital heart disease (Ebstein's anomaly, L-transposition of the great arteries, cardiomyopathy, and intracardiac tumors). Six to nine percent of patients who have WPW syndrome and congenital heart disease are more likely to have multiple pathways. Approximately a quarter of patients with Ebstein's anomaly also have preexcitation, the most common association. In addition, up to 43 % of patients with WPW and Ebstein's anomaly have multiple pathways. In patients with other forms of congenital heart disease, 25 % had multiple pathways. Pathway location is also associated with congenital heart disease: right-sided pathways are more common in congenital heart disease (63 %) whereas left-sided pathways are more common in the structurally normal heart (61 %). Interestingly, the appearance of preexcitation in patients with congenital heart disease may be misleading, as some malformations—tricuspid atresia and hypoplastic left heart syndrome—may be associated with "pseudo-preexcitation" or the appearance of preexcitation and not have an accessory pathway.

The management of the asymptomatic patient with WPW has been addressed by the Pediatric and Congenital Electrophysiology Society in a recent consensus statement (2012). Patients who are 8 years of age or older and are found to have manifest preexcitation on an ECG without symptoms are recommended to undergo risk stratification, initially with noninvasive studies (i.e., exercise treadmill test; Holter monitor tracings). If inconclusive, invasive studies can be considered to determine those at higher risk for sudden cardiac arrest. In asymptomatic individuals under 8 years of age, the low risk of sudden death due to atrial fibrillation, allow conservative management and continued follow-up.

Atrioventricular and Mahaim Fibers

Mahaim fibers, as first described in 1938, are direct histologic links between either the AV node and the right ventricle (nodoventricular fibers) or the His bundle and the right ventricle (fasciculoventricular fibers). These nodo or fascicular ventricular fibers are anatomically common (though often inactive, i.e., not resulting in preexcitation or tachycardia) When they do produce ventricular preexcitation, it may be only in a "by-stander" roles and not participate in an arrhythmia reentrant circuit. In patients with a nodoventricular fiber, the PR interval varies relative to the fiber's take-off from the node. In those with a fascicular-ventricular fiber arising from the His bundle and inserting into the ventricular myocardium the PR interval is normal. Rarely the nodoventricular fibers produce a wide QRS complex in the context of a different mechanism for SVT, such as AVNRT (Fig. 4.7), or even more rarely participate as a true antegrade limb of an atrioventricular circuit. Fasciculoventricular fibers have not been shown to participate in a reentrant circuit other than as a bystander. These bystander pathways are often best left alone and not ablated.

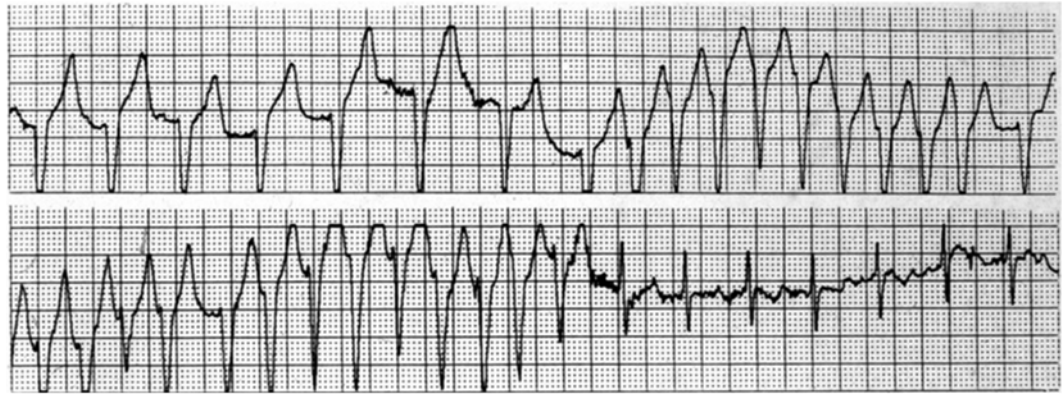


Fig. 4.7 Wide QRS rhythm and tachycardia followed by narrow QRS sinus rhythm in a 9-year-old girl. Electrophysiology study demonstrated a nodoventricular fiber (not involved in the reentrant circuit), which was ablated. Narrow QRS tachycardia was demonstrated post ablation of the Mahaim fiber and was found to be due to AVNRT. The slow pathway and arrhythmia were ablated

An uncommon right-sided atriofascicular fiber (somewhat confusingly also referred to as a Mahaim fiber) is located in the right posterior AV groove (Fig. 4.8). This accessory pathway has several features: (1) it typically conducts in only an antegrade direction producing preexcitation in a left bundle branch block configuration; (2) it inserts deep (not along the AV ring) in the right ventricle, often near the distal fascicle of the right bundle (moderator band); (3) the pathway demonstrates decremental conduction; (4) if present, the tachycardia is antidromic resulting in a wide QRS left bundle branch pattern SVT. These fibers were shown to be the cause of preexcitation characterized by left bundle branch block QRS morphology and wide QRS tachycardia. Intracardiac electrophysiologic studies demonstrate that the preexcitation and the wide QRS tachycardia are due to an atriofascicular accessory pathway coursing from the lateral right atrial tricuspid valve annular area to insert deeper in the right bundle rather than at the AV groove. As these fibers often have AV nodal properties, they may exhibit slow conduction velocity and "decremental conduction" with atrial extrastimulus and adenosine sensitive, resulting in AV block with adenosine administration. The hallmark of identifying the site for ablation is the identification of a fast action specialized conduction tissue electrogram distant in both location and timing from the His bundle electrogram, often near the moderator band. Ablation at that site terminates conduction within this pathway (eliminates the preexcitation), as well as the wide QRS tachycardia (Fig. 4.8). It can also be ablated on the right lateral annulus.

Diagnostic Evaluation of AVRT

Exercise Treadmill Testing and Holter Monitoring

Abrupt disappearance of ventricular preexcitation on the electrocardiogram during exercise suggests an accessory pathway effective refractory period perhaps as long as 360–390 ms, placing the patient in a lower risk category (Fig. 4.9). Exercise testing or Holter monitoring during activity has been used as a noninvasive method to evaluate the conduction properties of a manifest accessory pathway. Abrupt loss of preexcitation during exercise treadmill testing occurred in 15 % of a predominately s pediatric group of patients. However, in practice, disappearance of ventricular preexcitation exercise testing can be difficult to interpret due to movement artifact on the ECG and enhanced AV node conduction from increased adrenergic tone during exercise resulting in gradual (and less) not abrupt diminution of the ventricular preexcitation.

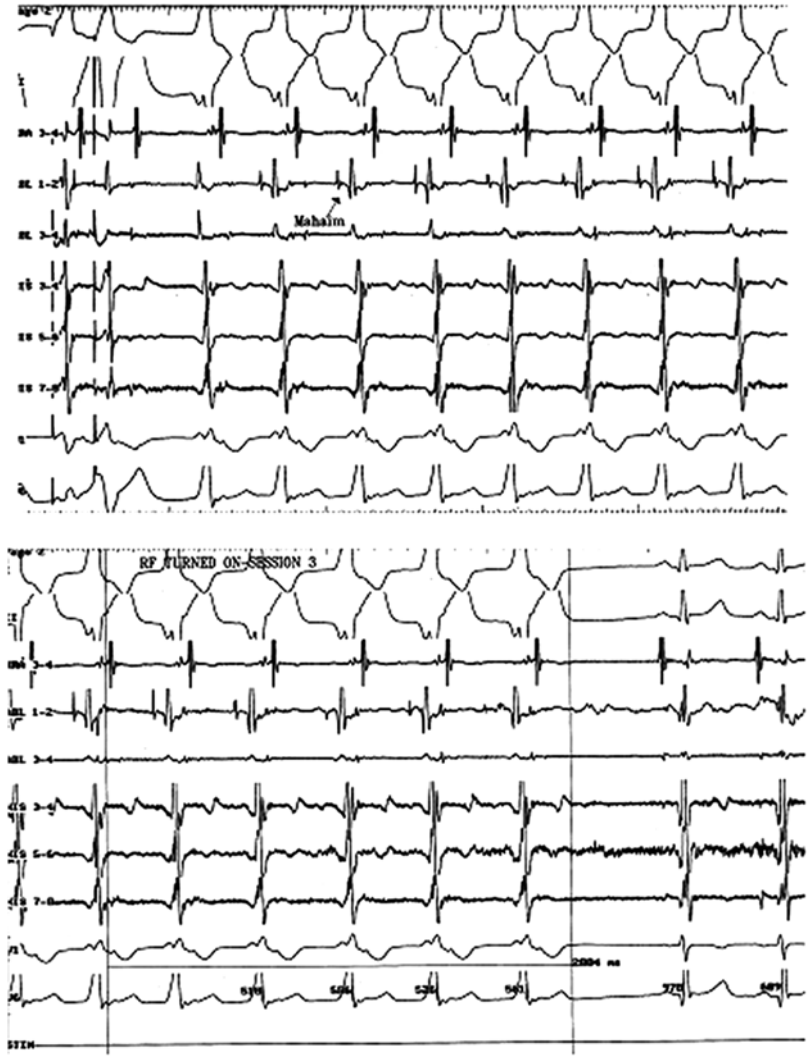


Fig. 4.8 Patient with an atrioventricular fiber causing wide QRS tachycardia. *Top panel*: Initiation of wide QRS tachycardia with antegrade conduction through the Mahaim fiber (note fast action deflection of atriofascicular fiber activation) and retrograde conduction through the normal His-Purkinje–AV node system. *Bottom panel*: Radiofrequency ablation of antegrade conduction in the atriofascicular fiber, terminating the tachycardia. Note the His bundle electrogram in the two sinus beats, as well as the absence of fast action deflection of the atrioventricular fiber in the mapping/ablation catheter post ablation

Holter monitoring of patients with WPW may demonstrate intermittent ventricular preexcitation. This intermittent conduction down the manifest accessory pathway is thought to confer low-risk attributes for the ability to conduct atrial fibrillation rapidly. This finding can be reassuring in the risk stratification of patients for sudden cardiac arrest, but does not exclude the possibility of SVT.

Electrophysiology Study

The electrophysiology study (see Chap. 3) is an essential tool in the assessment of the patient with documented SVT. Although atrial extrastimuli can be delivered through a transvenous catheter or transesophageal catheter (particularly useful for infants and small children), the transcatheter intracardiac technique is necessary for a

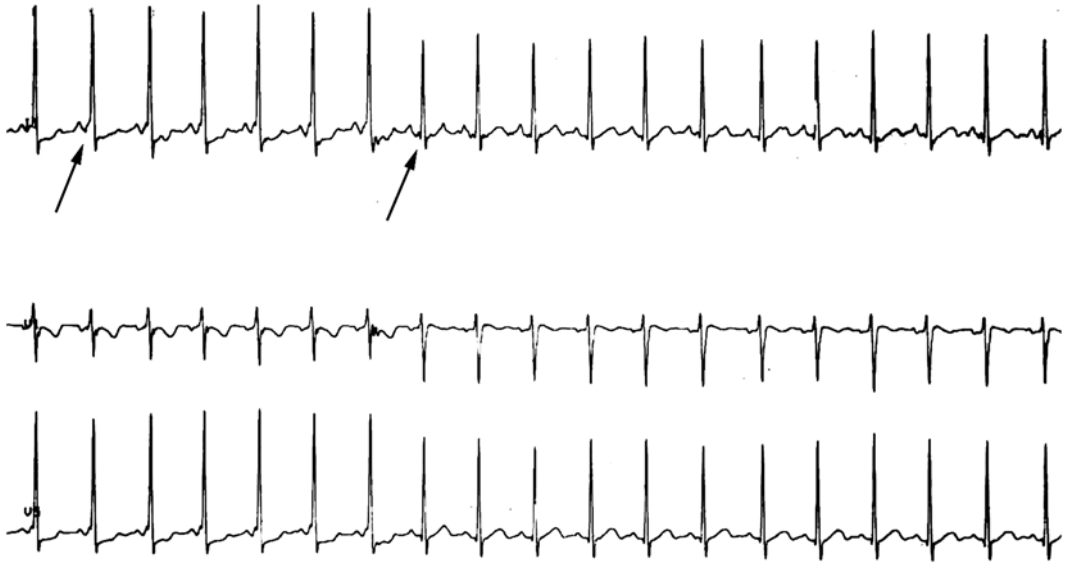


Fig. 4.9 Leads II, V1, and V5 during an exercise treadmill test. Note the delta wave in the onset of the QRS (*left arrow*) and abrupt loss over 2–3 beats (*right arrow* and next two beats) as the heart slightly increases, suggesting a slowly conducting accessory pathway

definitive examination of the properties and location of the accessory pathway as well as for transcatheter ablation.

Baseline Studies

The patient is usually placed under general anesthesia supervised by an anesthesiologist; conscious sedation is usually well tolerated in the adolescent but in many centers still requires the presence of the anesthesiology service. At the start of the electrophysiology study, baseline surface electrocardiogram and electrogram recordings are obtained. Baseline intracardiac intervals measured in patients with manifest accessory pathway conduction typically reveal an HV interval (Fig. 4.10) much less than normal (40 ms) or at times <0 ms (ventricular activation occurring before the His electrogram). When the patient has manifested accessory pathway conduction, the earliest area of early ventricular activation (prior to the onset of the surface QRS complex) during antegrade conduction through the accessory pathway can identify the location of ventricular insertion of the accessory pathway.

Antegrade and retrograde electrophysiologic properties of the AV node and accessory pathway can then be determined. Atrial pacing is performed at a cycle length slightly shorter than the sinus rate, and this is gradually decreased in 10–20 ms increments until 1:1 AV conduction is no longer seen (Wenckebach cycle length), or for a sudden loss of preexcitation. The loss of 1:1 AV conduction represents either the accessory pathway Wenckebach cycle length (if the preceding beats were preexcited), or the AV node Wenckebach cycle length (if the preceding beats were conducting through the AV node, typically narrow complex).

The antegrade effective refractory period of the AV node and accessory pathway can then be determined by delivering extra stimuli after an 8–10 beat drive train cycle length (e.g., at both 600 and 400 ms. The S2 stimulus is decremented by 10–20 ms observing for a loss of AV conduction reflecting the antegrade effective refractory period of the AV node or the loss of preexcitation representing the effective refractory period of the accessory pathway or both (Fig. 4.11). In rare cases, it may be possible to differentiate between two separate antegrade conducting pathways noted by alterations in the pre-excited QRS

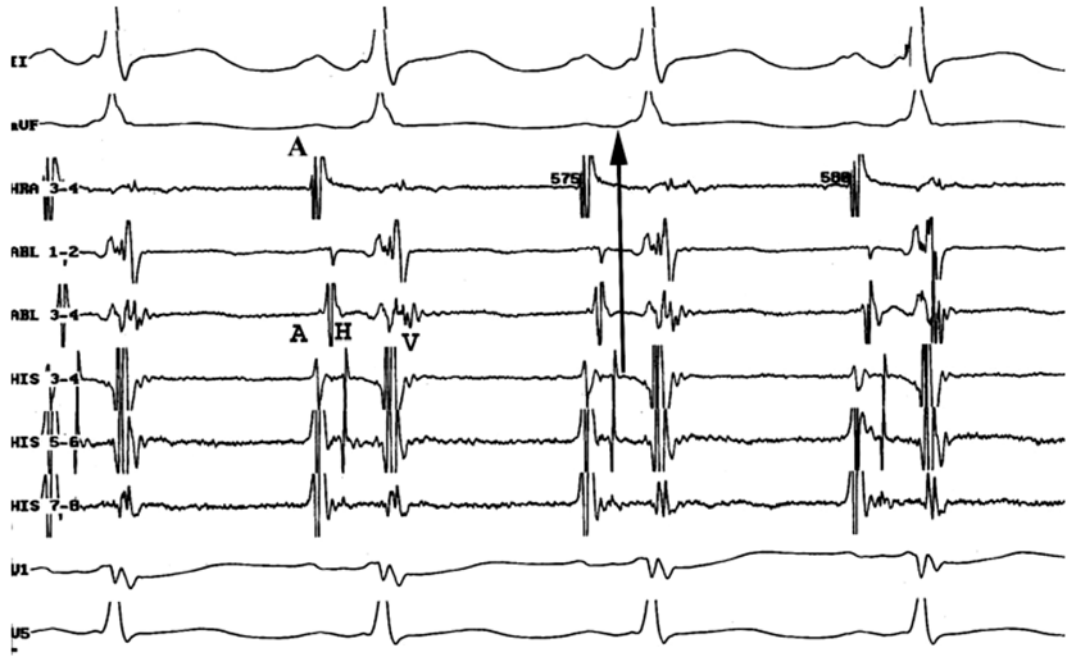


Fig. 4.10 Surface electrocardiograms (II, aVF, V1, V5) and intracardiac electrograms obtained during sinus rhythm in a patient with a left lateral accessory pathway. A very short HV interval (H to arrow) is seen in the His electrogram tracings indicating that ventricular activation is reaching the ventricles earlier than expected if the wave front from the sinus impulse were only traversing the atrioventricular nodal–His-Purkinje axis (i.e., the ventricles are pre-excited). *A* atrial electrogram, *HRA* high right atrium, *HIS = H* His, *Abl* ablation catheter in RA

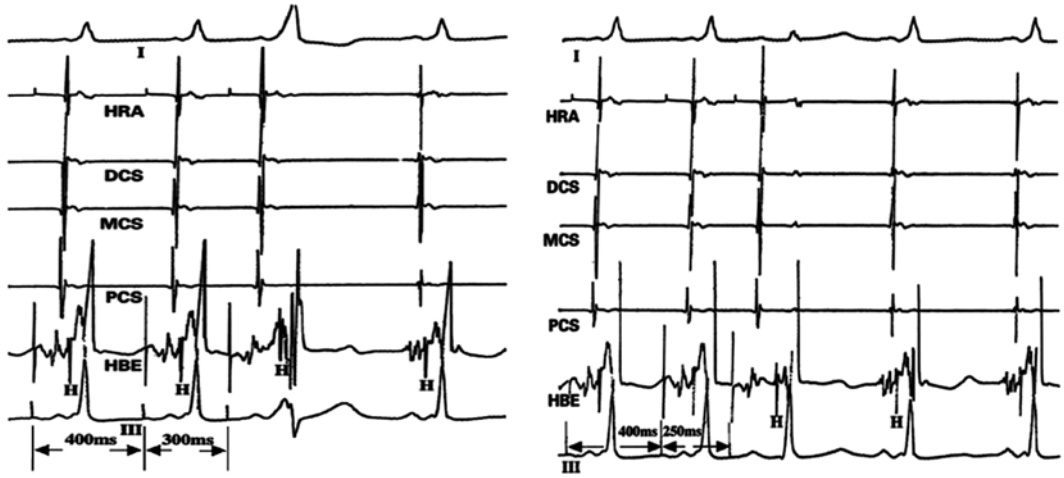


Fig. 4.11 Surface electrocardiograms and intracardiac electrograms obtained during an atrial extrastimulus in a patient with preexcitation. In the *left panel*, the premature atrial stimulus (300 ms coupling interval conducts antegrade through the accessory pathway resulting in more pronounced ventricular preexcitation and a short AV interval in the distal CS electrode pair. By shortening the atrial extrastimulus by 40 ms, the accessory pathway becomes refractory resulting in normal conduction through the AV node, a narrow QRS complex, and lengthening of the AV interval in the coronary sinus electrodes. *HRA* high right atrium, *HIS* His, *CS* coronary sinus, *RVA* right ventricular apex

morphology. In a similar manner, retrograde properties of the AV node and accessory pathway can be determined using the same techniques but pacing from the ventricle and monitoring for loss of VA conduction or eccentric accessory pathway conduction. If the manifest accessory pathway is noted to have decremental conduction, this may be indicative of an atriofascicular pathway.

Electrophysiologic Evaluation of the Manifest Accessory Pathway

As part of a risk stratification strategy for WPW syndrome, induction OD atrial fibrillation during the electrophysiology study provides useful information. Once atrial fibrillation is induced, by burst atrial pacing, the pre-excited R–R intervals are monitored. In a study of 60 children, a short, pre-excited R–R interval during rapid atrial fibrillation was the most sensitive predictor of sudden cardiac death (Chap. 20, Fig. 20.2), with all patients with a cardiac arrest having an interval <220 ms (though not all patients in this group had previously had an arrest). In this group, an interval <220 ms was potentially associated (the natural history and risk was eliminated by surgery in some subjects with <220 ms pre-excited R–R interval) with a positive predicted value for cardiac arrest of 68 %. In some patients, atrial fibrillation may not be inducible or sustained; rapid atrial pacing with or without isoproterenol, although used, is not a good surrogate for atrial fibrillation. The antegrade accessory pathway effective refractory period has also been used for risk stratification but has been less well correlated than atrial fibrillation. Multiple manifest accessory pathways have also been demonstrated to confer a higher risk for ventricular fibrillation. Conversely, intermittent loss of preexcitation during sinus rhythm suggests a low-risk pathway.

Electrophysiologic Evaluation of the Concealed Accessory Pathway

By definition, concealed accessory pathways cannot be evaluated during atrial pacing due to lack of antegrade conduction. However, both manifest and concealed accessory pathways can be evaluated by retrograde assessment using ventricular pacing. A straightforward method to determine the presence of a concealed accessory pathway is performed by ventricular pacing during a bolus infusion of IV adenosine (200 mcg/kg up to 12–18 mg) followed by a rapid flush (Fig. 4.12). Ventricular pacing at fast enough rates (<500 ms cycle length, 120 bpm) assures that the pacing rate is faster than the reflex sinus tachycardia that follows adenosine infusion in 15–20 s. As adenosine usually blocks retrograde conduction in the AV node a change in the atrial activation sequence suggests a shift of retrograde conduction from the AV node to the accessory pathway (Fig. 4.12), particularly evident with a left-sided accessory pathway. At times, a significant change in the retrograde atrial activation may not be seen due to either a paraHisian or anterior pathway accessory pathway or an adenosine-resistant AV node. Occasionally, a concealed accessory pathway conducting slowly retrograde will block with an adenosine bolus during ventricular pacing.

Similar to antegrade assessment, the retrograde Wenckebach cycle length and retrograde effective refractory periods of the AV node and accessory pathway are determined by rapid ventricular pacing and extrastimulus pacing. Though uncommon, the presence of multiple concealed pathways can be determined during extrastimulus pacing observing for multiple changes in the retrograde atrial activation sequence or after ablation of one pathway.

Induction of SVT and Diagnostic Pacing Maneuvers

During the atrial and ventricular pacing maneuvers, SVT is induced and usually well tolerated. However, the hemodynamic status is closely monitored for any compromise. If there is significant hemodynamic compromise, overdrive pacing maneuvers, adenosine, or rarely direct current cardioversion may be required. On occasion, an isoproterenol continuous infusion is required to initiate SVT. The starting dose of isoproterenol is 0.01–0.02 mcg/kg/min; rarely is more than

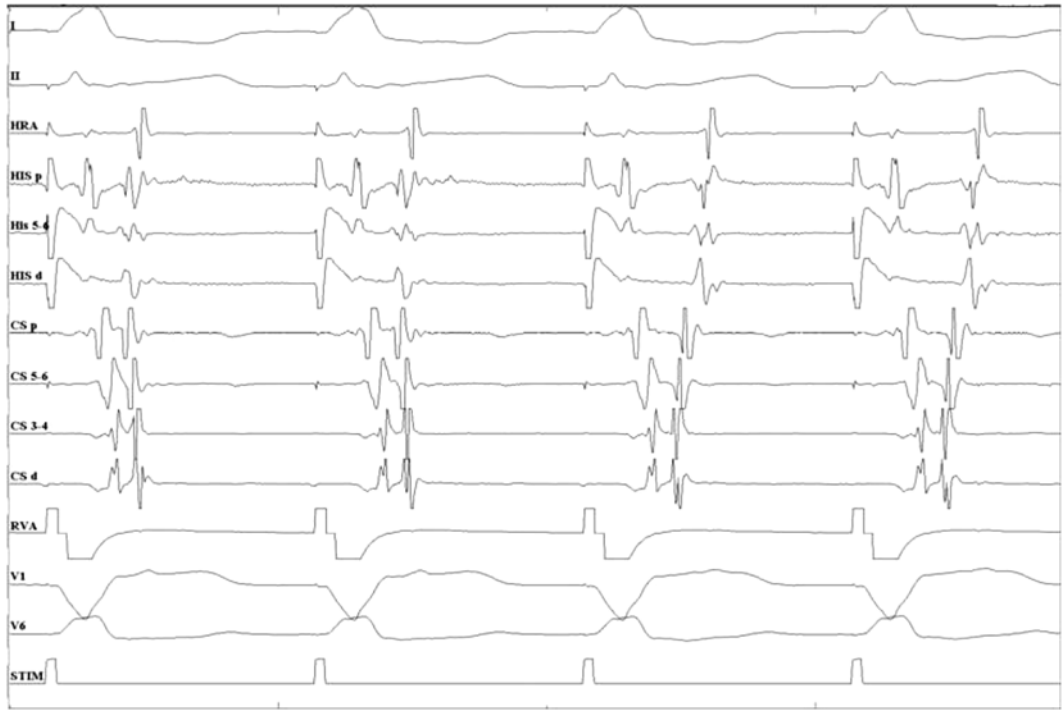


Fig. 4.12 Change in retrograde atrial activation sequence following adenosine infusion during ventricular pacing. At the far left the earliest atrial activation is seen in the proximal CS (CSp) and the His bipolar electrode pairs (His d, His 5–6, His p). As the adenosine blocks retrograde AV node conduction the earliest activation shifts (compare second and third complexes in CSp) to the distal coronary sinus bipolar electrode pairs (CS 5–6, CS 3–4). *HRA* high right atrium, *HIS* His, *CS* coronary sinus, *RVA* right ventricular apex

0.08 mcg/kg/min needed. When SVT cannot be induced with the previously described atrial and ventricular pacing maneuvers, two and three extrastimuli in the atrial or ventricle may be tried. Infrequently intravenous atropine, epinephrine, or caffeine may also be used in an attempt to induce arrhythmias.

If a bundle branch block pattern is seen during the initiation of the SVT, the difference in the cycle length in the SVT between wide QRS (bundle branch) and narrow QRS tachycardia (or changes in the cycle length as the bundle block branch pattern resolves) can be helpful in determining the location of the accessory pathway (Chap. 12, Fig. 12.6). An initially wide bundle block branch pattern during the tachycardia that prolongs the tachycardia cycle length is indicative of an ipsilateral accessory pathway (e.g., right bundle branch block lengthens the cycle length of orthodromic AVRT using the right-sided accessory pathway). This finding is explained by the slower conduction from myocyte to myocyte through the reentry circuit as compared to through the rapidly conducting His-Purkinje system. Therefore, a bundle branch block prolongs the ventricular transit time to the ipsilateral accessory pathway, thus lengthening the cycle length (Figs. 4.13 and 4.14). The corollary to this finding is that if the bundle branch block pattern does not alter the SVT cycle length, the bundle branch block is contralateral to the accessory pathway (e.g., the right bundle branch block pattern with left-sided accessory pathway does not alter SVT cycle length). Occasionally, this observation is confounded by a compensating faster conduction through the AV node neutralizing the cycle length change. This confounder is corrected by examining the AV conduction (time) as the AV conduction time remains constant regardless of cycle length change in the presence of an ipsilateral accessory pathway.

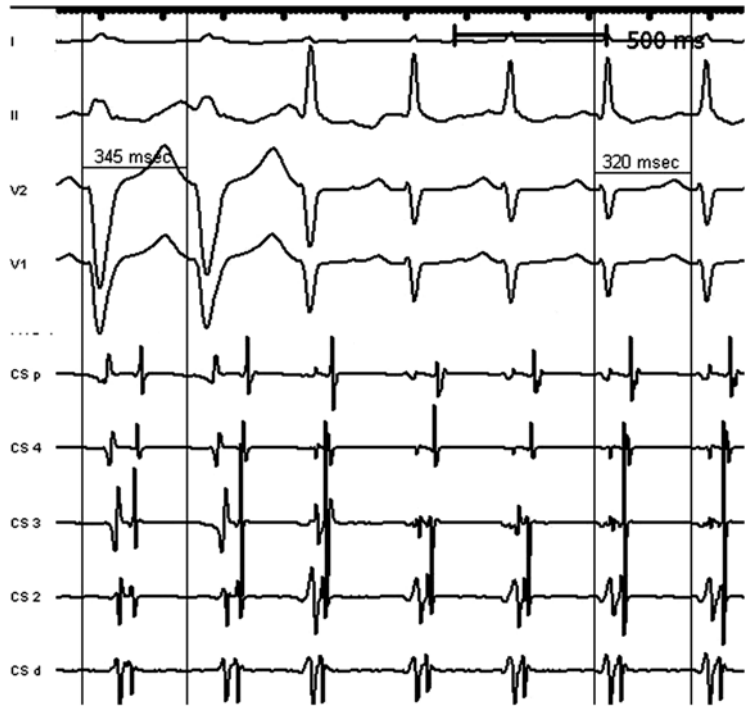


Fig. 4.13 A change in the cycle length of the tachycardia is noted concurrently to a normalization of the rate-related aberrancy (left bundle block configuration) to a narrow QRS complex on the surface and intracardiac electrograms. The electrograms in the CS catheters during narrow QRS tachycardia show left to right atrial activation from the distal CS to the proximal CS indicating a left-sided pathway with a slower tachycardia cycle length during the LBBB seen in the first two beats. This change suggests that the reentry circuit proceeds through an accessory pathway ipsilateral to the left bundle branch block

Various pacing maneuvers can be important diagnostic procedures. Premature ventricular beats introduced into the SVT can be helpful in distinguishing between AVRT and AVNRT and can help determine the location of the accessory pathway. The degree of preexcitation may help in deciphering between left- and right-sided accessory pathways as right-sided pathways typical pre-excite more prominently with right-sided pacing. Conversely, pacing from the left side (e.g., via the coronary sinus or left ventricle) may preferentially engage a left sided pathway. To ensure that retrograde conduction is not through the His bundle but rather the accessory pathway, premature beats may be given during His refractoriness (i.e., not earlier than 10–25 ms prior to the His deflection). If the ventricular stimulus is delivered during SVT while the His bundle is refractory in the presence of an accessory pathway, the retrograde conduction is through the accessory pathway shortening the atrial cycle length. The preexcitation index may be calculated to assist with localization of the accessory pathway and is determined by subtracting the longest premature ventricular pacing interval that shortened the atrial cycle length from the SVT cycle length (Fig. 4.14). The shorter the preexcitation index (longest PVC coupling interval), the more likely the pathway is to be on the right side. Posterior septal accessory pathways have a mean preexcitation index of 38 ms whereas anteroseptal septal accessory pathways have a mean preexcitation index of 17 ms. The longer the preexcitation index (shortest PVC coupling interval), the more likely the pathway is left-sided but the possibility of conduction through the His-Purkinje system/AV node should be considered, suggesting AVNRT. This can be usually distinguished by adenosine bolus infusion during ventricular pacing. Additionally, paraHisian pacing may be used to distinguish retrograde conduction through the AV node or an accessory pathway.

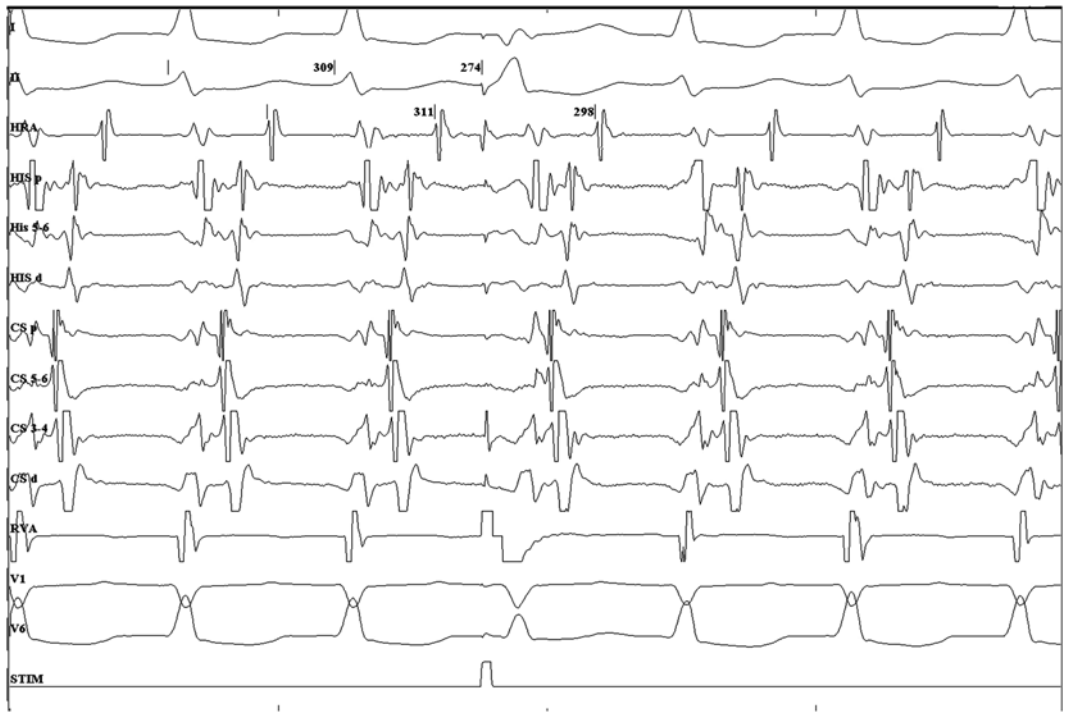


Fig. 4.14 Surface electrocardiograms and intracardiac electrograms obtained during orthodromic AVRT. A premature ventricular extrastimulus introduced during His refractoriness shortens the atrial cycle length by greater than 10 ms. The preexcitation index is calculated by subtracting the premature interval from the tachycardia cycle length (309–274 ms), resulting in a preexcitation index of 35 ms, consistent with a right-sided accessory pathway. *HRA* high right atrium, *HIS* His, *CS* coronary sinus, *RVA* right ventricular apex, *STIM* stimulation

The VA time can be measured after high output pacing at the His signal to capture both the His bundle (as noted with a more narrow QRS) and the ventricular myocardium. By slowly decreasing the pacing output until there is loss of His capture, with continued ventricular myocardial capture, the VA time is again measured. Accessory pathways continue to demonstrate consistent VA conduction time regardless of captured tissue (both or just heart muscle), while AV nodal retrograde conduction demonstrates an increase in the VA time consistent with the delay required for the ventricular myocardium to propagate into the His-Purkinje system.

Once an accessory pathway is identified a more precise method to determine the location of the pathway is by evaluating for the site of the shortest ventriculoatrial conduction time during ventricular pacing or orthodromic AVRT or the shortest AV conduction time during antidromic AVRT or in the presence of preexcitation. If the pathway is on the left side of the heart, a coronary sinus catheter advanced beyond the left-sided pathway may "bracket" the pathway (i.e., when there are bipolar electrograms from either side of the pathway that have longer VA or ventriculoatrial conduction times than the bipolar electrograms located near the accessory pathway during AVRT or ventricular pacing). If the accessory pathway is right-sided, a multipolar (e.g., duodecapolar) catheter or a roving catheter can be used to map around the tricuspid valve during SVT or ventricular pacing again observing for a short ventriculoatrial conduction time (or AV time with an antidromic SVT). 3-D mapping systems can enhance the ability to isolate the pathways using these techniques.

When mapping the accessory pathway during ventricular pacing (Chaps. 3 and 22), it is important to remember that when pacing the ventricle, retrograde conduction through both the accessory pathway and the AV node is likely. It is often

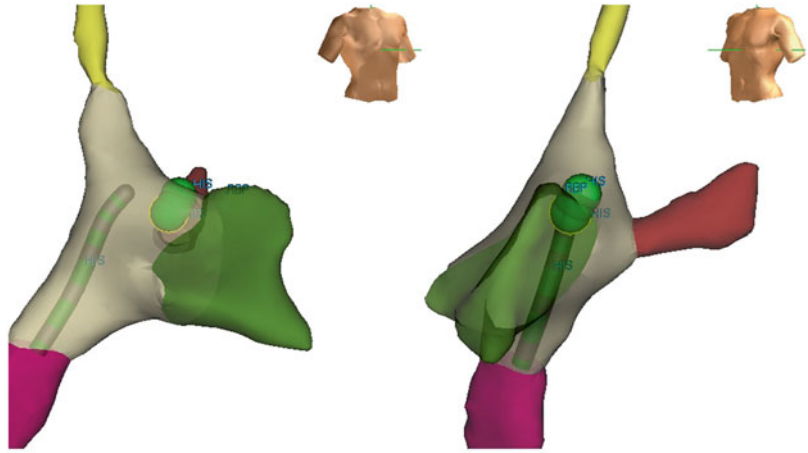


Fig. 4.15 RAO and LAO view of a paraHisian pathway mapped without radiation using 3-D mapping. The structures visualized include the SVC (*yellow*), IVC (*pink*), RA (*gray*), and RV (*green*). Note the location of the His labeled in close proximity to the ablation lesions (*green circles*). A small His signal was seen during the successful cryoablation of this accessory pathway. (Tie His catheter is seen in the RA and had been moved away from the His to facilitate cryoablation.) *HIS* His electrogram markings, *RBP* right bundle potential

possible to pace sufficiently fast to block conduction through the AV node and not the accessory pathway. If the pathway is located on the left side, pacing from the right ventricular outflow tract, LV apex or LV-free wall (retrograde through the aorta or transseptally across the atrial septum) may preferentially activate the left-sided accessory pathway prior to retrograde conduction through the AV node. Ventricular pacing at incrementally faster pacing rates may also be helpful in determining if there are multiple accessory pathways.

Complex anatomy and/or paraHisian pathways can make determination of the accessory pathway location more difficult. Three-dimensional mapping computer-based systems can prove to be extremely valuable in delineating the anatomy and precisely locating the area of His potentials (Fig. 4.15).

Treatment

Observation and Acute Treatment

As AVRT is rarely life threatening, and only rarely the cause of syncope (when orthodromic), several different options can be considered. For patients who have infrequent episodes that result in minimal or no symptoms, observation can be considered, especially in smaller children. In these patients, vagal maneuvers can be effective at terminating tachycardia (Chap. 23). If the tachycardia persists (>45–60 min) after vagal maneuvers, the patient should seek the assistance of a healthcare provider. In trained hands, esophageal overdrive pacing has been proven to be very effective, but is seldom used outside the infant age group. Medical cardioversion can also be very effective. Adenosine is 95–100 % effective in terminating AVRT. Typically when not effective, it is due to inadequate delivery of the medication to the coronary circulation and the AV node from too a slow flush, a distant delivery site that is too peripheral, or, in an infant, poor circulation. The advantage of adenosine is a very short half-life; its effects seldom last more than 10 s. However, once the adenosine effect is ended there is no further protection for recurrence of SVT and recurrences are not uncommon. When delivering adenosine, it is important to be prepared for atrial fibrillation that can occur as a result of adenosine infusion. Patients with Wolff–Parkinson–White syndrome and a fast conducting accessory pathway who develop atrial fibrillation after adenosine intervention are at risk for ventricular fibrillation. Although this combination is rare, an external

defibrillator should be readily available. Another option for medical cardioversion is verapamil, which is 80–95 % effective. Verapamil should not be used in infants (less than ~6 weeks old) and sparingly before 1 year of age, especially those in congestive heart failure as the calcium channel blocker effect can have a profound negative inotropic effect resulting in severe hypotension. Procainamide may have selective effect on the accessory pathway terminating the tachycardia but should be given slowly and with caution in the hypotensive patient.

For those patients who can tolerate their SVT but do not respond to vagal maneuvers, a "pill in the pocket" technique could be employed. These patients may take a beta-blocker or calcium channel blocker when the SVT begins, however if the SVT is not tolerated well, there may not be time for the antiarrhythmic medication to take effect.

Antiarrhythmic Medications

For those patients who have frequent events or do not tolerate their SVT, chronic antiarrhythmic medication is an option (Chap. 21). Digoxin for infants with SVT or a beta-blocker with or without digoxin have a long history and are safe when properly administered. However, as digoxin can shorten the accessory pathway effective refractory period, this should be avoided in patients who have Wolff–Parkinson–White syndrome. In older children digoxin has been largely replaced by others agents and beta-blockers are likely the most common antiarrhythmic medication used for daily prophylaxis. Sodium channel blockers and potassium channel blockers have are effective and there are liquid forms of all these antiarrhythmic medications. Amiodarone is an effective agent for especially resistant AVRT in infants and small children before they are candidates for ablation; however, duration of amiodarone should ideally not exceed 18–24 months. As noted previously, calcium channel blockers should not be used in children under ~6 weeks of age and caution in those less than 1 year. Some patients who have drug refractory SVT may require combination therapy such as sotalol (potassium with some beta blockade) and flecainide (sodium channel blockade) which has shown to be effective in a small group of children less than one year of age with refractory SVT.

Transcatheter Ablation

When antiarrhythmic therapy is ineffective or not desired, the ablation procedure offers the possibility of a definitive cure. Disruption of the accessory pathway was first performed surgically, followed by direct current ablation. Radiofrequency ablation was first introduced in 1987 and was reported in a series of pediatric patients in 1991. Today radiofrequency and cryotherapy are the most common energy sources used for transcatheter ablation and both have been shown to have excellent success and safety profiles.

Transcatheter ablation is discussed in Chap. 22. For patients who have paraHisian pathways or complex anatomy, 3-D mapping systems can be a useful adjunct to the electrophysiology study and the ablation procedure. Advances in mapping technology have resulted in 3-D spatial resolution of 1–2 mm, allowing for more precise localization of accessory pathways and reproducible targeting of an identical point within the heart. This technology cannot only increase the success rate and safety of the procedure but eliminate or decrease the fluoroscopic time and radiation dose. In patients with paraHisian pathways, accurate mapping of the AV node and accessory pathways using a 3-D system can allow for ablation with careful and consistent localization of the AV node and the accessory pathway (Fig. 4.15). For example, using the 3-D mapping system to map the AV node during ventricular pacing, then mapping the accessory pathway during adenosine infusion (blocking the retrograde conduction through the AV node) may facilitate a more precise location of the site of the accessory pathway, especially in those with initial failure. In patients who have congenital heart disease and AV tachycardia, 3-D mapping techniques can be used to better determine the complex anatomy and location of the His-Purkinje system, which can be

displaced secondary to the congenital defect or previous surgery.

Care should be taken when applying radiofrequency energy during SVT as the ablation catheter position on the AV ring can shift abruptly upon termination of the tachycardia. A technique to overcome this shift is to map the location of the accessory pathway during SVT, place the ablation catheter at that site, then entrain the tachycardia circuit by pacing the ventricle at a slightly faster rate than the SVT. This technique engages the pathway and because the ventricular pacing continues throughout the energy application, it prevents an abrupt shift of the catheter position away from the optimal site for ablation at the moment of successful ablation. Temperatures greater than 50 °C are desired. However, temperatures as low as 48 °C have been shown to cause irreversible damage. Seldom is it necessary to use temperatures greater than 65 °C. It is important to recognize that accessory pathways are in close proximity to other important structures (AV valve, coronary artery, coronary vein); therefore, excess temperature and time of energy radiofrequency application should be weighed against collateral injury. If success of radiofrequency does not occur within 10 s of the radiofrequency application, then the energy is turned off. Successful ablation within the 10 s frame usually leads to a full 30–60 s application (Chap. 22).

The advent of cryothermal ablation has added another energy source for ablation (Chap. 22). Cryothermal ablation affords catheter stability during ablation as the catheter adheres (frozen) to the tissue, even during SVT. Additionally, damage to surrounding structures has been demonstrated to be minimal during cryothermal ablation, including the AV node and coronary arteries. Although the surrounding regions of the site of ablation also cool, tissue injury has been found to be reversible. During ablation of accessory pathways, careful monitoring of the PR interval and ST segments can prevent permanent injury if the cryo-application is terminated promptly. However, cryothermal ablation has also been felt to have a slightly higher recurrence compared to radiofrequency ablation. Several recommendations have been made to reduce recurrence. Use of a larger tip catheter (i.e., 6 mm vs. 8 mm) has may reduce recurrence. Elimination of pathway conduction early during the cooling process (less than 20–30 s after initiation and at warmer temperatures) suggests probable success. Lesion placement such as a freeze–thaw–freeze technique can also help in permanent pathway elimination. Finally, extensive testing post ablation to monitor for recurrence (at least 45 min post first successful lesion) may reduce the risk of recurrence.

The success rate for accessory pathway ablation is now between 90 and 95 % with the highest success rates found in patients having left-sided accessory pathways. Patients with paraHisian pathways have the lowest success rate, understandably due to more cautious ablation therapy applications in an effort to avoid AV block. Data from the pediatric radiofrequency ablation registry prior to adoption of cryotherapy by many centers recorded a risk of heart block at 1.2 % with a risk as high as 10.4 % for patients with mid-septal ablation site.

The overall risk of complications in patients undergoing an ablation is reported to be between 3 and 4 %, with the most common complication being a hematoma. The risk of early death has been reported at 0.05 % with the risk of late death between 0.07 and 0.18 %. However, it should be noted that these data were primarily obtained in the earlier era (1991–2004) of conventional mapping using fluoroscopy and only radiofrequency energy.

Summary

AVRT is a common form of reentrant arrhythmias, commonly diagnosed in the newborn period. Spontaneous resolution of SVT after 1 year of age in patients with preexcitation or who have AVRT is uncommon. Observation and medical management play a role in the care of very young patients. However, transcatheter ablation offers the advantage of a lifelong cure in older patients, or in younger patients with poorly tolerated, medication refractory tachycardia. Three-dimensional mapping systems have been a major

advance in the management of children with AVRT, providing more precise pathway location data and reducing the exposure to ionizing radiation. Continued advances in technology will allow for continued improvement in outcome for young patients with AVRT.

Suggested Reading

Anderson RH, Becker AE, Arnold R, Wilkinson JL. The conducting tissues in congenitally corrected transposition. Circulation. 1974;50:911–23.

Bink-Boelkens MT. Pharmacologic management of arrhythmias. Pediatr Cardiol. 2000;21:508–15.

Bokenkamp R, Wibbelt G, Sturm M, et al. Effects of intracardiac radiofrequency current application on coronary artery vessels in young pigs. J Cardiovasc Electrophysiol. 2000;11:565–71.

Bricker JT, Porter CJ, Garson A, et al. Exercise testing in children with Wolff-Parkinson-White syndrome. Am J Cardiol. 1985;55:1001–4.

Bromberg BI, Lindsay BD, Cain ME, Cox JL. Impact of clinical history and electrophysiologic characterization of accessory pathways on management strategies to reduce sudden death among children with Wolff-Parkinson-White syndrome. J Am Coll Cardiol. 1996;27:690–5.

Chiang CE, Chen SA, Teo WS, et al. An accurate stepwise electrocardiographic algorithm for localization of accessory pathways in patients with Wolff-Parkinson-White syndrome from a comprehensive analysis of delta waves and R/S ratio during sinus rhythm. Am J Cardiol. 1995;76:40–6.

Erickson CC, Walsh EP, Triedman JK, Saul JP. Efficacy and safety of radiofrequency ablation in infants and young children <18 months of age. Am J Cardiol. 1994;74:944–7.

Fitzpatrick AP, Gonzales RP, Lesh MD, et al. New algorithm for the localization of accessory atrioventricular connections using a baseline electrocardiogram. J Am Coll Cardiol. 1994;23:107–16 [Erratum appears in J Am Coll Cardiol. 1994;23(5):1272].

Giardina AC, Ehlers KH, Engle MA. Wolff-Parkinson-White syndrome in infants and children. A long-term follow-up study. Br Heart J. 1972;34:839–46.

Hahurij ND, Gittenberger-De Groot AC, Kolditz DP, Bökenkamp R, Schalij MJ, Poelmann RE, Blom NA. Accessory atrioventricular myocardial connections in the developing human heart: relevance for perinatal supraventricular tachycardias. Circulation. 2008;117(22):2850–8.

Haissaguerre M, Cauchemez B, Marcus F, et al. Characteristics of the ventricular insertion sites of accessory pathways with anterograde decremental conduction properties. Circulation. 1995;91:1077–85.

Iturralde P, Araya-Gomez V, Colin L, Kershenovich S, de Micheli A, Gonzalez-Hermosillo JA. A new ECG algorithm for the localization of accessory pathways using only the polarity of the QRS complex. J Electrocardiol. 1996;29(4):289–99.

Ko JK, Deal BJ, Strasburger JF, Benson Jr DW. Supraventricular tachycardia mechanisms and their age distribution in pediatric patients. Am J Cardiol. 1992;69:1028–32.

Kugler JD, Danford DA, Deal BJ, The Pediatric Electrophysiology Society, et al. Radiofrequency catheter ablation for tachyarrhythmias in children and adolescents. N Engl J Med. 1994;330:1481–7.

Kugler JD, Danford DA, Houston K, Felix G. Radiofrequency catheter ablation for paroxysmal supraventricular tachycardia in children and adolescents without structural heart disease. Pediatric EP Society, Radiofrequency Catheter Ablation Registry. Am J Cardiol. 1997;80:1438–43.

Law IH, Fischbach PS, LeRoy S, Dick M. Access to the left atrium for delivery of radiofrequency ablation in young patients: retrograde aortic vs. transseptal approach. Pediatr Cardiol. 2001;22:204–9.

Lundberg A. Paroxysmal atrial tachycardia in infancy: long-term follow-up study of 49 subjects. Pediatrics. 1982;70:638–42.

Mahaim I, Benatt A. Nouvelles recherches sur les connexions superieures de la branche gauche du faisceau de His-Tawara avec la cloison interventriculaire. Cardiologia. 1938;1:61–73.

Mandapati R, Berul CI, Triedman KJ, et al. Radiofrequency catheter ablation of septal accessory pathways in the pediatric age group. Am J Cardiol. 2003;92(8):947–50.

Miles WM, Yee R, Klein GJ, et al. The preexcitation index: an aid in determining the mechanism of supraventricular tachycardia and localizing accessory pathways. Circulation. 1986;74:493–500.

Munger TM, Packer DL, Hammill SC, et al. A population study of the natural history of Wolff-Parkinson-White syndrome in Olmsted County, Minnesota, 1953–1989. Circulation. 1993;87:866–73.

O'Connor BK, Dick M. What every pediatrician should know about supraventricular tachycardia. Pediatr Ann. 1991;20(368):371–6.

Pappone C, Santinelli V, Manguso F, et al. A randomized study of prophylactic catheter ablation in asymptomatic patients with the Wolff-Parkinson-White syndrome. N Engl J Med. 2003a;349(19):1803–11.

Pappone C, Santinelli V, Rosanio S, Vicedomini G, et al. Usefulness of invasive electrophysiologic testing to stratify the risk of arrhythmic events in asymptomatic patients with Wolff-Parkinson-White pattern: results from a large prospective long-term follow-up study. J Am Coll Cardiol. 2003b;41:239–44.

Pappone C, Manguso F, Santinelli R, et al. Radiofrequency ablation in children with asymptomatic Wolff-Parkinson-White syndrome. N Engl J Med. 2004;351(12):1197–205.

Pediatric and Congenital Electrophysiology Society (PACES), Heart Rhythm Society (HRS), American College of Cardiology Foundation (ACCF), American Heart Association (AHA), American Academy of Pediatrics (AAP), Canadian Heart Rhythm Society (CHRS), Cohen MI, Triedman JK, Cannon BC, Davis AM, et al. PACES/HRS expert consensus statement on the management of the asymptomatic young patient with a Wolff-Parkinson-White (WPW, ventricular preexcitation) electrocardiographic pattern: Heart Rhythm. 2012;9(6):1006–24.

Riggs TW, Byrd JA, Weinhouse E. Recurrence risk of supraventricular tachycardia in pediatric patients. Cardiology. 1999;91:25–30.

Schaffer MS, Silka MJ, Ross BA, Kugler JD. Inadvertent atrioventricular block during radiofrequency catheter ablation. Results of the Pediatric Radiofrequency Ablation Registry. Pediatric Electrophysiology Society. Circulation. 1996;94:3214–20.

Scheinman MM, Wang YS, Van Hare GF, Lesh MD. Electrocardiographic and electrophysiologic characteristics of anterior, midseptal and right anterior free wall accessory pathways. J Am Coll Cardiol. 1992;20:1220–9.

Sternick EB, Timmermans C, Rodriguez LM, Wellens HJJ. Mahaim fiber: an atriofascicualr or long ventricular atrioventricular pathway. Heart Rhythm. 2004;1(6):724–7.

Weng KP, Wolff GS, Young ML. Multiple accessory pathways in pediatric patients with Wolff-Parkinson-White syndrome. Am J Cardiol. 2003;91:1178–83.

Wolff L, Parkinson J, White PD. Bundle-branch block with short P-R interval in healthy young people prone to paroxysmal tachycardia. Am Heart J. 1930; 10:685–704.

Atrioventricular Nodal Reentry Tachycardia

5

David J. Bradley, Nicholas Von Bergen, and Martin J. LaPage

Symptoms

As with other forms of paroxysmal tachycardia, the child with AVNRT complains of episodes of palpitations (heart racing, "hurting," fluttering, or "beeping"), often accompanied by malaise, pallor, nausea, and sweating, reflecting the sympathetic outpouring associated with the rapid heart rate. Shortness of breath may also occur, even with hemodynamically well-tolerated SVT; very rarely does the patient lose consciousness. Initiation of AVNRT is more influenced by sympathetic tone than accessory-connection-supported SVT, as it is often seen in patients during intense activity; SVT at rest suggests AVRT rather than AVNRT. In contrast to AVRT, AVNRT is less likely to be incessant, and therefore is virtually never implicated in tachycardia-induced cardiomyopathy.

D.J. Bradley, M.D. • M.J. LaPage, M.D., M.S. (✉)
Pediatric Cardiology, The University of Michigan Congenital Heart Center, Department of Pediatrics and Communicable Diseases, University of Michigan, Ann Arbor, MI, USA
e-mail: mlapage@med.umich.edu

N. Von Bergen, M.D.
Department of Pediatrics, University of Wisconsin—Madison, Madison, WI, USA

Incidence

AVNRT is relatively uncommon in small children, comprising less than 5 % of infant SVT. Its relative incidence increases across the pediatric age range, equaling, and then exceeding that of AVRT during the teenage years, making it the most common tachyarrhythmia until older adulthood, when atrial fibrillation predominates. A patient whose first episode of SVT occurs in late adolescence is most likely to have AVNRT as the mechanism; conversely, a child or adolescent relating a history of palpitations since early childhood is most likely to have accessory pathway SVT.

Electrocardiogram

The electrocardiogram (ECG) during AVNRT reveals regular, narrow, QRS complexes at a virtually constant rate; rarely, fluctuating conduction velocity (oscillation) in the AV node will render the tachycardia somewhat irregular. In its most common form, typical "slow–fast" antegrade conduction is through the "slow" pathway and retrograde conduction through the "fast" pathway during AVNRT. The retrograde P-waves are difficult to discern, as they begin less than 65–70 ms after the QRS onset and the QRS complexes are largely superimposed on them (Figs. 5.1 and 5.2). When P-waves are not coincident with the QRS,

M. Dick, II (ed.), *Clinical Cardiac Electrophysiology in the Young*,
DOI 10.1007/978-1-4939-2739-5_5

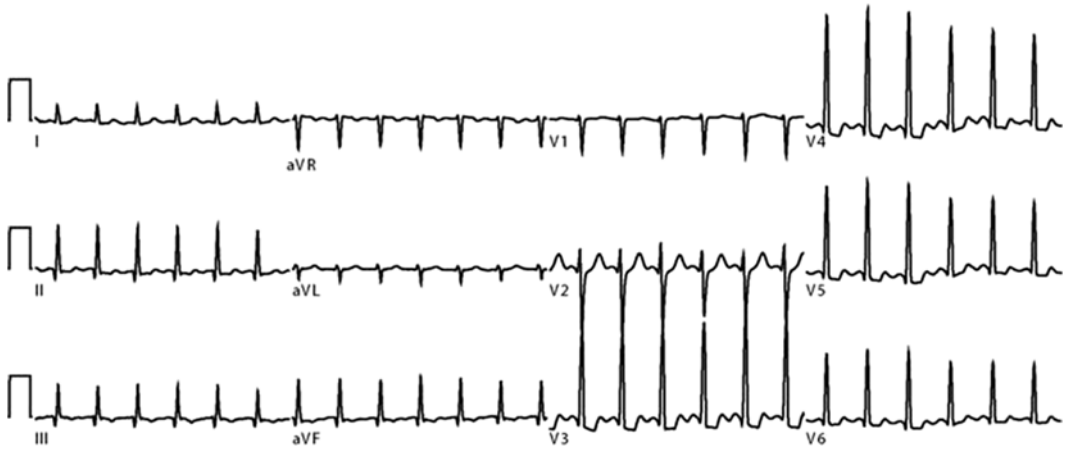


Fig. 5.1 12-Lead electrocardiogram of AVNRT. Note that distinct P-waves are not visible

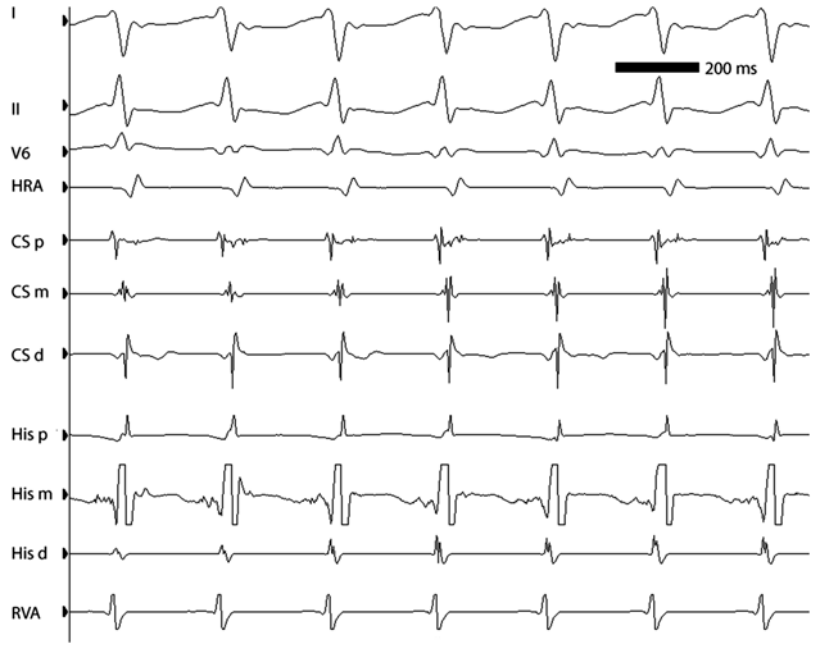


Fig. 5.2 ECG leads I, II, and V5 and intracardiac electrograms in a 13-year-old girl with AVNRT at approximately 260 bpm. Note the simultaneity of ventricular and atrial activation, characteristic of "typical" AVNRT. *HRA* high right atrium, *CSp*, *CSm*, *CSd* proximal, middle, and distal coronary sinus electrograms, respectively, *HIS P*, *HIS M HIS D* proximal, middle, and distal His bundle electrograms, respectively, *RVA* right ventricular apex

as in the less common atypical ("fast–slow" and "slow–slow") forms, the P-wave axis may be seen to be superior, reflecting atrial activation beginning at the AV node at the septal tricuspid annulus. These P-waves are usually visible following the QRS complex due to a retrograde P-wave beginning greater than 80 ms after the QRS complex (Fig. 5.3).

As in other forms of SVT, rate-related bundle branch-block may be seen, producing an "aberrant" wide-QRS tachycardia (Fig. 5.3) that is usually transient but can be mistaken for ventricular

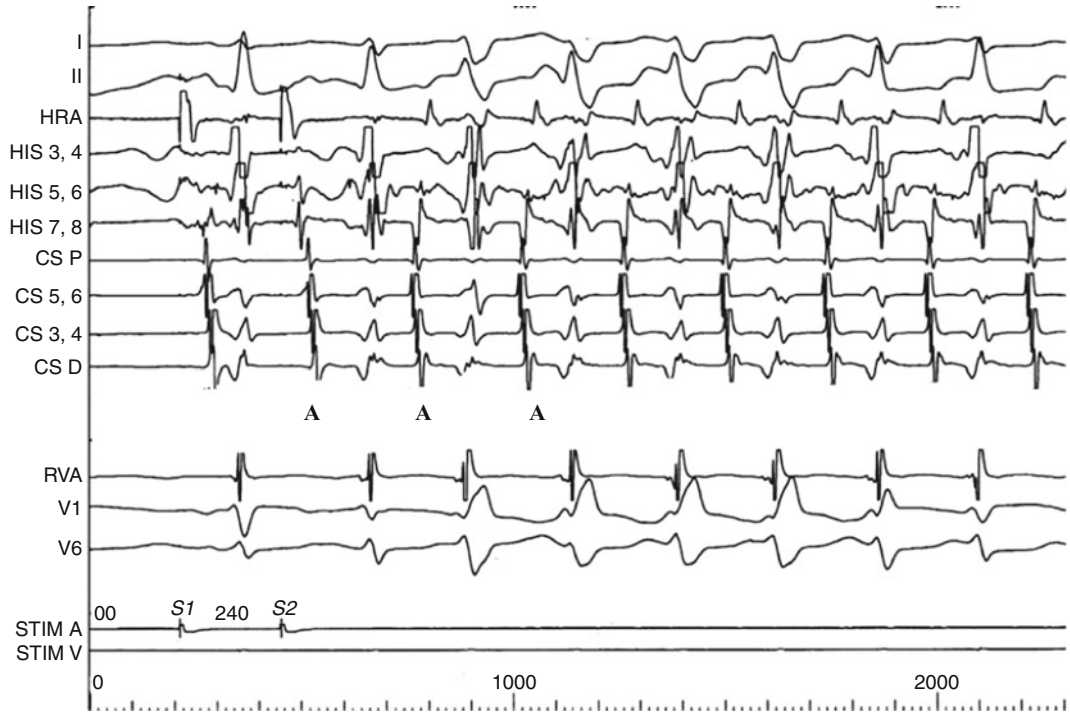


Fig. 5.3 "Atypical AVNRT" (slow–slow) initiated by programmed atrial stimulation in a 10-year-old girl. Note the long A2V2 and PR interval indicating slow conduction to the ventricle (third QRS complex from the left) and the echo beat (A) beginning the tachycardia. Note that the atrial echoes are not simultaneous with the QRS complex as in "typical AVNRT but are equidistant between the ventricular complexes. Note the rate-related right bundle branch bloc in the first four beats of the tachycardia followed by two narrow QRS complexes. The tachycardia cycle length does not lengthen during RBBB indicating that if there were an accessory pathway, it would not be on the right side (Chap. 4)

ectopy or tachycardia on ECG (Chap. 13). Depending on the patient's autonomic state and individual AV node characteristics, the rate of typical AVNRT can range from 120 to 300 bpm, with rates typically 180–250 bpm.

Dual AV Node Physiology

The term "dual AV nodal physiology" denotes the underlying functional substrate required for AVNRT to occur. In dual AV node physiology, two functional conducting pathways exist between the atrium and the penetrating His bundle (Fig. 5.4). In the typical example, the anterosuperior atrial connections ("fast" pathway) to the AV node comprise a pathway with a faster conduction velocity but a longer refractory period relative to the more slowly conducting postero-inferior atrial fibers ("slow" pathway), which have a shorter refractory period. As a result, an appropriately timed atrial premature beat (Fig. 5.4a) that fails to conduct through the refractory "fast pathway" may be successfully conducted through the AV node via the "slow pathway" (as it is not refractory, Fig. 5.4b). During the increased time which elapses as the impulse traverses the slow pathway, the fast pathway recovers excitability (no longer refractory) and is available for retrograde impulse propagation; the impulse also enters the His-Purkinje system activating the ventricles (Fig. 5.4c). In AVNRT, the atrium is therefore activated retrogradely at approximately the same time as the ventricle antegradely (Figs. 5.1 and 5.2). The reentrant circuit continues through atrial tissue, then antegradely through the slow AV nodal pathway and retrogradely through the

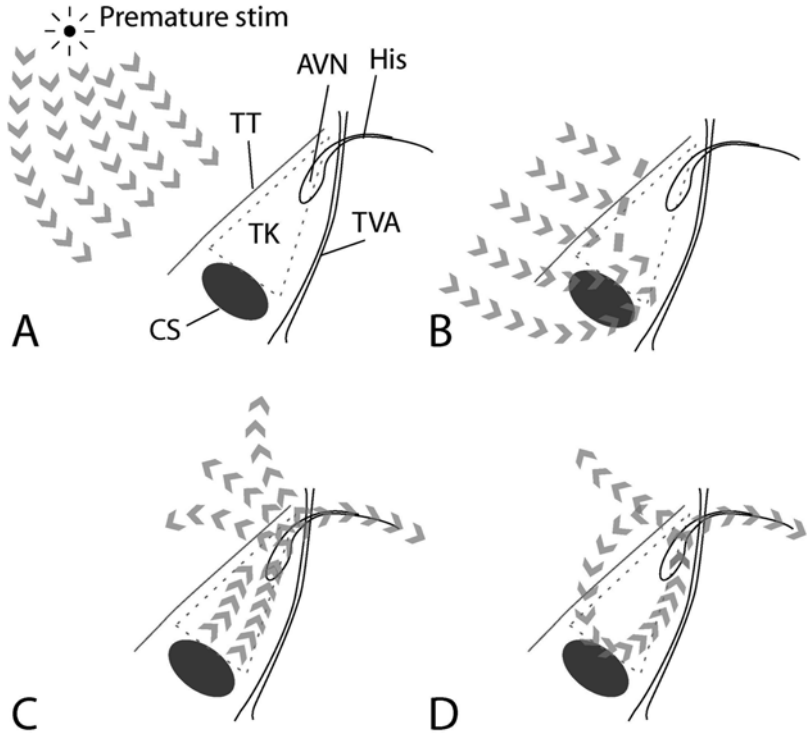


Fig. 5.4 Initiation of AVNRT by a premature atrial stimulus. (**a**) Atrial activation proceeds from the source of the premature stimulus. (**b**) The premature atrial activation approaches the AV node, but the anterior inputs ("fast pathway") to the AV node are still refractory, and thus block conduction. (**c**) In contrast, the posterior inputs ("slow pathway") to the AV node have a shorter refractory period, and are excitable. Here, conduction persists. The node is activated, leading to activation of the ventricle and (i.e., now the anterior aspect of the atrio-nodal junction is excitable) atrial tissues. (**d**) The reentrant circuit is established, with activation of atria and ventricles with each "lap" or revolution through the circuit. *Abbreviations*: *AVN* AV node, *His* His bundle, *Stim* stimulus, *TK* triangle of Koch, *TT* tendon of Todaro, *TVA* tricuspid valve annulus, *CS* ostium of the coronary sinus

fast, reactivating the atrium and ventricle with each cycle (Fig. 5.4d).

Programmed atrial stimulation is the standard technique to demonstrate the presence of these functionally separate conduction pathways. As the coupling interval of the premature atrial extra-stimulus is progressively shortened, the septal atrial to His bundle (A-H) interval progressively lengthens, due to decremental conduction through the atrioventricular node (Fig. 5.5). At a critical coupling interval, the "fast" anterior conduction pathway is refractory. Conduction, however, persists through the slower posterior connections, resulting in an abrupt increase or "jump" in both the resultant A-H interval (defined conventionally as ≥50 ms or greater) and in the H1-H2 interval (Fig. 5.5), induced by only a 10 ms decrease in the premature coupling interval. This "jump" indicates a shift in conduction from the fast pathway to the slow pathway (i.e., dual AV node physiology) and fulfills two of the three conditions for reentry (unidirectional block in one pathway and slow conduction in the other pathway (Chap. 3). Single atrial echoes or multiple beats of tachycardia complete the reentry triad (recovery of excitability in the tissue of origin).

Although typical "slow–fast" AVNRT (Figs. 5.1 and 5.2) is the most common pattern seen with dual AV node physiology, variants exist. In the first variant, the so-called fast–slow form, the impulse travels antegradely in the fast pathway and retrogradely in the slow pathway (a reversed circuit compared to the typical form), transcribing

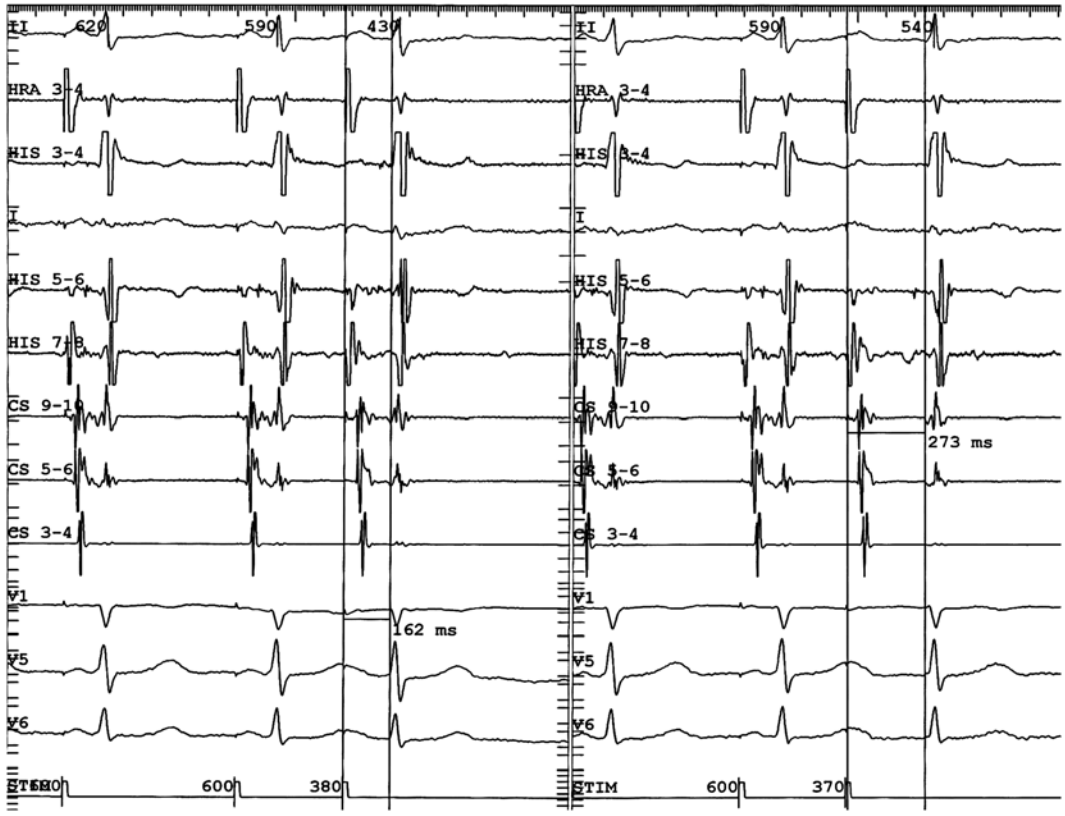


Fig. 5.5 Demonstration of dual AV nodal physiology at EP study. In the left panel atrial programmed extra-stimulation is performed using a drive cycle length (S1) of 600 ms and an extra-stimulus (S2) of 380 ms. The resultant A2-H2 was 162 ms as measured by the vertical caliper and the H1-H2 interval about 390 ms. In the right panel, the S1-S1 is again 600 ms but the S1-S2 is now 370 ms. The resultant A2-H2 is now 273 ms (and the H1-H2 interval increased by more than 100 ms) indicating conduction is blocked in the fast pathway but continues antegradely in the slow pathway

a longer RP interval. A third infrequent variant has similar conduction velocity in both pathways of the reentry circuit (e.g., "slow–slow") (Fig. 5.3). This form is characterized by a retrograde P-wave (negative in II, III, aVF) transcribed in the middle of the tachycardia cycle length. An important characteristic of the reentrant circuit of AVNRT is its independence from excitable tissues distal to the circuit, including the bundle of His and ventricles. It is therefore possible to observe AVNRT with 2:1 conduction to the ventricle (Fig. 5.6), which must be distinguished from atrial tachycardias.

On occasion atrial-programmed stimulation does not demonstrate dual AV node pathway physiology. Using ventricular extra-stimulation, retrograde conduction block occurs first in the fast pathway (longer refractory period) followed by conduction retrogradely through the slow pathway in the triangle of Koch and then antegrade conduction through the fast pathway, resulting in the "fast–slow" atypical form of AVNRT.

Noninvasive Treatment

As for all well-tolerated tachycardias, the decision to treat is largely governed by the findings of the individual patient. They include frequency and duration of episodes, intensity of symptoms with episodes, response to medications, and the

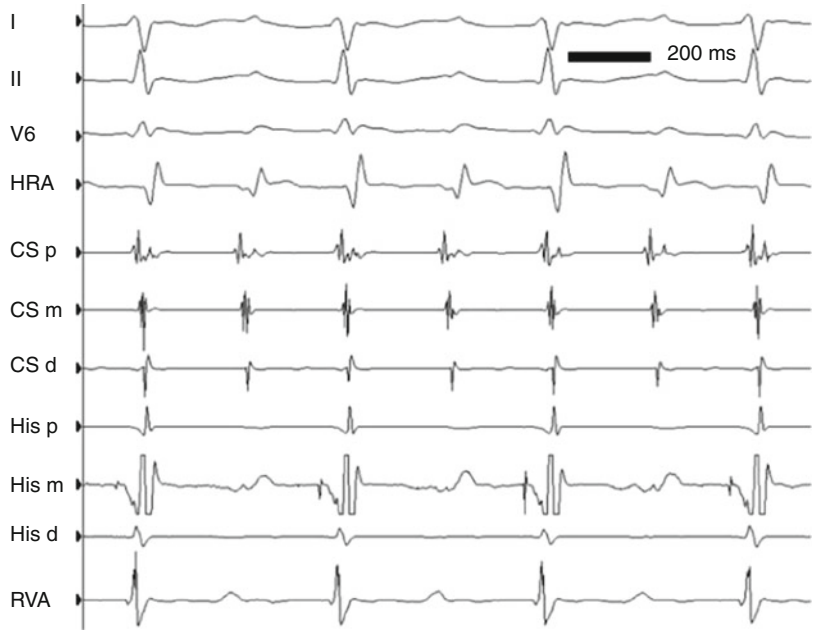


Fig. 5.6 The tracing demonstrates typical AVNRT, with a 2:1 A-V relationship between the atria and ventricles

patient's and family's views regarding the various options. Patients who have minimal symptoms with episodes that are short and self-terminating or that respond to vagal maneuvers may rightly pursue no further treatment. However, some patients in whom the response of the arrhythmia to vagal maneuvers is highly variable, or the symptoms are disruptive of activities of daily living elect treatment—either a trial of antiarrhythmic medication or ablation.

Because β-blockers are safe and available in convenient dosing (Table 5.1), they are the medication of first choice for many patients. This group of medications acts by reducing the excitability and probably also the conduction disparities of dual AV nodal pathways. Fatigue, malaise, and exercise limitations are common, even with the newer, more selective, and longer acting β_1-blockers such as atenolol or nadalol, which cross the blood–brain barrier to a lesser degree. The young athlete taking β-blockers often reports fatigue during vigorous exertion; even the nonathlete may unilaterally discontinue β-blockers due to fatigue.

Digoxin, at one time a common first-line therapy for SVT in children, is rarely used by pediatric electrophysiologists, except in infants without preexcitation. Its comparative efficacy remains debated, but digoxin may be preferable in the patient with a contraindication to β-blockers, such as asthma or prior unwanted side effects. Its use in the child with preexcitation on resting ECG is considered contraindicated, but in AVNRT it would not be expected to have significant risks.

Calcium-channel blockers also represent a satisfactory treatment option for some patients with AVNRT. The lack of availability of suspensions and the requirement of frequent dosing makes these somewhat more difficult to use in younger children, though they are typically well tolerated. Calcium-channel blockers should be avoided in infants less than 6 weeks of age.

Class I and III agents such as flecainide (I), sotalol (III), and amiodarone (III) are often effective in refractory AVNRT maybe useful in situations where catheter ablation is not an option.

Table 5.1 Drugs used in the treatment of AVNRT

Drug	Class	Dose (mg/kg/24 h)	Dose interval (h)	Comment
Digoxin	Glycoside	8–10 mcg	12	Decreasing use, minimal antiarrhythmic effect
Propranolol	β-Blocker	1–4	8	Depression, fatigue may occur
Atenolol	β-Blocker	0.5–1.5	12–24	Fewer CNS effects than propranolol
Diltiazem	Ca^{2+} channel blocker	1.5–3.5	6–8	Sustained-release form available
Flecainide	Na^{+} channel blocker	1–5	8–12	Structural heart disease a contraindication

Table 5.2 Components of electrophysiologic study for SVT

Study component	Information provided
Adenosine bolus during right ventricular pacing	If V-A block occurs, unlikely to have a V-A conduction pathway other than AV node
Atrial extra-stimulus	Anterograde refractory period of AV node pathway(s), atrium, arrhythmia induction
Ventricular extra-stimulus	Retrograde refractory period of AV node pathway(s), arrhythmia induction (less commonly)
Incremental pacing—atrial and ventricular	Determination of Wenckebach cycle length, antegrade and retrograde, arrhythmia induction
Isoproterenol infusion	"Unmasking" of dual AV node physiology and arrhythmias not demonstrable in the baseline state, arrhythmia induction
Premature ventricular stimuli during SVT	Confirms involvement of an accessory pathway in supraventricular tachycardia
Ventricular overdrive pacing	Distinguishes AVRT and AVNRT from atrial tachycardias

Antiarrhythmic agents no longer have the dominant role in treatment of SVT, especially in older, larger children. Many patients and families decide not to begin a daily medication for what is a sporadic symptom, but to proceed to ablation if SVT has become an unacceptable intrusion on their life.

Electrophysiology Study and Ablation

Ablation of the SVT substrate, with either transcatheter radiofrequency (RF) ablation or cryoablation, while carrying small but important risks, is regularly performed for the elimination of symptomatic SVT in children (Chap. 22).

The age at which ablation can safely be performed is declining. Early experience from the Pediatric Electrophysiology Society Registry suggested that patients under 15 kg had a significantly increased risk of serious complications. Some animal models of ablation suggested that RF lesions grow significantly when performed in young individuals, particularly when they are delivered to the ventricles. The clinical experience of large-volume centers and the long-term follow-up of children enrolled in the Prospective Assessment of Pediatric Catheter Ablation (PAPCA), however, support the use of ablation even in selected infants and toddlers.

Techniques for electrophysiologic study unique to children and young patients are reviewed in Chap. 3. Programmed stimulation, as used in adult patients, demonstrates the underlying physiology and usually induces the clinical tachycardia (Table 5.2). When performing an electrophysiology study of SVT, it is useful to begin with a bolus infusion of intravenous adenosine (200 mcg/kg) while pacing the right ventricle. Adenosine is a potent—and short-acting—blocker of the AV node, but does not block most accessory AV pathways. Ventricular-atrial (VA) block after the adenosine bolus suggests the absence of an accessory pathway, and that the diagnosis of AVNRT should be pursued. If VA conduction persists after a bolus of adenosine, the retrograde activation sequence of the atrium will help identify the location of an accessory pathway (Chap. 4). Next, programmed stimulation is used to define the refractory periods of the cardiac tissues, particularly those of the "fast" and "slow" components of the AV node (see above and Chap. 3).

It is important to note that dual AV node physiology is often discovered in patients during electrophysiologic testing for other reasons. This finding is much less frequent in younger children than in adolescents and adults. Interestingly, 38 % of children with AVNRT as their tachycardia mechanism do not demonstrate classical dual AV node physiology in the baseline state. In preparation for ablation, the clinical tachycardia should be induced at EP study. If this cannot be achieved in the baseline state, intravenous isoproterenol 0.02–0.1 mcg/kg/min should be infused, such that the baseline heart rate is increased by about 25 %. A small number of patients in whom dual AV nodal physiology is not found in the baseline state will show such physiology when receiving isoproterenol. The extra-stimulus testing and decremental pacing should be repeated during isoproterenol infusion to induce tachycardia. In patients in whom documented SVT on an ECG, dual AV node physiology, evidence for an accessory pathway, and inducible SVT are lacking, proceeding to slow pathway ablation is appropriate to eliminate the most likely substrate.

Intracardiac tracings of typical AVNRT have a characteristic appearance of nearly simultaneous atrial and ventricular activation (Fig. 5.2); V-A times in SVT of 50 ms or less essentially exclude the diagnosis of accessory pathway SVT. After AVNRT is established as the SVT mechanism, cryoablation or radiofrequency ablation lesions are placed in the slow pathway region, within the triangle of Koch. This triangle comprises the atrial tissues bounded by the coronary sinus ostium and the tendon of Todaro on the upstream side and the tricuspid annulus on the downstream side. It extends anteriorly up the annular edge of the tricuspid valve to its apex at the central fibrous body. The AV node rests just below the apex (Fig. 5.7).

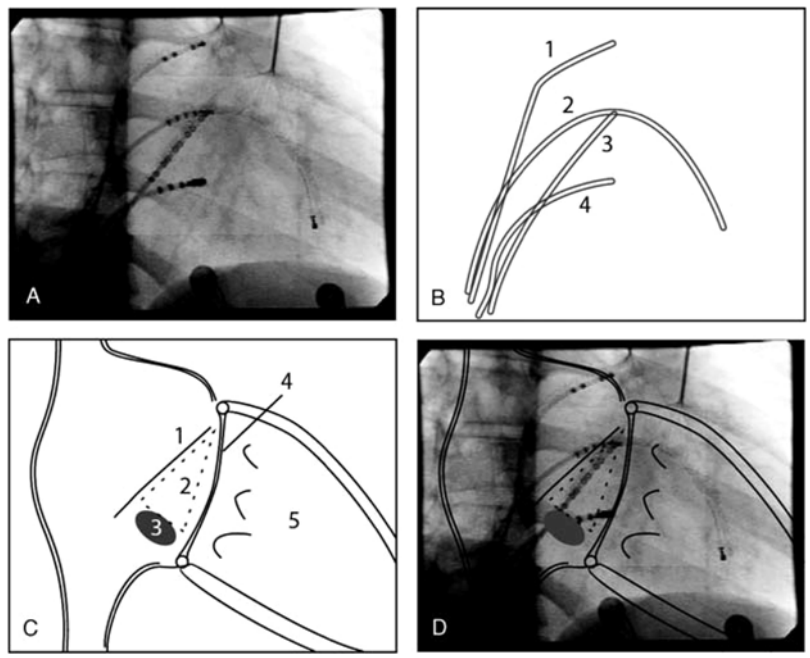


Fig. 5.7 Fluoroscopic-anatomic correlation of catheter positions relevant to AVNRT. (**a**) Right anterior oblique (30° angle) fluoroscopic image of the heart with catheters in position. (**b**) Key to catheter positions: (*1*) high right atrium; (*2*) combined His bundle/right ventricular apex catheter; (*3*) coronary sinus; (*4*) ablation catheter resting in slow pathway region. (**c**) Relevant anatomic structures: (*1*) tendon of Todaro/Eustachian ridge; (*2*) triangle of Koch; (*3*) coronary sinus ostium; (*4*) septal tricuspid valve annulus; (*5*) body of the right ventricle. (**d**) Anatomic cartoon overlying the fluoroscopic image

Mapping

Identification of the ablation site is primarily anatomic. The electrograms recorded by the distal bipolar pair of electrodes may be used to guide appropriate positioning: "ideal" sites typically include both atrial and ventricular components, where the ventricular amplitude exceeds the atrial signal by about 3–5 times (Fig. 5.8). Detailed mapping in early studies (see Jackman et al. 1992) delineated the presence of a "slow pathway potential" (sharp potential following a lower amplitude atrial potential) at the site of successful RF ablation. The most common site of slow pathway ablation success was between the CS ostium and the tricuspid valve annulus or immediately superior to this location. Additional investigations have revealed some alternative but infrequent circuits which must be considered in the difficult case. The slow pathway extensions of the AV node can extend to the left side of the intra-atrial septum along the roof of the coronary sinus—in these cases ablation at the roof of the proximal CS can be effective. This very rare typical AVNRT variant can be ablated from the left atrium at the inferior-lateral mitral valve annulus. This leftward variant should be considered in patients with typical AVNRT when the earliest atrial activation is clearly lateral on the mitral valve annulus.

The current paradigm shift to the use of catheter navigation systems attempts to minimize or eliminate fluoroscopy use and rely on computerized 3-D electro-anatomic mapping systems (Fig. 5.9). This technique is especially adaptable to cryoablation because of the low risk of AV node damage. Low fluoroscopy RF ablation is also possible but with some additional caution to

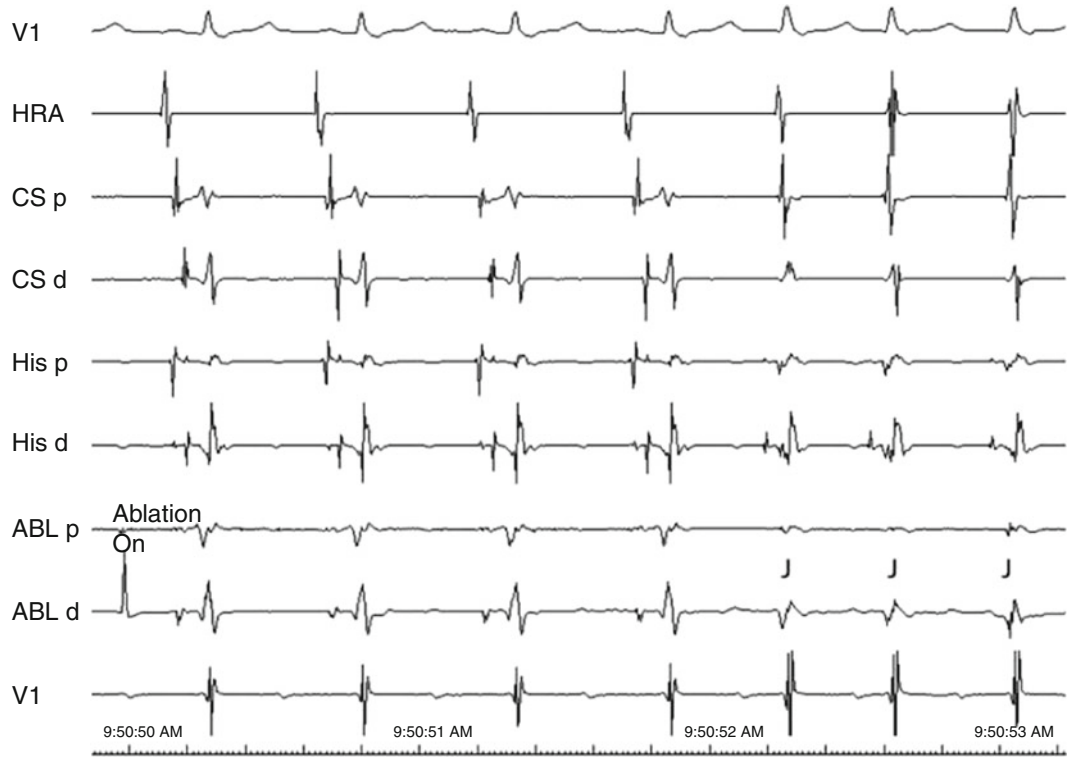


Fig. 5.8 Optimal electrograms recorded through the distal closely spaced pair of electrodes on the ablation catheter (ABLd). Note the electrogram recorded through ABL d with small "a" and larger "V". Radiofrequency energy is turned on, and accelerated junctional beats (labeled "J") begin. Note the "JA" association between the a-wave in the CS electrogram and the v-wave in the His electrogram and QRS in V1

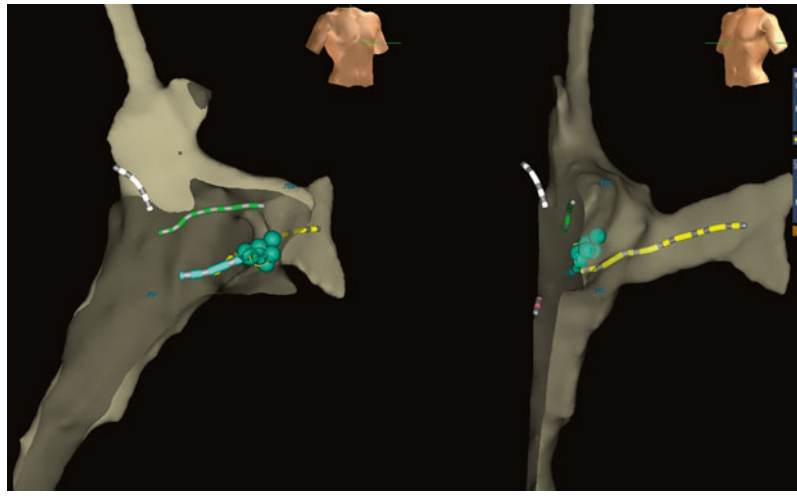


Fig. 5.9 Screen image from 3-D mapping (Ensite Velocity) system during cryoablation of slow pathway in 14-year-old girl with AVNRT. The gray shell is the modeled right atrial endocardial surface. Blue dots indicate cryoablation sites, and the segments of the catheters which have electrodes are also shown: His bundle (*green*), coronary sinus (*yellow*), right ventricle (*pink*), right atrial (*white*), and ablation (*blue*)

assure distance from the AV node tissues. Using RF energy, successful ablation of the slow pathway can usually be accomplished at a safe distance (≥5 mm) from sites where a His potential is recorded.

Radiofrequency Ablation

With RF ablation, care must be taken to confirm that the catheter tip position is sufficiently inferior to the site of the His bundle and AV node. Ablation is often performed in temperature control mode, with a 50 W power limit and a temperature cutoff of 47–55 °C. With good catheter–tissue contact, a slow-pathway ablation may not require more than 15 W (of the generator's available 50–100 W) to achieve satisfactory ablation. The induction of a junctional rhythm (<100 bpm) during or after a 10–15 s RF application can be a marker of a successful ablation site. After a successful RF application, EP testing assesses continued presence of the tachycardia or its substrate. Though it is common for operators to initiate ablation low in the triangle of Koch and then progress towards the AV node, conventional slow pathway ablation sites are uncommon higher in the Triangle of Koch and in the roof of the coronary sinus ostium. During the ablation and junctional rhythm, the presence of V (or J)-A conduction suggests persistent integrity of the "fast" pathway, and of intact atrioventricular nodal conduction. If either a fast junctional rhythm or interruption of V-A association appears during the RF ablation, the RF energy should be stopped immediately. This is a sign of likely injury to the fast AV node pathway, and a harbinger of iatrogenic heart block. Prolongation of the PR interval can also be an indication of injury to the AV node and may be permanent.

Cryoablation

Cryoablation (Fig. 5.9) has evolved as a widely used technique for AVNRT ablation (Chap. 23), especially in children, due to the apparent risk of AV nodal damage. It is our preferred ablation approach for AVNRT in children. Due to longer ablation application times, this technique is a longer process but justified by the lack of cases of iatrogenic heart block in the literature. Early studies of cryoablation showed a lower success rate and higher recurrence rate compared to RF ablation. However, evolution of the procedure and cryoablation technology have resulted in more favorable results and lower recurrence rates;

recent studies show acute success rates equivalent to that of RF. A specific benefit of the cryocatheter is adherence to the tissue, which allows for stable catheter position and ablation during tachycardia. Ongoing AVNRT may render selection of ablation sites more difficult (with A and V nearly superimposed), so sites maybe chosen in sinus rhythm. However, ablation during SVT may also be desirable to allow prompt identification of slow pathway effect. Re-induction attempts and testing for dual AV node physiology can be performed during ablation after catheter adhesion without fear of dislodging the catheter. The 6 and 8 mm tip catheters have largely replaced the 4 mm tip catheter due to their superior efficacy. The site of success is reinforced with a "freeze–thaw–refreeze" cycle; additional lesions are delivered around this site and in a linear fashion from tricuspid valve annulus to CS ostium, as these techniques have been shown to improve outcome. Cryoablation is a forgiving modality; ablation in a site that causes heart block, if promptly terminated, permits full conduction recovery.

Diligent re-testing after ablation is another important aspect of the procedure in the young patient. Whether or not the patient had tachycardia induced in the resting state or with isoproterenol infusion, a meta-analysis of adult literature has shown that post-ablation testing on isoproterenol is important to identify those at risk of recurrence. Additional lesions are placed if tachycardia or more than a single echo beat is seen during testing.

Overall, slow pathway modification by ablation is acutely successful (no tachycardia upon the electrophysiology laboratory) in greater than 95 % of children. Depending on the specific technique, recurrence rates as low as 6 % are achievable at 3–5 year follow-up.

The AV Node in Patients with Abnormal Cardiac Anatomy

AVNRT has been identified in patients having a variety of congenital anatomic defects, before and after their surgical repair or palliation. In such patients, the hemodynamic compromise associated with AVNRT episodes can be significant. Modification of the slow pathway region can be performed successfully even in complex anatomic situations, which may call for an unconventional (trans-aortic valve, trans-septal, trans-baffle) approach, or with limited catheter access due altered venous connections. When possible, the location of the His bundle should be mapped and tagged using a 3-D mapping system, or identified with a catheter consistently recording a His potential, to minimize the chance of injury to the fast AV node pathway.

In patients with complete AV canal defect, the conduction system is displaced posteriorly and inferiorly, due to incomplete septation. Disparity in mitral and tricuspid annular size may make the triangle of Koch difficult to localize. Successful ablation of AVNRT in such subjects requires a methodical positioning of catheters, defining landmarks, and careful selection of appropriate electrograms on the ablation catheter. In these patients, 3-D mapping may be of substantial benefit.

Complications of Ablation for AVNRT

The most evident serious risk is that of permanently interrupting AV conduction, for which a pacemaker is the usual required treatment. AV block may occur in two ways: either by direct injury to the AV node or His bundle by ablating too close to these structures, or by disruption of the vascular supply of the AV node. The AV node artery generally arises from the posteroinferior atrium as a branch of the posterior descending coronary artery. Histologic studies have demonstrated the variability both in its position and depth beneath the endocardial surface. Further, the shape and dimensions of the triangle of Koch in children vary. The risks of damage to these structures should be dichotomized by ablation technique—cryoablation versus RF. The risk of AV block with the use of cryoablation is extremely low, and at this time of this writing there have been no published reports of permanent AV nodal block with cryotherapy in AVNRT. Complete AV block has been documented with the application of RF energy

proximate to the coronary sinus ostium, in what would be considered "safe" locations. Although these anatomic features place the AV node at risk, recent experience indicates the likelihood of complete permanent heart block due to RF ablation is also low, typically estimated between 0.5 and 1 %. Nonetheless, it is the practice of experienced operators to limit ablation temperature, power, duration, and number of RF applications in smaller children. For most pediatric patients, recurrent tachycardia is preferable to AV block.

Summary

Atrioventricular nodal reentry tachycardia is the second most common mechanism of paroxysmal supraventricular tachycardia in pediatric patients and occurs more frequently in older children and adolescents. Although often responsive to vagal maneuvers and often manageable by antiarrhythmic medications, ablation has emerged as the primary therapy for significantly affected patients. Slow AV nodal pathway ablation can be achieved with a high degree of success and a low rate of complications.

Suggested Reading

Cohen MI, Wieand TS, Rhodes LA, Vetter VL. Electrophysiologic properties of the atrioventricular node in pediatric patients. J Am Coll Cardiol. 1997;29(2):403–7.

Crosson JE, Hesslein PS, Thilenius OG, Dunnigan A. AV node reentry tachycardia in infants. Pacing Clin Electrophysiol. 1995;18(12 part 1):2144–49.

Das S, Law IH, Von Bergen NH, Bradley DJ, et al. Cryoablation therapy for atrioventricular nodal reentrant tachycardia in children: a multicenter experience of efficacy. Pediatr Cardiol. 2012;33(7):1147–53.

De Sisti A, Tonet J. Cryoablation of atrioventricular nodal reentrant tachycardia: a clinical review. Pacing Clin Electrophysiol. 2012;35:233–40.

Denes P, Wu D, Dhingra RC, et al. Demonstration of dual A-V nodal pathways in patients with paroxysmal supraventricular tachycardia. Circulation. 1973;48:549–55.

Eckhardt LLL, Leal M, Hollis Z, Tanega J, Alberte C. Cryoablation for AVNRT: importance of ablation endpoint criteria. J Cardiovasc Electrophysiol. 2012;23:729–34.

Fishberger SB. Radiofrequency ablation of probable atrioventricular nodal reentrant tachycardia in children with documented supraventricular tachycardia without inducible tachycardia. Pacing Clin Electrophysiol. 2003;26:1679–83.

Friedman PL, Dubuc M, Green MS, Jackman WM, et al. Catheter cryoablation of supraventricular tachycardia: results of the multicenter prospective "frosty" trial. Heart Rhythm. 2004;1(2):129–38.

Hanninen M, Yeun-Lai-Wai N, Massel D, Gula LJ, et al. Cryoablation versus RF ablation for AVNRT: a meta-analysis and systemic review. J Cardiovasc Electrophysiol. 2013;24:1354–60.

Jackman WM, Beckman KJ, McClelland JH, Wang X, et al. Treatment of supraventricular tachycardia due to atrioventricular nodal reentry by radiofrequency catheter ablation of slow-pathway conduction. N Engl J Med. 1992;327:313–8.

Kannankeril PJ, Fish FA. Sustained slow pathway conduction: superior to dual atrioventricular node physiology in young patients with atrioventricular nodal reentry tachycardia? Pacing Clin Electrophysiol. 2006;29:159–63.

Ko JK, Deal BJ, Strasburger JF, Benson DW. Supraventricular tachycardia mechanisms and their age distribution in pediatric patients. Am J Cardiol. 1992;69:1028–32.

Ro PS, Rhodes LA. Atrioventricular node re-entry tachycardia in pediatric patients. Prog Pediatr Cardiol. 2001;13:3–10.

Scheinman MM, Yang Y. The history of AV nodal reentry. Pacing Clin Electrophysiol. 2005;28:1232–7.

Persistent Junctional Reciprocating Tachycardia

6

Parvin Dorostkar

Anatomy

Based on an analogy of the known anatomy in patients with Wolff–Parkinson–White syndrome, the hypothetical anatomy of the PJRT circuit consists of an antegrade limb through the normal atrioventricular (AV) nodal conduction system and a retrograde limb to the atrium via a slowly conducting concealed retrograde accessory pathway with decremental conduction properties (Fig. 6.1). By electrophysiologic study, the accessory pathway can usually be found in the posteroseptal area of the heart, but left and anterior locations—and even epicardial locations—have been reported.

Clinical and Electrocardiographic Findings

Persistent junctional reciprocating tachycardia usually presents during childhood <18 years and in approximately 50 % of patients during the first year of life. With advancing technology, the diagnosis can be entertained in utero and further evaluated using M-mode echocardiography to study the relationship of atrial and ventricular contractions in the fetus, supporting the diagnosis of PJRT. There is one familial case of PJRT where grandmother and grandson were noted to have PJRT. A 72-year-old female and in her 16-year-old grandson underwent evaluation and HLA typing. The Bw41 antigen was found in the patients as well as in the boy's paternal uncle. This is the first documented familial case of PJRT. The possible significance and correlation with the Bw41 antigen is still under scrutiny.

Persistent junctional reciprocating tachycardia heart rates usually range from 100 to 250 beats per minute. The criteria for diagnosis of PJRT include a narrow complex tachycardia, a long R-P interval, and inverted P-waves in leads II, III, AVF, and the left lateral precordial leads (Fig. 6.2). Unusual forms of suspected PJRT have been described where similar pathway behavior supports suspected a "PJRT-like" diagnosis. In one case (see Medeiros in Suggested Reading), there was a near-incessant tachycardia, with a 1:1 atrioventricular relationship and a retrograde P wave (P)′ occurring closer to the succeeding QRS complex, i.e., with a P-R interval shorter than the RP′ interval. The tachycardia episode was characterized by alternating short and long cardiac cycles due to alternation of retrograde conduction time (RP′ interval) in a retrograde Wenckebach periodicity pattern. The authors proposed that the accessory atrioventricular connection had decremental

P. Dorostkar, M.D., M.S., M.B.A. (✉)
Department of Pediatrics, Pediatric Cardiology, University of Minnesota, 225 North Smith Ave., Ste 504, Saint Paul, MN 55102, USA
e-mail: pcd@umn.edu

M. Dick, II (ed.), *Clinical Cardiac Electrophysiology in the Young*,
DOI 10.1007/978-1-4939-2739-5_6

functional properties that arborized into two atrial branches or categories with different conduction times. The fast branch initially exhibiting a 3:2 retrograde conduction block followed by a cycle length-dependent 2:1 retrograde conduction block, thereby permitting alternate use of the slow branch, which was thought to be the weakest component of the reciprocating process.

In pediatric patients with PJRT, the heart rate decreases with a PJRT cycle length increase from 200 to 300 beats per minute in the first 2 years of life, settling around heart rates of about 120–150 beats per minute as the patient matures, as can be seen in Fig. 6.3. Furthermore, as the PJRT cycle length increases the principal component appears to be associated with slowing of conduction in the concealed retrograde limb of the reentrant circuit, accounting for 64 % of the increase in the tachycardia cycle length as shown in Fig. 6.4. In contrast, the PR interval is relatively stable, accounting for only 36 % of the total increase in the tachycardia cycle length Fig. 6.5.

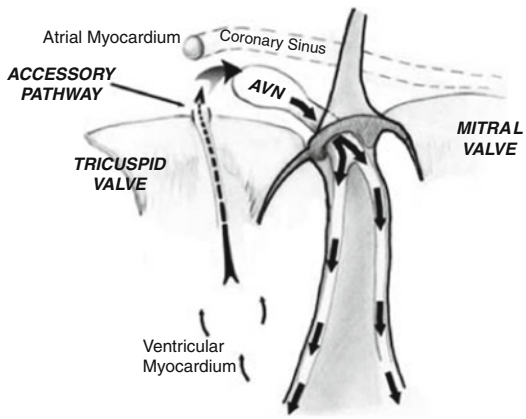


Fig. 6.1 Drawing of normal atrioventricular conduction tissue and concealed slowly only conducting retrograde accessory pathway supporting PJRT

Although very young patients <2 years with PJRT tend to have incessant tachycardia, older subjects with slower retrograde conduction through the accessory pathway also tend to exhibit an incessant form. This apparent contradiction is most likely related to the shorter refractoriness and faster conduction velocity of all cardiac excitable tissue found in young individuals, facilitating, in the presence of the necessary anatomic substrate, i.e., another conducting pathway such as in patients with PJRT, the establishment of a fast conducting reentrant circuit. As the individual gets older and these properties lengthen, the increasingly slow retrograde conduction of the abnormal accessory pathway compensates for the longer refractoriness of the return tissues, i.e., atrium, allowing for recovery of excitability and incessant tachycardia, but at a slower rate.

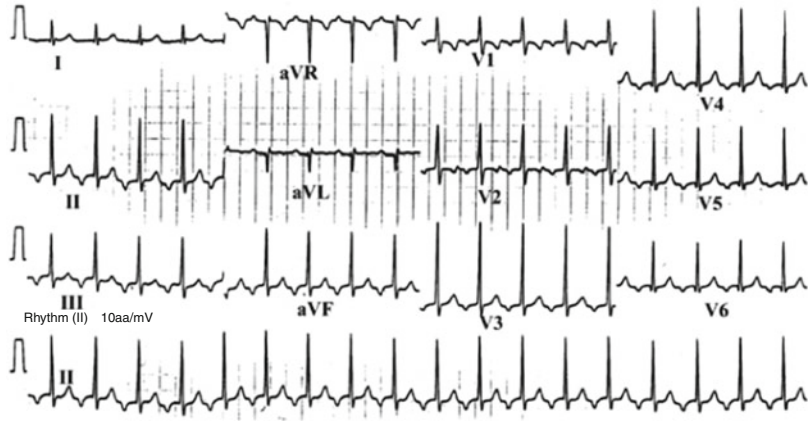


Fig. 6.2 12-Lead electrocardiogram and rhythm (bottom tracing) in a 5-year-old girl with PJRT. Note the negative P-waves in leads II, III, aVF, and the lateral precordial leads along with the long RP interval. [Reprinted from Dorostkar, P, et al., Clinical course of PJRT. Journal of the American College of Cardiology 1999;33(2):366–375. With permission from Elsevier.]

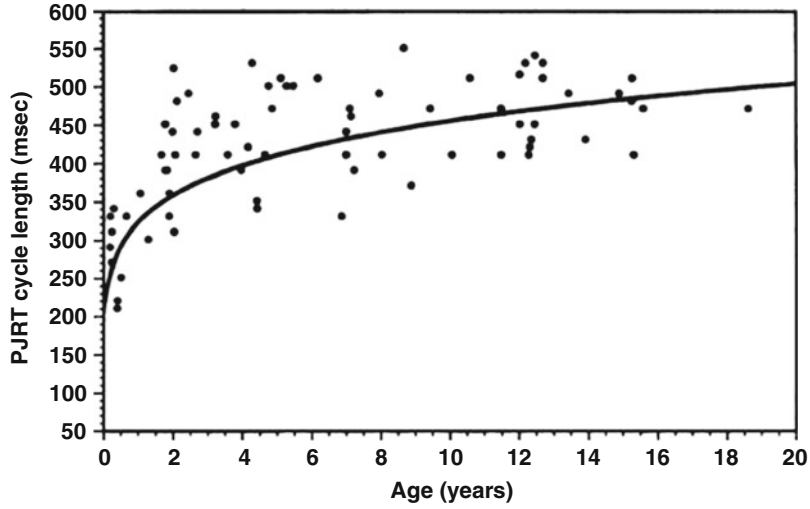


Fig. 6.3 Plot of serial tachycardia cycle length versus age years in 9 children with PJRT. Note the trend of an increase in cycle length slowing of the tachycardia with age. [Reprinted from Dorostkar, P, et al., Clinical course of PJRT. Journal of the American College of Cardiology 1999;33(2):366–375. With permission from Elsevier.]

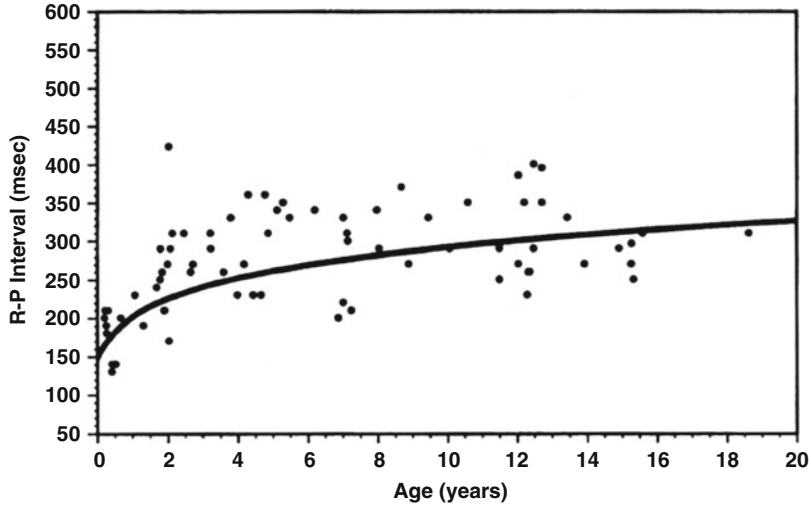


Fig. 6.4 Plot of age versus R-P interval demonstrating a slowing in the retrograde conduction limb increased R-P interval of the reentrant circuit over time. [Reprinted from Dorostkar, P, et al., Clinical course of PJRT. Journal of the American College of Cardiology 1999;33(2):366–375. With permission from Elsevier.]

Although PJRT in most patients is incessant, some subjects exhibit a paroxysmal form (Fig. 6.6). One factor that may contribute to this observation is the variation in the cardiac electrophysiologic properties between individuals and even within a single individual at different ages and physiologic states. When a longer refractory period in the atria is coupled with a faster retrograde conduction velocity in the accessory pathway, even for one cycle, the reentry circuit may be interrupted and the tachycardia transiently terminated. Clearly, the state of the autonomic nervous system and circulating catecholamines will influence the electrophysiologic properties of the

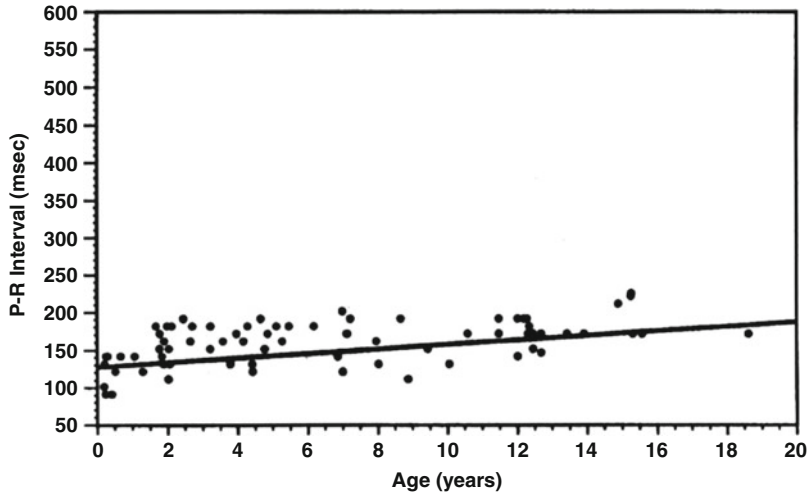


Fig. 6.5 Plot of age versus P-R interval demonstrating slow gradual increase in the P-R interval with time. [Reprinted from Dorostkar, P, et al., Clinical course of PJRT. Journal of the American College of Cardiology 1999;33(2):366–375. With permission from Elsevier.]

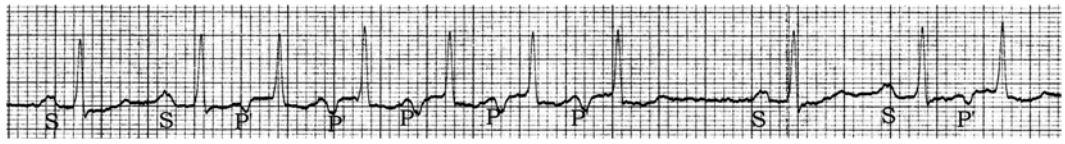


Fig. 6.6 Intermittent PJRT. S = sinus impulse; P′ = retrograde P-wave due to reciprocating PJRT impulse

circuit and vary the PJRT rate and pattern. In addition, because of the above noted variation in the electrophysiologic properties of the heart, along with the slowing of heart rate with increasing age, the arrhythmia may not be detected until later in childhood or even adulthood. Permanent junctional reciprocating tachycardia is often an asymptomatic tachycardia in an adult; however, unusual presentations have been described including presenting with complaints of syncope.

Despite the increase in tachycardia cycle length with age, PJRT may continue to be incessant, and, thus, may lead to tachycardia-mediated cardiomyopathy. The age-related decrease in both the heart rate and the persistence of tachycardia may mask the diagnosis of cardiomyopathy until later in life. Some patients may present with tachycardia-related symptoms or palpitations, as well as decreased exercise tolerance, fatigue, or syncope due to an associated decreased ventricular function. Patients with PJRT may also present with clinical signs of congestive heart failure or echocardiographic findings of impaired ventricular function compatible with cardiomyopathy. Limited series of patients with PJRT have documented diminished left ventricular function in as many as 75 % of patients. Signs and symptoms of congestive heart failure may be especially evident in infants with faster PJRT heart rates, but may be absent in the adult and go undiagnosed or misdiagnosed. The tachycardia will most likely slow as the patient gets older, and some patients have infrequent, spontaneous, and intermittent periods of remission. In some patients, the ventricular shortening fraction or ejection fraction measured by echocardiogram may improve, either spontaneously with time as the tachycardia cycle length lengthens with age, or the tachycardia becomes intermittent or goes away due to successful ablation of the accessory

pathway. However, multiple case reports document the benefit of ablation for control or abolition of tachycardia in patients who have incessant tachycardia-mediated myopathy. One report with a larger and older cohort of patients with PJRT, comprising 49 patients with a mean age of 43 years, noted that 16 % presented with tachycardia-induced cardiomyopathy, which was associated with a ventricular rate of about 146 ± 30 beats/min. In all cases, the myopathy regressed after successful ablation.

Electrophysiology

The tachycardia circuit traverses the normal AV nodal conduction system antegradely and returns to the atrium through a slowly conducting concealed pathway with decremental conduction properties (Fig. 6.1). The incessant nature of the tachycardia is probably due to its characteristically slow, retrograde, and unidirectional (no antegrade) conducting pathway, allowing the refractory period of the upstream cardiac tissue atria to recover so that they always present "an excitable gap" to the reciprocating impulse. The conduction velocity is typically faster and the antegrade effective refractory period of the AV node usually shorter than the conduction velocity and the retrograde effective refractory period of the accessory pathway, indicating less robust retrograde conduction. The introduction of a ventricular extrastimulus either from the right ventricular apex or the right ventricular summit during tachycardia while the His bundle is refractory, may advance, delay, or not affect the next recorded atrial electrogram and may or may not reset the tachycardia. A foreshortening of the atrial electrogram interval or termination of the tachycardia, even for only one beat, following the premature ventricular extrastimulus, strongly suggests the presence of an accessory pathway, and a delay in the next recorded atrial electrogram confirms that the slowly conducting retrograde accessory pathway is crucial to support the reentrant circuit during tachycardia. Rarely, PJRT may coexist with pre-excitation, as well as other concealed accessory pathways. In patients ≥10 years of age with shorter tachycardia cycle lengths, retrograde conduction through the accessory pathway is significantly faster in the paroxysmal form of PJRT as compared to the persistent form of PJRT.

Treatment

PJRT is often resistant to medical therapy, even with the use of one or multiple antiarrhythmic medications. A few case reports indicate limited efficacy of amiodarone therapy in patients with PJRT; one study reported that control of the incessant nature of the tachycardia was primarily related to the effects of amiodarone on the AV node rather than the accessory pathway associated with PJRT. In another cohort of patients aged 59 ± 62 months, the tachycardia was variably controlled with combinations of antiarrhythmic agents. Because of relative risks in smaller patients, deferment of definitive treatment with transcatheter ablation may be delayed until the patient is older. On the other hand, radiofrequency ablation of the accessory pathway is clearly the treatment of choice when it is judged safe to do.

Electrophysiologic Mapping and Ablation

Electrophysiologic evaluation includes assessment of retrograde conduction. The differential diagnosis of long RP tachycardias includes PJRT, atypical atrioventricular nodal reentry tachycardia, and atrial tachycardia. Delivery of a ventricular extrastimulus while the His bundle is refractory can differentiate this tachycardia from the other forms of long R-P tachycardia. The extrastimulus may advance, delay or not have any effect on the next inscribed atrial electrogram. If the atrial electrogram is delayed, the diagnosis of PJRT is confirmed. If the atrial electrogram is advanced and the tachycardia is reset, the atrioventricular reentry tachycardia and atrial tachycardia are highly unlikely. During entrainment from the ventricle, the difference between

the post-pacing interval and tachycardia cycle length is shorter for patients with PJRT compared to those with atrioventricular reentry tachycardia. Ventriculo-atrial dissociation during tachycardia rules out PJRT. The slowly conducting accessory pathway of PJRT usually bridges the AV groove in the right posterior septal (inferior-septal) area where it can be mapped.

The most common site of the accessory pathway location was noted to be just superior to the coronary sinus ostium (53 %) in one series of 21 patients and right posterior septal (inferior-septal) in 25 of 32 and 28 of 37 in two other series (Fig. 6.7). Unusual locations for this pathway have been reported. The PJRT accessory pathway has been noted in the right lateral area, left posterior (inferior) and left posteroseptal (inferior-septal) regions, and even left anterior (superior) and left lateral locations. There is one case report of an epicardial location. Ablation of the earliest atrial activation during tachycardia is associated with successful ablation of the accessory pathway. Even though an accessory pathway potential is usually not noted in the target area, one case report of PJRT documents an accessory pathway potential recording at the site of successful ablation. Intuitively, it appears that ablation in smaller children might be more difficult, but there are reports of successful ablation in patients as young as infants and even pre-term neonates. With advances in technology, PJRT has been ablated successfully using remote magnetic catheter ablation techniques and non-fluoroscopic techniques. The presence of more than one pathway has also been reported with PJRT. There is one case report of antegrade conduction across the accessory pathway.

Because the pathway is usually located in the septal area, it is thought that the risk of AV block is not insignificant, especially if a midseptal pathway is present that is anatomically closer to the normal atrioventricular node and His bundle. In such cases, one might consider the option of cryoablation. Although the success of radiofrequency ablation (Fig. 6.8) of the PJRT accessory pathway has been well documented, recurrent pathway conduction is well known. In such patients, repeat electrophysiologic study with ablation is usually successful.

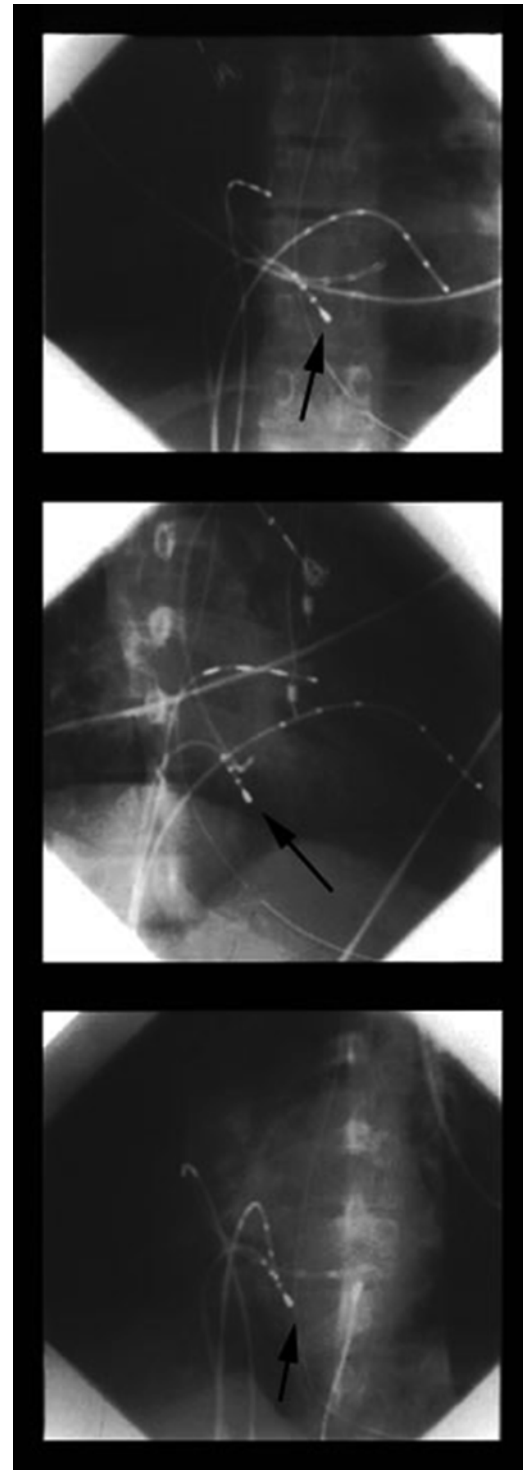


Fig. 6.7 *Top*: Posterior-anterior; *Middle*: Right anterior oblique; *Bottom*: Left anterior oblique radiographs during an electrophysiology study and radiofrequency ablation in a patient with PJRT. *Note*: the large electrode-tipped catheter arrow with the tip placed in the right infero septal area

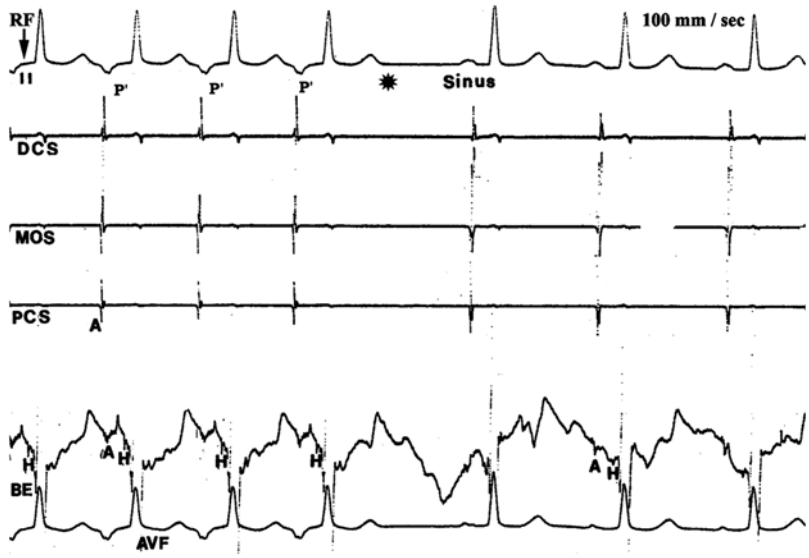


Fig. 6.8 Shortly after radiofrequency energy is started RF *arrow*, the PJRT is terminated by interruption of the retrograde pathway, indicated by absence asterisk of the retrograde P-wave P′

Reviewing a number of reported series, radiofrequency catheter ablation appears highly effective and safe and should be considered as the treatment of first choice in children and adult patients with PJRT. In infants, the risks and benefits of transcatheter ablation should be carefully weighed and the decision should be tailored to the specific needs of the patient.

Follow-up

It appears that children and young adults do well after ablation of the accessory pathway that supports PJRT. Several cohorts document safety and successful ablation with resolution of tachycardia-induced cardiomyopathy. In addition, in a study of older patients with a mean age of 42 years, 23 of 24 patients underwent radiofrequency catheter ablation. One of these patient's accessory pathways was not ablated because it was in the mid-septal area. In patients where there was myocardial dysfunction, ablation resulted in improvement of myocardial function and in some cases even normalization, suggesting that even at older ages, ablation may support an improvement in myocardial function. In older patients, if myocardial dysfunction is present post-ablation monitoring is advised due to possible increased proarrhythmia effects after ablative therapy.

Conclusions

Persistent junctional reciprocating tachycardia is an arrhythmia that usually presents in infancy or childhood but may not be recognized until adulthood. In older patients, the heart rate may not be sufficiently fast to result in enough symptoms to provoke further examination or evaluation by a physician. Age-related changes in both the rate and the intermittent nature of the tachycardia may mask the diagnosis. Thus, the diagnosis may be delayed until tachycardia-related symptoms or palpitations become more apparent. Presentation with heart failure is more common in younger patients. Since the heart rates associated with PJRT will most likely slow with age, radiofrequency ablation may be deferred in small children with this tachycardia. Because the PJRT has a possible spontaneous or intermittent resolution, as well as variable expression of impaired ventricular function, definitive therapy, whether radiofrequency current or cryotherapy, may be

delayed in small patients (≤15 kg). On the other hand, since ablation is effective and can be delivered safely, it is the preferred strategy for management of this arrhythmia.

Suggested Reading

Aguinaga L, Primo J, Anguera I, et al. Long-term follow-up in patients with the permanent form of junctional reciprocating tachycardia treated with radiofrequency ablation. Pacing Clin Electrophysiol. 1998;21:2073–8.

Ali H, Vitali-Serdoz L, Ferrero P, Pittalis M, Belotti G, Cappato R. An unusual case of permanent junctional reciprocating tachycardia: Successful ablation at the mitral annulus-aorta junction. J Interv Card Electrophysiol. 2008;23:213–7.

Amara W, Monsel F. Permanent junctional reciprocating tachycardia: a rare but curable form of tachycardia. Ann Cardiol Angeiol. 2013;62:361–3.

Amasyali B, Kose S, Aytemir K, Kilic A, Kursaklioglu H, Isik E. A permanent junctional reciprocating tachycardia with an atypically located accessory pathway successfully ablated from within the middle cardiac vein. Heart Vessels. 2006;21:188–91.

Arribas Ynsaurriaga F, Lopez Gil M, Ruiz Campa R, Gutierrez Larraya F, Merino Batres G, Garcia-Cosio Mir F. The curative treatment of incessant atrioventricular tachycardia by radiofrequency ablation. Rev Esp Cardiol. 1993;46:765–9.

Balaji S, Gillette PC, Case CL. Successful radiofrequency ablation of permanent junctional reciprocating tachycardia in an 18-month-old child. Am Heart J. 1994;127:1420–1.

Belhassen B, Glick A, Laniado S. Comparative clinical and electrophysiologic effects of adenosine triphosphate and verapamil on paroxysmal reciprocating junctional tachycardia. Circulation. 1988;77:795–805.

Benito Bartolome F, Fernandez-Bernal CS, Moreno Granado F. Radiofrequency catheter ablation in permanent atrioventricular junctional reciprocating tachycardia in children. Rev Esp Cardiol. 1996;49:48–55.

Bensler JM, Frank CM, Razavi M, et al. Tachycardia-mediated cardiomyopathy and the permanent form of junctional reciprocating tachycardia. Tex Heart Inst J. 2010;37:695–8.

Blomstrom-Lundqvist C, Scheinman MM, Aliot EM, et al. ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias—executive summary. A report of the American college of cardiology/American heart association task force on practice guidelines and the European society of cardiology committee for practice guidelines writing committee to develop guidelines for the management of patients with supraventricular arrhythmias developed in collaboration with NASPE-Heart Rhythm Society. J Am Coll Cardiol. 2003;42:1493–531.

Celiker A, Kafali G, Karagoz T, Ceviz N, Ozer S. The results of electrophysiological study and radiofrequency catheter ablation in pediatric patients with tachyarrhythmia. Turkish J Pediatr. 2003;45:209–16.

Chien WW, Cohen TJ, Lee MA, et al. Electrophysiological findings and long-term follow-up of patients with the permanent form of junctional reciprocating tachycardia treated by catheter ablation. Circulation. 1992;85:1329–36.

Collins KK, Schaffer MS. Use of cryoablation for treatment of tachyarrhythmias in 2010: survey of current practices of pediatric electrophysiologists. Pacing Clin Electrophysiol. 2011;34:304–8.

Coumel P. Junctional reciprocating tachycardias. The permanent and paroxysmal forms of A-V nodal reciprocating tachycardias. J Electrocardiol. 1975;8:79–90.

Coumel PCC, Fabiato A, et al. Tachycardie permanent par rhythm reciproque. Arch Mal Coeur Vaiss. 1967;60:1830–64.

Critelli G. Permanent junctional reciprocating tachycardia. Pacing Clin Electrophysiol. 1996;19:256–7.

Critelli G. Recognizing and managing permanent junctional reciprocating tachycardia in the catheter ablation era. J Cardiovasc Electrophysiol. 1997;8:226–36.

Critelli G, Gallagher JJ, Monda V, Coltorti F, Scherillo M, Rossi L. Anatomic and electrophysiologic substrate of the permanent form of junctional reciprocating tachycardia. J Am Coll Cardiol. 1984;4:601–10.

Critelli G, Gallagher JJ, Perticone F, Monda V, Scherillo M, Condorelli M. Transvenous catheter ablation of the accessory atrioventricular pathway in the permanent form of junctional reciprocating tachycardia. Am J Cardiol. 1985a;55:1639–41.

Critelli G, Gallagher JJ, Monda V, Scherillo M, Condorelli M. Catheter ablation of accessory pathway in the permanent form of junctional reciprocating tachycardia. Arch Mal Coeur Vaiss. 1985b;78:49–55.

D'Alto M, Russo MG, Paladini D, et al. The challenge of fetal dysrhythmias: echocardiographic diagnosis and clinical management. J Cardiovasc Med. 2008;9:153–60.

Dorostkar PC, Silka MJ, Morady F, Dick II M. Clinical course of persistent junctional reciprocating tachycardia. J Am Coll Cardiol. 1999;33:366–75.

Drago F, Silvetti MS, Mazza A, et al. Permanent junctional reciprocating tachycardia in infants and children: effectiveness of medical and non-medical treatment. Ital Heart J. 2001;2:456–61.

Elbaz M, Fourcade J, Carrie D, et al. Atrial insertion of accessory pathways in permanent reciprocating junctional tachycardia. Arch Mal Coeur Vaiss. 1995;88:1399–405.

Femenia F, Sarquella-Brugada G, Brugada J. Single-catheter radiofrequency ablation of a permanent junctional reciprocating tachycardia in a premature neonate. Cardiol Young. 2012;22:606–9.

Fouron JC, Fournier A, Proulx F, et al. Management of fetal tachyarrhythmia based on superior vena cava/aorta Doppler flow recordings. Heart (British Cardiac Soc). 2003;89:1211–6.

Gaita F, Haissaguerre M, Giustetto C, et al. Catheter ablation of permanent junctional reciprocating tachycardia with radiofrequency current. J Am Coll Cardiol. 1995;25:648–54.

Giani P, Maggioni AP, Volpi A, et al. Blood levels and electrophysiological effects of intravenous amiodarone in patients with junctional reciprocating tachycardia. Preliminary observations. Acta Cardiol. 1984;39:9–17.

Grimm W, Hoffmann J, Menz V, Maisch B. Transient QT prolongation with torsades de pointes tachycardia after ablation of permanent junctional reciprocating tachycardia. J Cardiovasc Electrophysiol. 1999;10:1631–5.

Guarnieri T, Sealy WC, German LD, Gallagher JJ. Utilization of an accessory pathway as the anterograde limb during the permanent form of junctional reciprocating tachycardia. Am J Cardiol. 1984;53: 365–8.

Ho RT, Frisch DR, Pavri BB, Levi SA, Greenspon AJ. Electrophysiological features differentiating the atypical atrioventricular node-dependent long RP supraventricular tachycardias. Circulation. 2013;6:597–605.

Isa R, Gonzalez R, Vergara I, Baeza M. Paroxysmal tachycardia in a patient with a permanent form of junctional reciprocating tachycardia. A case report. Rev Med Chil. 2004;132:608–13.

Jaeggi E, Fouron JC, Fournier A, van Doesburg N, Drblik SP, Proulx F. Ventriculo-atrial time interval measured on M mode echocardiography: a determining element in diagnosis, treatment, and prognosis of fetal supraventricular tachycardia. Heart (British Cardiac Soc). 1998;79:582–7.

Jaeggi E, Lau KC, Cooper SG. Successful radiofrequency ablation in an infant with drug-resistant permanent junctional reciprocating tachycardia. Cardiol Young. 1999;9:621–3.

Juneja R, Shah S, Naik N, Kothari SS, Saxena A, Talwar KK. Management of cardiomyopathy resulting from incessant supraventricular tachycardia in infants and children. Indian Heart J. 2002;54:176–80.

Kalbfleisch SJ, Rhodes TE. A rare case of permanent junctional reciprocating tachycardia ablated on the roof of the left atrium. J Cardiovasc Electrophysiol. 2013;24:464–7.

Klein GJ, Kostuk WJ, Ko P, Gulamhusein S. Permanent junctional reciprocating tachycardia in an asymptomatic adult: further evidence for an accessory ventriculoatrial nodal structure. Am Heart J. 1981;102:282–6.

Kose S, Iyisoy A, Barcin C. A permanent junctional reciprocating tachycardia with atypical location, treated with radiofrequency catheter ablation. Acta Cardiol. 2002;57:371–5.

Kose S, Amasyali B, Kursaklioglu H, Kilic A, Isik E. Permanent junctional reciprocating tachycardia: an unusual presentation. Int J Clin Pract. 2009;63:518–21.

Kozluk E, Gawrysiak M, Piatkowska A, et al. Radiofrequency ablation without the use of fluoroscopy—in what kind of patients is it feasible? Arch Med Sci. 2013;9:821–5.

Kusano KF, Morita H, Fujimoto Y, Hirose E, Ohe T. Catheter ablation of an epicardial accessory pathway via the middle cardiac vein guided by monophasic action potential recordings. Europace. 2001;3:164–7.

Lindinger A, Heisel A, von Bernuth G, et al. Permanent junctional re-entry tachycardia. A multicentre long-term follow-up study in infants, children and young adults. Eur Heart J. 1998;19:936–42.

Malcic I, Buljevic B, Kaltenbrunner W, Jelasic D, Mustapic Z. Permanent junctional reciprocating tachycardia PJRT and dilated cardiomyopathy. Lijec Vjesn. 2007;129:66–9.

Maurier F, Delisle G, Guay M. Paroxysmal junctional reciprocal tachycardia and fetoplacental anasarca. Arch Mal Coeur Vaiss. 1985;78:275–8.

McGuire MA, Lau KC, Davis LM, Knight P, Uther JB, Ross DL. Permanent junctional reciprocating tachycardia misdiagnosed as 'cardiomyopathy'. Aust N Z J Med. 1991;21:239–41.

Medeiros CM, Lucchese FA. Permanent form of junctional reciprocating tachycardia with only even-numbered beats. J Electrocardiol. 1989;22:249–56.

Meiltz A, Weber R, Halimi F, et al. Permanent form of junctional reciprocating tachycardia in adults: peculiar features and results of radiofrequency catheter ablation. Europace. 2006;8:21–8.

Menafoglio A, Schlapfer J, Kappenberger L, Fromer M. Permanent junctional reciprocating tachycardia: a little-known clinical entity curable with radiofrequency ablation. Schweiz Med Wochenschr. 1995;125:1980–8.

Montenero AS, Drago F, Crea F, et al. Transcatheter radiofrequency ablation in supraventricular tachycardia in children: immediate results and mid-term follow-up. G Ital Cardiol. 1996;26:31–40.

Oudijk MA, Stoutenbeek P, Sreeram N, Visser GH, Meijboom EJ. Persistent junctional reciprocating tachycardia in the fetus. J Matern Fetal Neonatal Med. 2003;13:191–6.

Perticone F, Marsico SA. Familial case of permanent form of junctional reciprocating tachycardia: possible role of the HLA system. Clin Cardiol. 1988;11:345–8.

Pflaumer A, Hessling G, Luik A, Wu J, Zrenner B. Remote magnetic catheter mapping and ablation of permanent junctional reciprocating tachycardia in a seven-year-old child. J Cardiovasc Electrophysiol. 2007;18:882–5.

Rodriguez DA, Rosas F, Jumbo LA, Velasco VM. Permanent AV junction Coumel type reciprocal tachycardia. Arch Cardiol Mex. 2001;71:50–8.

Scaglione M, Caponi D, Riccardi R, et al. Accessory pathway potential recording in a case of permanent junctional reciprocating tachycardia with decremental conduction localized on the atrial site. Ital Heart J. 2001;2:147–51.

Schleich JM, Vaksmann G, Khanoyan P, Rey C, Dupuis C. Permanent junctional reciprocating tachycardia in children and adolescents. Efficacy of medical treatment. Arch Mal Coeur Vaiss. 1992;85:553–9.

Semizel E, Ayabakan C, Ceviz N, Celiker A. Permanent form of junctional reciprocating tachycardia and

tachycardia-induced cardiomyopathy treated by catheter ablation: a case report. Turkish J Pediatr. 2003;45:338–41.

Shih HT, Miles WM, Klein LS, Hubbard JE, Zipes DP. Multiple accessory pathways in the permanent form of junctional reciprocating tachycardia. Am J Cardiol. 1994;73:361–7.

Sternick EB, Gerken LM, God EG. Concealed accessory pathway with long conduction times and incremental properties: a case report. J Cardiovasc Electrophysiol. 2001;12:103–7.

Trigo C, Paixao A, da Silva MN, Kaku S. Permanent junctional reciprocating tachycardia: an incessant tachycardia in children. Rev Port Cardiol. 2003;22:767–74.

Vaksmann G, D'Hoinne C, Lucet V, et al. Permanent junctional reciprocating tachycardia in children: a multicentre study on clinical profile and outcome. Heart British Cardiac Soc. 2006;92:101–4.

Sinoatrial Reentrant Tachycardia: Inappropriate Sinus Tachycardia

7

Macdonald Dick II

Sinoatrial reentrant tachycardia (Figs. 7.1, 7.2, and 7.3), a rare form of supraventricular tachycardia in children, involves reentry in and around the sinoatrial node. It is postulated that the sinus impulse, as it emerges from the sinoatrial node, enters an area of slow conduction within the atrium. It then recycles through peri-sinoatrial nodal tissue to reenter the site of origin. Clinical criteria for establishing this diagnosis are outlined in Table 7.1. This form of supraventricular tachycardia accounts for considerably less than 1 % of SVT in children.

When considering the diagnosis of this tachycardia, one must exclude other physiologic or pathologic states that can cause a sustained acceleration of sinus rhythm. It is very unusual for the sinus rate to exceed 220 bpm under any physiologic or pathologic state; the maximal heart rate of an elite athlete is usually approximately 220 bpm under maximal sustained exercise. A good formula for the maximal attainable heart rate is: 208 bpm minus 0.7 times the subject's age.

Hyperthyroidism, febrile illnesses, and hypovolemic states can increase the heart rate (Fig. 7.3) above what the apparent metabolic needs of the patient are at the time. Hyperthyroidism may present with an accelerated sustained heart rate usually about 120 bpm in the absence of other signs or symptoms. Febrile illnesses or hypovolemic states rarely exceed the maximal heart rate appropriate for the patient's age.

Inappropriate sinus tachycardia, defined as a sinus tachycardia without discernible cause, is usually seen in anxious older children and adolescents who are experiencing increased stress in their lives. A 24-h ECG Holter monitor will uncover normal heart rate variability without the findings of abrupt onset or termination of a tachycardia. The postural orthostatic tachycardia syndrome (POTS) is a form of dysautonomic regulation resulting in an abrupt accelerated sinus rhythm when the person arises from the supine or sitting position to the standing position. It is a form of neurocardiogenic syncope (Chap. 16).

If an underlying condition is present, treatment is specific for that disorder. The sinoatrial reentrant tachycardia can be converted with either adenosine, intracardiac or transesophageal overdrive pacing or DC cardioversion. Chronic treatment is rarely necessary in children. Radiofrequency ablation has mixed results in children; although success has been reported in adults. It is often difficult to ablate the entire SA node and another focus within the node may emerge (Fig. 7.4).

Inappropriate sinus tachycardia (Fig. 7.5) and POTS can be addressed with beta blockade

M. Dick II, M.D. (✉)
Pediatric Cardiology, The University of Michigan Congenital Heart Center, Department of Pediatrics and Communicable Diseases, University of Michigan, Ann Arbor, MI, USA
e-mail: mdick@umich.edu

M. Dick, II (ed.), *Clinical Cardiac Electrophysiology in the Young*,
DOI 10.1007/978-1-4939-2739-5_7

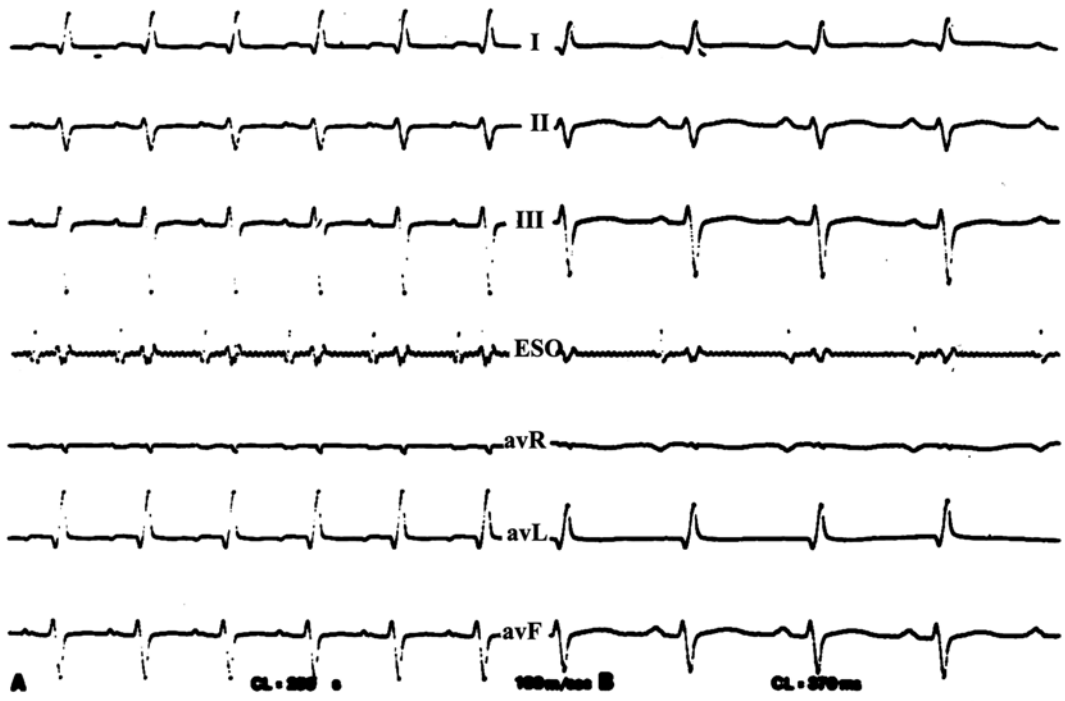


Fig. 7.1 Six (limb) lead electrocardiogram (*top* three and *bottom* three tracings) with an esophageal bipolar lead recording (middle tracing), all at paper speed of 100 mm/s, in a 2-month-old boy with tricuspid atresia. Panel A on the left demonstrates supraventricular tachycardia at 270 bpm. Panel B demonstrates sinus rhythm at 160 bpm. Note the PR interval and P-wave morphology and axis during the tachycardia are virtually identical to the PR and P-wave morphology and axis observed during sinus rhythm, suggesting the origin of the tachycardia to be around the sinoatrial (sinus) node

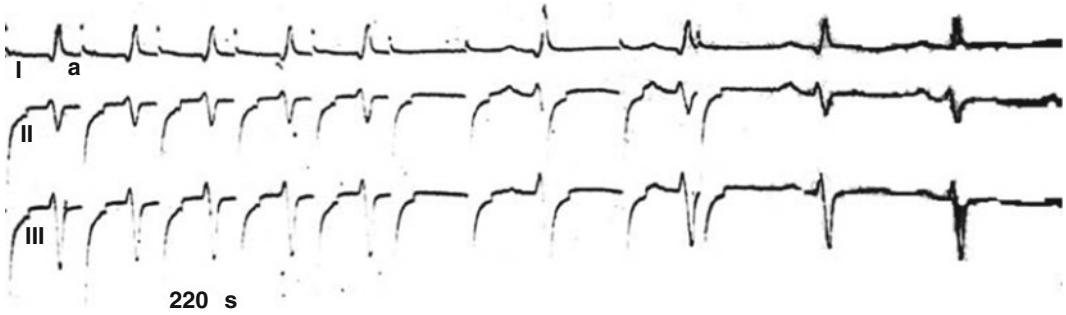


Fig. 7.2 Transesophageal atrial overdrive pacing (stimulus rate -s- at a pacing cycle length of 220 ms) in the patient from Fig. 7.1. Successful cardioversion to sinus rhythm is achieved, supporting the diagnosis of a reentrant mechanism in the region of the sinus node (inferred from Fig. 7.1), i.e., sinoatrial reentrant tachycardia

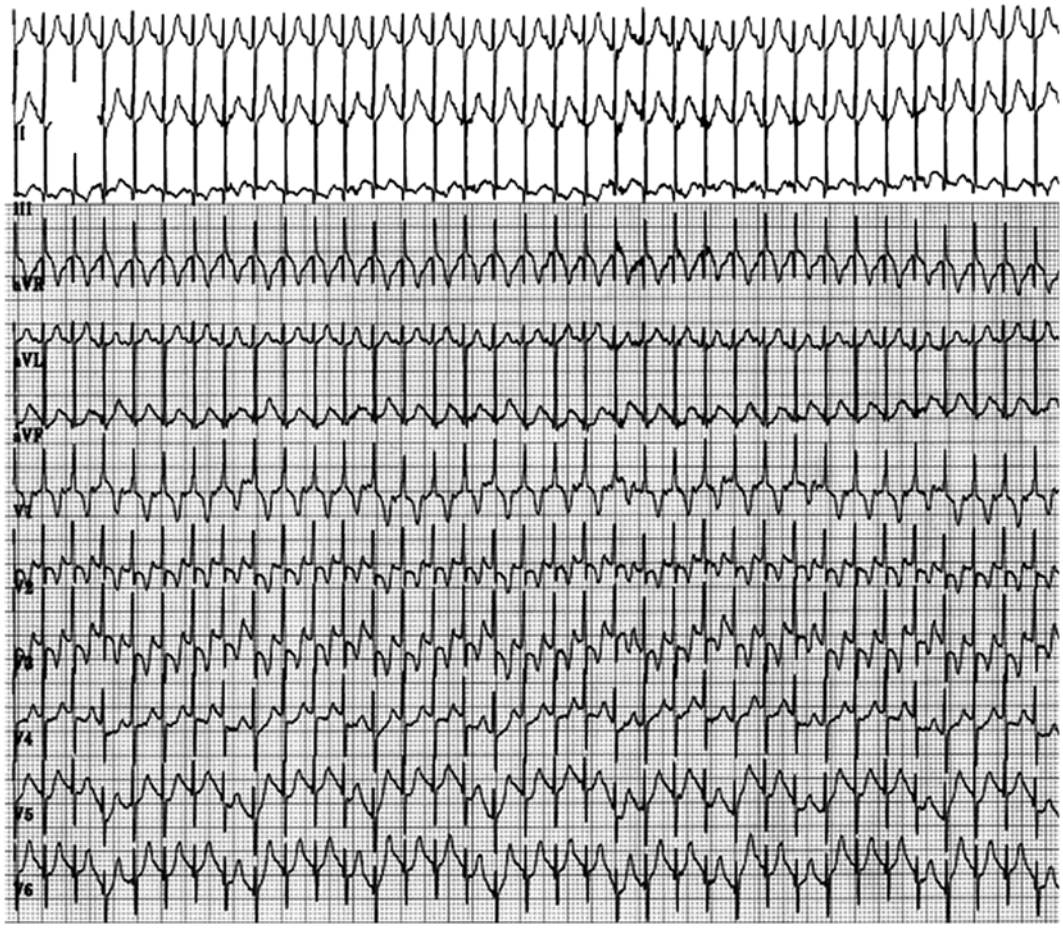


Fig. 7.3 Sinus tachycardia at 250 bpm in a 14-month-old girl with a urinary tract infection and fever of 40 °C

Table 7.1 Criteria for diagnosis of sinoatrial reentrant tachycardia

Sinus-like P-waves (positive P waves in limb leads 1, 2, 3, and negative P-wave in aVR) during the tachycardia
Initiation (and resetting and termination) by appropriately timed single premature atrial (or sinus) stimuli, over an echo zone either spontaneous or through programmed extrasimulation independent of atrioventricular nodal conduction slowing (Fig. 7.1)
Normal PR interval (identical to that during sinus rhythm) with a long RP interval during the tachycardia (Fig. 7.2)
Termination of the tachycardia by vagal maneuvers or adenosine
Exclusion of other mechanisms

if simple measures such as fluid and electrolyte replacement are unsuccessful. In contrast to sinoatrial node reentrant tachycardia, inappropriate sinus tachycardia does not respond to adenosine. Although often vexing to the patient, especially an adolescent, inappropriate sinus tachycardia appears to be benign. Ivabradine, a new medication—recently approved in the USA, acts on the I_f (funny) ion current, which is highly expressed in the sinoatrial node and serves to generate the cardiac impulse (pacemaker current). Ivabradine selectively inhibits the pacemaker I_f current in a dose-dependent manner. Ivabradine

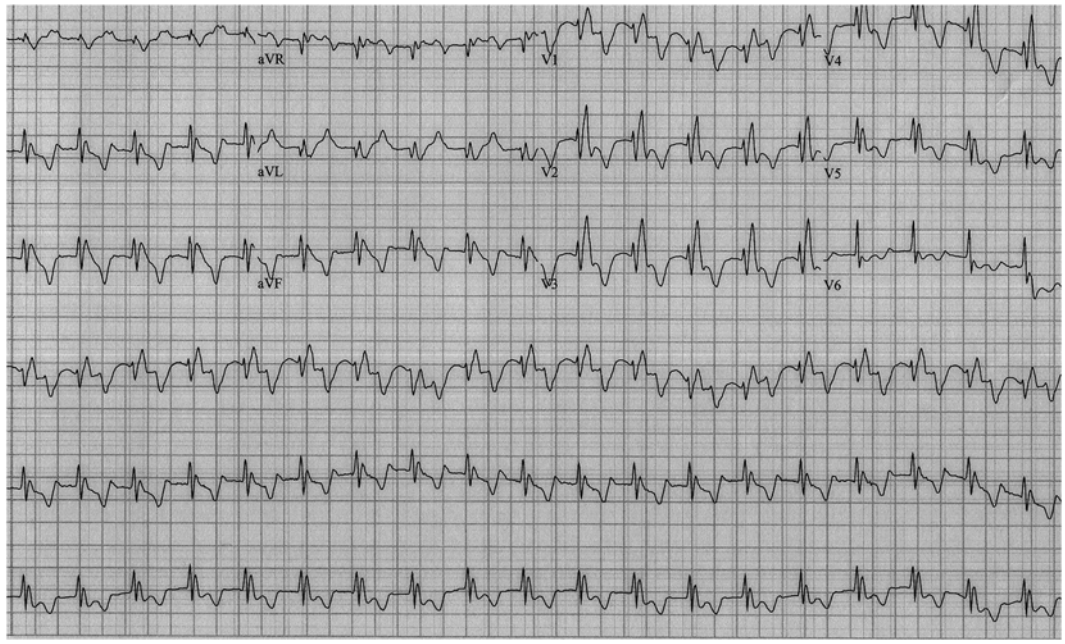


Fig. 7.4 12 lead tracing from a 28-year-old woman with Ebstein's anomaly of the tricuspid valve and sinoatrial reentrant tachycardia. She had both atrioventricular reentrant tachycardia and atrioventricular nodal reentry tachycardia—both successfully ablated with radiofrequency energy. She then developed sinoatrial reentrant tachycardia that could not be ablated by radiofrequency energy on several attempts. At repair of her tricuspid valve, surgical excision of the sinoatrial node and placement of a dual chamber pacemaker eliminated her tachycardia

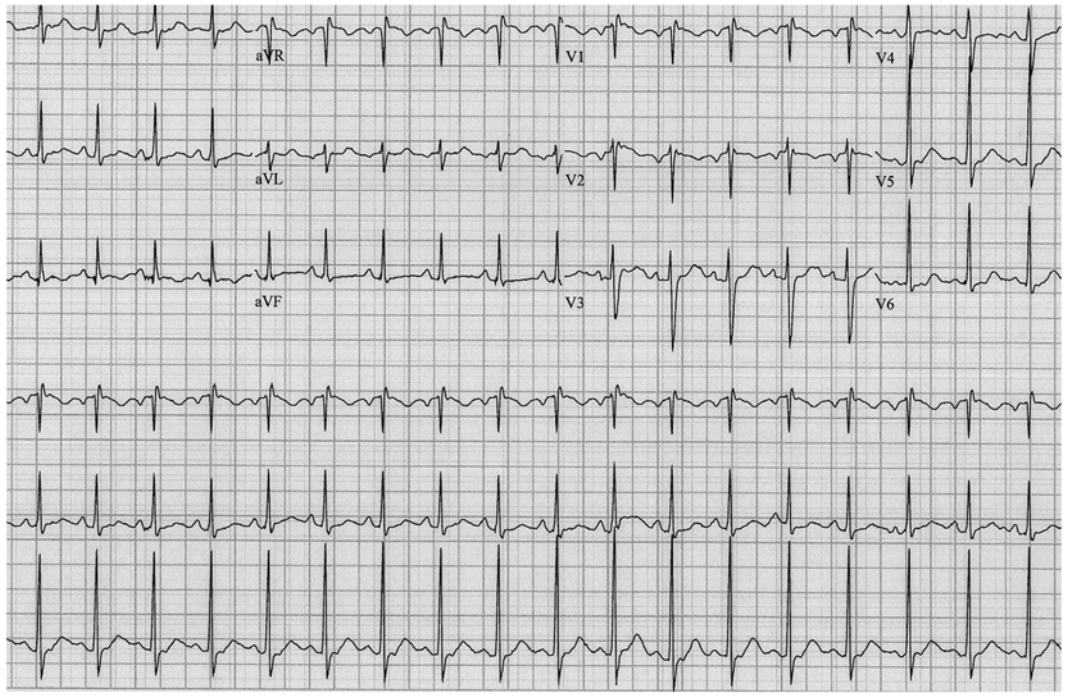


Fig. 7.5 12 lead EG tracing from a symptomatic 16-year-old girl with inappropriate sinus tachycardia. Note the normal P wave axis—in the frontal plane—inferior and to the left. Repeated ECGs and Holters demonstrated a near constant heart rate of 120–130 bpm when awake and 90–100 bpm when asleep

has been approved for the treatment of patients with angina pectoris who have contraindications to β-adrenoreceptor blockade in the European Union; its use is currently off-label for patients with inappropriate sinus tachycardia (Chap. 22).

In summary, both sinoatrial reentrant tachycardia and inappropriate sinus tachycardia are unusual findings in the young; their management must, therefore, be customized to the individual patient.

Suggested Reading

Blaufox AD, Numan M, Knick BJ, Saul JP. Sinoatrial node reentrant tachycardia in infants with congenital heart disease. Am J Cardiol. 2001;88:1050–4.

Fischer DJ, Gross DM, Garson Jr A. Rapid sinus tachycardia. Differentiation from supraventricular tachycardia. Am J Disease Children. 1983;137:164–6.

Heidbuchel H. Sinus node reentrant tachycardia versus ectopic atrial tachycardia: where lies the difference. Cardiac Arrhythmias Pacing Electrophysiol. 1988;201:3–9.

Kanjwal MY, Kosinski DJ, Grubb BP. Treatment of postural orthostatic tachycardia syndrome and inappropriate sinus tachycardia. Curr Cardiol Rep. 2003; 5:402–6.

Sanders Jr WE, Sorrentino RA, Greenfield RA, et al. Catheter ablation of sinoatrial node reentrant tachycardia. J Am Coll Cardiol. 1994;23:926–34.

Shen WK. Modification and ablation for inappropriate sinus tachycardia: current status. Card Electrophysiol Rev. 2002;6:349–55.

Still A-M, Huikuri HV, Airaksinen KE, et al. Impaired negative chronotropic response to adenosine in patients with inappropriate sinus tachycardia. J Cardiovasc Electrophysiol. 2002;13:557–62.

Atrial Flutter Intra-Atrial Reentrant Tachycardia

8

Nicholas Von Bergen, Ian H. Law, and Macdonald Dick II

Atrial flutter, a subtype of intra-atrial reentry tachycardia (IART) is characterized by the reentrant circuit progressing between the tricuspid valve (TV) and the inferior vena cava (IVC; Fig. 8.1) and a fixed atrial cycle length of 200 ms (300 atrial bpm); it is common in adults, especially those with heart disease. In contrast, atrial flutter in the infant with an atrial cycle length of 120–160 ms (atrial rate 300–400 bpm; Fig. 8.2) and incisional IART are far more common in the young. In the patient with surgically corrected or palliated congenital heart disease, incisional IART is an increasingly prevalent and important arrhythmia.

This chapter will focus on the diagnosis and management of both atrial flutter in the child and incisional IART in the patient following congenital heart disease surgery.

Background

Atrial flutter comprises less than 1 % of arrhythmias in children with a structurally normal heart; most are infants (Fig. 8.2). In infants, atrial flutter is commonly an isolated event with infrequent recurrence; some authors report a late association with other forms of SVT. On the other hand, only 6–7 % of older children with atrial flutter or IART have a structurally normal heart.

Mechanism of Atrial Flutter

Experimental animal studies and clinical observations have shown that in order for atrial flutter to develop, suitable substrates are required. Prerequisites include:

1. A corridor or isthmus bounded by structural barriers such as the tricuspid valve, the coronary sinus, the superior or inferior vena cava, or a "scar."
2. A functional change in the myocardium resulting in prolonged intra-atrial or inter-atrial conduction and increasing atrial refractoriness.

N. Von Bergen, M.D. (✉)
Department of Pediatrics, University of Wisconsin—Madison, 1675 Highland Ave., Madison, WI 53792, USA
e-mail: vonbergen@pediatrics.wisc.edu

I.H. Law, B.S.E., M.D.
Division of Cardiology, Department of Pediatrics, University of Iowa Children's Hospital, University of Iowa Carver College of Medicine, Iowa City, IA, USA

M. Dick II, M.D.
PPediatric Cardiology, The University of Michigan Congenital Heart Center, Department of Pediatrics and Communicable Diseases, University of Michigan, Ann Arbor, MI, USA

M. Dick, II (ed.), *Clinical Cardiac Electrophysiology in the Young*,
DOI 10.1007/978-1-4939-2739-5_8

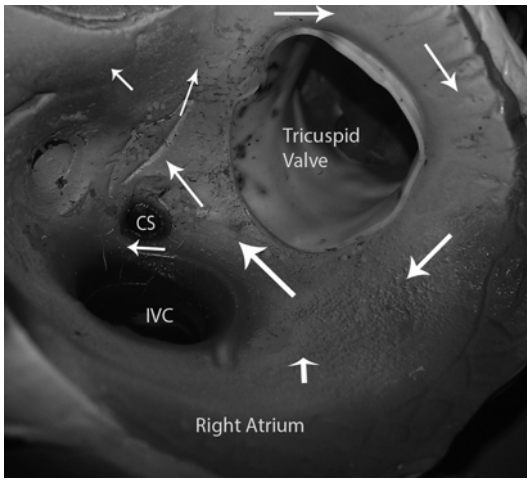


Fig. 8.1 The inner geometry of the right atrium showing the reentrant loop of a typical flutter circuit. Notice that the typical flutter circuit passes between the IVC and the TV passes in a counterclockwise loop around the TV. This mechanism results in the classic P-wave morphology as the circuit proceeds from low RA near the CS to depolarize the atrium, then reenter the IVC/TV isthmus

3. An eccentric premature depolarization allowing the extrasystole to enter and propagate around the structural barriers.

Functional barriers, such as the crista terminalis with its anisotropic properties, may play an important role in the initiation and maintenance of atrial flutter.

ECG Characteristics

Type I atrial flutter has characteristic inverted "saw tooth" P-waves in leads II, III, and AVF, implying inferior to superior atrial activation typically the reentrant loop consists of a counterclockwise rotation around the tricuspid valve through the cavo-tricuspid isthmus. The anatomic barriers are the tricuspid valve annulus, coronary sinus, inferior and superior vena cavae, and crista terminalis (Fig. 8.1). In infants, these rates are typically very fast, ranging from 350 to 500 bpm (Fig. 8.2). Atrial rates in older children and adults are usually around 300 bpm (range: 240–350 bpm). There is usually variable atrioventricular (AV) conduction yielding a pulse rate of near 150 bpm; in clinical practice, a fixed heart rate of 120–150 bpm strongly suggests the presence of atrial flutter with 2:1 AV block (Fig. 8.3). A second form, atypical atrial flutter, has positive P-waves in leads II, III, and AVF, and usually has slower atrial rates around 200 bpm. The upright P-waves imply superior to inferior atrial activation typically with a clockwise rotation around the tricuspid valve still passing through the cavo-tricuspid isthmus.

Treatment of Typical Atrial Flutter During an Event

There are several methods of treating this arrhythmia including observation, antiarrhythmic medications, atrial overdrive pacing, and DC cardioversion. For the treatment during an acute arrhythmia, the initial goal of management in the young is termination of the arrhythmia. Rate control is less often employed because of the infrequent recurrence in the child with a normal structural heart, the difficulty in slowing the ventricular rate with cardiac glycosides, beta receptor, or calcium channel blockers (Chap. 22) due to relatively rapid conduction in the young AV node, the desire to avoid anticoagulation in the young, the risk of a negative inotropic effect, especially in the very young, and the success of overdrive pacing or DC cardioversion.

In the newborn and infant, spontaneous conversion is common; however, if the arrhythmia lasts longer than 24 h or if there is clinical deterioration, either cardioversion or overdrive pacing is warranted. Because the atrial flutter is usually composed of a single highly organized reentrant circuit, minimal biphasic energy (0.5–1.0 J/kg or less) delivered through patches placed in the anterior/posterior position is typically all that is necessary.

Transesophageal atrial overdrive pacing (Fig. 8.4) offers the advantage of rapid termination with targeted electrical energy (i.e., to the atria not the entire myocardium). As the atrial flutter rates are often 400 bpm or greater in the newborn and infant, very rapid atrial pacing is required. Transesophageal pacing stimuli are delivered at rates 20–25 % faster than the flutter rate until the flutter circuit is entrained (Chap. 3). When both the orthodromic limb and the antidromic limb of the reentrant circuit are suf-

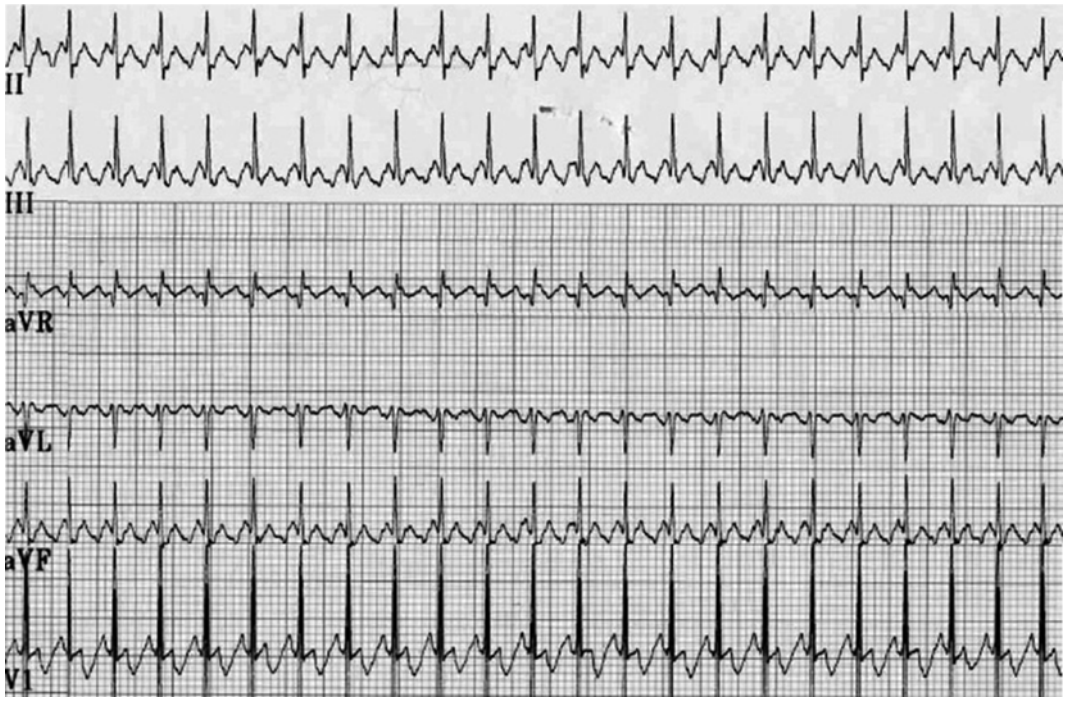


Fig. 8.2 A partial ECG of atrial flutter in an infant. Note the saw tooth appearance with an atrial cycle length of 160 ms and with the 2:1 A:V conduction

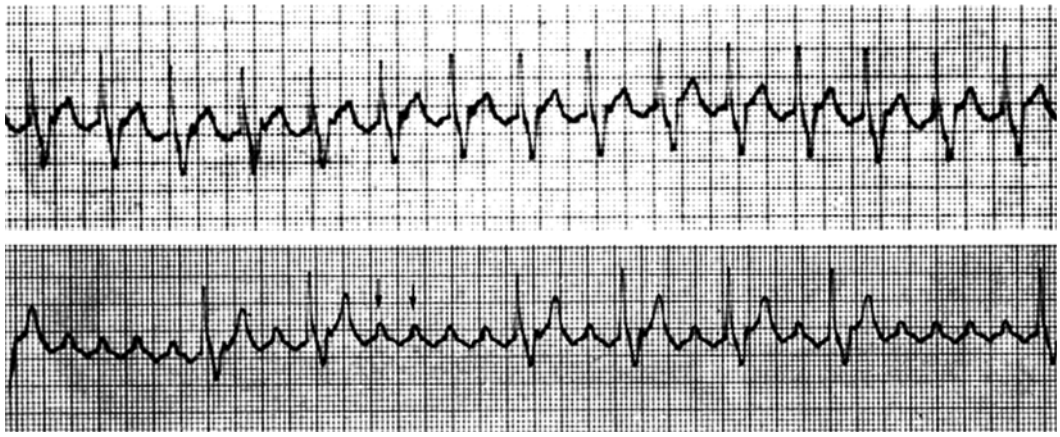


Fig. 8.3 Tracings from a 24-h Holter monitor in a 15-year-old boy with Ebstein's anomaly of the tricuspid valve. *Top tracing*: The fixed ventricular rate of 130 bpm strongly suggests atrial flutter with 2:1 conduction, which is confirmed in the lower tracing when greater AV block occurs and the flutter waves become more striking and clear (*arrows*). Notice the saw tooth appearance

ficiently engaged by the pacing impulse (wavefront) so as to collide and self-extinguish within the circuit, the pacing is terminated and sinus (or a slower atrial) rhythm will restart. These steps are repeated with faster pacing rates until there is either termination of the flutter or loss of atrial capture. Transesophageal atrial pacing requires higher pacing outputs about 10–15 mA at 4–6 ms pulse duration or greater.

Medication for chemical cardioversion may also be considered, and sotalol, ibutilide, and amiodarone have all been shown to be successful in

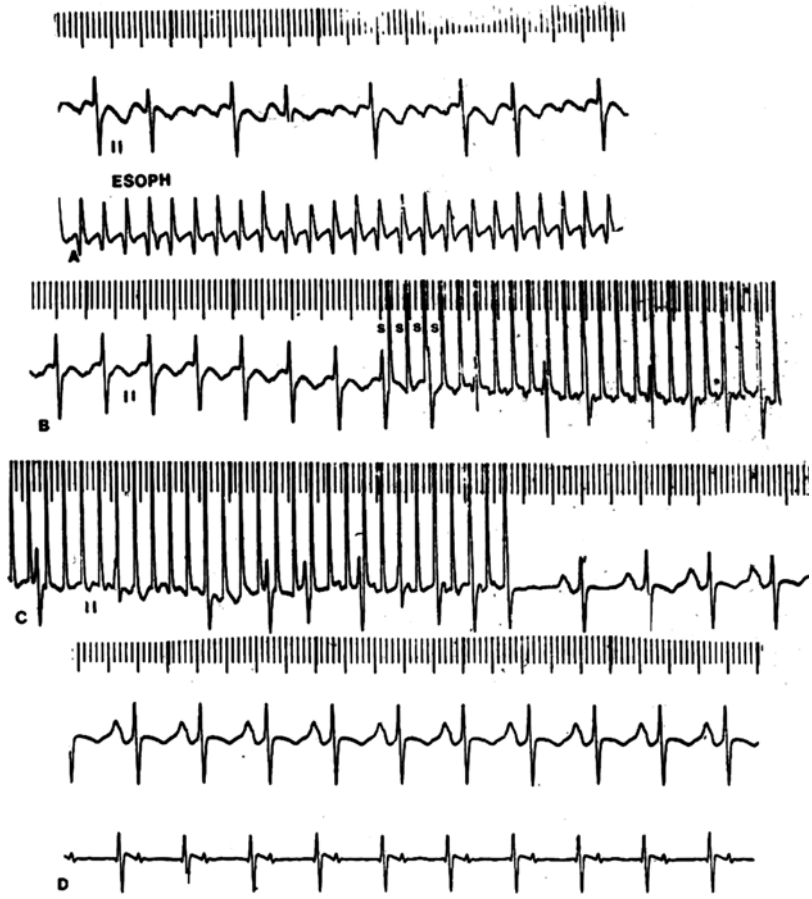


Fig. 8.4 Transesophageal overdrive pacing and conversion of Atrial Flutter (A) in a 12-year-old girl. The pacing cycle length is slightly shorter (B) than the tachycardia cycle length and engages both the orthodromic and antidromic limbs of the reentrant circuit (C) where the impulse traversing both limb collides and self-extinguishes, terminating the flutter followed by emergence of the sinus impulse (D)

acute conversion ≥60 % of the time when given as an infusion or a bolus in the acute. However, these patients must be carefully monitored as these treatments may be associated with an increased risk of ventricular arrhythmias during their delivery.

To Prevent Further Episodes of Atrial Flutter

Patients with a single episode of atrial flutter, especially if presenting as a neonate, often do not need long-term medical prophylaxis. If deciding to use prophylactic medications for arrhythmia control, beta-blockers, sotalol, propafenone, amiodarone, and dofetilide have shown some promise for long-term control of atrial flutter. For the older patient who has recurrence of atrial flutter and does not respond to pharmacological management, radiofrequency ablation is an option and has been shown in adult subjects to have a greater success (80 % vs. 50 %) than pharmacological management. In patients with repeated episodes of IART, anticoagulation may need to be considered.

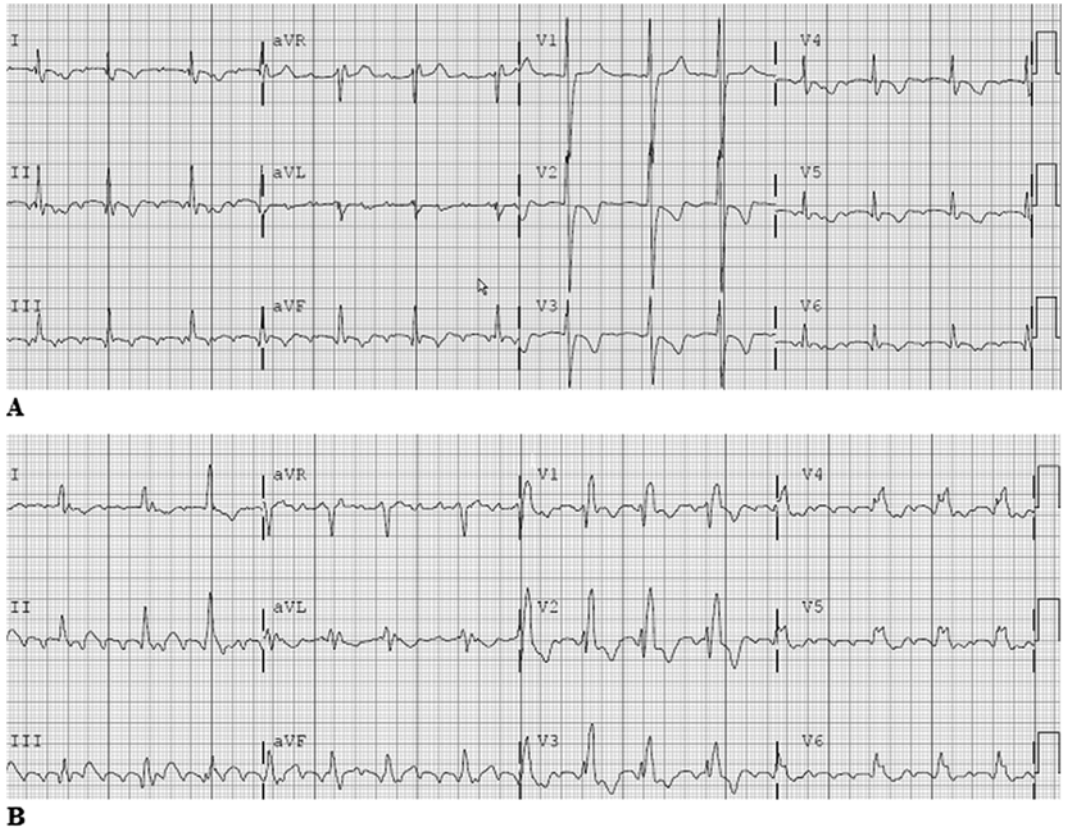


Fig. 8.5 A 12-Lead electrocardiogram in a young adult with L-transposition of the great arteries, Ebstein's anomaly with tricuspid valve replacement and intra-atrial tachycardia. Note the very small reentry P-waves, especially in the limb and lateral precordial leads. B 12-Lead electrocardiogram in a young adult with repaired Tetralogy of Fallot. This incisional IART was located near the atriotomy incision

Incisional Intra-Atrial Reentrant Tachycardia

Incidence

In contrast to typical atrial flutter, incisional intra-atrial reentrant tachycardia (IART; Fig. 8.5a, b) is an increasingly more prevalent arrhythmia in the young cardiac patient following heart surgery. The vast majority of young patients presenting with IART have heart disease (about 84 %), most of them following surgery. The incidence of incisional IART is related to both the underlying congenital heart defect and the type of surgical repair. In general, the more complex the defect and the surgery (number of incisions and suture lines within the atria), the higher is the incidence. However with the development and widespread success of the arterial switch operation, replacing the atrial switch operation, the incidence of IART in patients with transposition has markedly decreased.

A unique and increasingly prevalent group of patients is those who underwent single ventricle palliations (Fontan sequence). The incidence of incisional IART appears to increase with age and to be directly related to the age at operation, the type of operation (most prevalent in the direct atriopulmonary connection), and the presence of sinus node dysfunction. Thus, a substantial number of Fontan patients (16–50 %) may

develop incisional IART in their lifetime. Additionally, IART may be associated with an increased mortality, as one study of atrial flutter in the young; the congenital heart disease population had a mortality rate of 5 % in patients with medically controlled IART, and 20 % in medically uncontrolled patients.

ECG Characteristics of Incisional IART

In contrast to typical atrial flutter, incisional IART usually has a slower atrial rate—often less than 300 bpm (cycle length ≥200 ms). Atrial rates of 185–270 bpm (cycle length: 325–220 ms) are seen in Mustard patients and rates of 220–325 bpm (cycle length: 230–470 ms) in Fontan patients. The P-wave morphology is variable, often smaller and fractionated, and at times can be difficult to detect, particularly when evaluating on a few leads, typical with many event monitors. A multiple-lead ECG tracing is often necessary to detect the small P-waves, though a fixed ventricular rate of 100 to 150 bpm in patients following extensive atrial surgery or abnormality should suggest IART with 2:1 conduction to the ventricles. Furthermore, as the atrial rate slows, the possibility of 1:1 AV conduction increases, resulting in faster ventricular rates and an increased risk of hemodynamic compromise.

Etiology

The primary difference between the typical form of atrial flutter and incisional IART is the nature of the barriers around which the reentry impulse circulates. In contrast to typical atrial flutter, incisional IART may involve not only the anatomically fixed structural barriers but also incisions, suture lines, patches, and baffles within the atria, as well as areas of fibrosis. The atria of patients with heart disease are also often subjected to increased pressure and volume loads, resulting in progressive fibrosis and changes in the electrophysiological properties. Clinical intracardiac electrophysiologic studies have confirmed the vulnerability of patients for IART after the Senning, Mustard, and Fontan procedures. This liability is likely due surgically created atrial discontinuities; focal atrial scarring and conduction block associated with suture lines; atrial fibrosis and thickening caused by pericardial inflammation and abnormal wall stress; abnormal atrial size and anatomy; increased atrial refractoriness associated with sinus node dysfunction; and prolonged duration of atrial activation. Many of these abnormalities may even be present before any of their operations. A number of experimental animal studies have reinforced the critical importance of the natural anatomical barriers in typical atrial flutter and found that surgical incisions and suture lines could facilitate IART, especially the crista terminalis, as well as potentially prevent inducibility of IART.

Mustard or Senning Patients

A major vulnerable site for IART in Mustard or Senning patients is near the triangle of Koch (location of AV nodal reentry tachycardia) and the IVC to TV isthmus, both of which are often separated from the systemic venous drainage by the baffle so that some or all of the target triangle is not easily accessible (requiring trans-baffle approach to the target area). Thus, the critical isthmus may either be near the coronary sinus on the systemic venous side or near the tricuspid annulus on the pulmonary venous side or involve both sites. A second common site for IART in this population is the junction between the superior vena cava and systemic venous atrium (Fig. 8.6).

Fontan Patients

In post Fontan patients with IART, intra-atrial mapping studies have demonstrated several conduction corridors or isthmuses between the atriotomy incision and the crista terminalis, around the atrial septal defect patches or between the inferior vena cava and tricuspid valve (Fig. 8.7, Table 8.1).

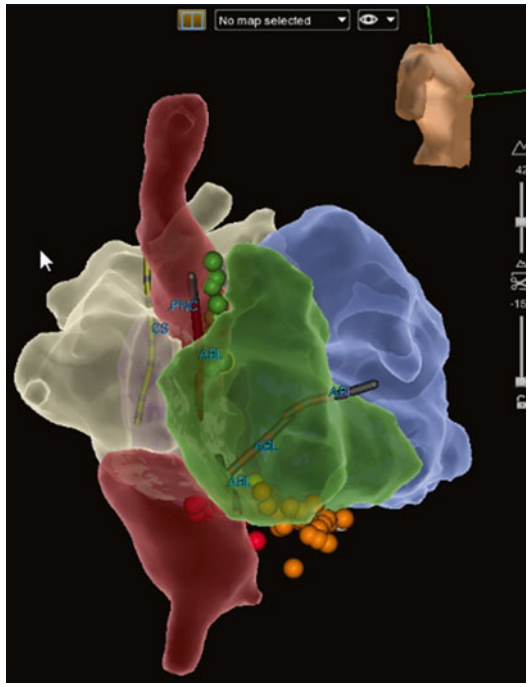


Fig. 8.6 A right lateral, slightly RAO 3-D map (St. Jude, Ensite Velocity) of an adult patient with D-Transposition of the Great Arteries who underwent a Mustard procedure as an infant. The systemic venous pathway (SVC and IVC baffle side) is displayed in red, the pulmonary venous pathway (pulmonary vein baffle side), in white; RV (*green*) and LV (*blue*). Two IART circuits were ablated, one on the pulmonary venous side across the TV/IVC isthmus (*red* and *orange* lesions markers), and a second in the SVC to atriotomy area (*green* lesion markers)

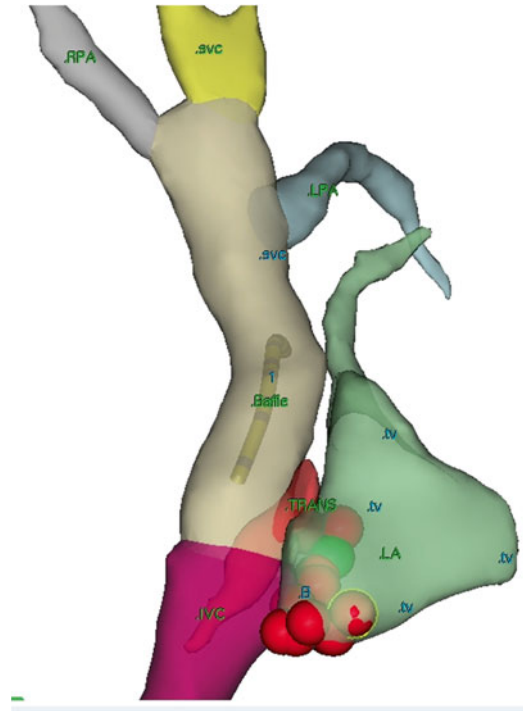


Fig. 8.7 An RAO view using 3-D mapping of a lateral tunnel Fontan with IART near the TV/IVC isthmus with successful ablation after a trans-baffle procedure. The SVC IVC and baffle are seen connecting to the *right* and *left* pulmonary arteries

Treatment of Incisional IART or IART in a Patient with Congenital Heart Disease

Observation

Treatment of IART is dependent on several factors including: associated heart disease, frequency and duration of episodes, associated hemodynamic compromise, patient/parental preference, and failure of previous management strategies. For patients who have had a single, well tolerated, self-limited episode of incisional IART, observation as the initial strategy after cardioversion or atrial overdrive pacing is an option. These patients are advised on the importance of early physician notification of recurrence as

Table 8.1 Types of congenital heart disease and their associated surgeries and common locations of IART

Congenital heart disease	Common locations for IART
D-TGA with Mustard or Senning	IVC and tricuspid valve isthmus—often on the pulmonary venous side SVC and systemic venous atrium junction
Fontan	Isthmuses between atriotomy incision and the crista terminalis Around the atrial septal defect patches IVC and tricuspid valve isthmus Combination of all the above
ASD (and procedures with ASD repair)	IVC and tricuspid valve isthmus Atriotomy site ASD patch

sustained tachycardia increases the risk of both hemodynamic compromise and thrombus formation (anticoagulation discussed below).

Medical Management

As incisional IART tends to be a progressive disease, most patients will require antiarrhythmic therapy at some point (Chap. 22) and anticoagulation will need to be considered. Unfortunately, this arrhythmia can be difficult to control, and, not uncommonly, as many as 2–3 antiarrhythmic drugs per patient may yield only suboptimal results. In patients who have infrequent episodes of IART or have had significant hemodynamic compromise due to rapid AV conduction, rate control should be considered in addition to antiplatelet or anticoagulation therapy. Beta-blocker and calcium channel blockers (diltiazem) are first-line agents. Beta-blockers may suppress sinus node function in an at-risk population, as well as possibly depressing ventricular function. Calcium channel blockers can exert a negative inotropic effect, but usually are well tolerated.

For patients with frequent or poorly tolerated episodes of IART, both rate and rhythm control is desirable. The mainstays of rhythm control agents include sodium channel blockers and potassium channel blockers as individual agents or in combination. In part, the antiarrhythmic mechanism of action of sodium channel blockers is to slow myocardial conduction velocity. While this can help in preventing reentrant atrial arrhythmias, it can also slow an IART, converting what once was a hemodynamically well-tolerated rapid atrial tachycardia with 2:1 AV conduction to a slower reentrant tachycardia with 1:1 AV conduction and a paradoxically faster ventricular rate. If a sodium channel blocker is used, consideration should be given to the addition of a rate control agent to protect against this adverse effect.

Potassium channel blockers, sotalol and amiodarone, and more recently dofetilide, which prolong the myocardial effective refractory period, are valuable agents in preventing IART. Sotalol and amiodarone also have the beneficial effect of slowing AV conduction. Nevertheless, the side effect profile of these mediations should be considered as dofetilide and sotalol have a higher risk of proarrhythmia while amiodarone has a greater risk of systemic adverse reactions (Chap. 22).

Anticoagulation

While the risk of thrombus formation is unknown, prophylactic anti-platelet or warfarin therapy is recommended for those with frequent or incessant IART, and aspirin should be considered in many patients with IART, even with only infrequent events. For patients with frequent and/or poorly tolerated episodes of IART anticoagulation therapy should also be considered for at least 3–6 months before considering weaning from the anticoagulation if arrhythmia suppression is obtained. In those with an acute episode of IART, the risk of thrombus formation increases with tachycardia duration. Therefore, cardioversion should be considered within the first 24 h if not anticoagulated. An echocardiogram, often transesophageal, is useful to exclude a preexisting thrombus before cardioversion. If one is seen, warfarin therapy should be instituted for at least 3 weeks prior to cardioversion if the clinical state permits.

Electrophysiology Study

Goals for electrophysiologic evaluation include:

1. Evaluation of possible arrhythmia-related symptoms (palpitations, tachycardia, and syncope) in patients with repaired or palliated congenital heart disease.
2. Evaluation of antiarrhythmic therapy.
3. Mapping of intra-atrial reentrant circuits followed by transcatheter ablation.

There are a number of challenges to consider during an EP study, especially in those with prior cardiac surgery. These include that the clinical IART may not be induced in the laboratory; the tachycardia induced may not be the clinical

tachycardia; multiple reentry circuits (and tachycardias) may be induced in the catheterization laboratory; and the clinical IART may exhibit different cycle lengths. Therefore, careful sorting out of the clinical IART from nonclinical laboratory artifacts is essential. A full understanding of the patient's specific cardiac malformation and surgical interventions is imperative. All surgical notes should be reviewed for a detailed description of the atrial anatomy, as well as a precise description of the surgical intervention. Attention needs to be directed toward location of atriotomy incisions, atrial septal defect patches, bypass cannula insertion sites, atrial appendage anatomy, intra-atrial baffle placement, and coronary sinus position in relation to the intra-atrial baffle. A heart catheterization with appropriate contrast injections can define anatomic (and hemodynamic) features absent from the surgical record such as the configuration of intra-atrial baffles, the drainage of the coronary sinus, and the size and hemodynamic load of the atria. On occasion, patients will present to the electrophysiology laboratory in IART, permitting immediate evaluation and mapping of the clinical arrhythmia.

Ablation of typical atrial flutter requires electrophysiologic stimulation and recording systems and fluoroscopy or 3-D computer-assisted mapping-navigation systems along with the several different ablation energy sources. Mapping can be done with a multi-pole (duo-decapolar) catheter placed around the tricuspid valve (fluoroscopy), or with the use of 3-D mapping equipment. Both these techniques allow the operator to determine the course and rotation [counter clockwise looking from the right ventricular apex (the usual rotation) or clockwise] of the flutter circuit. In addition, a multi-polar catheter in the coronary sinus (to monitor left atrial activation) or occasionally a temporary active fixation lead can serve as a stable electrical reference and pacing site. A His bundle catheter is usually not necessary, although it may be helpful in demarcating the area of the AV node. Often in patients with complex anatomy, the His bundle as well as the ventricular chambers may not be accessible. As the anatomy becomes more complex, the use of three-dimensional mapping and advanced computer-based navigation systems as well as other multi-pole catheters placed between the superior vena cava and inferior vena cava in the abnormal atria is useful to delineating the reentry circuits and delivering ablation.

In addition, study and ablation of incisional IART usually require more time, personnel, as well as deeper lesion formation with a larger or irrigated tip catheter. Nonetheless, radiofrequency ablation of both the typical form of atrial flutter and incisional IART utilizes the same principle: creation of a line of block across a critical isthmus of the reentrant circuit.

When the patients presents in sinus rhythm, a basic electrophysiology study is performed, including assessment of sinus node and AV node function (Chap. 3). This information can prove valuable when considering antiarrhythmic therapy or determining whether an IART is capable of rapid conduction through the AV node. The atrial anatomy can also be determined by endocardial mapping, paying close attention to anatomical landmarks such as the vena cavae, coronary sinus, atriotomy scars, anastomotic sites, the His bundle area, and baffles or patches. In patients with congenital heart disease the sinus node and AV node may be markedly displaced and therefore at risk of inadvertent injury. Identification of these structures is essential before ablation.

Intra-atrial reentrant tachycardia is induced by either incrementally more rapid atrial pacing or programmed atrial extra-stimulation with 1–3 extrastimuli. Isoproterenol continuous infusion may be required (0.02–0.06 mcg/kg/min). Upon induction of the tachycardia, a brief hemodynamic assessment should be performed to assure adequate blood pressure and perfusion. When hypotension is encountered, intravenous phenylephrine can be helpful in increasing the blood pressure and reflexively slowing conduction through the AV node. Discontinuation of isoproterenol or additional of beta-blocking may also be used to prevent rapid AV conduction. The induced tachycardia can be confirmed to be a truly IART by verifying that the AV node and ventricle are not critical to the reentrant circuit, such as observing variable AV conduction, by

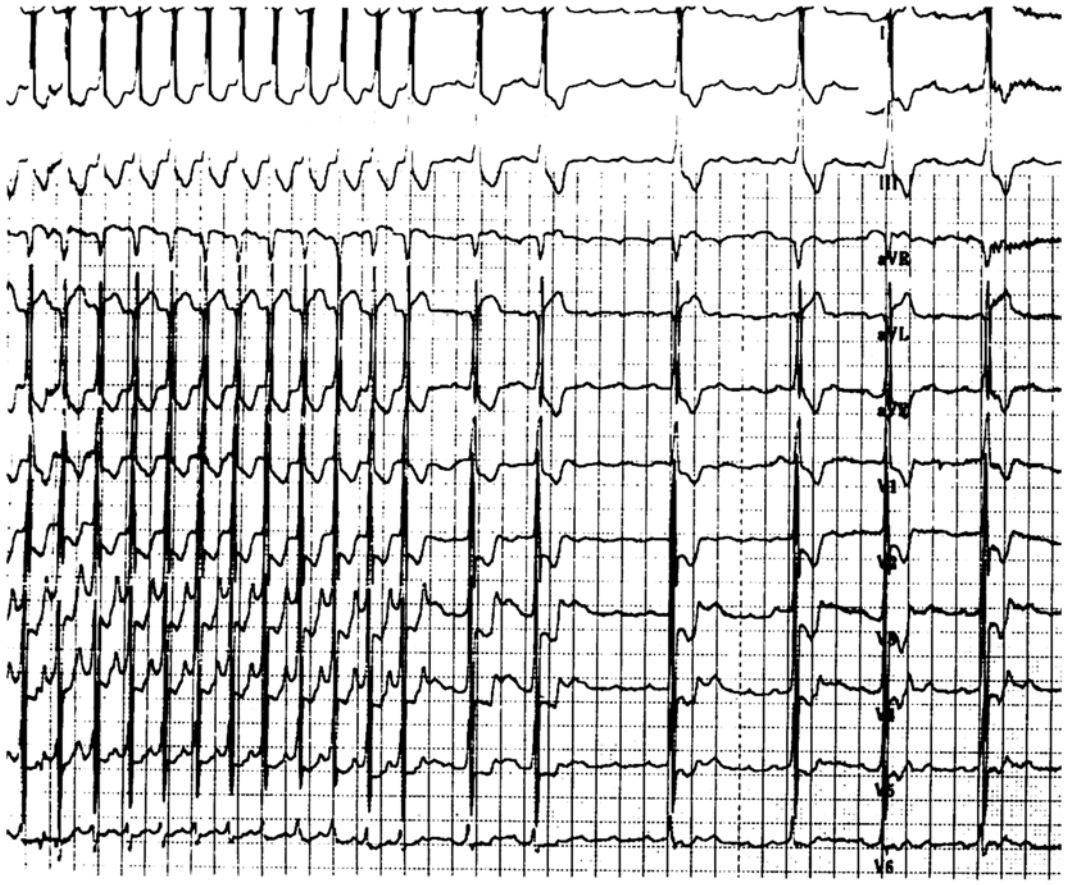


Fig. 8.8 12-Lead electrocardiogram rhythm strip obtained on a 6-year-old Fontan patient during intra-atrial reentrant tachycardia. During 1:1 AV conduction the P-waves are difficult to visualize. Following adenosine infusion, the small, low amplitude P-waves are seen

entraining the tachycardia (see entrainment mapping below) with atrial pacing or by confirming persistence of the arrhythmia with AV block using adenosine (Fig. 8.8).

Entrainment Mapping

Entrainment mapping (Chap. 3) is performed by pacing (through the mapping catheter distal electrode pair) at 10–30 ms less than the spontaneous IART cycle length for at least 10 beats at twice the diastolic threshold and confirming atrial capture (change in the atrial cycle length to the pacing cycle length). Pacing too rapidly may terminate the tachycardia or initiate a different reentrant tachycardia. Pacing too slowly may not achieve constant capture. Upon consistent capture, the presence of either manifest or concealed entrainment is determined. Manifest entrainment occurs when there is progressive fusion of the paced P-wave (atrial activation) with the tachycardia P-wave (different atrial activation) on the 12-lead electrocardiogram, indicating that the pacing site is remote from the reentrant circuit. This change of atrial activation can also be seen on the intracardiac electrograms. During manifest entrainment, the post-pacing interval is greater than the tachycardia cycle length when judged from the entraining catheter (Fig. 8.9). Concealed entrainment occurs when there is no surface fusion noted and a delay is seen between the stimulus artifact and the paced P-wave, indicating that the pacing site is within the isthmus of

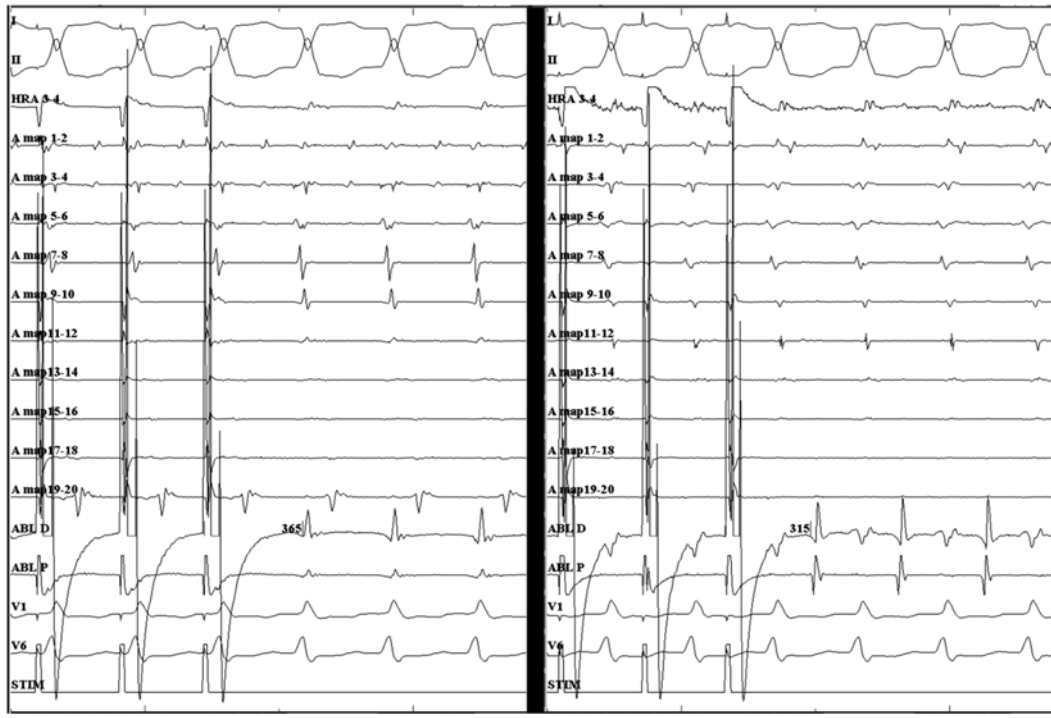


Fig. 8.9 Surface electrocardiograms and intracardiac electrograms obtained on a 19-year-old Fontan patient while performing entrainment mapping during IART (atrial cycle length = 310 ms). Pacing through the ablation electrode pair 1–2 at a slightly faster cycle length (300 ms) reveals consistent atrial capture. In the *left panel*, the post-pacing cycle length (365 ms) is significantly longer than the tachycardia cycle length, which indicates that the site of atrial pacing is not within the reentrant circuit. In the *right panel*, the post-pacing cycle length (315 ms) is nearly identical to the tachycardia cycle length, which indicates that the pacing site is within the reentrant circuit. *HRA* high right atrial reference catheter, *A map* ablation D (fourth tracing from bottom) is the ablation catheter with the distal electrode one two pair. Ablation T is the proximal electrode pair on the ablation catheter, three four. *STIM* stimulation channel marker

the reentrant circuit. When concealed entrainment is obtained at different pacing cycle lengths, the site of pacing is felt to be within the protected isthmus of conduction. This is confirmed by evaluating the interval between the last captured atrial beat during entrainment and the first spontaneous atrial activation on the same intracardiac electrode pair used for pacing during the IART. If the post-pacing interval is equal to or only 10–20 ms longer (infrequently up to 50–60 ms in slow IART) than the tachycardia cycle length, the pacing site is said to be "inside" the reentry circuit. If the post-pacing interval is greater than 20 ms longer (≥50–60 ms in slow IART), then the tachycardia cycle length, the pacing site is "outside" the IART circuit (Fig. 8.9). Finally, an isthmus or narrow corridor of slow conduction may be identified by examining the timing of the local electrogram relative to the onset of the surface electrocardiogram P-wave. Optimally, the local electrogram should be found 20–40 ms prior to the onset of the P-wave.

In patients who have numerous intra-atrial tachycardia circuits, a transcatheter atrial Maze procedure, creating a number of lines of block between several anatomical barriers, can not only address the current clinical arrhythmia but also areas of potential future reentrant circuits.

Three-Dimensional Mapping

Due to the complexity of incisional IART circuits, and the possibility of multiple circuits, three-dimensional mapping systems are a valuable adjunct to traditional mapping techniques.

As the available systems each have limitations, it is important to confirm any findings with conventional techniques, such as entrainment or endocardial (relative timing of the local electrogram with the onset of the P-wave) mapping. Recent studies have suggested that the reentry circuit may be dependent on areas of low voltage "bridges" that are responsible for the slow conduction across the isthmus-dependent portion of the circuit. These areas may also be able to be identified on 3-D mapping. Additionally, the use of 3-D mapping may significantly reduce or eliminate the use of radiation for these procedures. There are two main types of 3-D mapping, contact and non-contact mapping.

Contact Three-Dimensional Mapping

Contact three-dimensional mapping consists of an electro-anatomical mapping system allowing catheter localization while operating within a low intensity energy or magnetic field. The 3-D position of the catheter within the chamber allows cardiac geometry to be created which can then be linked to 3-D localized electrical activity in a point-by-point manner allowing the 3-D intracardiac geometry to be reconstructed with the overlying atrial signals (Figs. 8.6 and 8.7). Therefore, the 3-D inner atrial geometry can be created and areas of atrial activation of scars and anatomical landmarks that serve as barriers for the reentrant circuit can be identified. Because low amplitude signals suggest abnormal tissue or scar, voltage maps can construct a 3-D image of these areas, typically with an anatomic resolution less than 1 mm. After the atrial geometry is created, the catheter can be manipulated without fluoroscopic guidance. The major disadvantage of the system is that it requires a stable rhythm to obtain meaningful data. In patients who have multiple reentrant circuits, a new map must be created each time a different cycle length is induced. This disadvantage can be minimized by finding common areas critical to each of the circuits. Another approach is to map in sinus rhythm, identify the barriers, and target these areas for ablation lesions.

Non-contact Endocardial Mapping

The non-contact mapping technology (EnSite, St. Jude Inc.) utilizes a specialized 64-electrode balloon array to simultaneously record far-field electrical activity, compute virtual electrograms, and project them on a 3-D recreation of the chamber of interest using a reversed Laplace transformation. The 3-D model is created by tracing the endocardial surface with a roving catheter and computing the distance from the axis of the balloon by triangulation from specialized electrodes on either side of the balloon array itself. After the atrial geometry has been created, non-contact endocardial mapping allows for instantaneous identification of an IART circuit and, as opposed to contact mapping, has the advantage of identifying a new circuit without creating a new geometry. As this technique records the wave front at all points simultaneously, it negates the need to map the arrhythmia with a roving catheter. This may be especially helpful in patients with non-sustained arrhythmias, in patients having multiple reentrant circuits with different cycle lengths or in those with poorly tolerated arrhythmias. Low voltage may also be identified to allow creation of an ablation line across an isthmus which conducts the IART. Post ablation, pacing on either side of the line while mapping can rapidly identify "gaps" that require additional energy delivery.

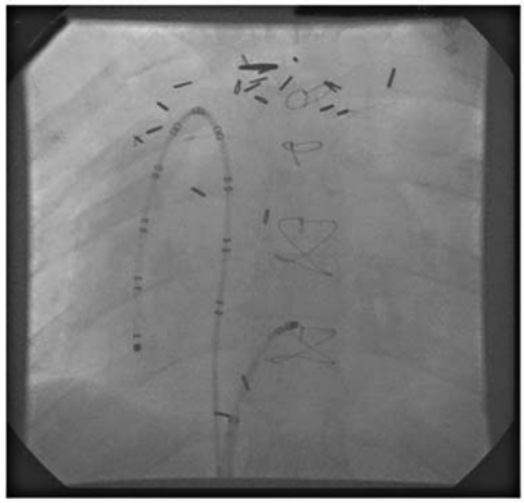
As with the contact method system, after the balloon is in place, the catheter can be guided without the use of fluoroscopy, reducing radiation exposure. A disadvantage of the non-contact method system is the concern of thrombus formation on the deployed balloon array; therefore, activated clotting times should be maintained between 250 and 300 s. A second disadvantage is that the balloon array has a relatively large profile and requires a 9 French sheath for introduction. In addition, when the balloon array is fully expanded, it occupies a large amount of space within the right atrium, which can limit ablation catheter manipulation, and possibly impede flow in and out of the atrium. While the resolution of the non-contact method system is quite good, edge detection beyond 4–5 cm from the center of

the balloon diminishes as does resolution obtained from the superior or inferior aspects of the balloon, limiting its use in a commonly dilated atrium. A final disadvantage of the non-contact method system is that far-field ventricular activity can be interpreted as atrial activity because the electrograms are unipolar. This can be particularly problematic in patients who have 1:1 AV conduction where the atrial activation may occur during ventricular depolarization or repolarization, leading to false identification of the atrial activation. This problem can be minimized by administering adenosine during the IART, allowing numerous cycles of the atrial activity to be mapped during AV block.

Transcatheter Ablation of IART

After the IART circuit has been characterized using the techniques described above (3-D mapping, entrainment mapping), attention is directed toward ablation.

In typical atrial flutter, the usual site for ablation is the isthmus between the tricuspid valve annulus and the inferior vena. As this is the most prevalent isthmus for all forms of IART, and a relatively easily accessible area, a prophylactic line of block in this area is also prudent when ablating intra-atrial reentrant circuits in patients with complex anatomy. A successful lesion should reduce the amplitude of the atrial electrogram by 90 % and often terminates the tachycardia (Fig. 8.10). Criteria for an effective "line of block" include the inability to induce the atrial reentrant tachycardia and the presence of bidirectional conduction block across the isthmus. Bidirectional conduction block is confirmed by pacing within the proximal coronary sinus and observing prolonged conduction to the low lateral right atrium as conduction proceeds counterclockwise around the tricuspid valve, and similarly, delayed conduction to the proximal coronary sinus when from pacing in the low lateral right atrium, with clockwise conduction around the tricuspid valve to the coronary sinus



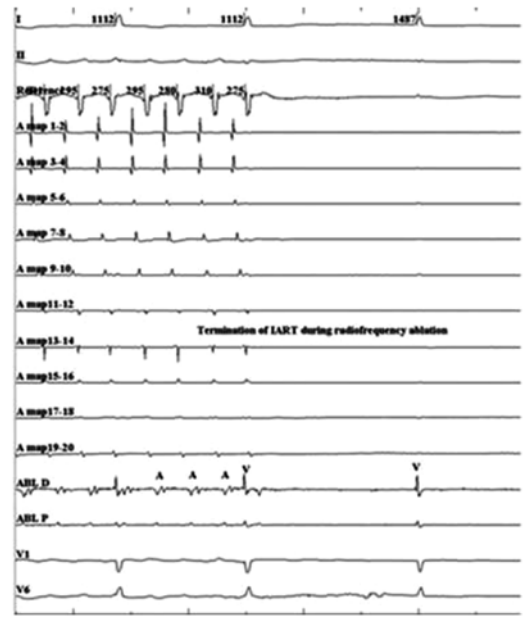


Fig. 8.10 AP X-ray image (*left panel*) and surface electrocardiogram and intracardiac electrograms obtained on a 22-year-old Fontan patient while applying radiofrequency energy during IART. The radiofrequency energy terminates the tachycardia resulting in a prolonged period of atrial asystole and a junctional escape rhythm. Ablation *ABL D* distal electrode pair, *ABL P* proximal electrode pair, *ABL* ablation catheter, *A* atrial electrogram, *V* ventricular electrogram

(viewing the tricuspid orifice from the right ventricular apex). Three-dimensional mapping can assist in identifying areas of breakthrough conduction along the line of block, allowing targeted ablation lesions to close the gap.

In patients with incisional IART, the isthmus block between the tricuspid valve and inferior vena cava is seldom sufficient to treat the arrhythmia. The optimal site to target for radiofrequency ablation is an isthmus that is narrow, has low voltage electrograms, exhibits concealed entrainment, has local electrograms that precede the P-wave by 20 or more milliseconds, and the line of block terminates the tachycardia. When these criteria cannot be met, a next best step is to find a narrow area between two barriers where a linear lesion can be made. In patients that have multiple inducible intra-atrial reentrant circuits, a shared isthmus can sometimes be found (dual figure of eight circuits). On occasion, when IART cannot be induced or sustained in the laboratory, substrate mapping (i.e., identifying barriers or scars and possible corridors) can serve as surrogates for mapping of the intra-atrial reentrant circuit, using similar criteria as during IART to identify the area for ablation.

In patients with multiple inducible intra-atrial reentrant circuits and no clear isthmus, an endocardial "Maze" procedure can be performed. This is accomplished by creating lines of block through potential areas of reentrant conduction. Typical lesion sets include a line from the superior vena cava to the inferior vena cava, the tricuspid valve to the inferior vena cava with or without incorporating the coronary sinus os, the atrial septal defect patch/scar to the line adjoining the vena cavae, and the right atrial appendage to the line adjoining the vena cavae. Other lesion lines may be required to disrupt potential circuits around anatomical boundaries depending on the individual electro-anatomic characteristics.

After identifying the critical isthmus and/or other areas to be targeted for disruption of the IART circuit(s), lesions are created. To be effective, a non-interrupted transmural lesion is required. Unfortunately, in patients with incisional IART, there are many obstacles that stand in the way of lesion formation. The endocardium is often thick, reducing the likelihood of a transmural lesion, and fibrotic, limiting the transmission of the radiofrequency energy. The low blood flow within the dilated atria also limits the blood cooling effects on the catheter tip, also limiting deep lesion formation.

Most commonly radiofrequency ablation is performed due to its tissue penetration, the speed of lesion formation, lesion permanency, and ease of catheter movement. However, cryotherapy has an advantage of reversibility when used only for short applications; therefore, it can be considered when ablations are in an area which could cause collateral damage; such as when near the AV node, phrenic nerves, or SA node. Disadvantages include a greater time for the ablation lesion therapy, and it may be associated with an increased risk of recurrence.

Ablation in incisional IART, although an effective tool, is not as acutely successful (75 %, with a recurrence as high as 50 %) as ablation for typical atrial flutter. This lower success rate and higher recurrence rate is most likely due to the thicker, diseased atrial myocardium, a greater number of anatomical barriers and circuits, and a high prevalence of concurrent sinus node disease. To overcome the obstacles for better lesion formation, several techniques can be undertaken. The two most common techniques are the use of a larger tip catheter (8 mm) or the use of an irrigated tip catheter that infuses saline through the ablation catheter tip. Attention should be paid to the additional amount of fluid given if using an irrigated tip catheter. Also, when incorporating techniques that assist in deeper radiofrequency lesion formation, the potential for adverse effects such as myocardial perforation and damage to surrounding tissue such as the phrenic nerve is increased.

The phrenic nerves, which lie along the lateral walls of the right and left atria, can be injured in the process of performing long linear lesions in this area. Therefore, high output pacing on the lateral atrial wall prior to ablation and observing for phrenic nerve stimulation, can help prevent collateral damage to this structure.

In rare circumstances when antiarrhythmic and ablative therapy is unsuccessful, one could consider a surgical Maze, an antitachycardia pacemaker or an AV node ablation. AV nodal ablation may be considered in patients who have rapid AV conduction with chronic IART which is not controlled with medications, or cured with ablation in patients with complex congenital disease, such as those following the atrial switch or Fontan operations with complicated intra-atrial batch patches and baffles can be challenging. These patients may require transvenous pacemakers or even epicardial pacemaker system placement and be rendered pacemaker dependent.

Surgical Management

Patients with incisional IART may have associated cardiac structural abnormalities resulting in significant hemodynamic compromise that requires surgical correction. In these patients, concurrent surgery for both arrhythmia management and correction of the structural abnormalities is a possible approach, such as concurrent arrhythmia surgery performed during Fontan conversion to a total cavopulmonary anastomosis Fontan. The arrhythmia surgery consists of an isthmus cryoablation and a right-sided maze (or a Cox III maze for patients with atrial fibrillation). Consideration for this surgical strategy is appropriate after failed medical and/or catheter-based management. Because of the inherent risks associated with an open heart procedure, surgical arrhythmia management is best reserved for those patients who require surgical intervention for structural problems or failed transcatheter ablation. These procedures may also result in worsening sinus node function; therefore, concurrent pacemaker placement should be considered especially in whose with any presurgical evidence of sinus node dysfunction.

Pacemaker Management

Pacemakers have long been used for the treatment of sinus and AV node disease that is associated with congenital heart disease (Chap. 18). In selected patients, the use of atrial antitachycardia pacemakers has been shown to be effective for the treatment of IART. These devices not only can treat the atrial arrhythmias with overdrive pacing protocols but also has pacing prevention algorithms that provide rate stabilization, minimizing the triggers for atrial arrhythmias. An antitachycardia pacing protocol can convert up to 50 % of atrial tachycardias and may be even more effective in patients who have had the Mustard or Senning operations. The overall success rate of the atrial antitachycardia pacemaker in the congenital heart disease population is similar to that of the adult population and appears particularly suited for patients with indications for atrial or dual chamber pacing and IART (Fig. 8.11). The applicability of this device for

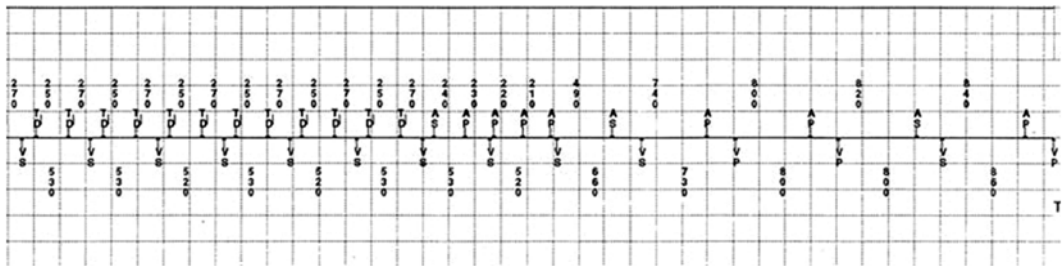


Fig. 8.11 Pacemaker marker channel strip from a 25-year-old woman D transposition of the great arteries, palliated with a Senning operation. The rhythm at the beginning of the pacemaker strip is suggestive of IART having 2:1 atrioventricular conduction. The pacemaker appropriately detects the arrhythmia (TD notations), and successfully atrial overdrive paces (AP) the patient into a sinus (AS), then an atrial paced rhythm

the treatment of IART is limited by its dependence on 2:1 or greater AV conduction for the classification and treatment of the atrial arrhythmia. When there is 1:1 AV conduction, the overdrive pacing protocol is automatically disabled. Modifications of future devices (or plugging the ventricular port) may allow the ability to manually override the disabled overdrive pacing therapies in patients with confirmed IART and a low risk of rapid AV conduction.

Prevention of Future IART at the Time of Initial Surgery

The treatment of postoperative IART has been reactive. As our understanding of this atrial arrhythmia has grown, a greater effort has been put forth in the area of prevention. The idea of modifying surgical procedures to prevent arrhythmias is not new; in fact, modifications of the atrial switch and Fontan operations were in part driven to by the desire to prevent sinus node disease and IART. This has included alteration of the site of atriotomy, baffle placement and even placing prophylactic atrial incisions to disrupt potential atrial reentry circuits. Unfortunately, these past attempts have not lived up to expectations.

Summary

The prognosis of typical atrial flutter in the pediatric population is excellent; the majority of infants do not have recurrence beyond their first episode. In contrast, incisional IART, when untreated, is progressive and can be associated with significant morbidity and mortality. Antiarrhythmic agents can be effective in both rate and rhythm control but often multiple medications are required, and proarrhythmic effects and other adverse reactions limit usage and decrease compliance.

Ablative therapy for typical atrial flutter, when needed, has a high success rate, though ablation for incisional IART averages 75 % short-term success rates and up to 50 % recurrence. Advances in mapping and ablation technology may greatly improve the long-term success rates. Arrhythmia surgery is advocated strongly by several groups, but due to its inherent increased risk, this procedure, in our experience, is limited to patients who require an open heart procedure or who fail transcatheter techniques.

Atrial antitachycardia pacemaker therapy for patients with IART is particularly suitable if other indications (sick sinus syndrome) for pacing are present. While the reported arrhythmia treatment success rate in the repaired or palliated congenital heart disease population is less than ideal, atrial rate stabilization algorithms may decrease the atrial arrhythmia burden. Also, patients with the atrial switch have shown a greater success rate of atrial overdrive pacing and therefore may be more suitable for this treatment.

Ideally, prevention of the IART is the goal. Addressing the reported risk factors, modifying surgical approaches (i.e., minimizing injury to the sinus node) and incorporating strategic incisions through well-described isthmus regions may reduce the incidence of IART. Long-term follow-up of current studies will clarify this issue.

Suggested Reading

Baker BM, Lindsay BD, Bromberg BI, Frazier DW, et al. Catheter ablation of clinical intra-atrial reentrant tachycardias resulting from previous atrial surgery: localizing and transecting the critical isthmus. J Am Coll Cardiol. 1996;28(2):411–7.

Balaji S, Johnson TB, Sade RM, Case CL, Gillette PC, et al. Management of atrial flutter after the Fontan procedure. J Am Coll Cardiol. 1994;23(5):1209–15.

Campbell RM, Dick M, Jenkins JM, Spicer RL, et al. Atrial overdrive pacing for conversion of atrial flutter in children. Pediatrics. 1985;75:730–40.

Casey FA, McCrindle BW, Hamilton RM, Gow RM. Neonatal atrial flutter: significant early morbidity and excellent long-term prognosis. Am Heart J. 1997; 133(3):302–6.

Castells F, Meste O, Quesada A, Guillem MS, et al. Characterization of typical and atypical atrial flutter loops from the vectorcardiogram. IEEE Eng Med Biol Soc. 2011;2011:4976–9.

Fishberger SB, Wernovsky G, Gentles TL, Gauvreau K, et al. Factors that influence the development of atrial flutter after the Fontan operation. J Thorac Cardiovasc Surg. 1997;113(1):80–6.

Frame LH, Page RL, Boyden PA, Fenoglio Jr JJ, Hoffman BF. Circus movement in the canine atrium around the tricuspid ring during experimental atrial flutter and during reentry in vitro. Circulation. 1987;76(5):1155–75.

Garson Jr A, Bink-Boelkens M, Hesslein PS, Hordof AJ, et al. Atrial flutter in the young: a collaborative study of 380 cases. J Am Coll Cardiol. 1985;6(4):871–8.

Kalman JM, Van Hare GF, Olgin JE, Saxon LA, et al. Ablation of 'incisional' reentrant atrial tachycardia complicating surgery for congenital heart disease. Use of entrainment to define a critical isthmus of conduction. Circulation. 1996;93(3):502–12.

Kanter RJ, Papagiannis J, Carboni MP, Ungerleider R, et al. Radiofrequency catheter ablation of supraventricular tachycardia substrates after Mustard and Senning operations for d-transposition of the great arteries. J Am Coll Cardiol. 2000;35(2):428–41.

Kurer CC, Tanner CS, Vetter VL. Electrophysiologic findings after Fontan repair of functional single ventricle. J Am Coll Cardiol. 1991;17(1):174–81.

Law IH, Fischbach PS, Goldberg C, Mosca RS, et al. Inducibility of intra-atrial reentrant tachycardia after the first two stages of the Fontan sequence. J Am Coll Cardiol. 2001;37(1):231–7.

Law IH, Alam A, Bove EL, Ohye RG, et.al. Strategy to reduce intra-atrial reentry tachycardia following the Fontan operation (abstract). Scientific Sessions American Heart Association, 2013, Dallas TX, p. 381

Mavroudis C, Backer CL, Deal BJ, Johnsrude CL. Fontan conversion to cavopulmonary connection and arrhythmia circuit cryoablation. J Thorac Cardiovasc Surg. 1998;115(3):547–56.

Mavroudis C, Backer CL, Deal BJ, Johnsrude C, Strasburger J. Total cavopulmonary conversion and maze procedure for patients with failure of the Fontan operation. J Thorac Cardiovasc Surg. 2001;122(5): 863–71.

Mendelsohn A, Dick M, Serwer GA. Natural history of isolated atrial flutter in infancy. J Pediatr. 1991;119(3): 386–91.

Natale A, Newby KH, Pisanó E, Leonelli F, et al. Prospective randomized comparison of antiarrhythmic therapy versus first-line radiofrequency ablation in patients with atrial flutter. J Am Coll Cardiol. 2000;35(7):1898–904.

Olgin JE, Kalman JM, Fitzpatrick AP, Lesh MD. Role of right atrial endocardial structures as barriers to conduction during human type I atrial flutter. Activation and entrainment mapping guided by intracardiac echocardiography. Circulation. 1995;92(7):1839–48.

Prasad SM, Maniar HS, Camillo CJ, Schuessler RB, et al. The Cox maze III procedure for atrial fibrillation: long-term efficacy in patients undergoing lone versus concomitant procedures. J Thorac Cardiovasc Surg. 2003;126(6):1822–8.

Rosenblueth A, Garcia Ramos A. Studies on flutter and fibrillation. Part II. The influence of artificial obstacles on experimental auricular flutter. Am Heart J. 1947; 33:677–84.

Rowland TW, Mathew R, Chameides L, Keane JF. Idiopathic atrial flutter in infancy: a review of eight cases. Pediatrics. 1978;61(1):52–6.

Russell MW, Dorostkar PC, Dick 2nd M, Craenen J, et al. Catheter interruption of atrioventricular conduction using radiofrequency energy in a patient with transposition of the great arteries. Pacing Clin Electrophysiol. 1995;18(1 Pt 1):113–6.

Stephenson EA, Casavant D, Tuzi J, Alexander ME, Law I, et al. Efficacy of atrial antitachycardia pacing using the Medtronic AT500 pacemaker in patients with congenital heart disease. Am J Cardiol. 2003;92(7):871–6.

Texter KM, Kertesz NJ, Friedman RA, Fenrich Jr AL. Atrial flutter in infants. J Am Coll Cardiol. 2006; 48(5):1040–6.

Theodoro DA, Danielson GK, Porter CJ, Warnes CA. Right-sided maze procedure for right atrial arrhythmias in congenital heart disease. Ann Thorac Surg. 1998;65(1):149–53. discussion 153–154.

Triedman JK, Jenkins KJ, Colan SD, Saul JP, Walsh EP. Intra-atrial reentrant tachycardia after palliation of congenital heart disease: characterization of multiple macroreentrant circuits using fluoroscopically based three-dimensional endocardial mapping. J Cardiovasc Electrophysiol. 1997;8(3):259–70.

Triedman JK, Alexander ME, Love BA, Collins KK, et al. Influence of patient factors and ablative technologies on outcomes of radiofrequency ablation of intra-atrial re-entrant tachycardia in patients with congenital heart disease. J Am Coll Cardiol. 2002;39(11):1827–35.

Van Hare GF, Lesh MD, Ross BA, Perry JC, Dorostkar PC, et al. Mapping and radiofrequency ablation of intra-atrial reentrant tachycardia after the Senning or Mustard procedure for transposition of the great arteries. Am J Cardiol. 1996;77(11):985–91.

Walsh EP, Cecchin F. Arrhythmias in adult patients with congenital heart disease. Circulation. 2007;115:534–45.

Watson RM, Josephson ME. Atrial flutter. I. Electrophysiologic substrates and modes of initiation and termination. Am J Cardiol. 1980;45(4):732–41.

Atrial Fibrillation

9

Peter S. Fischbach

Atrial fibrillation is a supraventricular tachycardia characterized by a disorganized electrical activation and thus contraction of the atrium. The characteristic "irregularly irregular" rhythm is generated by the rapid irregular bombardment of the atrioventricular (AV) node with electrical impulses emanating from the atrial myocardium with variable conduction of the atrial impulses through the AV node (Figs. 9.1 and 9.2). The ventricular response is dependent on the ability of the AV node to transmit electrical signals (i.e., its refractory state). This is determined by its inherent electrophysiologic properties as well as autonomic tone.

Incidence

Atrial fibrillation is the most common rhythm disorder seen in man; prevalence in the general population is estimated at 0.4 %. There is a significant age-related distribution of the arrhythmia with 6 % of the population greater than 80 years of age suffering from atrial fibrillation. Atrial fibrillation remains an extremely rare arrhythmia in the pediatric population. Interestingly, genetic mutations in the KCNQ1 channel have been associated with atrial fibrillation as has the mutation related to the short QT syndrome (Figs. 9.3 and 9.4) has been reported (Chap. 18). Familial atrial fibrillation has involved an addition of nine different genetic defects from 13 loci; many of the genes are implicated in other cardiac arrhythmias (Chap. 19).

Associated Disease

Atrial fibrillation commonly occurs as a comorbid condition with other cardiovascular abnormalities. It is found in patients with congestive heart failure, mitral valve stenosis and insufficiency, hypertension, hyperthyroidism, and some forms of repaired congenital heart malformations. In addition, it is well recognized in the child and young adult with complex, functionally impaired congenital heart malformation, particularly those with extensive atrial incisions or suture lines (Figs. 9.5 and 9.6). Atrial fibrillation is also associated with Wolff–Parkinson–White syndrome. Atrial fibrillation occurring in conjunction with Wolff–Parkinson–White syndrome is a potentially life-threatening situation due to the lack of decremental conduction through the accessory pathway. Some accessory pathways are capable of rapidly conducting the atrial signals to the ventricle leading to ventricular fibrillation (Chaps. 4 and 21).

P.S. Fischbach, M.D., M.S. (✉)
Sibley Heart Center, Children's Healthcare of Atlanta, Department of Pediatrics, Emory University School of Medicine, Atlanta, GA, USA
e-mail: fischbachp@kidsheart.com

M. Dick, II (ed.), *Clinical Cardiac Electrophysiology in the Young*,
DOI 10.1007/978-1-4939-2739-5_9

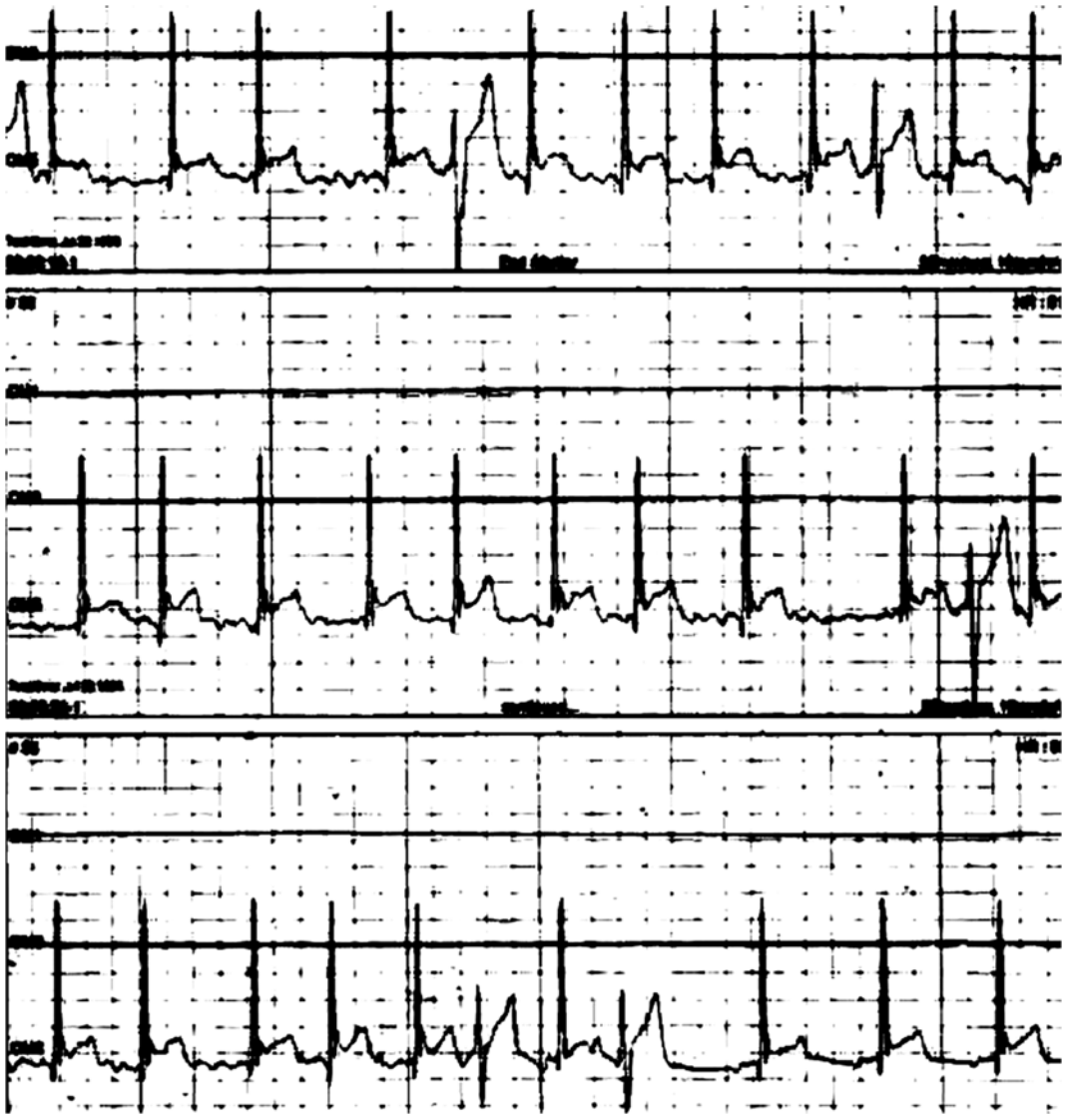


Fig. 9.1 Paroxysmal atrial fibrillation in a 17-year-old boy. Note the low amplitude fast waveforms (atrial fibrillatory waves) between the "irregularly irregular" QRS intervals. There are a few different QRS morphologies due to aberrant conduction. The atrial fibrillation spontaneously terminates (*bottom tracing*) as it frequently does in the paroxysmal form in patients without structural heart disease

Following elimination of the accessory pathway either surgically or via radiofrequency ablation, atrial fibrillation resolves in a large portion of these patients. Atrial fibrillation also may be associated with several other forms of supraventricular tachycardia in young patients. Our experience and that of others has been that young patients presenting with atrial fibrillation will frequently have other underlying mechanisms of SVT such as AVNRT, AVRT, ectopic atrial tachycardia, or atrial flutter. Ablation of these other tachycardia substrates results in the resolution of atrial fibrillation. Conversion of these forms of SVT with adenosine may result in transient atrial fibrillation (Fig. 9.7) as adenosine shortens atrial refractoriness.

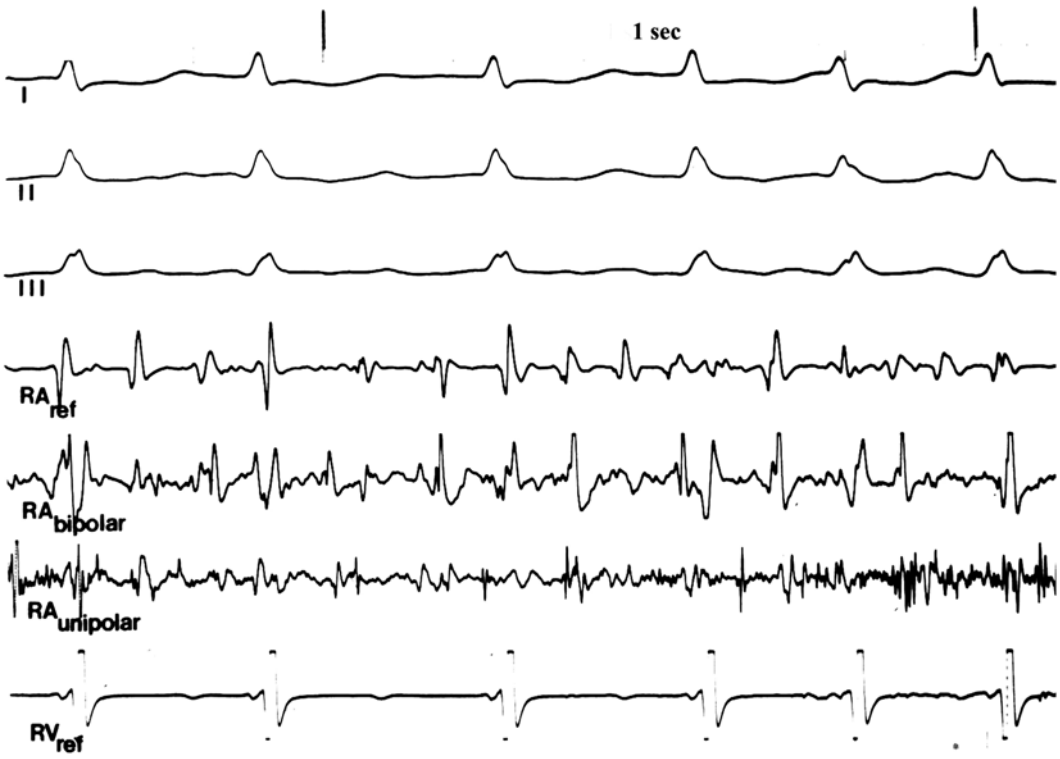


Fig. 9.2 Three electrocardiographic leads and four intracardiac electrograms [three in the right atrium (RA) and one from the right ventricular apex (RV)] illustrating the multi-phasic variable amplitude of the atrial fibrillation wave fronts

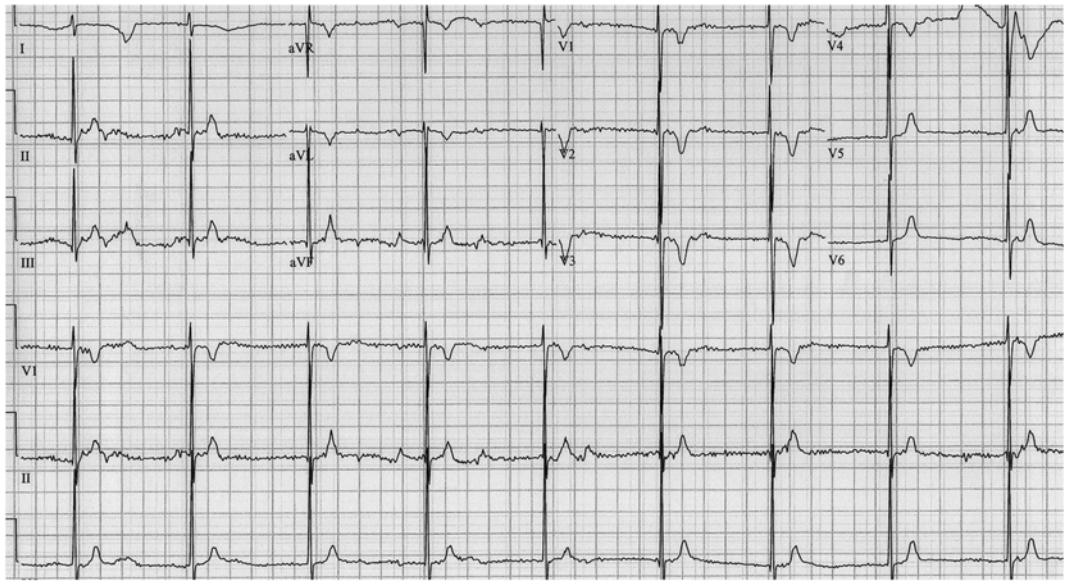


Fig. 9.3 One-week-old girl with congenital atrial fibrillation—the baseline shows a fine fibrillatory waveform, confirmed by esophageal electrogram (not shown)

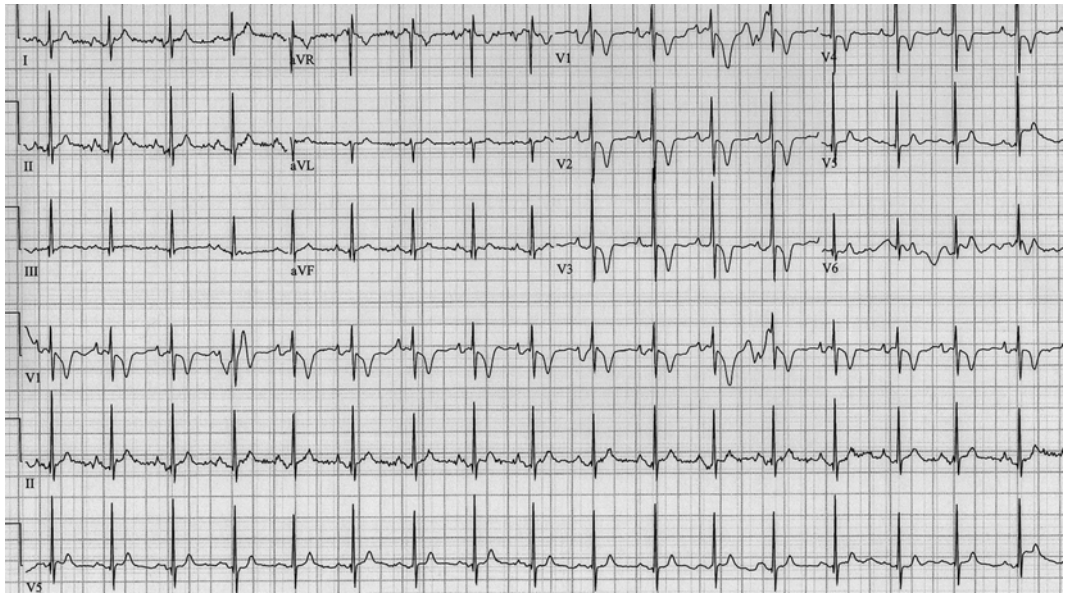


Fig. 9.4 Same patient as in Fig. 9.3—now in sinus rhythm (only for several hours; usual rhythm is atrial fibrillation). Note the very short QT interval (see text)

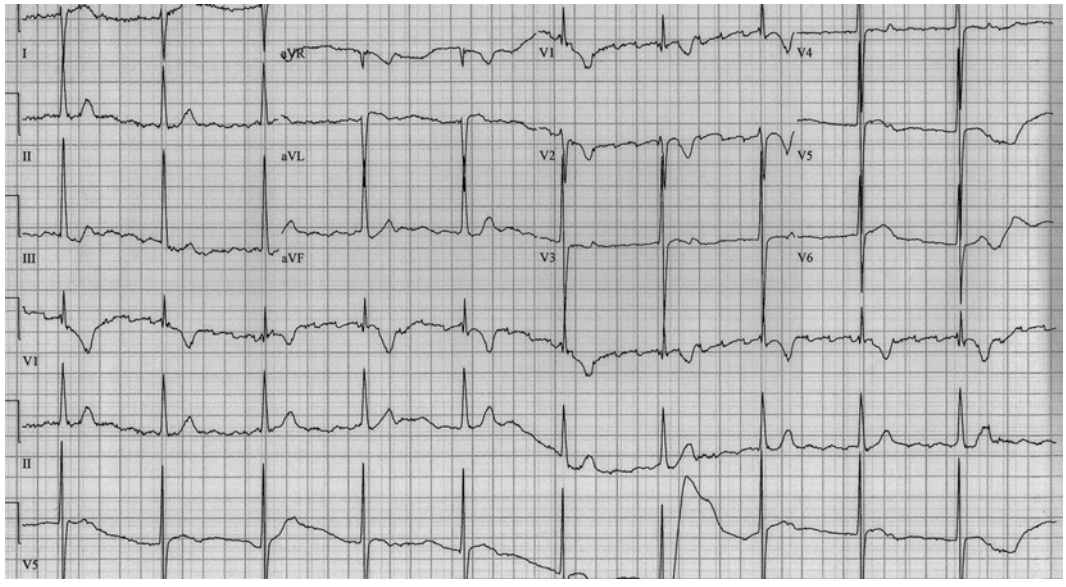


Fig. 9.5 Lead ECG in a 14 months boy after the double switch operation for congenitally corrected transposition of the great arteries. Note the atrial flutter-fibrillatory baseline

Another interesting association of atrial fibrillation is with obesity. This link has been demonstrated in adults as well as with pediatric patients. The exact physiological mechanism for this connection is unknown currently. We have also seen patients with atrial fibrillation that has probably resulted from enhanced vagal tone. Very strong vagal input can significantly shorten

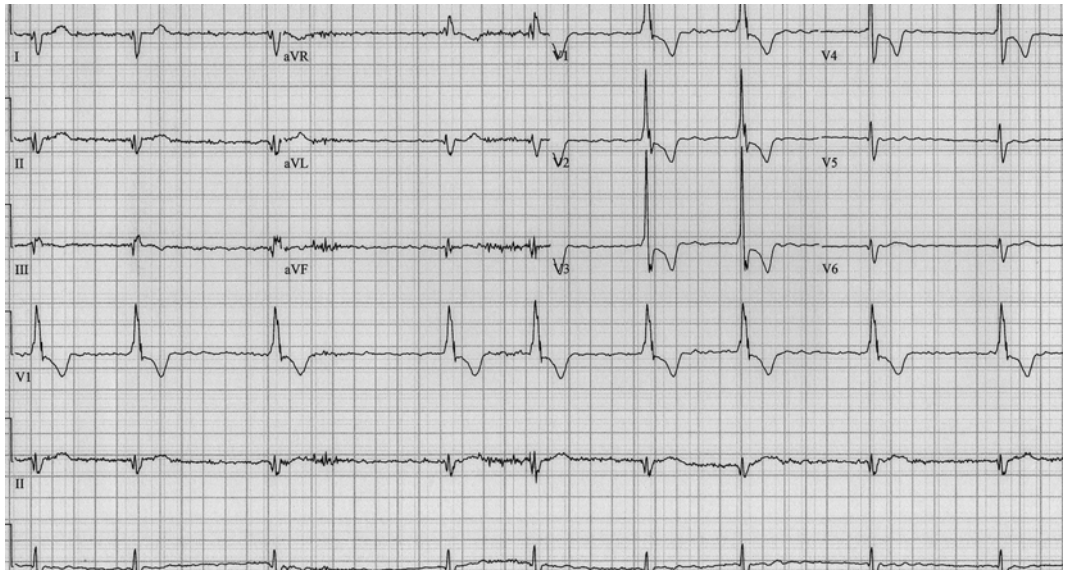


Fig. 9.6 12 Lead ECG from a 30-year-old man following the Mustard operation for D-transposition of the great arteries. Note the fine fibrillatory baseline and the "irregular irregularity" of the ventricular response

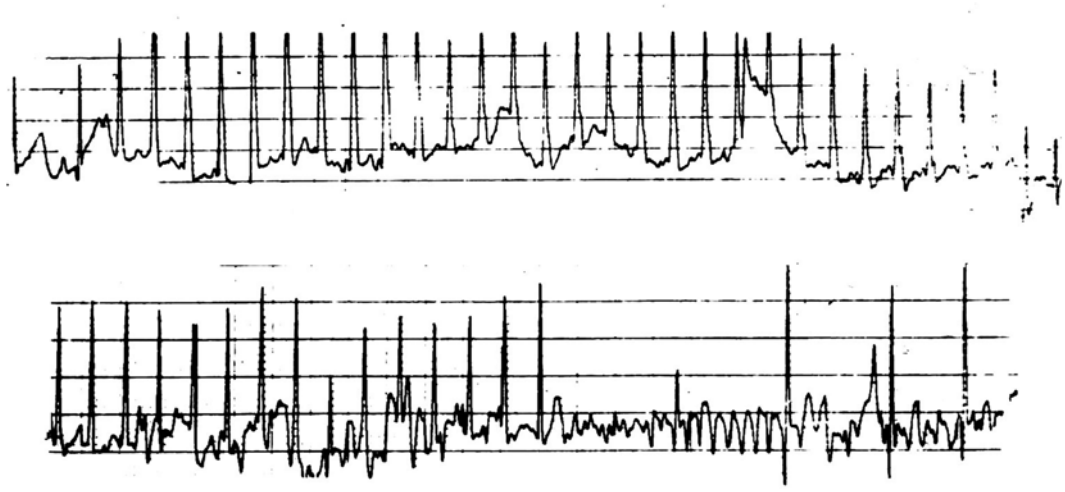


Fig. 9.7 Six hundred gram premature infant with SVT administered 120 mcg of adenosine. *Note*: The termination of the SVT but emergence of atrial fibrillation. The fibrillation spontaneously ceased several seconds later

the refractory period of atrial myocardium making the atria more susceptible to microreentrant circuits which underlie atrial fibrillation (see below). This is the physiological mechanism which leads to atrial fibrillation after adenosine administration (Fig. 9.7).

Recurrence

Two different recent reports demonstrated both a recurrence rate and an incidence of inducible supraventricular tachycardia in young patients

studied by programmed extra-stimulation of 39 %. Both of these findings support continued follow-up of these patients, if not electrophysiologic study after one episode of atrial fibrillation.

Mechanism

The pathophysiologic mechanisms underlying the initiation and perpetuation of atrial fibrillation remain under investigation (Fig. 9.2). It is possible that the mechanisms that support the initiation of atrial fibrillation are different from those that sustain the arrhythmia. The three most likely mechanisms include the multiple wavelet theory, single-circuit reentry, and multiple-circuit reentry with ectopic excitatory pulmonary vein foci. In this last model, multiple reentrant waves continuously circulate through the atrium using migrating central cores of refractory tissue to rotate around. The multiple wavelets circulate throughout the atrium following ever-changing pathways created by myocardium recovering from refractoriness. A critical mass of atrial tissue in this model is necessary to support a minimum number of wavelets in order to sustain atrial fibrillation. This has been cited as a rationale for the low incidence of atrial fibrillation in infants and children, as well as in small mammals (Chaps. 2 and 3). The second proposed mechanism for atrial fibrillation is the single-circuit reentrant model. In this model, a single "mother rotor" serves as the hub with multiple accessory circuits emanating from it. The third potential mechanism is atrial fibrillation arising from a rapidly discharging ectopic focus with fibrillatory conduction. This mechanism has come into favor with recent findings of excitatory loci occurring within the pulmonary veins, perhaps serving as the "trigger" of the "wavelets or of the "mother rotor." Recent clinical experience has demonstrated that focal radiofrequency ablation within the pulmonary veins as well as pulmonary vein isolation has successfully treated atrial fibrillation.

Sustained atrial fibrillation produces profound changes within the atrial myocardium, creating a substrate more conducive to supporting sustained atrial fibrillation. The electrical and structural remodeling of the atrium includes increasing fibrosis, as well as alterations in the expression of gap junctions and ion channels. These changes alter the mechanical and electrical properties of the atrial tissue by slowing the conduction velocity and a shortening of the refractory period in the atrium leading to tissue that is more likely to sustain atrial fibrillation.

The mechanism of the genetic mutation of atrial fibrillation and short QT appears to be a gain in function of the I_{Ks} in the KCNQ1 channel.

Therapy

Atrial fibrillation has proven to be an extremely difficult arrhythmia to manage with pharmacological therapy, achieving far less than optimal results. Multiple large clinical trials have been performed using nearly all of the currently available antiarrhythmic drugs, each of them with disappointing results. Large trials have also been performed comparing rate control (inhibition of conduction through the AV node) with rhythm control (restoration of sinus rhythm) for the ideal therapy. These studies have demonstrated no significant difference between these treatment options using total mortality, congestive heart failure, and rehospitalization as end points. Much of the difficulty with pharmacological therapy lies in the ever-present risk of ventricular proarrhythmia.

There are several non-pharmacological treatment strategies that have recently emerged. The Cox maze procedure creates multiple surgical incisions that are then repaired in the atrium in an attempt to channel the electrical signal between the sinus node and the AV-node while minimizing the formation of a reentrant loop. The surgical maze procedure has proven to have a reasonably high success rate, albeit with considerable associated surgical morbidity. An attempt to recreate this treatment principle using radiofrequency ablation has been attempted using long linear lesions, but with relatively poor results. The understanding of the role of rapidly discharging ectopic foci residing within the pulmonary veins has refocused the transcatheter therapies. Application of radiofrequency energy

or cryotherapy are now directed at either electrically isolating the pulmonary veins from the left atrium or at directly ablating the ectopic focus within the veins. A large meta-analysis published in 2013 sited a success rate of a single ablation procedure of just over 50 % for paroxysmal AF and just over 40 % for sustained AF. There was a considerable degree of variability in the reported results in the different studies cited. The long-term success rates (freedom from AF) after multiple procedures increased to almost 80 %, again with great variability between studies. When the total number of ablation procedures was evaluated, the average number of ablation procedures in the cohort was 1.5. A recent large study has demonstrated rhythm control (return to normal sinus rhythm) using radiofrequency ablation that is superior to either rate control or rhythm control using pharmacological agents. The difference between rhythm control using radiofrequency ablation and pharmacological agents likely rests in the proarrhythmia associated with pharmacological therapy.

Finally, pacemakers and implanted defibrillators have been used in an attempt to treat atrial fibrillation or to prevent its onset. To date, no significant improvement has been achieved relative to pharmacological therapies.

In conclusion, while atrial fibrillation is a common arrhythmia in older patients, it remains rare in pediatric and young adult patients. When encountered in pediatric patients, it often is the paroxysmal form with spontaneous remission and infrequent episodes. In addition, it can occur in the setting of other forms of supraventricular tachycardia, which are amenable to radiofrequency ablation therapy resulting in the resolution of the atrial fibrillation. For older patients with symptomatic or hemodynamic consequences, new ablation strategies aimed at eliminating or isolating the triggers within the pulmonary veins appears promising. Due to the infrequency of this arrhythmia in the young, transcatheter treatment targeted directly to atrial fibrillation is rarely indicated or necessary.

Suggested Reading

Ceresnak SR, Liberman L, Silver ES, Fishberger SB, et al. Lone atrial fibrillation in the young—perhaps not so "lone"? J Pediatr. 2013;162(4):827–31.

Ganesan AN, Shipp NJ, Brooks AG, et al. Long-term outcomes of catheter ablation of atrial fibrillation: a systematic review and meta-analysis. J Am Heart Assoc. 2013;2:e004549.

Heist EK, Mansour M, Ruskin JN. Rate control in atrial fibrillation: targets, methods, resynchronization considerations. Circulation. 2011;124:2746–55.

Hohnloser SH, Kuck KH, Lilienthal J. Rhythm or rate control in atrial fibrillation—pharmacological intervention in atrial fibrillation (PIAF): a randomised trial. Lancet. 2000;356:1789–94.

Hong K, Piper DR, Diaz-Valdecantos A, Brugada J, et al. De novo KCNQ1 mutation responsible for atrial fibrillation and short QT syndrome in utero. Cardiovasc Res. 2005;68(3):433–40.

Jais P, Haissaguerre M, Shah DC, et al. A focal source of atrial fibrillation treated by discrete radiofrequency ablation. Circulation. 1997;95:572–6.

Mills LC, Gow RM, Myers K, Kantoch MJ, et al. Lone atrial fibrillation in the pediatric population. Can J Cardiol. 2013;29(10):1227–33.

Nattel S, Burstein B, Dobrev D. Atrial remodeling and atrial fibrillation: mechanisms and implications. Circ Arrhythm Electrophysiol. 2008;1:62–73.

Schotten U, Verheule S, Kirchhof P, Goette A. Pathophysiological mechanisms of atrial fibrillation: a translational appraisal. Physiol Rev. 2011;91(1):265–325.

The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med. 2002;347:1825–33.

Wijffels MC, Kirchhof CJ, Dorland R, Allessie M. Atrial fibrillation begets atrial fibrillation: a study in awake chronically instrumented goats. Circulation. 1995;92:1954–68.

Zimetbaum P. Antiarrhythmic drug therapy for atrial fibrillation. Circulation. 2012;125:381–9.

Atrial Ectopic Tachycardias

10

Burt I. Bromberg and Andrew Papez

Atrial Ectopic Tachycardia

Clinical Presentation

Atrial ectopic tachycardia (AET) is the most common manifestation of abnormal automaticity in otherwise healthy children. Typically AET is seen in children with no structural heart disease. Infants and toddlers may have a longstanding tachycardia that may smolder for weeks or months until symptoms and signs of congestive heart failure develop, producing a tachycardia-related cardiomyopathy. In contrast, older patients typically present with palpitations, although occasionally they too may first be identified with the onset of a tachycardia-related cardiomyopathy.

The heart rate in AET tends to be slower than in reentrant supraventricular tachycardia (SVT), typically in the range of 120–160 bpm. Both a paroxysmal form, which may mimic in some aspects the reentrant forms of SVT, and a more chronic form have been described. It is the chronic form, often at relatively slow rates (<150 bpm), that can lead to a tachycardia-induced cardiomyopathy. Occasionally, these tachycardias resolve spontaneously. On rare occasions, they may be follow device placement, presumably due to direct mechanical perturbation (stimulation) of adjacent cardiac tissue.

Diagnosis

AET can be diagnosed from the ECG. Each QRS complex of the tachycardia is preceded by a P-wave, although at faster rates this may be difficult to detect since the P-wave may become fused with the preceding T-wave (Fig. 10.1). The ectopic P-wave has a different morphology from the sinus beat, but this may not always be a reliable indicator if the ectopic focus is near the sinus node. Algorithms have been developed to localize the ectopic focus, thereby aiding in the planning of catheter ablation procedures. In a study of 126 consecutive patients, it has been reported that a P-wave morphology during the tachycardia in V1 that was either positive or biphasic with an initial positive component was associated with 100 % specificity and 100 % positive predictive value for a right atrial focus. A negative or biphasic P-wave with an initial negative component had 100 % sensitivity and 100 % positive predictive value for a left atrial focus. In a smaller study, Tang found that a positive or biphasic P-wave morphology in

B.I. Bromberg, M.D. (✉)
Department of Pediatrics, Mercy Clinic,
621 South New Ballas Road, Suite 198A, St. Louis,
MO 63141, USA
e-mail: burt.bromberg@mercy.net

A. Papez, M.D.
Pediatric Cardiology, Arizona Pediatric Cardiology/
Phoenix Children's Hospital, Phoenix, AZ, USA

M. Dick, II (ed.), *Clinical Cardiac Electrophysiology in the Young*,
DOI 10.1007/978-1-4939-2739-5_10

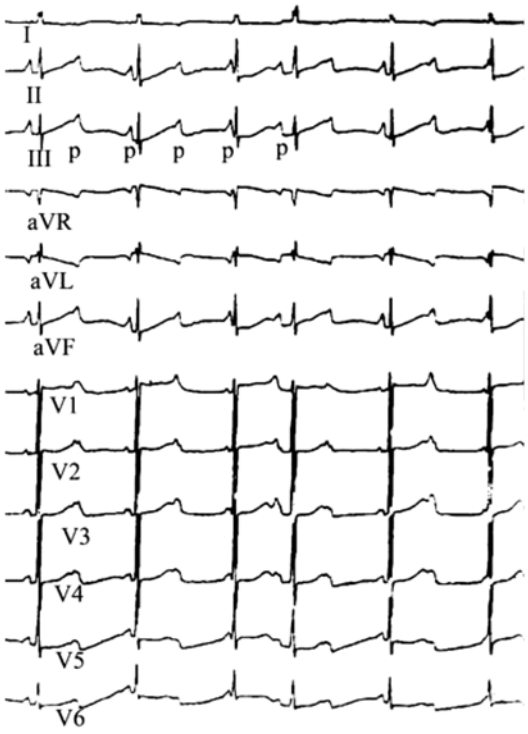


Fig. 10.1 12-Lead ECG from a 9-month-old boy with atrial ectopic tachycardia at 150 bpm. There is variable A-V conduction. The P-wave is large in many leads and has a leftward inferior (positive in leads I, II, aVF) but anterior (positive in lead V1) axis suggesting a high left atrial origin near the right upper pulmonary vein

Table 10.1 Criteria for automatic atrial tachycardia

P-wave preceding each QRS
P-wave of different morphology from sinus
Persistence of tachycardia in the presence of AV block
"Warm-up" period
Catecholamine sensitive

Modified from Josephson ME. Superventricular Tachycardias. In: Josephson ME (ed). Clinical Cardiac Electrophysiology: Techniques and Interpretations, 4th Edition. Philadelphia, PA: Lippincott Williams & Wilkins; 2008: 175–284. With permission from Wolters Kluwer Health

V1 was 88 % sensitive for a tachycardia originated in the right atrium, with a positive predictive value of 83 %.

Noninvasive testing may clarify the diagnosis (Table 10.1). In contrast to reentrant forms of SVT, Holter monitoring may demonstrate a characteristic gradual acceleration of the heart rate in AET, the so-called warm-up period. The first beat of the tachycardia typically occurs late in the cycle, and the initial P-wave will have the same morphology as subsequent P-waves. Participation of the ventricle in the tachycardia is not required, excluding an accessory pathway in these patients. During periods of reduced adrenergic tone and heightened parasympathetic tone (sleep, carotid sinus massage), the P-waves of an AET may not conduct to the ventricles, resulting in varying degrees of atrioventricular block. On occasion, this block can be induced with adenosine (Fig. 10.2); on the other hand, some AETs may be transiently suppressed with adenosine, limiting the usefulness of this test.

AET also has distinguishing features observed at electrophysiology study. First, it cannot be terminated by overdrive pacing. If ventricular participation can be excluded during either spontaneous or adenosine-induced AV node Wenckebach, the remaining diagnostic possibility for a narrow QRS tachycardia with P-waves preceding each QRS complex is atrial flutter (intra-atrial reentrant tachycardia). While macroreentrant tachycardia, including atrial flutter, can be interrupted with appropriate atrial overdrive pacing, an automatic tachycardia is only momentarily suppressed before the ectopic focus gradually warms up and returns. Another diagnostic finding is the sequence of atrial-atrial-ventricular electrograms (A-A-V) following cessation of ventricular burst pacing, elicited in almost 80 % of patients with a paroxysmal form of this arrhythmia. Use of catecholamine to induce AET may make it difficult to identify the mechanism of the tachycardia (Fig. 10.3).

Treatment

Treatment presents two options: antiarrhythmic medications or radiofrequency ablation. There are no controlled, randomized series to evaluate drug therapy; available data are difficult to interpret because of selection bias in retrospective studies. Digoxin, propranolol, and verapamil are

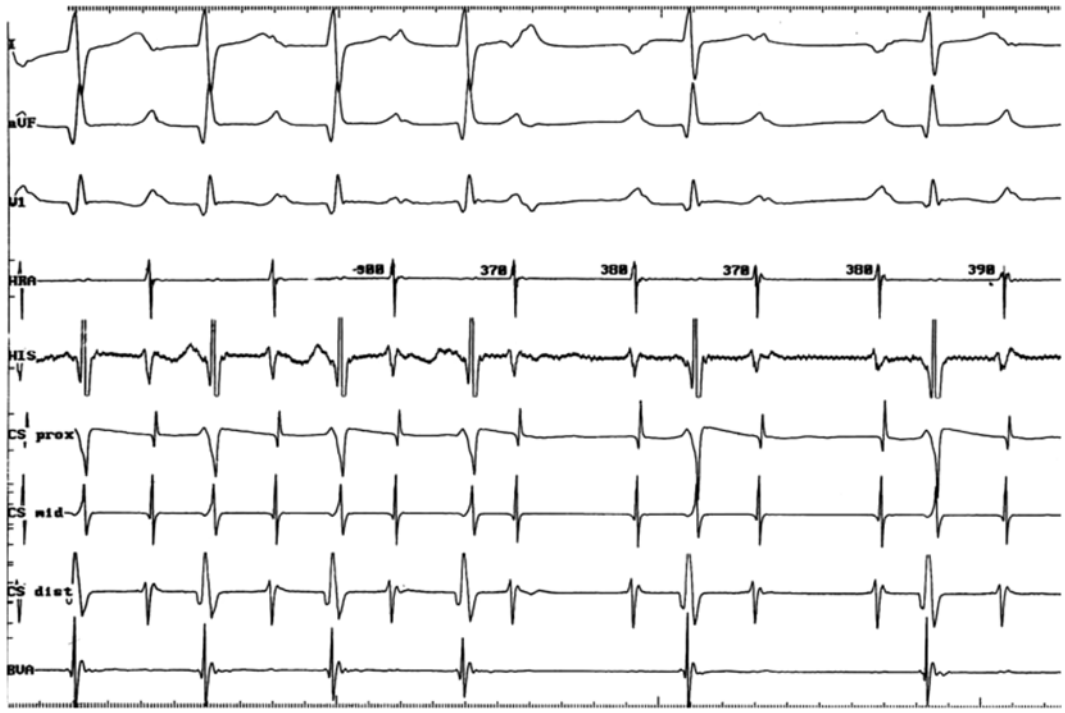


Fig. 10.2 Atrioventricular block with adenosine during AAT. The atrial tachycardia persists at a cycle length of 370–390 ms despite AV block induced by adenosine. In addition to demonstrating that the ventricular is not a participant in the tachycardia, the P-wave, which had been buried within the preceding T-wave, becomes clearly discernable

ineffective. Class III drugs like amiodarone and sotalol, and IC drugs (propafenone and flecainide) have been more successful in small retrospective series. The addition of a beta-blocker to flecainide may be helpful, and in refractory cases, flecainide in combination with amiodarone may be considered. AET may be a complication of transcatheter atrial septal defect closure devices; treatment requires removal of the device; however, the tachycardia may persist and ablation of the identified site be necessary (Fig. 10.4).

The acute success rate of radiofrequency ablation for AET approaches 95–100 %. Experience in children demonstrates that a majority of the foci are in the left atrium, particularly near the right pulmonary veins and in the atrial appendage. In contrast, the anatomic distribution in adult patients is predominantly on the right side, particularly near the SVC/RA junction, right atrial appendage, and the coronary sinus os. When the focus (i) in children is on the right side, they cluster in and around the right atrial appendage. The technical aspects of successful ablation include identification of the earliest intra-atrial electrogram preceding the onset of the surface P-wave by at least 20 ms, pace-mapping to assure that P-waves originating from the pacing site are identical to those of the AAT and computer-based intra-cardiac mapping techniques (Figs. 10.5 and 10.6).

In view of the possibility of spontaneous resolution, as well as the availability of drugs with perhaps modest efficacy and a low incidence of adverse effects, a trial with flecainide or amiodarone for symptomatic patients with AET is reasonable. However, for patients who have poor control of the tachycardia, especially with evidence of diminished ventricular function, or who remain dependent on pharmacologic therapy after 1–2 years, radiofrequency catheter ablation is indicated (Fig. 10.6).

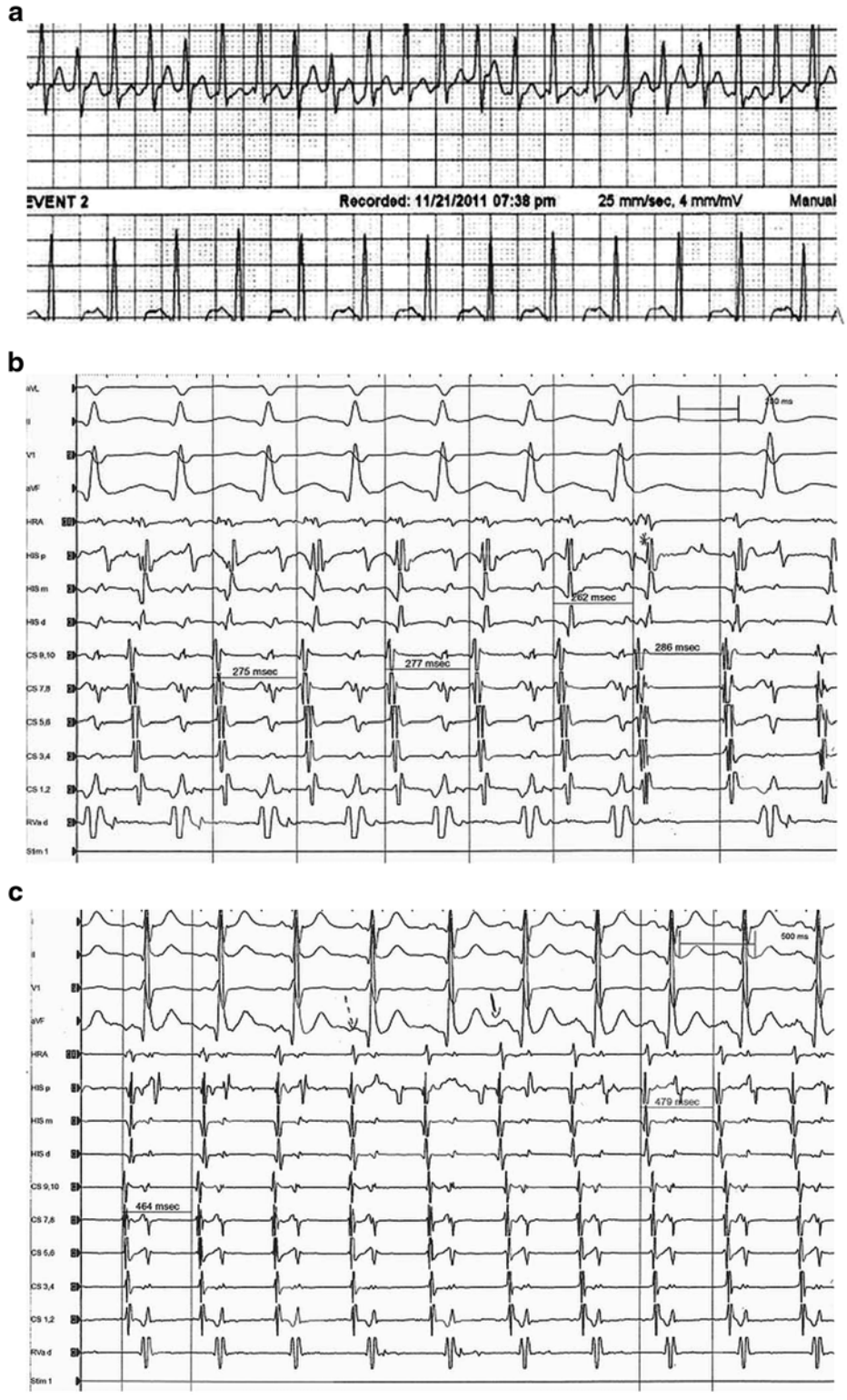


Fig. 10.3 Panel **a**: Rhythm strip from a 16-year-old with exertional palpitations. Rhythm strip shows narrow QRS tachycardia, with slight cycle length variability, 260–280 ms, and also a suggestion of P-waves. Panel **b**: Atrial burst pacing on isoproterenol induces clinical tachycardia, initially with 1:1 AV conduction, where P-wave is buried in preceding T-wave. Block of an atrial premature beat #7 (*asterisk*) suppresses the following atrial beat with identical atrial activation sequences during the tachycardia consistent with an abnormal automatic mechanism and thus eliminates tachycardia mediated by concealed accessory pathway. Panel **c**: After discontinuing isoproterenol, AET slowing leads to resumption of sinus rhythm, as evidenced by the change in P-wave morphology and atrial activation sequence

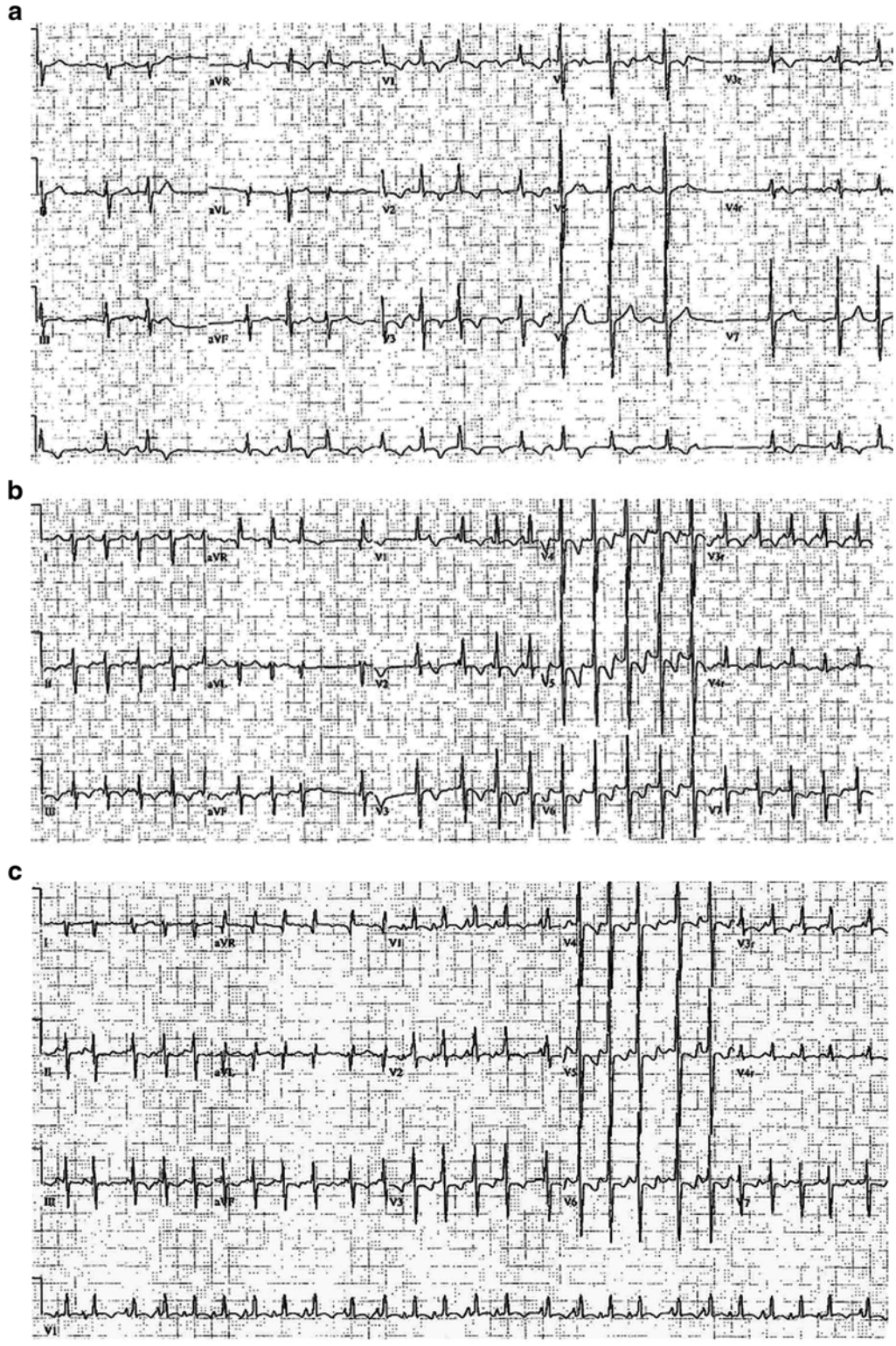


Fig. 10.4 13 Lead ECGs from 5-year-old child, s/p Amplatzer septal occluder for secundum ASD. Panel **a**: Atrial ectopy following device implant subsequently progressed to non-sustained AET (panel **b**) and the development of mild LV systolic dysfunction. Pharmacologic treatment was ineffective, which led 1 year later to surgical explant of the device and patch closure of the ASD. Panel **c**: AET became almost incessant, prompting catheter radiofrequency ablation. Lesions on the left side at the lower margin of the patch slowed the tachycardia, and subsequent lesions on the right side of the patch, near the CS os terminated the tachycardia. LV function subsequently normalized

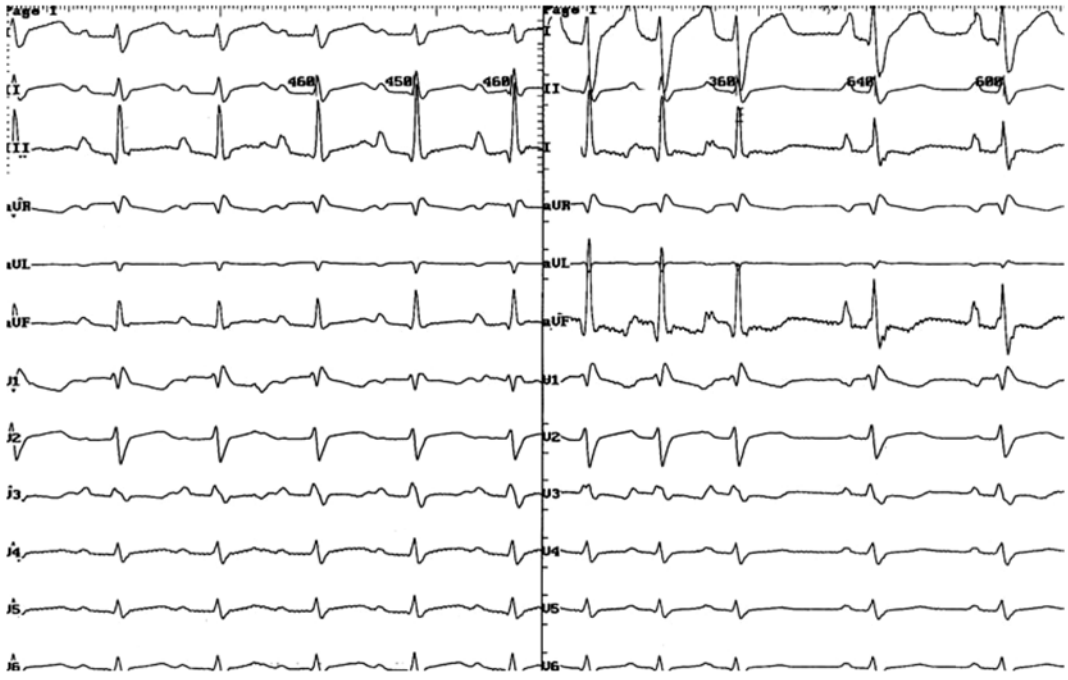


Fig. 10.5 Atrial ectopic tachycardia originating from the atrial mid-septum. *Left panel*: At a slower cycle length, the P-wave of the tachycardia preceding the QRS is easily discernable, but not obviously distinguishable in shape from a sinus beat. *Right panel*: During radiofrequency catheter ablation, the ectopic focus heats up, the tachycardia cycle length shortens, and the P-wave cannot be clearly identified within the preceding T-wave. After the third beat, the tachycardia terminates. Cycle lengths are displayed in lead II. Successful ablation of the ectopic focus is often preceded by an acceleration of the tachycardia, followed by a sudden prolongation of the cycle length of the normal sinus impulse. The morphology of the ensuing sinus beats is only subtly different from that of the automatic tachycardia (see leads I, aVR, V1-2)

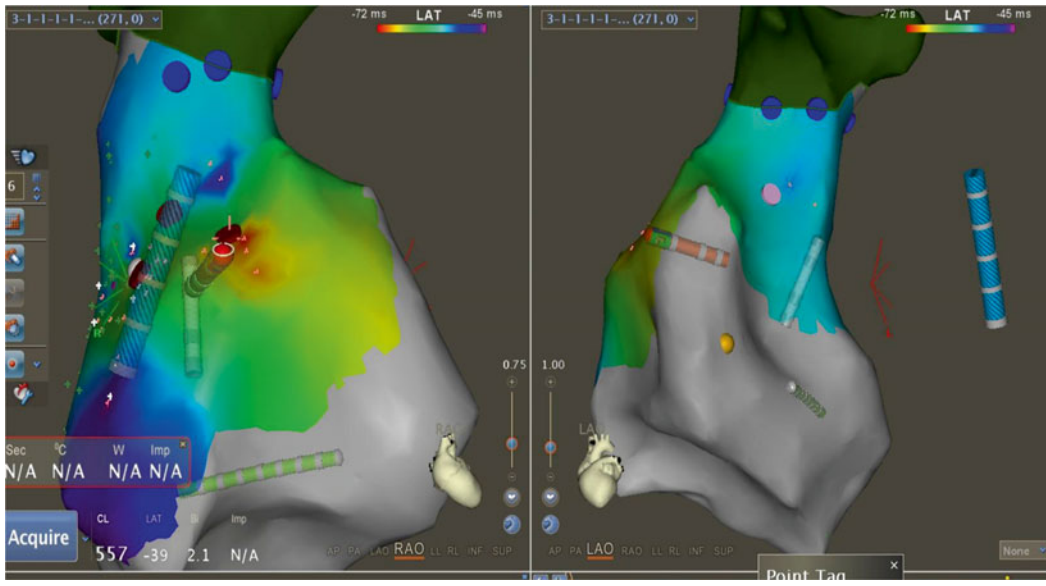


Fig. 10.6 CARTO electro-anatomic map (right [*left image*] and left [*right image*] anterior oblique projection) of AET arising from the right anterior free wall of the right atrium, moving through the right atrium (*red* to *green* to *blue*). Radiofrequency ablation was successful at this site (*red*). The *gray areas* represent atrial geometry without local activation measurements. *Blue* electrode catheter is in the esophagus

Suggested Reading

Bauersfeld U, Gow RM, Hamilton RM, Izukawa T. Treatment of atrial ectopic tachycardia in infants <6 months old. Am Heart J. 1995;129:1145–8.

Bisset GS, Seigel SF, Gaum WE, Kaplan S. Chaotic atrial tachycardia in childhood. Am Heart J. 1981;101: 268–72.

Dodge-Khatami A, Miller OI, Anderson RH, et al. Surgical substrates of postoperative junctional ectopic tachycardia in congenital heart defects. J Thorac Cardiovasc Surg. 2002;123(4):624–30.

Dodo H, Gow RM, Hamilton RM, Freedom RM. Chaotic atrial rhythm in children. Am Heart J. 1995;129: 990–5.

Fenrich Jr A, Perry JC, Friedman RA. Flecainide and amiodarone: combined therapy for refractory tachyarrhythmias in infancy. J Am Coll Cardiol. 1995;25: 1195–8.

Fish FA, Gillette PC, Benson Jr DW. Proarrhythmia, cardiac arrest and death in young patients receiving encainide and flecainide. The Pediatric Electrophysiology Group. J Am Coll Cardiol. 1991;18: 356–65.

Fish FA, Mehta AV, Johns JA. Characteristics and management of chaotic atrial tachycardia of infancy. Am J Cardiol. 1996;78:1052–5.

Gillette PC, Garson Jr A. Electrophysiologic and pharmacologic characteristic of automatic ectopic atrial tachycardia. Circulation. 1977;56:571–5.

Gillette PC, Wampler DG, Garson Jr A, Zinner A, Ott D, Cooley D. Treatment of atrial automatic tachycardia by ablation procedures. J Am Coll Cardiol. 1985;6:405–9.

Horenstein MS, Saarel E, Dick II M, Karpawich PP. Reversible symptomatic dilated cardiomyopathy in older children and young adolescents due to primary non-sinus supraventricular tachycardia. Pediatr Cardiol. 2003;24(4):274–9.

Huikuri HV, Poutiainen A, Makikallio TH, et al. Dynamic behavior and autonomic regulation of ectopic atrial pacemakers. Circulation. 1999;100:1322–416.

Josephson ME. Clinical cardiac electrophysiology. 2nd ed. Philadelphia: Lea & Febiger; 1993.

Josephson ME, Spear JF, Harken AH, et al. Surgical excision of automatic atrial tachycardia: anatomic and electrophysiologic correlates. Am Heart J. 1982;104: 1076–85.

Kang KT, Etheridge SP, Kantoch MJ, Tisma-Dupanovic S, Bradley DJ, Balaji S, Hamilton RM, Singh AK, Cannon BC, Schaffer MS, Potts JE, Sanatani S. Circ Arrhythm Electrophysiol. 2014;(4):664–70.

Kay GN, Chong F, Epstein AE, et al. Radiofrequency ablation for treatment of primary atrial tachycardias. J Am Coll Cardiol. 1993;21:910–9.

Kistler PM, Roberts-Thomson KC, Haqqani HM, et al. P-wave morphology in focal atrial tachycardia. J Am Coll Cardiol. 2006;48:1010–7.

Knight BP, Zivin A, Souza J, et al. A technique for the rapid diagnosis of atrial tachycardia in the electrophysiology laboratory. J Am Coll Cardiol. 1999;33: 775–81.

Koike K, Hesslein PS, Finlay CD, et al. Atrial automatic tachycardia in children. Am J Cardiol. 1988;61: 1127–30.

Rosales AM, Walsh EP, Wessel DL, Triedman JK. Postoperative ectopic atrial tachycardia in children with congenital heart disease. Am J Cardiol. 2001; 88(10):1169–72.

Rosen MR, Gelband H, Merker C, Hoffman BF. Mechanisms of digitalis toxicity: effects of ouabain on phase four of canine Purkinje fiber transmembrane potentials. Circulation. 1973;47:681–9.

Salim MA, Case CL, Gillette PC. Chaotic atrial tachycardia in children. Am Heart J. 1995;129:831–3.

Tang CW, Scheinman MM, Van Hare GF, et al. Use of P wave configuration during atrial tachycardia to predict site of origin. J Am Coll Cardiol. 1995;26:1315–24.

Tracy CM, Swartz JF, Fletcher RD, et al. Radiofrequency catheter ablation of ectopic atrial tachycardia using paced activation sequence mapping. J Am Coll Cardiol. 1993;21:910–7.

Walsh EP, Saul JP, Hulse JE, et al. Transcatheter ablation of ectopic atrial tachycardia in young patients using radiofrequency current. Circulation. 1992;86: 1138–46.

Walsh EP, Saul JP, Sholter GF, et al. Evaluation of a staged treatment protocol for rapid automatic junctional tachycardia after operation for congenital heart disease. J Am Coll Cardiol. 1997;29:1046–53.

Yeager SB, Hougen TJ, Levy AM. Sudden death in infants with chaotic atrial rhythm. Am J Dis Child. 1984;138: 689–92.

Junctional Tachycardia: Congenital, Acquired, Postoperative

11

Adam C. Kean, Matthew Hazle, Martin J. LaPage, and Burt I. Bromberg

Intracardiac Electrophysiology of Junctional Tachycardia

Postoperative junctional ectopic tachycardia (JET) does not require invasive electrophysiology evaluation or treatment. However, both congenital JET and focal junctional tachycardia (FJT) may be successfully treated with catheter ablation. Electrophysiologic study demonstrates a His bundle electrogram preceding the QRS with normal His-V interval (Fig. 11.1). There is usually at least transient AV dissociation; when retrograde AV node conduction is present (Fig. 11.2), VA time is short, with earliest retrograde A preceding or buried within the QRS complex. Atrial activation is concentric but can be seen anywhere along the atrial septum. The observation of AV dissociation with a longer AA interval than HH interval eliminates both atrial tachycardia and AV reentry via a concealed septal accessory pathway as possible etiologies. While this observation also makes AV nodal reentrant tachycardia (AVNRT) unlikely, additional maneuvers are helpful to confirm the diagnosis and rule out typical AVNRT.

Junctional tachycardia is not reproducibly initiated or terminated with programmed stimulation. Tachycardia initiation is not dependent on a critical A-H interval. During junctional tachycardia, a carefully timed single premature atrial complex (PAC) delivered during His refractoriness does not affect the timing of the subsequent His. In the case of AVNRT, a carefully timed single delivered during His refractoriness will conduct antegradely down the AV nodal slow pathway resulting in either perturbation of the subsequent His or termination of tachycardia (Chap. 3, Fig. 3.22). The ability to advance the immediate His with PAC placed before depolarization of the junctional area is 100 % specific for junctional tachycardia. If atrial overdrive pacing at a cycle length shorter than that of the tachycardia shortens the AV interval, the presence of dual AV node pathways (and thus AVNRT) can be eliminated (Fig. 11.3). Response to cessation of atrial pacing demonstrating an A-H-H-A response indicates junctional tachycardia, similar to V-A-A-V response of atrial tachycardia to ventricular overdrive pacing and A-H-A response during AVNRT.

A.C. Kean, M.D., M.P.H. (✉)
Section of Pediatric Cardiology, Indiana University School of Medicine, 705 Riley Hospital Drive, Riley research Room 127, Indianapolis, IN 46202, USA
e-mail: akean@iu.edu; ackean@gmail.com

M. Hazle, M.D.
Pediatric Cardiology, Wake Forest Baptist Health, Wake Forest University, Winston Salem, NC, USA

M.J. LaPage, M.D., M.S.
Pediatric Cardiology, The University of Michigan Congenital Heart Center, Department of Pediatrics and Communicable Diseases, University of Michigan, Ann Arbor, MI, USA

B.I. Bromberg, M.D.
Department of Pediatrics, Mercy Clinic, St. Louis, MO, USA

M. Dick, II (ed.), *Clinical Cardiac Electrophysiology in the Young*,
DOI 10.1007/978-1-4939-2739-5_11

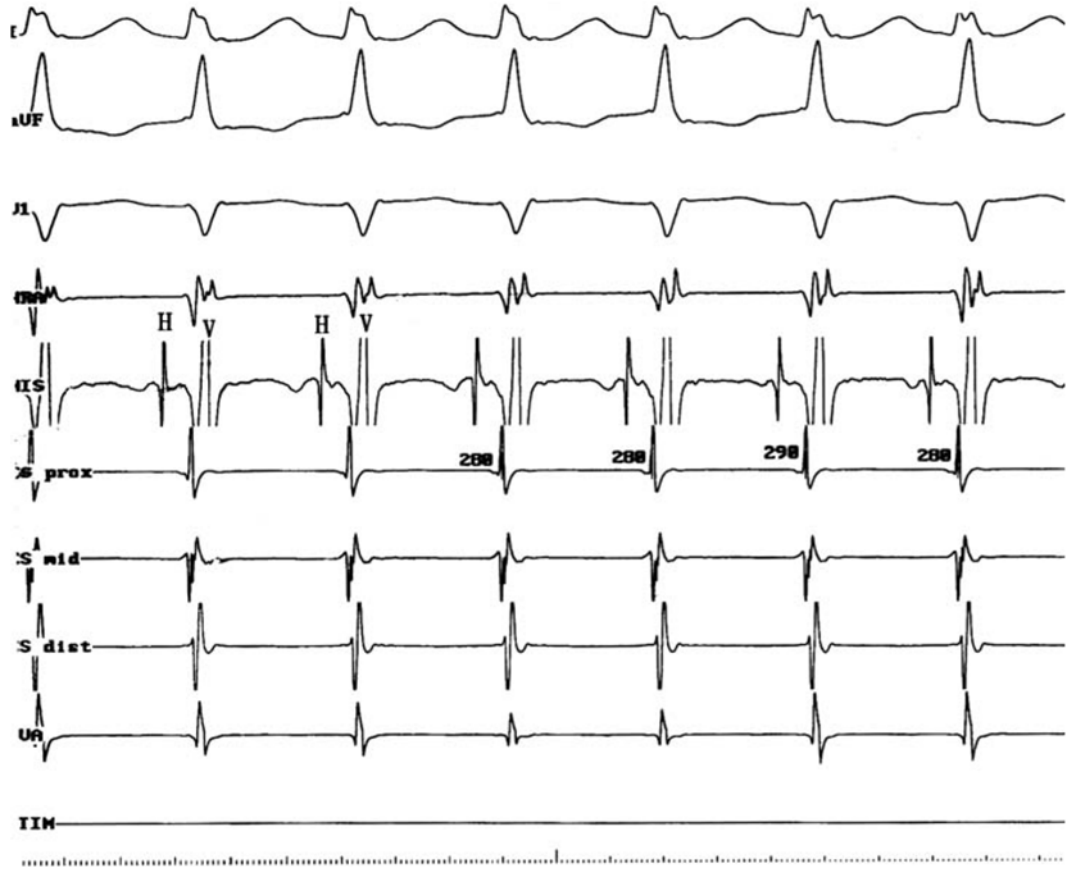


Fig. 11.1 Junctional ectopic tachycardia. The AH interval is 240 ms during the junctional ectopic tachycardia, which has a cycle length of 290 ms. The long AH interval and short or negative VA interval is consistent with both typical AV node reentry tachycardia (AVNRT), where antegrade conduction proceeds down the slow pathway and junctional tachycardia

Postoperative Junctional Ectopic Tachycardia

Natural History

Postoperative JET (PO-JET) is the most common form of an abnormal automatic rhythm in children. The exact mechanism for this arrhythmia is unknown; however, the fluid and electrolyte shifts of the early postoperative state, trauma, stretch, local edema, or ischemia in the region of the AV node and/or His bundle are likely candidates. Similar to the non-postoperative forms of junctional tachycardia, PO-JET is an automatic arrhythmia displaying warm-up and cool-down transitions to sinus rhythm. The onset is typically during the first 72 h post-op and in the great majority of patients, during the first 24 h. The heart rate during PO-JET can range from 150 to 240 bpm, potentially compromising cardiac output (Fig. 11.4). The atria and ventricles are activated nearly simultaneously from impulses originating within the His bundle causing the contraction of the atria against closed atrioventricular valves (Fig. 11.5). This lack of atrioventricular synchrony compromises the cardiac output by decreasing ventricular filling. Uncontrolled, this tachycardia may further lead to a fall in blood pressure, initiating a downward

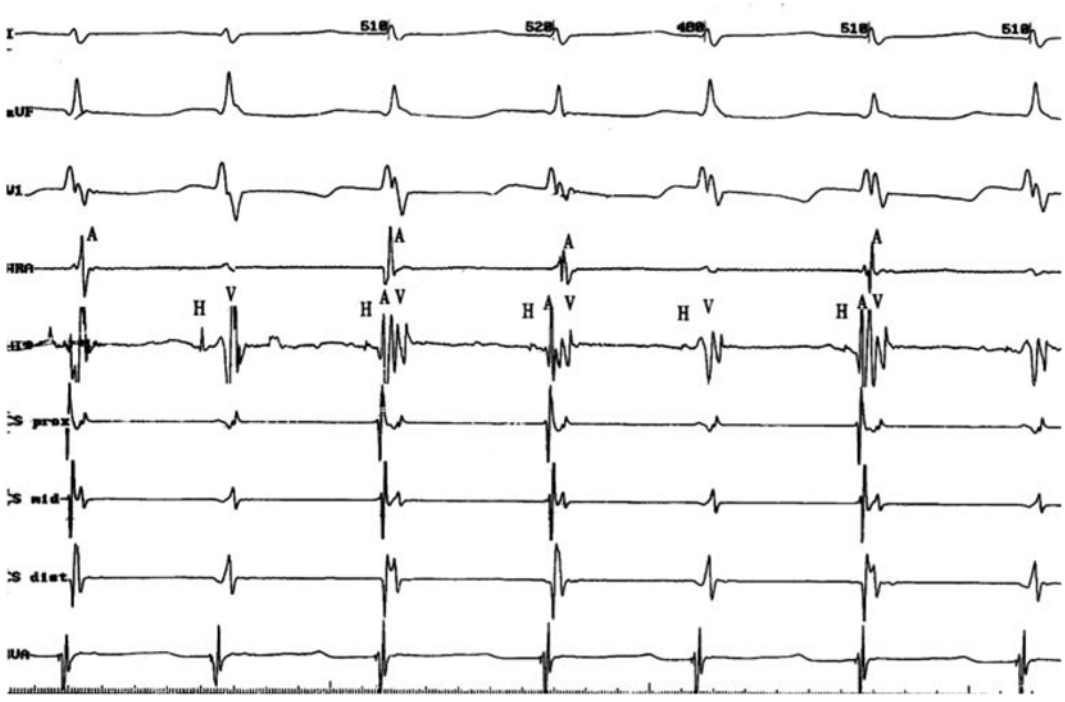


Fig. 11.2 JET with V-A dissociation. V-A dissociation without interruption of the tachycardia is most apparent in the HRA and CSp tracings. *HRA* high right atrium, *His* His bundle, *CSp* coronary sinus proximal, *CSd* coronary sinus distal, *RVA* right ventricular apex

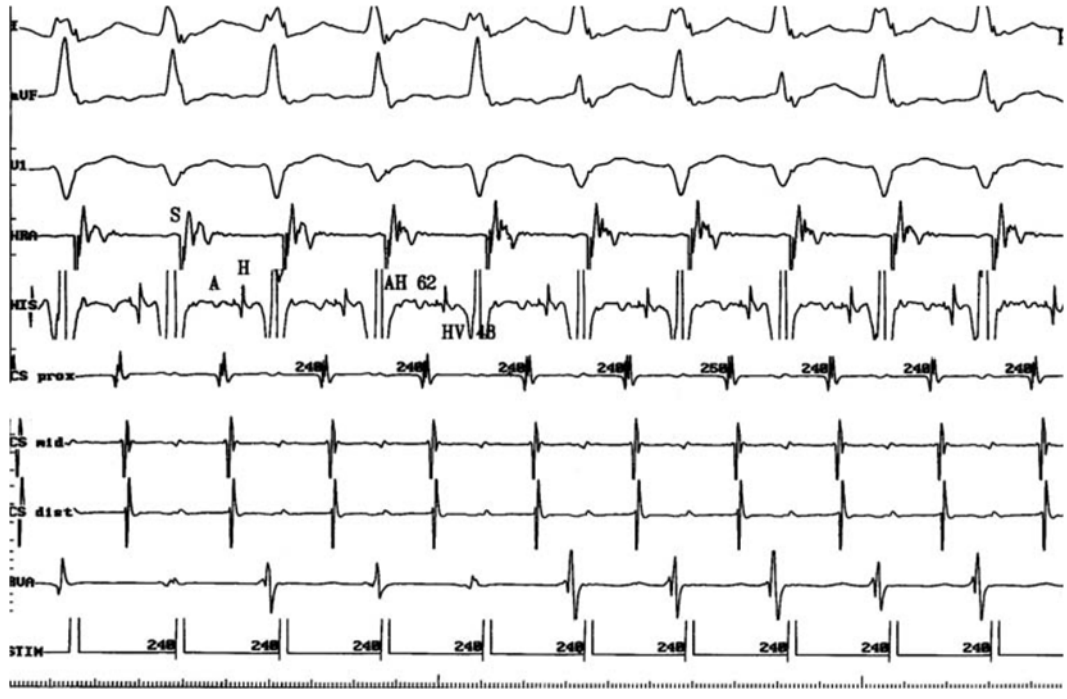


Fig. 11.3 Atrial pacing at a slightly faster rate (cycle length 240 ms) *reduces* the AH interval to 62 ms. This eliminates slow pathway conduction as a consideration, thereby excluding typical AVNRT as a possible mechanism

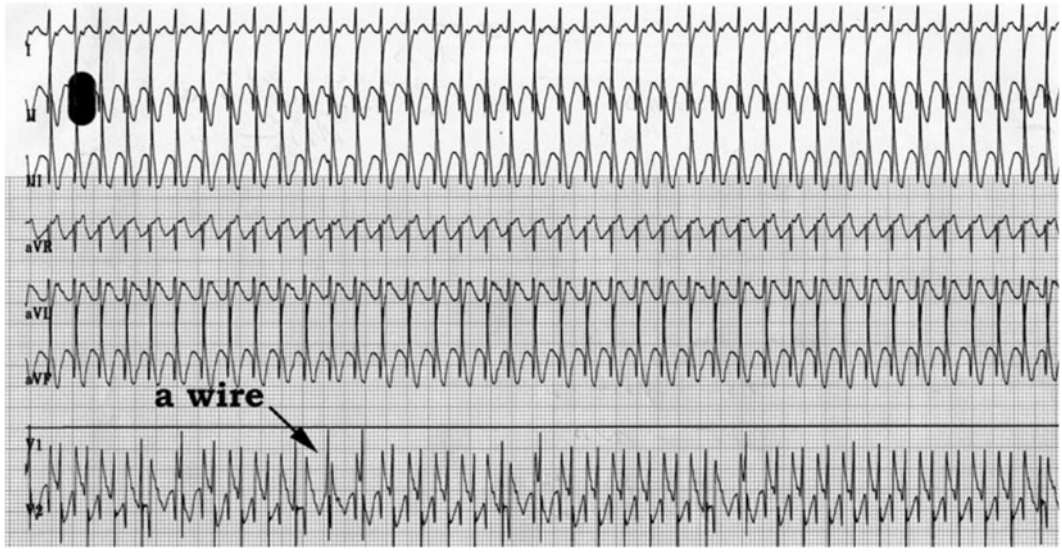


Fig. 11.4 Postoperative JET in 4-month-old girl following a repair of an atrioventricular septal defect (complete). The heart rate is approximately 260 bpm. Note the atrioventricular dissociation clearly demonstrated by recording of the atrial electrogram through the transthoracic temporary atrial epicardial electrode "a wire"; the "a" rate is approximately 160 bpm; there is variable retrograde conduction from (or capture of the atrium by) the ectopic junctional focus to the atrium. She responded to amiodarone and had an otherwise normal postoperative course. This illustration underscores the importance of postoperative transthoracic wires in diagnosing arrhythmias

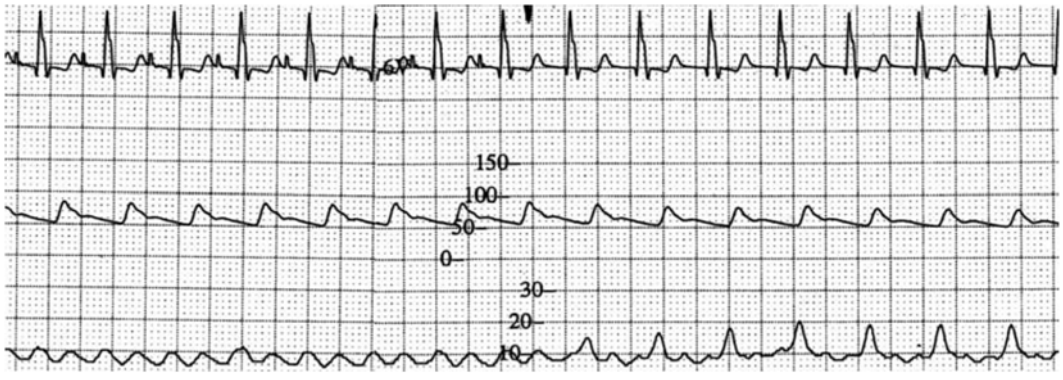


Fig. 11.5 ECG tracing, blood pressure (*middle*), and right atrial recording (*bottom*) in a 2-year-old post-Fontan patient in the intensive care unit. In the left-hand part of the tracing, there is sinus tachycardia (CL = 410 ms) with a blood pressure of 85/50 mmHg, and a right atrial pressure of peak 10 mmHg. In the right-hand part of the tracings, there is junctional rhythm (CL = 430 ms) with "canon" waves of 15–20 mmHg and a blood pressure of 75/50 mmHg, due to loss of atrioventricular synchrony and thus atrial "kick"

spiral characterized by increased endogenous catecholamines and increased inotropic support to maintain adequate blood pressure and renal perfusion. As a result of vasoconstriction, the patient's skin may feel cool, but the core temperature rises because of an inability to dissipate heat. This increase in endogenous and exogenous adrenergic input as well as the elevation in core temperature exacerbates the tachycardia. Thus, it is critical to interrupt this cycle of escalating heart rate, increasing vasoconstriction, and falling cardiac output. Although postoperative JET

is often self-limited, slowing to a tolerable heart rate within 48 h, rapid rates (≥180–190 bpm) associated with decreasing blood pressure require intervention. The slower rates often do not need treatment or only need atrial pacing at a slightly higher rate than the junctional rate to provide atrial-ventricular synchrony, and they rarely persist beyond 5–7 days.

The natural history of postoperative JET is time-dependent resolution, regardless of treatment, usually within 24–48 h. Early reports cited up to a 16% mortality. More recently with improved understanding and treatment, a fatal outcome is now uncommon, though there is an increased risk of perioperative death in patients experiencing JET compared to those without JET.

Incidence and Risk Factors

Many studies over the past two decades have attempted to establish the incidence and risks of developing postoperative JET. The reported incidence of JET varies widely from 1.4 to 15 % when all open cardiac operations for congenital malformations are considered. However, a number of lesions are the predominate ones at risk, including tetralogy of Fallot (14–37 %), repair of anomalous pulmonary venous return (36 %), arterial switch operation (23 %), atrioventricular canal (10–21 %), Norwood procedure (20 %), and interrupted aortic arch repair (17 %). Even Blalock–Taussig shunt placement has been reported to result in PO-JET, despite the fact that no intracardiac manipulation is performed. Other risk factors are longer duration of cardiopulmonary bypass, longer aortic cross clamp time, patient temperature, and elevated biomarkers of cardiac injury. Inotrope use, especially dopamine and milrinone, have been correlated to higher risk of JET. Specific genetic polymorphisms, such as the angiotensin-converting enzyme insertion/deletion polymorphism also appear to predispose to JET.

The wide variation in incidence is likely dependent on multiple factors, including an era effect and different center practices. One major cause of variation is the lack of a standard definition of JET across these studies. Early studies on PO-JET differentiated it from other tachyarrhythmias by failure of overdrive pacing or DC cardioversion. Even today the precise definition of JET remains unclear—either exclusively having VA dissociation or inclusive of both VA dissociated and 1:1 conducting arrhythmias provided the tachycardia is diagnosed "JET" in the patient's medical record. The former criteria will underdiagnose those patients who conduct 1:1 retrograde consistently during JET. The latter interpretation will overdiagnose JET, including other normal complex QRS tachycardias with 1:1 conduction and simultaneous VA or short VA conduction. Visualization of the onset or offset of the tachycardia or other diagnostic maneuvers (overdrive pacing, adenosine) is necessary for a completely accurate diagnosis.

Treatment

The treatment of postoperative JET has evolved over the past two decades. The initial steps are reduction of catecholaminergic stimuli along with, hypothermia, atrial pacing, antiarrhythmic medications, and time.

Hypothermia induction to 32–34° using extracorporeal cooling or intravenous cooling is effective for slowing the rate. This strategy is also used to allow atrial pacing at 10–20 bpm above the JET rate, thereby restoring atrioventricular synchrony. The JET rate typically needs to be <180 bpm to successfully overdrive the rhythm. This goal can also be achieved with antiarrhythmic medications.

Nearly all intravenous antiarrhythmic medications have been evaluated as therapy for PO-JET. The earliest studies showed that digoxin has some effect, but beta-blockers, phenytoin, and calcium channel blockers were found to be relatively ineffective and carried an increased risk of complication due to their negative inotropic effects. The class IC antiarrhythmics, flecainide, and propafenone have been the subjects of favorable reports in small single center studies. Importantly, procainamide reduces JET rates in a dose-dependent manner. Despite the demonstra-

tion of efficacy and the absence of side effects in these prospective studies, procainamide may lead to significant causing hypotension secondary to sympathetic ganglion blockade.

Amiodarone is the most widely studied antiarrhythmic for the treatment of PO-JET. It appears most efficacious when administered as 1 or 2 loading doses of 5 mg/kg followed by a continuous infusion. A double-blind randomized controlled drug trial evaluated the efficacy of three different amiodarone dosing strategies on incessant tachyarrhythmias in pediatrics. While a dose-dependent time to effect was found for the entire dosing level cohorts, JET as a subgroup did not show significant difference in efficacy across dosing levels cohort. The study also found a dose-dependent risk of side effects: 36 % of patients experienced hypotension (undefined); 20 %, bradycardia (undefined); and 15 %, atrioventricular conduction block. Amiodarone has also been used prophylactically after tetralogy of Fallot repair as a 48 h continuous infusion (2 mg/kg/day) with a decrease in the occurrence of JET (10 %) as compared to a control group (37 %). It is important to remember the high incidence of acute, chronic, and potentially severe side effects of amiodarone when considering it as a treatment strategy for this self-limited arrhythmia.

Magnesium supplementation during cardiopulmonary bypass for repair of congenital heart defects (unspecified) was the subject of a prospective randomized double-blind trial to reduce PO-JET. It reduced the incidence of PO-JET in the high dose group, 50 mg/kg of magnesium sulfate ($n=40$) to zero. Dexmedetomidine, an alpha-2-adrenergic receptor agonist has shown some early promise as a treatment as well.

Many centers employ a staged treatment protocol to address PO-JET, utilizing a sequential combination of treatments. Initial interventions include reduction of inotropic support and catecholaminergic stimuli, if possible, including sedation and paralysis. Cooling followed by active cooling and antiarrhythmic medications are instituted subsequently. Atrial pacing above the JET rate should be considered at any stage. The rapidity that one moves through the levels of treatment is dependent on the patient's clinical status and response to intervention. Because PO-JET is a transient arrhythmia, it is important to weigh the use of treatment with the clinical need. Stable PO-JET, without significant hemodynamic consequence, can be treated solely by removal of stimuli, cooling, and patience.

Congenital Junctional Ectopic Tachycardia

Congenital JET (Fig. 11.6) is a rare arrhythmia occurring in patients 6 months of age or younger, not associated with a cardiac operation. Affected infants often present with symptoms of congestive heart failure or fetal hydrops in the setting of an incessant tachycardia. Some infants may initially appear compensated only to subsequently develop cardiovascular collapse. Patients with congenital JET are most likely to have incessant tachycardia and more likely to have sustained rather than sporadic tachycardia. The heart rate typically is >200 bpm, although it may be as slow as 130–150 bpm. Criteria for diagnosis are identical to those for PO-JET, but given the rarity of the disorder, a high index of suspicion is needed.

Congenital JET is associated with a relatively high mortality risk. The incessant nature of the tachycardia may lead to secondary cardiomyopathy and congestive heart failure. An early large multicenter report showed an overall mortality rate of 35 % in 27 congenital JET patients gathered over 17 years. In a larger, more recent cohort, mortality was 9 %. Those patients who do not succumb to early hemodynamic compromise will show spontaneous slowing of the junctional rate; yet follow-up Holter evaluation >5 years after apparent symptom resolution may show persistent JET at slower rates during periods of sleep when the sinus rate slows.

Incidence and Risk Factors

Congenital JET is rare. A review of all non-postoperative JET patients from 22 centers over

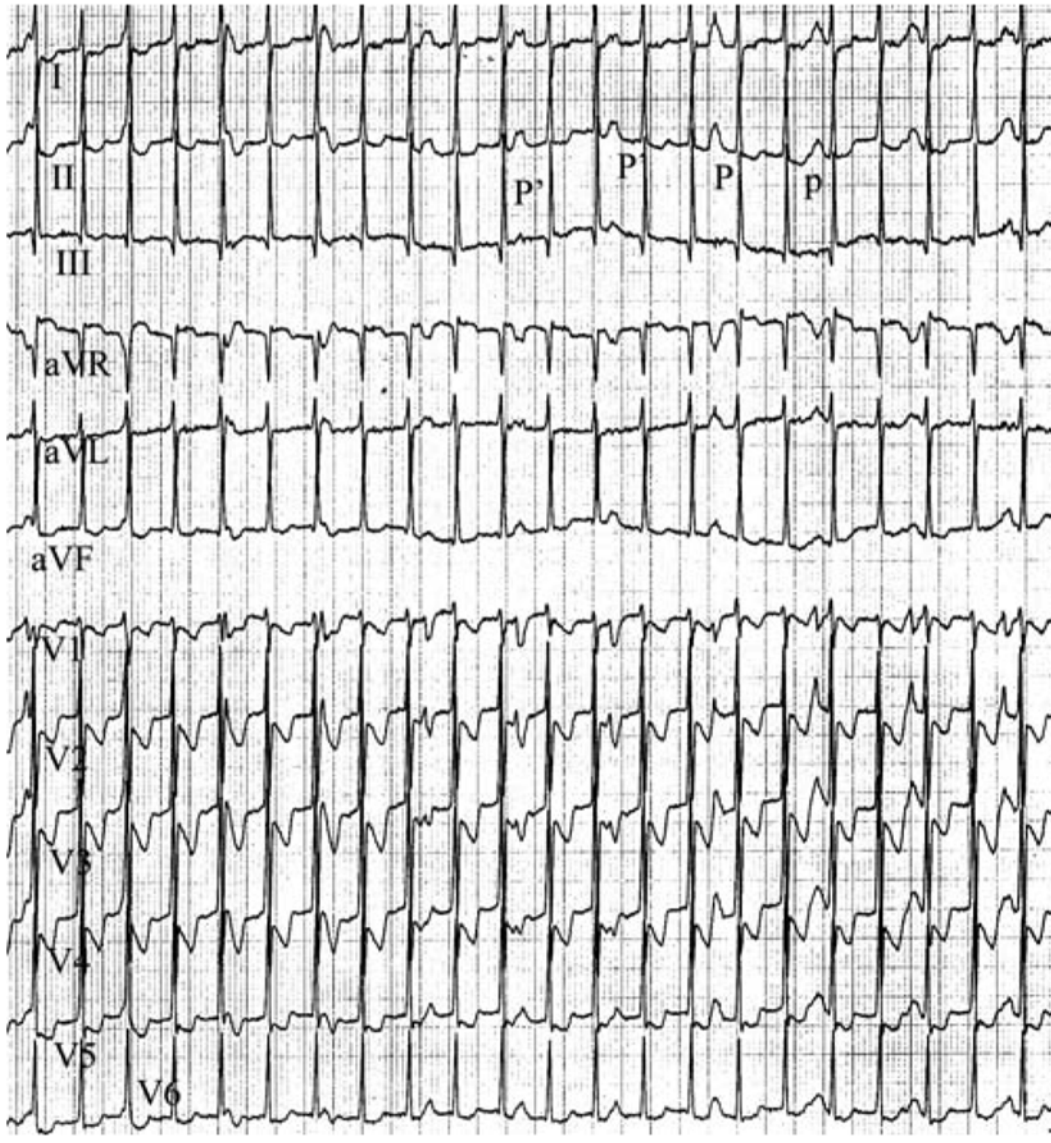


Fig. 11.6 12-Lead ECG of congenital JET in a 9-month-old girl. Note the narrow QRS tachycardia at 170 bpm and AV dissociation (large P-waves in lead II. Note brief period of 2:1 retrograde conduction to the atria (P′). This girl was treated with amiodarone for 12 months and the arrhythmia subsided. The amiodarone was discontinued and JET has not returned after 9 years

40 years identified just 44 patients with tachycardia at 6 months or less. Maternal and neonatal risk factors are unclear due to the rarity of the diagnosis. Fetal tachycardia was found in 36 % of the congenital JET population and an association with family history of JET and minor congenital heart defects was noted. The influence of maternal auto-antibodies is unknown.

Etiology

The mechanism of congenital JET involves the area of the atrioventricular junction (Fig. 11.7). Histologic abnormalities of the AV node and His bundle identified at autopsy include entrapment, distortion, and division of the AV node within the central fibrous body, left-sided AV node,

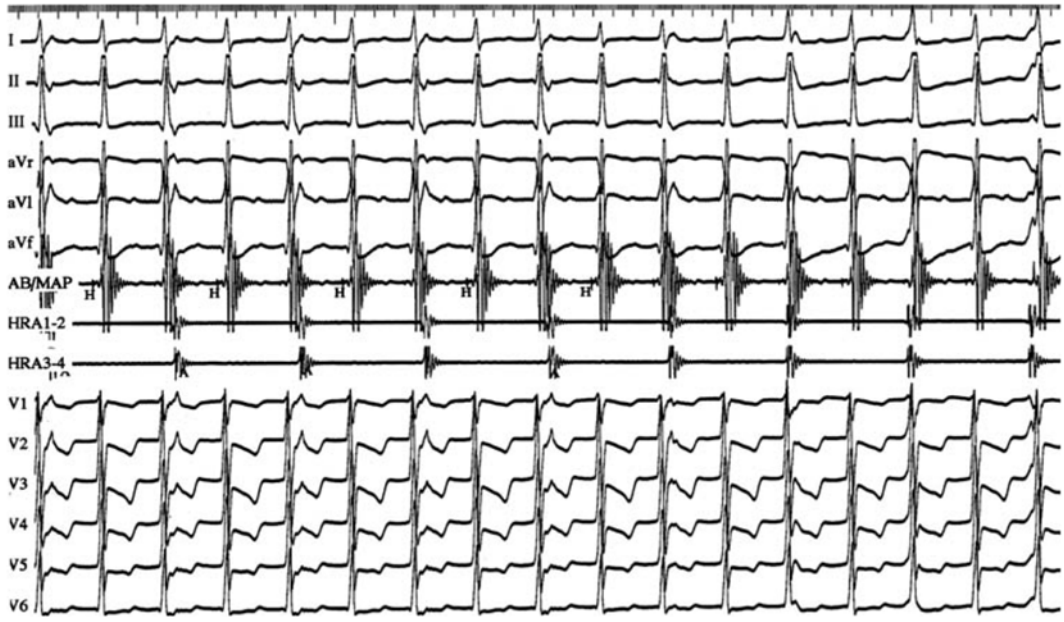


Fig. 11.7 Same patient as in Fig. 11.6. There is a His bundle (H) tracing (ABMAP) and intra-atrial electrograms (HRA 1–2 and 3–4) recorded through closely spaced bipolar electrodes, along with 12-lead ECG. The tracing shows a ventricular rate of 100 bpm, each V preceded by an H potential. There is atrioventricular dissociation with an atrial rate of about 50 bpm. The His bundle rhythm confirms the anatomic region of congenital JET

fibrosis, inflammation, and focal degeneration. This has led to speculation that in addition to tachycardia-induced cardiomyopathy, sudden death in these patients may be due to complete heart block. Furthermore, a familial pattern observed in half of the patients implicates an apoptotic degeneration of the AV node and His bundle in some cases.

Treatment

Because of the rarity of congenital JET, treatment is empiric. Initial therapy is antiarrhythmic medication in all but those few requiring first-line ablation. A wide variety of agents have been used, and in most cases two or more agents are necessary to either convert or reduce the tachycardia burden. Amiodarone appears to be the treatment of choice, most frequently cited as a single agent or as part of a successful treatment regimen. Beta-blockers are the next most common medication used. In a single case report, ivabradine, a new agent that inhibits the cardiac pacemaker "funny" current I(f) was successful in terminating the tachycardia after amiodarone and beta-blocker failed and the combined use of flecainide and sotalol produced only periodic rate control.

In the absence of hemodynamic improvement secondary to spontaneous or pharmacological resolution of the tachycardia, ablation is the definitive treatment. Prior to the availability of intravenous amiodarone in the United States, intentional AV node radiofrequency ablation followed by permanent ventricular pacing was an option; however, it is now rarely used. With increased experience, radiofrequency and cryoablation of the arrhythmia focus can be successfully performed with preservation of atrioventricular conduction. In a cohort involving both congenital and older FJT patients, initial success and

recurrence rates were similar for RF and cryo at 82–85 % and 13–14 %, respectively. Pacemaker implantation was required in 14 % of these, 10 % due to complete AV block.

Focal Junctional Tachycardia

Focal junctional tachycardia (FJT; Fig. 11.8) also referred to as automatic junctional tachycardia can present as either a paroxysmal or non-paroxysmal arrhythmia. The paroxysmal form is usually seen in otherwise healthy children, adolescents, and adults without structural heart disease, although cases in patients with congenital heart disease have also been described. In contrast to congenital JET, FJT is not typically incessant. It demonstrates sudden onset and termination with durations lasting from seconds to hours (Fig. 11.9). Episodes can occur infrequently or multiple times per day, often triggered by catecholaminergic stress. Children may report episodic palpitations, headache, lightheadedness, or presyncope. However, they are often asymptomatic and clinical suspicion arises based on physical exam demonstrating a rapid or irregular heart rate. The non-paroxysmal form of FJT is most commonly observed in adults with acute myocardial ischemia, digoxin toxicity, chronic obstructive pulmonary disease, rheumatic carditis, electrolyte disturbances (hyperkalemia, hypercalcemia), or postcardiac surgery. Although the tachycardia is usually more frequent, the rates are slower, in the 70–120 bpm range, therefore symptoms may be minimal or absent.

The diagnosis is based on ECG evaluation (see above). In the non-paroxysmal form, ECG typically shows gradual tachycardia onset in which the junctional rate overtakes the sinus rate (Fig. 11.10). At times of increased adrenergic stimulation (e.g., fever, stress, exertion), the tachycardia is often sustained and more rapid. While rapid prolonged episodes may precipitate symptoms, Holter monitoring frequently demonstrates slower tachycardia rates of which the patient is unaware.

Unlike the incessant postoperative and congenital forms, FJT tends to be clinically well tolerated due to its brief duration. However, symptoms and hemodynamic instability (syncope) have been described in pediatric and adult patients. The non-paroxysmal form may persist for decades before diagnosis. The risk for tachycardia-induced cardiomyopathy appears to be related to tachycardia burden. Sudden death is rare in otherwise healthy patients.

Etiology

Consistent with the other junctional tachycardias, the mechanism of paroxysmal FJT appears to be one of enhanced automaticity within the AV node. This is supported by clinical tachycardia features (catecholamine sensitivity, warm-up period) and invasive data showing antegrade AV block above the level of the His bundle in response to beta-blocker administration. Although rare, rapid atrial or ventricular pacing can, at times, initiate tachycardia and there have been reports of adenosine sensitivity, suggesting triggered activity in the AV node region.

Treatment

The decision to treat is based largely on symptom intensity, duration, and frequency. In asymptomatic cases, this type of arrhythmia can be monitored without therapy. Ambulatory Holter monitoring or exercise stress testing should be performed to assess tachycardia burden during catecholamine stimulation. Serial echocardiograms may be indicated to monitor ventricular function. For symptomatic patients, beta-blockers are an appropriate initial choice for rate control. For refractory cases, class I agents (flecainide, propafenone) and class III agents (sotalol, amiodarone) are commonly used either alone, in combination with beta-blocker or digoxin, or with each other with various degrees of success. Given the potential side effects of these medications, persistent and/or symptomatic cases are typically treated with radiofrequency or cryothermal catheter ablation, especially in the setting of deteriorating ventricular function.

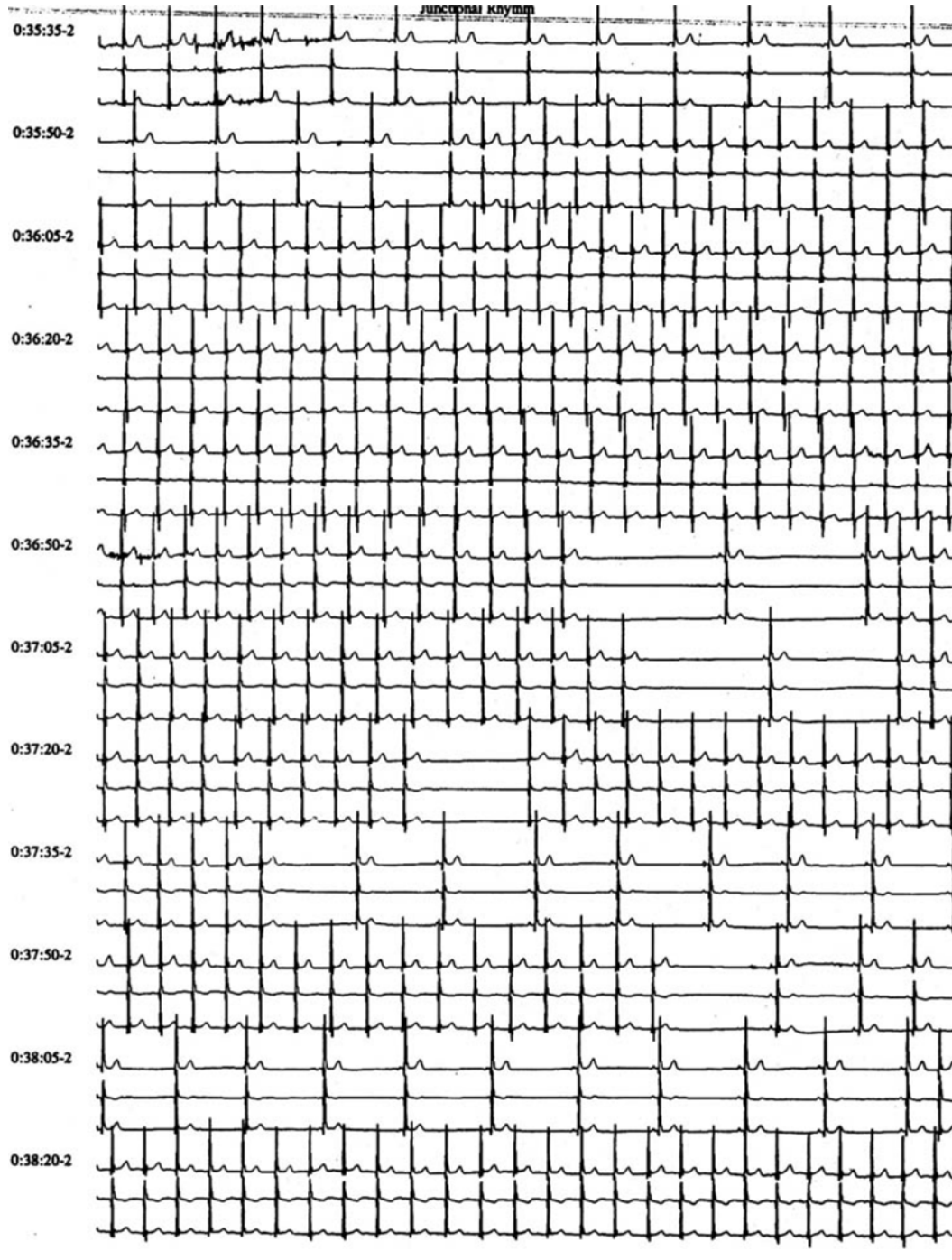


Fig. 11.8 Holter tracing of a 7-year-old boy with focal junctional tachycardia. Note the junctional tachycardia (no P-wave) and post-tachycardia suppression of the escape beats. His tachycardia was successfully ablated using cryothermal energy

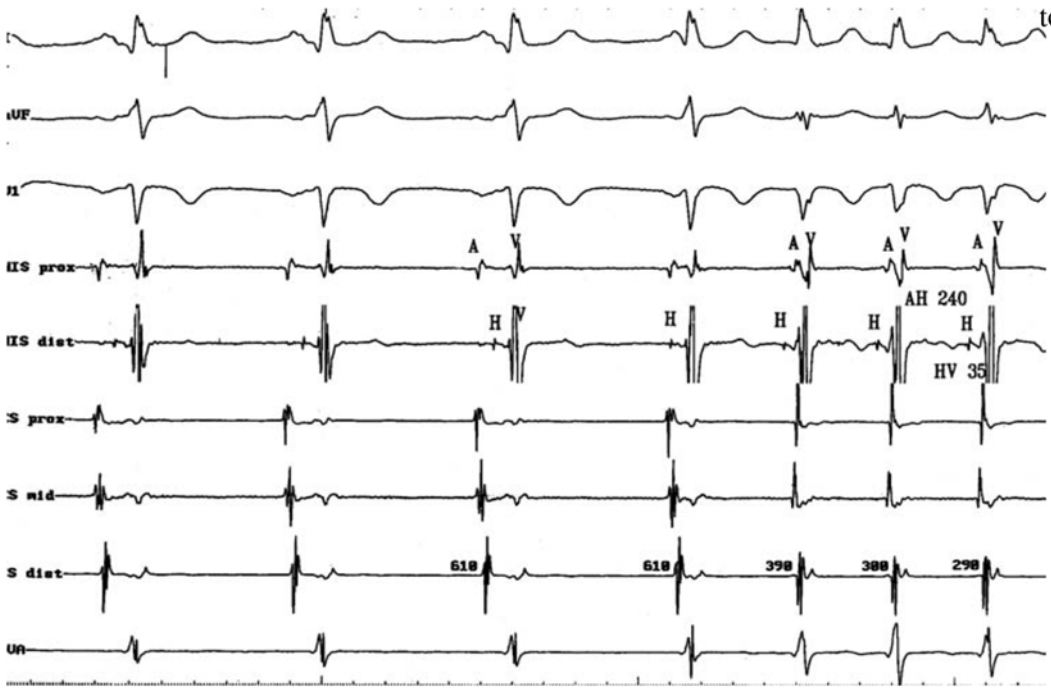


Fig. 11.9 Three ECG leads (I, aVR, V1) and His bundle tracings (fourth and fifth from the *top*) and three coronary sinus electrograms with right ventricular (bottom training) electrogram. The tracing initially demonstrates sinus rhythm, with a PR interval of 120 ms. The junctional rhythm suddenly accelerates capturing the atrium retrograde

Transcatheter Ablation

The goal of catheter ablation is to eliminate the arrhythmia focus while preserving AV nodal function. Modern mapping systems facilitate identification of the location of the His potentials, guiding placement of ablation lesions appropriately to minimize damage to the compact AV node. While the origin of tachycardia is often immediately adjacent to the His bundle, initial ablation at the site of earliest atrial activation during tachycardia has been shown to be a successful strategy. Isoproterenol can be used to increase tachycardia frequency during the EP study to facilitate mapping and to support post-ablation success. In the absence of VA conduction, empiric ablation in the AV node slow pathway region, followed by progressive applications in the mid-septal, then followed by superior septal locations may be necessary. Ablation at the site of tachycardia termination during catheter manipulation and cryomapping has also been described. Cryotherapy is often used first line in order to avoid permanent damage to the compact AV node.

Treatment outcomes are generally favorable. Acute success and recurrence rates are approximately 85–100 % and 0–15 %, respectively. Among the cohort of all non-postoperative JET (about half of which was congenital), at a mean 4.5-year follow-up, 75 % were well without need for medical therapy. Of this group 46 % were patients that had undergone successful ablation, 30 % had spontaneous resolution, 16 % had persistent but well-tolerated JET at slower rates, and 8 % had permanent pacing and no JET. While reported cases of complete heart block range from 5 to 18 % with radiofrequency ablation of FJT, there have been no reported cases of permanent heart block with cryotherapy.

In summary, junctional tachycardia describes three distinct clinical entities: PO-JET, Congenital JET, and FJT, all likely due to abnormal (increased) automaticity of the AV junction.

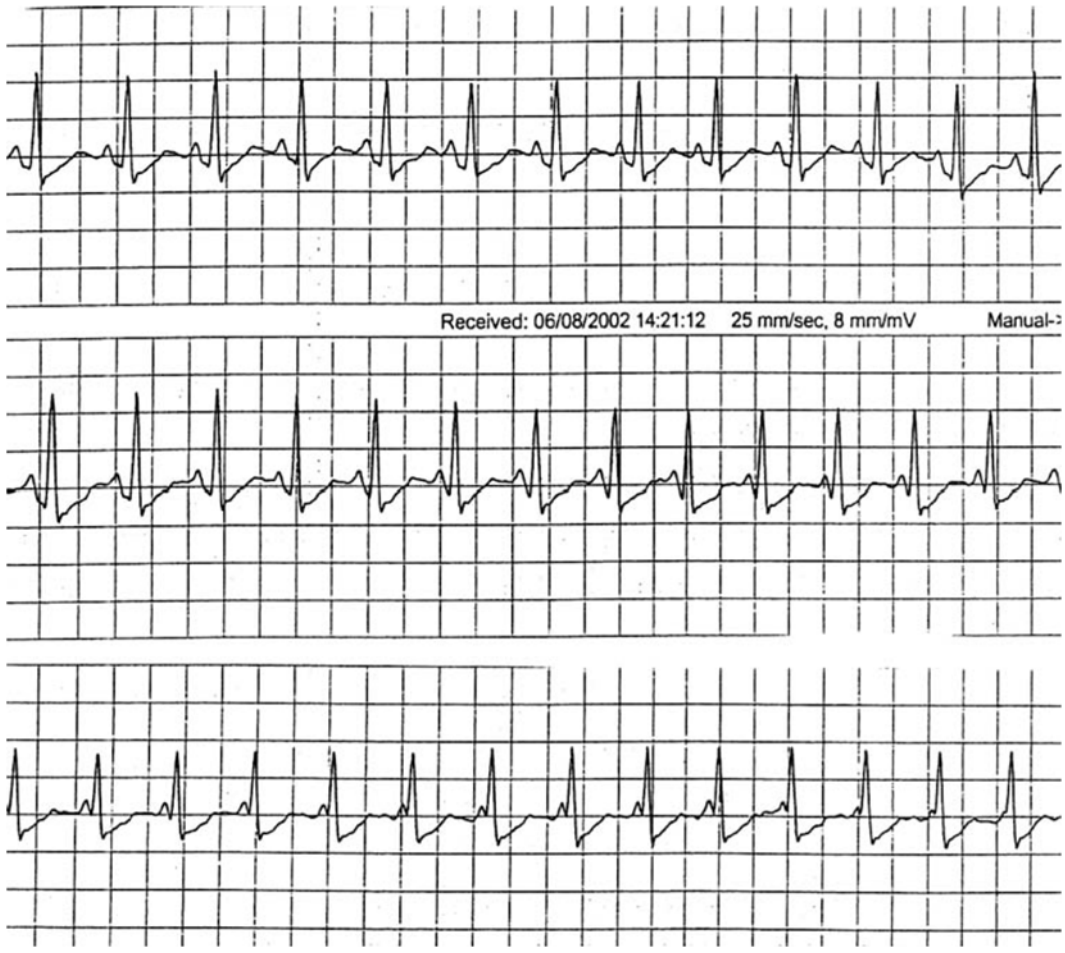


Fig. 11.10 JET on Holter monitoring. The tracing initially demonstrates sinus rhythm, with a PR interval of 120 ms. However, the PR interval gradually shortens as the junctional focus accelerates. Eventually, the P-wave is buried within the QRS complex, clearly implying a tachycardia that originates independently within the AV node or His bundle

PO-JET continues to account for significant morbidity in the postoperative patient, but is often treatable, and always time limited. Congenital JET is rare though often presents with hemodynamic compromise requiring urgent treatment. FJT is usually well tolerated and increasingly well treated by ablation in the EP lab.

Suggested Reading

Al-Ghamdi S, Al-Fayyadh M, Hamilton RM. Potential new indication for ivabradine: treatment of a patient with congenital junctional ectopic tachycardia. J Cardiovasc Electrophysiol. 2013;24:822–4.

Andreasen JB, Johnson SP, Ravn HB. Junctional ectopic tachycardia after surgery for congenital heart disease in children. Intensive Care Med. 2008;34:895–902.

Bash SE, Shah JJ, Albers WH, Geiss DM. Hypothermia for the treatment of postsurgical greatly accelerated junctional ectopic tachycardia. J Am Coll Cardiol. 1987;10:1095–9.

Batra AS, Chun DS, Johnson TR, Maldonado EM, Kashyap BA, Maiers J, Lindblade CL, Rodefeld M, Brown JW, Hubbard JE. A prospective analysis of the incidence and risk factors associated with junctional ectopic tachycardia following surgery for congenital heart disease. Pediatr Cardiol. 2006;27:51–5.

Borgman KY, Smith AH, Owen JP, Fish FA, et al. A genetic contribution to risk for postoperative junctional ectopic tachycardia in children undergoing surgery for congenital heart disease. Heart Rhythm. 2011;8:1900–4.

Bronzetti G, Formagari R, Giardini A, Frascaroli G, et al. Intravenous flecainide for the treatment of junctional ectopic tachycardia after surgery for congenital heart disease. Ann Thorac Surg. 2003;76:148–51.

Collins KK, Van Hare GF, Kertesz NJ, Law IH, et al. Pediatric non-postoperative junctional ectopic tachycardia medical management and interventional therapies. J Am Coll Cardiol. 2009;53:690–7.

Darst JR, Kaufman J. Case report: an infant with congenital junctional ectopic tachycardia requiring extracorporeal mechanical oxygenation. Curr Opin Pediatr. 2007;19:597–600.

Delaney JW, Moltedo JM, Dziura JD, et al. Early postoperative arrhythmias after pediatric cardiac surgery. J Thorac Cardiovasc Surg. 2006;131:1296–301.

Dodge-Khatami A, Miller OI, Anderson RH, Goldman AP, et al. Surgical substrates of postoperative junctional ectopic tachycardia in congenital heart defects. J Thorac Cardiovasc Surg. 2002;123:624–30.

Dubin AM, Cuneo BF, Strasburger JF, Wakai RT, et al. Congenital junctional ectopic tachycardia and congenital complete atrioventricular block: a shared etiology? Heart Rhythm. 2005;2(3):313–5.

Garson Jr A, Moak JP, Smith RT, Norton JB. Usefulness of intravenous propafenone for control of postoperative junctional ectopic tachycardia. Am J Cardiol. 1987;59:1422–4.

Gillette PC. Evolving concepts in the management of congenital junctional ectopic tachycardia. Circulation. 1990;81:1713–4.

Grant JW, Serwer GA, Armstrong BE, Oldham BE, et al. Junctional tachycardia in infants and children after open heart surgery for congenital heart disease. Am J Cardiol. 1987;59:1216–8.

Hoffman TM, Bush DM, Wernovsky G, Cohen M, Wieand TS, Gaynor JW, Spray TL, Rhodes LA. Postoperative junctional ectopic tachycardia in children: incidence, risk factors, and treatment. Ann Thorac Surg. 2002;74:1607–11.

Imamura M, Dossey AM, Garcia X, Shinkawa T, et al. Prophylactic amiodarone reduces junctional ectopic tachycardia after tetralogy of Fallow repair. J Thorac Cardiovasc Surg. 2012;143:152–6.

Kelly BP, Gajarski RJ, Ohye RG, Charpie JR. Intravenous induction of therapeutic hypothermia in the management of junctional ectopic tachycardia: a pilot study. Pediatr Cardiol. 2010;31:11–7.

Kovacikova L, Hakoacova N, Dobos D, Skrak P, et al. Amiodarone as a first line therapy for postoperative junctional ectopic tachycardia. Ann Thorac Surg. 2009;88:616–23.

Laird WP, Snyder CS, Kertesz NJ, Friedman RA, et al. Use of intravenous amiodarone for postoperative junctional ectopic tachycardia in children. Pediatr Cardiol. 2003;24:133–7.

Makhoul M, Oster M, Fischbach P, Das S, et al. Junctional ectopic tachycardia after congenital heart surgery in the current surgical era. Pediatr Cardiol. 2013;34:370–4.

Mandapati R, Byrum CJ, Kavey REW, et al. Procainamide for rate control of postsurgical junctional tachycardia. Pediatr Cardiol. 2000;21:123–8.

Manrique AM, Arroyo M, Lin Y, Khoudary SR, et al. Magnesium supplementation during cardiopulmonary bypass to prevent junctional ectopic tachycardia after pediatric cardiac surgery: a randomized controlled study. J Thorac Cardiovasc Surg. 2010;139:162–9.

Mildh L, Hiippala A, Rautiainen P, Pettila V, et al. Junctional ectopic tachycardia after surgery for congenital heart disease: incidence, risk factors, and outcome. Euro J Cardio Thorac Surg. 2011;39:75–80.

Moak JP, Arias P, Kaltman JR, Cheng Y, et al. Postoperative junctional ectopic tachycardia: risk factors for occurrence in the modern surgical era. PACE. 2013; 00:1–13.

Perry JC, Fenrich AL, Hulse JE, Triedman JK, et al. Pediatric use of intravenous amiodarone: efficacy and safety in critically ill patients from a multicenter protocol. J Am Coll Cardiol. 1996;27:1246–50.

Pfammatter J-P, Paul T, Ziemer G, Kallfelz HC. Successful management of junctional tachycardia by hypothermia after cardiac operations in infants. Ann Thorac Surg. 1995;60:556–60.

Plumpton K, Justo R, Haas N. Amiodarone for postoperative junctional ectopic tachycardia. Cardiol Young. 2005;15:13–8.

Raja P, Hawker RE, Chaikitpinyo A, Cooper SG, et al. Amiodarone management of junctional ectopic tachycardia after cardiac surgery in children. Br Heart J. 1994;72:261–5.

Sarubbi B, Vergara P, D'Alto M, Calabro R. Congenital junctional ectopic tachycardia: presentation and outcome. Indian Pacing Electrophysiol J. 2006;3(3):143–7.

Saul JP, Scott WA, Brown S, Marantz P, et al. Intravenous amiodarone for incessant tachyarrhythmias in children: a randomized, double-blind, antiarrhythmic drug trial. Circulation. 2005;112:3470–7.

Smith AH, Owen J, Borgman KY, Fish FA, Kannankeril PJ. Relation of milrinone after surgery for congenital heart disease to significant postoperative tachyarrhythmias. Am J Cardiol. 2011;108:1620–4.

Tobias JD, Chrysostomou C. Dexmedetomidine: antiarrhythmic effects in the pediatric cardiac patient. Pediatr Cardiol. 2013;34:779–85.

Villain E, Vetter VL, Garcia JM, Herre J, et al. Evolving concepts in the management of congenital junctional ectopic tachycardia. A multicenter study. Circulation. 1990;81:1544–9.

Walsh EP, Saul JP, Sholler GF, Triedman JK, et al. Evaluation of a staged treatment protocol for rapid automatic junctional tachycardia after operation for congenital heart disease. J Am Coll Cardiol. 1997; 29:1046–53.

Zampi JD, Hirsch JC, Gurney JG, Donohue JE, et al. Junctional ectopic tachycardia after infant heart surgery: incidence and outcomes. Pediatr Cardiol. 2012; 33:1362–9.

Multifocal Atrial Tachycardia

12

Johannes C. von Alvensleben and David J. Bradley

Clinical Context

Whereas adults have multifocal atrial tachycardia (MAT) primarily during exacerbations of chronic respiratory disease, pediatric patients are a heterogeneous group and comprise the healthiest to the most severely ill. Similar to adults, all large pediatric MAT series demonstrate a significant association (30–60 %) with respiratory illness, including both infectious processes, such as bronchiolitis or croup, and noninfectious conditions such as respiratory distress syndrome of prematurity and bronchomalacia. Resolution of the arrhythmia does not always exactly parallel recovery from the respiratory illness or its treatment. Nor does oxygen saturation per se appear linked to the presence of MAT. But the most common presentation of MAT, in approximately half of cases, is as an incidental finding in an otherwise healthy infant. The markedly rapid and irregular rhythm may be an unexpected observation in a presumed well child. A history of recent viral upper respiratory symptoms may be elicited, but in many patients there is none. Such children may give no hint of cardiac symptoms or congestive heart failure.

MAT in the context of severe, life-threatening illness, including myocarditis and birth asphyxia, has been described. As in other forms of supraventricular tachycardia, sustained or recurrent, rapid MAT has the potential to affect cardiac function, with reports of up to a third of patients presenting with cardiomyopathy. In our series, 27 % (4 of 15) patients who had echocardiograms demonstrated either dilation of cardiac chambers or abnormal indices of function. Longitudinal follow-up of these patients revealed that the cardiac function normalized once the arrhythmia resolved.

Patients with structural heart disease may comprise up to 33 % of pediatric MAT, though the routine monitoring of cardiac patients probably leads to over-representation of this patient subgroup. No particular cardiac lesion has emerged as associated with the incidence of MAT, although coarctation of the aorta, hypertrophic cardiomyopathy, atrial septal defect, tetralogy of Fallot, and complex single ventricle lesions have been reported. Thus, a thorough evaluation of the patient with newly diagnosed MAT is necessary to identify any coexisting conditions that may impact the patient's prognosis.

Patients may have other atrial arrhythmias before and after MAT develops. Atrial flutter and

J.C. von Alvensleben, M.D. (✉)
Department of Cardiology, Children's Hospital Denver, University of Colorado School of Medicine, Aurora, CO, USA
e-mail: jvonalve@med.umich.edu

D.J. Bradley, M.D.
Pediatric Cardiology, The University of Michigan Congenital Heart Center, Department of Pediatrics and Communicable Diseases, University of Michigan, Ann Arbor, MI, USA

M. Dick, II (ed.), *Clinical Cardiac Electrophysiology in the Young*,
DOI 10.1007/978-1-4939-2739-5_12

ectopic atrial tachycardia have been observed in pediatric patients, and atrial fibrillation, more commonly seen in adults, may be transiently induced by the rapid atrial activation of MAT.

Most children diagnosed with MAT are infants, although documentation in a fetus using echocardiography and fetal monitoring has been described in the later weeks of gestation. Patients over 5 years of age are unusual.

Incidence

MAT accounts for a very small proportion of arrhythmias treated in large pediatric cardiology centers. As an estimate of its incidence in healthy newborns, a survey of the heart rhythms of 3,383 infants by ambulatory monitoring identified two (0.02 %) with MAT.

Clinical Course

The course of MAT, regardless of treatment, is self-limited. Half of patients will have no residual evidence of MAT 5 months after diagnosis (Fig. 12.1). In our long-term follow-up study, late recurrence was not observed.

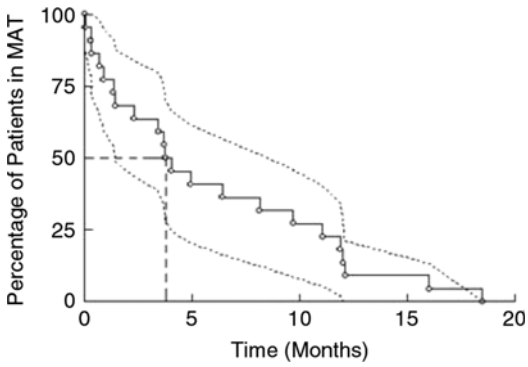


Fig. 12.1 Resolution of MAT. Fifty percent of patients (indicated by *broken line*) were free of arrhythmia 5 months after diagnosis. The dotted line indicates a 95 % confidence interval. [Reprinted from Bradley DJ, et al. The clinical course of multifocal atrial tachycardia in infants and children. *J Am Coll Cardiol* 2001;38(2): 401–408. With permission from Elsevier.]

Electrocardiographic Features

MAT is typically very irregular and can be rapid, with atrial rates as high as 400 beats per minute (Fig. 12.2). Care must be taken to identify different P-wave forms on the ECG, as the isoelectric period between discrete p-waves distinguishes this rhythm from the other irregularly irregular rhythms such as atrial fibrillation or atrial flutter with variable ventricular conduction. Often readily apparent on a surface ECG, the use of adenosine, beta-blockers, and calcium channel blockers has been described to slow the ventricular response allowing better delineation of the underlying p-wave morphology.

The effort to find the requisite P-waves for the diagnosis is often prompted by MAT's signature ECG appearance, which includes scattered, aberrantly conducted beats and pauses, due to sinus node suppression after a run of MAT beats as well as blocked conduction of premature atrial impulses (Fig. 12.2). Extended recordings demonstrate periods of sinus rhythm alternating with MAT in most patients.

Mechanism

Just as there is some disagreement about the correct term for this arrhythmia (some authors prefer the term "chaotic atrial tachycardia"), a conclusive mechanistic explanation for MAT remains elusive. Abnormal automaticity, ectopic foci, and triggered activity have all been suggested. Proponents of the term "multifocal" infer that different P-wave forms and irregular PP and PR intervals imply the presence of several ectopic foci in the atria. Ectopic atrial tachycardia, where a single ectopic focus is the source of the tachycardia, exhibits many of characteristics of MAT including resistance to cardioversion and a "warm up" and "cool down" response. However, if an ensemble of ectopic foci gives rise to the arrhythmia, it is unexpected that they would trigger each other's depolarization, rather than each creating spontaneous, unifocal atrial runs at separate times.

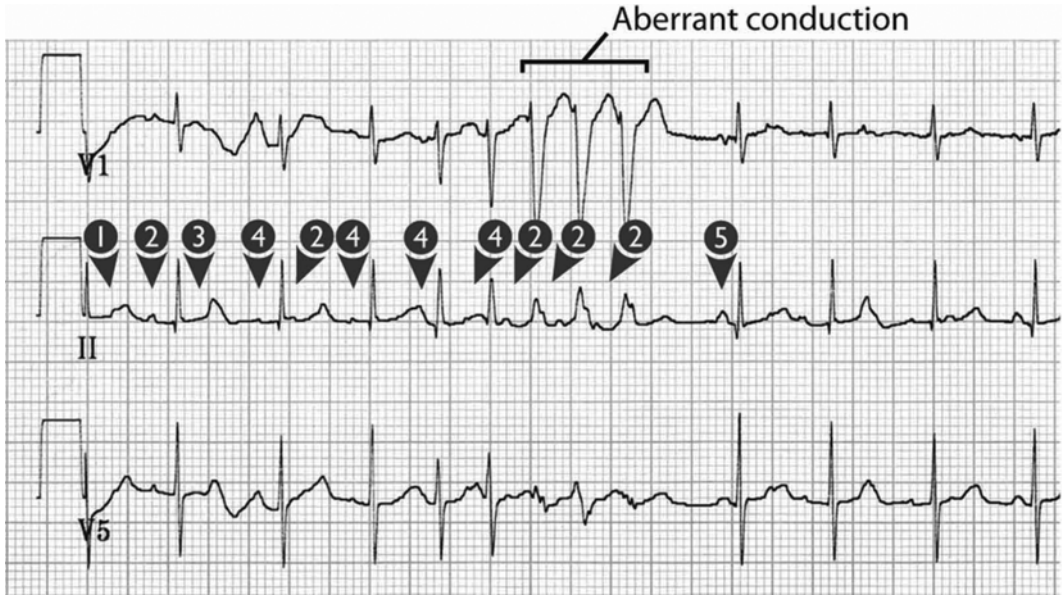


Fig. 12.2 Three electrocardiograph leads (V1, II, V5) in a 3-month-old boy with MAT. Note the five different P-wave morphologies (*arrows*), the fifth being that of sinus activation. Note also the aberrant conduction (complexes 8–10 from the *left*). [Reprinted from Bradley DJ, et al. The clinical course of multifocal atrial tachycardia in infants and children. *J Am Coll Cardiol* 2001;38(2): 401–408. With permission from Elsevier.]

An alternative mechanistic explanation is variable propagation through the atrium of rapid impulses from a single focus. Supportive of this concept is one report of successful radiofrequency ablation of MAT in an infant at a single atrial site.

In isolated atrial preparations, the conditions associated with MAT, i.e., hypoxia, beta-adrenergic stimulation, hypokalemia, and acidosis, have produced abnormal rhythmic behavior most consistent with triggered activity.

The poor response of MAT to direct current cardioversion and to overdrive pacing and the observed cycle length irregularity are strong evidence that the mechanism is not reentrant.

Antiarrhythmic Therapy

The poor response of MAT to standard, "first-line" antiarrhythmic agents compels the clinician to make the assessment whether treatment is necessary at all. Though correction of magnesium deficit, administration of beta-blockers (such as metoprolol) and calcium channel blockers (verapamil) are considered effective in adults, no consistent response to any of these agents has been described in pediatric patients. The reported treatment strategies are varied and future well-designed trials are unlikely given the rarity of the arrhythmia. With regard to beta-blockade, the reported patients with MAT treated with agents in this class have shown no clear response. And calcium channel blockers are—based on some evidence of their risks—usually avoided in infants, the core patient age group. Class IC agents, such as flecainide and propafenone, were effective in multiple small case series of children with both normal hearts and structural disease. Amiodarone appears to be the current treatment of choice for pediatric MAT, when treatment is necessary. The lack of pro-arrhythmic characteristics makes it an attractive option for those patients presenting in congestive heart failure or with cardiomyopathy; however, its long half-life and significant

side effects are problematic when treating a self-limited arrhythmia. In the sickest group of MAT patients, those with severe ventricular dysfunction, intravenous amiodarone must be administered with caution, as it may acutely exacerbate their already compromised state.

Patient Management

The asymptomatic infant with newly diagnosed MAT who has no evidence of intercurrent illness, cardiac malformation, or significant dysfunction may be observed regularly as an outpatient without further investigation. Follow-up should include ECG and ambulatory (Holter) monitoring, as MAT may occur sporadically and not be detected on ECG alone. The patient should be followed until there is no further evidence of MAT; an excellent outcome can be anticipated.

The patient with suspected cardiac pathology should have anatomy and function defined by echocardiogram. Concurrent illness should be treated. Periods of MAT can be expected to alternate with sinus rhythm on cardiac monitor. If the patient's reduction in cardiac function is significant or complicates other conditions, medical therapy with amiodarone or a class IC agent should be begun. Outcome in such patients will depend on recovery of function and resolution of the associated condition. Once the rhythm has normalized, recurrence is not expected.

Suggested Reading

Bradley DJ, Fischbach PS, Law IH, Serwer GA, et al. The clinical course of multifocal atrial tachycardia in infants and children. J Am Coll Cardiol. 2001;38(2):401–8.

Houyel L, Fournier A, Davignon A. Successful treatment of chaotic atrial tachycardia with oral flecainide. Int J Cardiol. 1990;27(1):27–9.

Hsieh MY, Lee PC, Hwang B, Meng CC. Multifocal atrial tachycardia in 2 children. J China Med Assoc. 2006;69(9):439–43.

Lapage MJ, Bradley DJ, Dick 2nd M. Verapamil in infants: an exaggerated fear? Pediatr Cardiol. 2013; 34(7):1532–4.

Shine KI, Kastor JA, Yurchak PM. Multifocal atrial tachycardia Clinical and electrocardiographic features in 32 patients. N Engl J Med. 1968;279(7):344–9.

Southall DP et al. Frequency and outcome of disorders of cardiac rhythm and conduction in a population of newborn infants. Pediatrics. 1981;68(1):58–66.

Yeager SB, Hougen TJ, Levy AM. Sudden death in infants with chaotic atrial rhythm. Am J Dis Child. 1984; 138(7):689–92.

Ventricular Tachycardia

13

Nicholas Von Bergen and Craig J. Byrum

Introduction

Physicians caring for the young, when faced with a wide QRS complex tachycardia on electrocardiogram, are often hesitant to assign a diagnosis of ventricular tachycardia (VT), especially since the patient is often minimally symptomatic. Though young patients frequently present with rate-related aberrancy associated with supraventricular tachycardia (SVT), VT accounts for an estimated ~80 % of all wide complex rhythms across all ages. The incidence of VT in the pediatric population has been estimated around 1 in 100,000, though studies have suggested that short undetected episodes of VT may occur rarely in the general population.

When confronted with a wide QRS complex tachyarrhythmia in a child, it is always important to first consider the diagnosis of VT, and then look for other causes of the wide complex tachyarrhythmias when the diagnosis of VT has been excluded. Although most VT in young patients occurs in the setting of a structurally normal heart, those with underlying heart disease are at greater risk. As many as 15 % of patients with complex congenital heart disease (native or repaired) may develop ventricular arrhythmias over a lifetime which may be associated with an increased risk sudden death or a cardiac arrest. In addition, VT may develop in the setting of acquired myocardial disease, which can be either acute (ischemic, toxic, or inflammatory) or chronic (myopathic, neoplastic) and either focal or diffuse. Examples of some of these myocardial disorders include myocarditis, Kawasaki disease, Chaga's disease, tricyclic poisoning, focal tumors, arrhythmogenic right ventricular dysplasia (AVRC, fatty replacement areas), peripartum cardiomyopathy, and dilated or hypertrophic cardiomyopathy.

As the clinical presentation is a function not only of the rate of the tachycardia but also the underlying state of the myocardium, and the resultant blood pressure, young individuals may tolerate even sustained VT for lengthy periods of time. Therefore, the clinical response to VT should be tailored to the individual presentation and may range from conservative management to emergent cardioversion and invasive management.

Ventricular tachycardia implies an arrhythmia that arises from the working ventricular myocardium. Some forms may arise from the distal branches and the Purkinje network. Thus, junctional ectopic tachycardia will be excluded from the present discussion as it originates from the AV node—His bundle area.

N. Von Bergen, M.D. (✉)
Department of Pediatrics, University of Wisconsin—Madison, 1675 Highland Ave., Madison, WI 53792, USA
e-mail: vonbergen@pediatrics.wisc.edu

C.J. Byrum, M.D.
Pediatrics–Cardiology, Syracuse, NY, USA

M. Dick, II (ed.), *Clinical Cardiac Electrophysiology in the Young*,
DOI 10.1007/978-1-4939-2739-5_13

Electrocardiographic (ECG) Diagnosis of VT

There continues to be debate among electrophysiologists regarding the most comprehensive ECG characteristics to diagnose VT. Using relatively intuitive criteria VT can be diagnosed by:

- A QRS complex greater in duration than normal for age—i.e., a wide QRS complex (Fig. 13.1).
- Atrial (A) and ventricular (V) dissociation with more ventricular complexes than atrial complexes (Fig. 13.2).
- A rate greater than 25 % above that of normal sinus rhythm, or greater than 120 bpm in adults.

However, these criteria are not necessarily applicable to the young patients. VT in infants may be associated with QRS durations of only ~80 ms, requiring comparison of the VT-QRS duration and morphology to age-appropriate norms. Although retrograde ventricular-atrial dissociation during VT is virtually diagnostic for VT, a good number of patients may display 1:1 (Fig. 13.1) or retrograde Wenckebach conduction during VT indicating that VA dissociation is not a prerequisite for VT. Because AV dissociation may be difficult to determine, a long rhythm strip may assist in its identification. Adenosine may be given to transiently block retrograde AV nodal conduction to assist in making the diagnosis (Fig. 13.2). Additionally, capture and fusion beats may be identified by a sinus-driven beat conducting antegrade through the AV node and influencing the initial deflection (fusion beat) or normalizing (capture beat) the QRS complex. When this is seen, it suggests a ventricular origin of the wide complex arrhythmia (Fig. 13.3). The likelihood of observing these beats is inversely proportional to the VT rate. In asymptomatic patients with a ventricular rate within ~125 % of the sinus rate an accelerated idioventricular rhythm (AIVR) is likely and is associated with a benign course. AIVR is somewhat more common in infants and children than adults.

In some cases, it may be difficult to distinguish VT from an atrial-driven rhythm with aberrancy of QRS conduction. To improve the diagnostic sensitivity suggested expanded criteria may be employed:

- A QRS complex with both an initial and a terminal conduction delay Fig. 13.4a
- A shift in the QRS axis by more than 40° from baseline
- Fusion beats or capture beats (Fig. 13.3)
- A QRS axis between −90 and 180°
- QRS duration greater than 0.14 s (with RBBB) or 0.16 s (LBBB)
- A taller initial (leftward) peak in the QRS complex in a right bundle branch complex
- A delayed S wave nadir with a notched S down stroke in a left bundle branch complex (Fig. 13.4b)

Though many of these criteria may be useful, they remain imperfect as the sensitivity may be

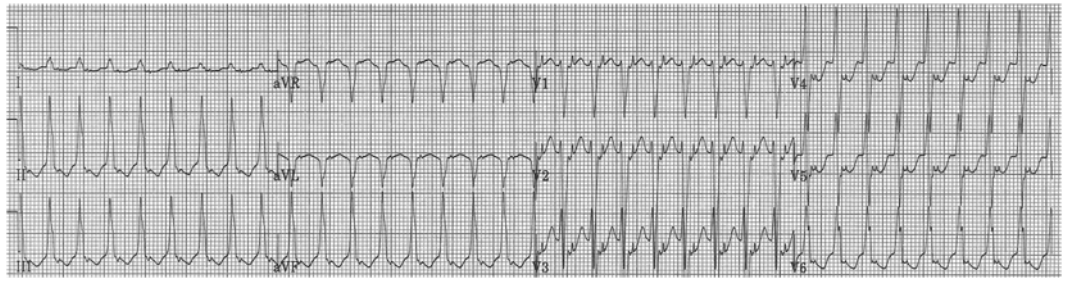


Fig. 13.1 An ECG of ventricular tachycardia presenting in a 3-day-old with mild LV dysfunction. The tachycardia exhibits a left bundle branch block with an inferior axis suggesting origin of the tachycardia from the right ventricular outflow tract. This VT has 1:1 VA conduction, with the P waves most easily seen in V1 and V2

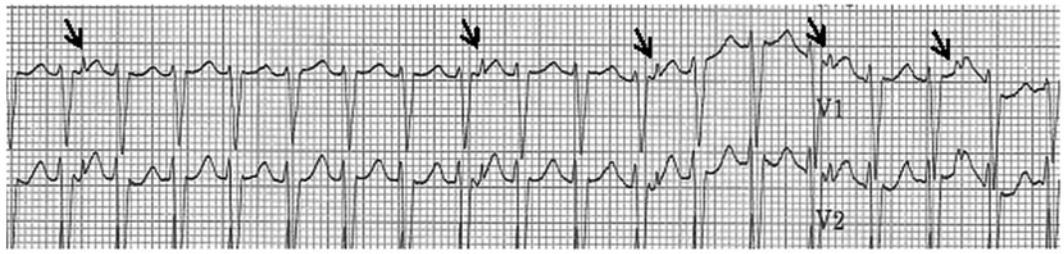


Fig. 13.2 An ECG rhythm strip on the patient from Fig. 13.1 after an adenosine bolus. Note the loss of retrograde VA conduction with adenosine administration confirming VT. Arrows indicate the retrograde P waves

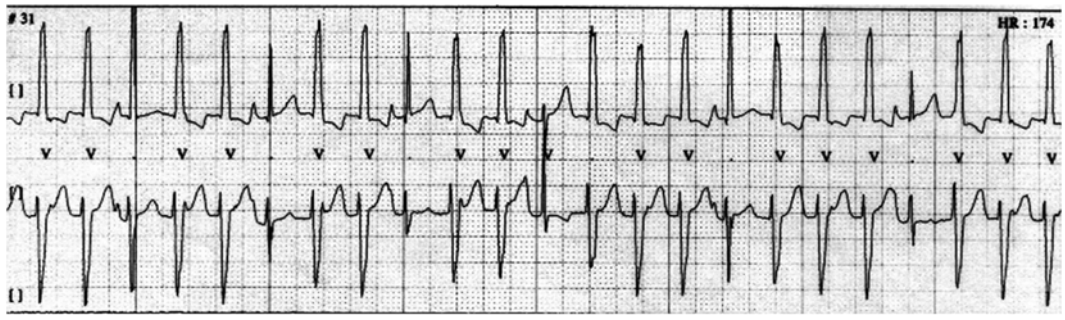


Fig. 13.3 A Holter monitor strip showing lack of VA conduction and fusion complexes (beat three and others) and sinus captures (beat six and others)

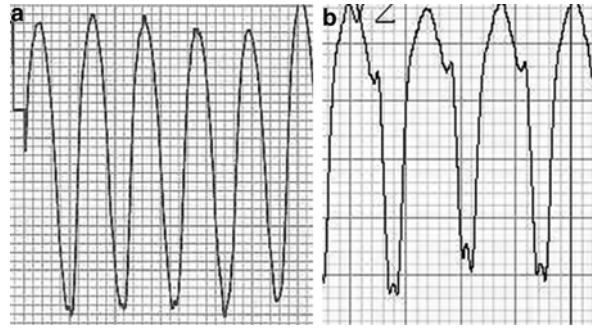


Fig. 13.4 (**a**) A 16-year-old male with VT associated with ARVC showing the initial and terminal conduction delay from V1. (**b**): A notched S negative deflection in a patient with an LBBB appearance VT from V2 from a different patient

below 50 %. Therefore, care should be used when applying them, and other potential criteria to wide QRS tachyarrhythmia diagnosis.

Often vector analysis can be employed to discern the origin of the VT. Because the wave front moves away from the point of origin, an ECG complex in the precordial leads that has predominately leftward forces (with an LBBB appearance) predicts an origin from the right ventricle and, conversely, predominately rightward forces (with an RBBB appearance) predicts an origin from the left ventricle. Further, a frontal plane (from the limb leads) superior QRS axis of the VT suggests origin from the inferior ventricular segments, and conversely, a frontal plane inferior QRS axis suggests origin of the VT from the base of the heart, usually the right ventricular outflow tract or coronary cusps.

Differential Diagnosis of Wide QRS Tachycardia

A wide QRS tachycardia in a young patient strongly suggests VT; however, other possibilities include (Fig. 13.5):

- Supraventricular arrhythmia with rate-related aberrancy (Figs. 13.5a and 13.6)
- Antidromic supraventricular tachycardia (Fig. 13.5b)
- An atrial tachycardia with preexcitation, including a Mahaim fiber (Fig. 13.5c, d)
- Ventricular tachycardia (Fig. 13.5e)
- Tachycardia with a preexisting bundle branch block
- A ventricular paced rhythm

Aberrant conduction (aberrancy) results from a delay in the recovery of the relative refractory period of the bundle branches (usually the right as it has a longer refractory period than the left) as the heart rate changes quickly producing a left or right bundle branch morphology (Figs. 13.5a and 13.6).

At times preexisting wide QRS morphology may manifest as an abnormal wide QRS tachycardia driven by an atrial tachycardia (Fig. 13.7). When possible, especially in patients with congenital heart disease, comparison of the tachycardia QRS morphology to a baseline ECG may be helpful in distinguishing a preexisting wide QRS from a true ventricular arrhythmia.

Other forms of wide QRS tachycardia include antegrade conduction during both sinus rhythm and SVT through a Mahaim fiber (Fig. 13.5d) or through an atriofascicular accessory pathway

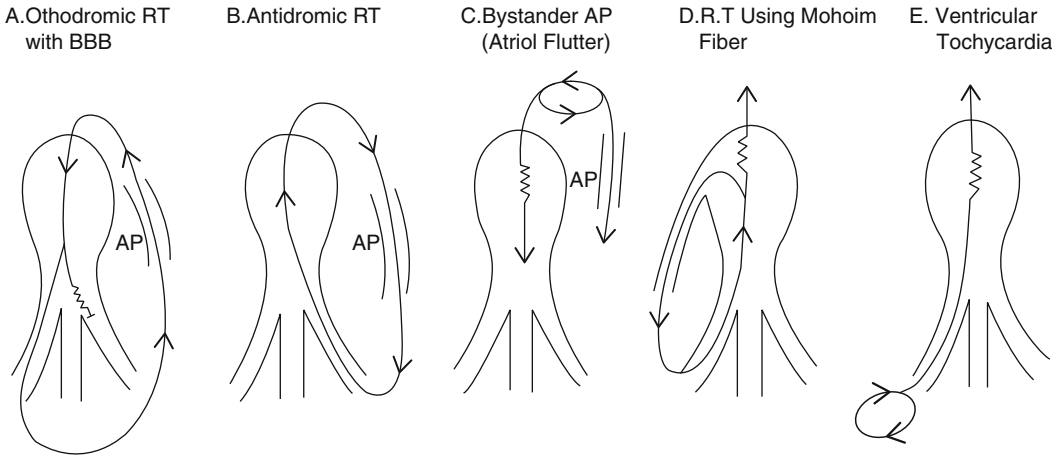


Fig. 13.5 See Differential Diagnosis [Reprinted from Benson DW, et al. Mechanisms of regular wide QRS tachycardia in infants and children. American Journal of Cardiology 1982;49(7):1778–1788. With permission from Elsevier.]

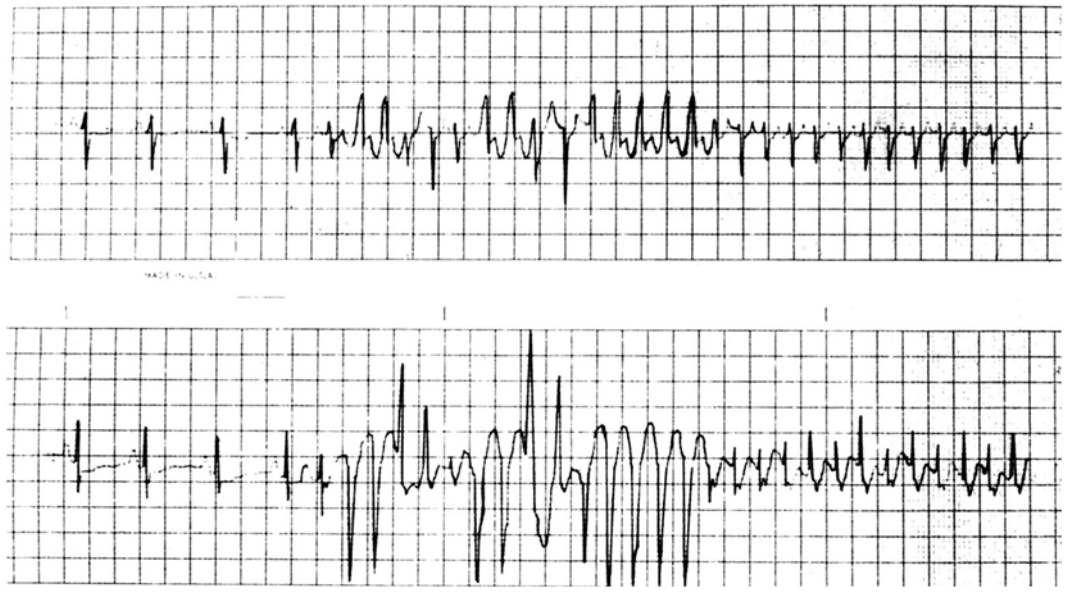


Fig. 13.6 Holter tracing of an infant with SVT and aberrancy [Figure is not a continuous ECG]—i.e., rate-related bundle branch block—both right (positive-wide QRS complexes) and left (negative-wide QRS complexes)—due to the atrial tachycardia impulses encountering relative refractoriness in the bundle branches. The refractory periods shorten in response to the shortened cycle lengths of the tachycardia, eventually normalizing the QRS complex (right-sided beats of upper and lower tracing)

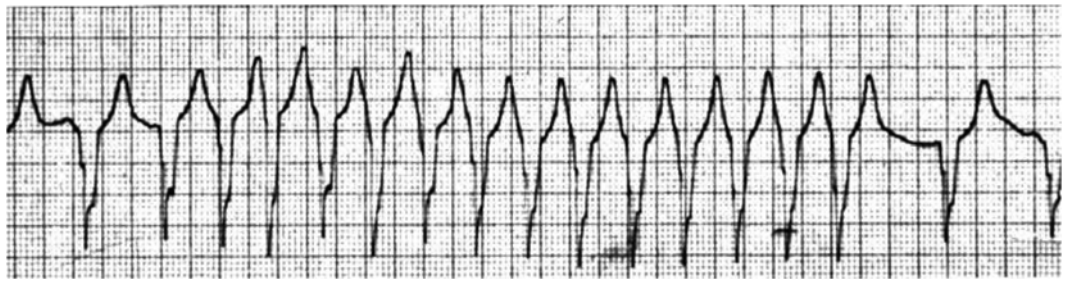


Fig. 13.7 Wide QRS tachycardia in a patient with transposition of the great arteries and ventricular septal defect following the Rastelli operation. Note the first and the last two slow wide QRS complexes are identical to the wide QRS complex tachyarrhythmia, indicating that the wide QRS complex tachycardia is due to a preexisting conduction abnormality

(not shown in Fig. 13.5); both of these anomalous connections are right sided so the wide QRS morphology in both sinus rhythm and SVT is similar and of a LBBB configuration. Rarely, atrial flutter or fibrillation (Fig. 13.5c) in the presence of preexcitation produces a wide complex rhythm due to rapid conduction through the accessory pathway. In other unusual cases, an accessory pathway may provide the atrioventricular limb of a reentrant circuit maximally activating (preexciting) the ventricular myocardium followed by retrograde (antidromic) conduction through the His–Purkinje system—AV node to "reenter" the chambers of origin (atria), resulting in an antidromic tachycardia (Fig. 13.5b); (see Chaps. 4 and 20).

Table 13.1 Factors to consider when classifying VT

Non-sustained	Sustained
Monomorphic	Polymorphic
No heart disease	Structural or function myocardial disease
Focal myocardial process	Diffuse myocardial process
Specific drug response (e.g., calcium blocker)	No specific drug response
Exercise suppressible	Exercise induced
Automatic or triggered automatic	Reentry or multiple reentrant
No underlying electrical disease	Underlying electrical disease

Table 13.2 Classification of VT by duration

Duration of VT	Description
Salvo	A few beats in a row
Non-sustained VT	Typically 3–4 beats in a row up to runs of 30s in duration
Sustained VT	An episode longer then 30s, or requiring termination due to hemodynamic compromise
Repetitive VT	Multiple salvos or non-sustained VT events in close proximity
Incessant VT	Lengthy sustained VT that often dominate the cardiac rhythm

Classification of Ventricular Tachycardia

One may classify VT from a variety of frames of reference including duration, morphology, etiology, association with underlying heart disease, relationship to physical activity and presumed origin of the tachycardia of the origin (Tables 13.1 and 13.2).

Electrocardiographic Morphology

Monomorphic VT refers to one dominant QRS form during VT whereas polymorphic refers to a changing QRS shape and beat-to-beat interval within the episode.

A form of polymorphic VT is "bidirectional tachycardia" where the QRS alters between one form and another, typically flipping its axis every other beat across the baseline. This may be seen in a portion of patients with catecholaminergic polymorphic VT (CPVT), with digoxin toxicity, or with some inherited arrhythmias. Polymorphic VT is considered more predisposed to degeneration to ventricular fibrillation.

Electrophysiologic Mechanism

Understanding of the mechanism of VT may be important in deciding on either medical management strategies or invasive management strategies. Three known arrhythmia mechanisms occur: reentry, automaticity, and triggered automaticity. Reentrant arrhythmias in pediatric and congenital heart patients are seen in the scar formation after cardiac surgery, with myocardial ischemia due to coronary artery anomalies, or with abnormal coronary perfusion related to chronic abnormal loading conditions. These the scarred areas, by virtue of their slow conduction property and their anatomic relationship to other scarred areas or to naturally occurring electrically inert borders like AV grove, may form corridors of slow electrical conduction through which electrical activity may enter, exit, and then reenter. Stretch on the myocardium may induce an extra depolarization and imitate a reentry VT in patients with abnormal loading condition.

Clinical Presentation

Ventricular tachycardia may present with a variety of clinical scenarios. It is not infrequent to encounter patients who are completely asymptomatic with the diagnosis. Often these young patients have no underlying structural heart disease and may have either repetitive non-sustained VT or sustained but rather slow VT. Those patients with non-sustained VT may be picked up by finding an irregular heartbeat during routine examination. There are some patients who have a sensation of a racing heart others, with minimal symptoms. Associated symptoms during tachycardia may include dizziness, particularly

at the onset of tachycardia, vague chest discomfort, some dyspnea, weakness and headache. Surveillance with regular ECG (Holter) monitoring may be helpful; to detect and evaluate this potential late complication.

Sustained VT over time may lead to tachycardia-mediated cardiomyopathy. In the young patient presenting with clinical congestive heart failure in the presence of a chronic, modestly increased rate, VT, in an otherwise structurally normal heart, presents a diagnostic challenge; determination of the primary cause—VT or primary myocardial disease—is required. VT secondary to a primary dilated cardiomyopathy may be best treated with medication and possibly implantable cardio-defibrillator, though the value of the defibrillator is unproven. On the other hand, tachycardia induced heart failure patients may best benefit from primary treatment of the tachycardia either through medication or catheter ablation. Often the cardiac function will return to normal with the elimination of symptoms.

The most serious but rare clinical presentation of VT in the young is syncope or sudden death. These presentations are unusual in a structurally normal heart save for those with underlying electrical disease (inheritable arrhythmia syndromes, see Chap. 19) or those with infiltrative or hypertrophic diseases of the myocardium. Rather, the number of patients with this presentation will be those who have had surgery for congenital heart disease or those who have an acutely or chronically dysfunctional myocardium after infectious or inflammatory insult.

Clinical Investigation

History

As seen in patients with supraventricular tachycardia, patients who perceive VT will typically report a sudden onset and cessation of the arrhythmia. A history of acquired or congenital heart disease and therapy, substance abuse, possible exposure to toxins or contact with infectious agents (viruses) is important. The family history should be explored vigorously, often with a trained genetic counselor, focus on syncope, seizures, sudden death, or specific inheritable cardiac arrhythmia diagnoses.

The Physical Exam

During an arrhythmia, the examination findings reflect the presence of the tachycardia as well as the inefficiency of cardiac contraction and the AV dissociation. The rate would be elevated and pulses may be weak. The observation of cannon waves in the neck reflecting episodic atrial contraction against a closed AV valve would be useful. Diastolic filling sounds may reflect underlying primary cardiomyopathic condition. Abnormal heart sounds, murmurs, rubs, and chest scars will suggest the likely presence of congenital heart disease and the related surgical palliations or corrections. Rarely will VT will respond to vagal maneuvers.

Echocardiogram

Patients with ventricular arrhythmias require an echocardiogram to rule out structural heart disease and to evaluate cardiac function. In addition for those without congenital heart disease, echocardiography (with Doppler) should focus on possible tumors, ventricular hypertrophy as well as myocardial dysfunction brought on by abnormalities of preload or afterload or by conditions primarily affecting contractility.

Cardiac Magnetic Resonance (CMR)

MRI appears to offer the advantage of viewing the ventricles in three dimensions and it may give a better view of both anatomy and function. In addition, it provides a useful sensitivity for detecting myocardial abnormalities such as areas of fatty replacement in the patient with arrhythmogenic right ventricular dysplasia. Delayed enhancement and the presence of fibrosis on CMR have also been suggested as a marker of risk for a patient to develop arrhythmias in hypertrophic cardiomyopathy and other congenital heart populations. In selected cases with scar-related VT, CMR may also assist in the planning process for scar/fibrosis mapping in patients who may undergo an electrophysiologic study and ablation. In selected cases, CMR images may be imported into and merged with electro-anatomical

mapping systems used during catheter electrophysiologic assessment to enhance and clarify points of intracardiac anatomy.

Holter Monitor

Holter monitoring is useful for assessing the results of ablation or medications. It can also give one a measure of the density (percentage of tachycardia beats relative to total beats) of non-sustained VT episodes that may serve to trigger sustained VT episodes.

Treadmill Exercise Testing

Treadmill exercise testing can be helpful for diagnosis of exercised-provoked VT (such as CVPT) and in ascertaining the effectiveness of antiarrhythmic therapy or ablative therapy. Some tachycardias are suppressed by exercise and increasing sinus rates but the prognostic significance of that observation is unclear.

Hemodynamic Catheterization

As part of the electrophysiologic study, hemodynamic data and angiography may be helpful to determine the current hemodynamic status of the heart and circulation, especially in patients with congenital heart disease. Since the primary goal in the management of ventricular tachyarrhythmias in this population is to first improve the hemodynamic status with medical or surgical therapy when appropriate, hemodynamic catheterization and angiography can provide directions. In addition, the coronary arteries are best imaged by the transcatheter-selective coronary approach.

Electrophysiology Study With/Without Ablation

Electrophysiologic investigation may be indicated for those patients with documented non-sustained VT, symptoms suspicious for tachyarrhythmia or a high density of premature ventricular systoles. It may also be indicated to evaluate for sustained VT in those patients with underlying structural heart disease and the effectiveness of orally administered antiarrhythmic therapy. The goal is to determine if the patient has inducible VT that places the individual at higher risk. Even so, sensitivity and specificity of an EP study remains imperfect for prognosis of an arrhythmia.

An ablation may be considered in patients presenting VT if there is substrate that may be effectively eliminated. This is often considered the first line for patients with a monomorphic VT associated with symptoms or functional/structural abnormalities. In others, without a substrate that can be reliably ablated such as channelopathies, or polymorphic VT, an ICD should be considered in place of ablation therapy.

Common Types of Ventricular Tachycardia in the Pediatric Population

Accelerated Ventricular Rhythm (AVR)

This arrhythmia simulates VT but is usually not considered a VT. It has characteristics similar to VT (Figs. 13.8 and 13.9).

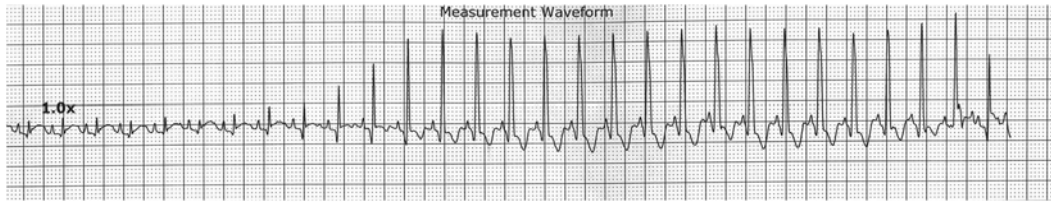


Fig. 13.8 Accelerated ventricular rhythm in 22-day-old infant at virtually the same rate as the sinus tachycardias. Note the fusion beats at the beginning of the AVR and at the end as the sinus impulse partially captures ventricular activation. Note also the more narrow QRS of the AVR that is likely age related

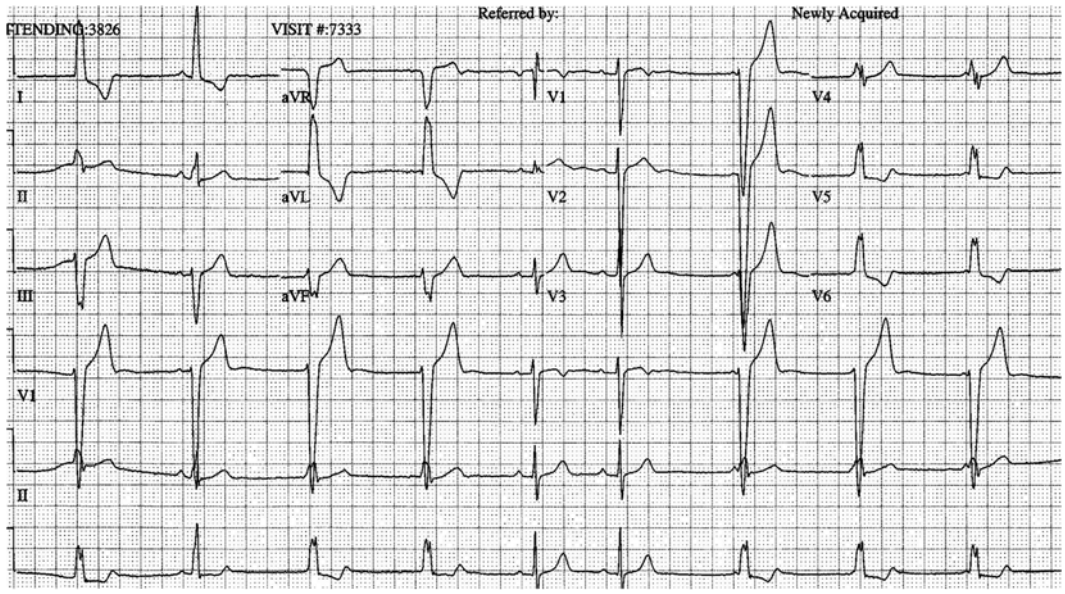


Fig. 13.9 Ten-year-old girl with a normal structural heart and a "slow" ventricular rhythm

Diagnostic ECG Features of AVR

(a) At least three beats of a ventricular rhythm which is ≤125 % of the rate of the sinus rhythm.
(b) Fusion beats often appear at the onset and termination of the arrhythmia.

Background

AVR is seen in all age groups and has been described in the presence of heart disease. In pediatrics, it segregates to the infant age group and is usually found in patients with a normal heart while in older adults it may be associated with coronary artery disease. It has also been seen with medications, digitalis intoxication, myocarditis, and other cardiomyopathies.

If the surrounding sinus rate is elevated, an accelerated idioventricular rhythm will also be proportionately elevated. Care needs to be taken when diagnosing AVR so as not to label it the more serious ventricular tachycardia.

Evaluation

The diagnosis and evaluation of AVR is similar to the evaluation for premature ventricular beats that includes evaluation for symptoms and density (frequency relative to total beats).

Treatment

Treatment, if necessary, of AVR should be done under the guidance of a pediatric cardiologist.

(a) Accelerated ventricular rhythm is benign so usually no treatment is necessary.
(b) If an etiology is identified, then it should be addressed if possible.
(c) If there is evidence of ventricular dysfunction or symptoms, then medication or electrophysiology study and ablation be may considered, but this would be the exception.

Outcome

AVR is well tolerated and often spontaneously resolves. If AVR is associated with an inciting

cause (such as a medication or myocarditis), then AVR will likely resolve once the cause is removed. In patients with structurally normal hearts and no obvious etiology, the course can range from resolution to intermittent sustained runs of AVR.

Right Ventricular Outflow Tract Ventricular Tachycardia

ECG features:

(a) Wide complex with a left bundle branch block morphology.
(b) An inferior QRS axis.

Background

Right ventricular outflow tract tachycardias are the most common form and site of origin of VT in the pediatric population. The posterior wall of the conal septum of the RVOT is in close proximity to the aortic outflow tract, valve and coronary cusps, all just posterior to it. Therefore, careful evaluation of the left-sided outflow tract and coronary cusps should be considered when approaching an ablation of RVOT-VT, especially if ambiguity is encountered in mapping the VT origin. Lead I may help distinguish if this arrhythmia is more likely to be RVOT-free wall (more upright), or RVOT septal (more isoelectric or negative; more detailed localization techniques have been described. RVOT-VTs may be either suppressed or evoked with exercise. Consideration of other causes of RV tachycardia such as Arrhythmogenic Right Ventricular Tachycardia (ARVC) needs to be entertained when evaluating patients with right-sided arrhythmias as this disorder carries a more serious prognosis (Figs. 13.10, 13.11, and 13.12).

Outcome

The decision to treat patients with RVOT tachycardia depends on patient symptoms in combination with cardiac function. If RVOT-VT is most often just a single beat or 2–3 beats and without symptoms, it is usually well tolerated. However, it may present with episodes of sustained arrhythmias. In rare cases, this arrhythmia may cause tachycardia-induced cardiomyopathy. Fortunately, RVOT-VT can often be successfully ablated, restoring cardiac function.

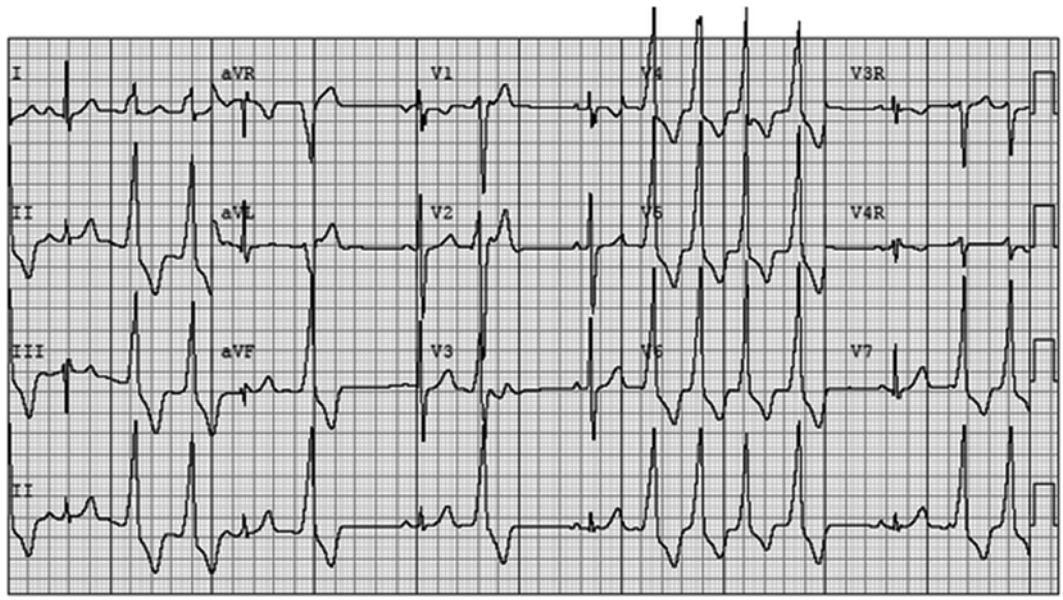


Fig. 13.10 This ECG shows ventricular ectopic activity occurring in single PVCs and repetitively as VT salvos in a 12-year-old with no symptoms but with mild LV dilation. This ECG is consistent with an RVOT-VT, however, because the origin of this RVOT-VT was mapped to the left side of the right ventricular outflow tract—i.e., high on left side of the conal or infundibular septum—it was successfully ablated in the left coronary cusp

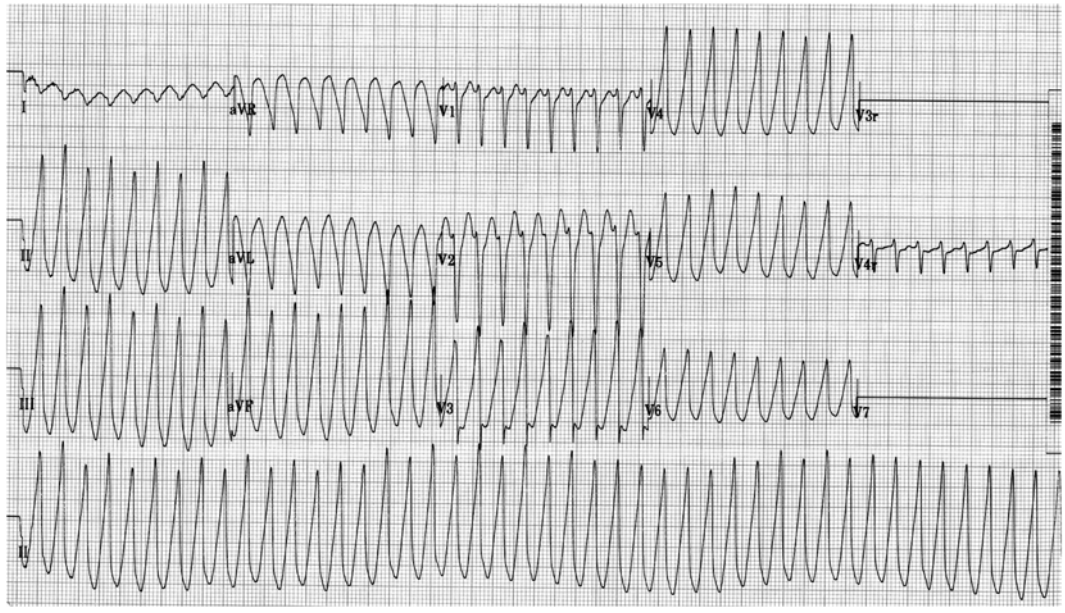


Fig. 13.11 RVOT-VT in a 16-year-old boy with an otherwise normal heart. Cryoablation was successful in the left coronary cusp

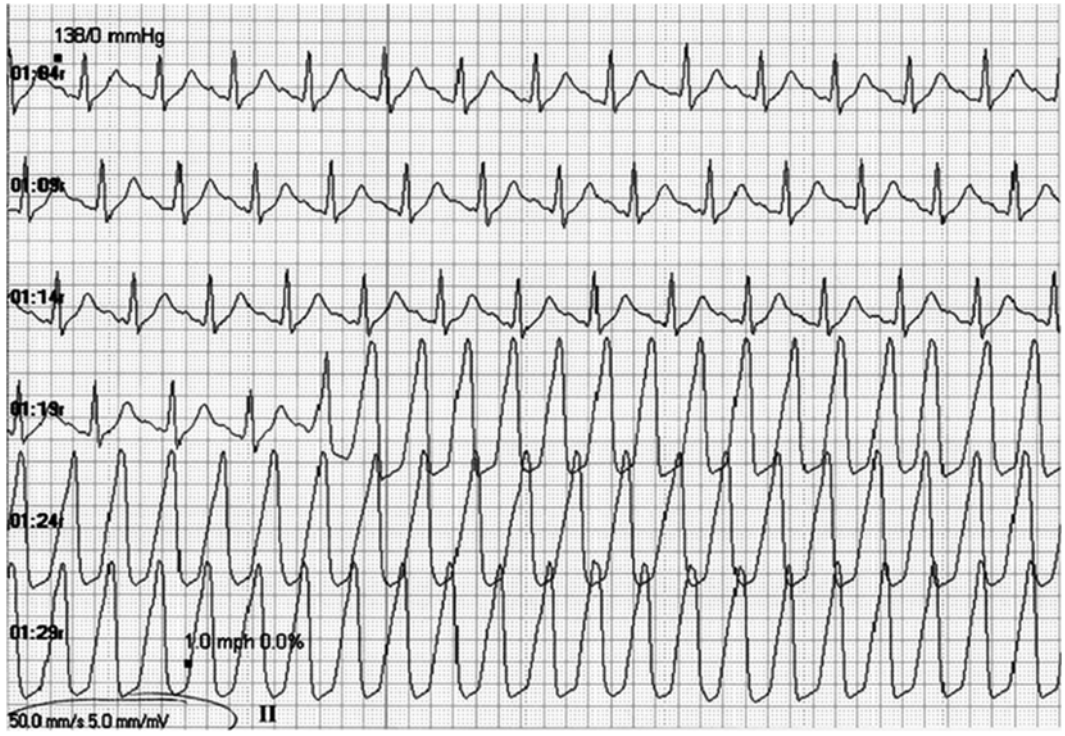


Fig. 13.12 Initiation of VT during treadmill exercise test—same patient as in Fig. 13.10

Left Posterior Fascicular Reentrant Tachycardia

ECG features:

(a) Wide complex with right bundle branch block morphology.
(b) A superior QRS axis (Figs. 13.13, 13.14, and 13.15).

Background

Although less common than RVOT tachycardia, left ventricular posterior fascicular VT is well known in pediatric patients and is most often associated with a structurally normal heart. This arrhythmia is supported by a reentry circuit within the distal fibers of the left posterior fascicle. The impulse propagates retrogradely through the left side of the His–Purkinje system to the contralateral right bundle branch slightly later as manifested by the right bundle branch block configuration, resulting in a slightly narrower QRS complex.

Outcome

Left posterior fascicular reentrant tachycardia is generally unresponsive to adenosine and

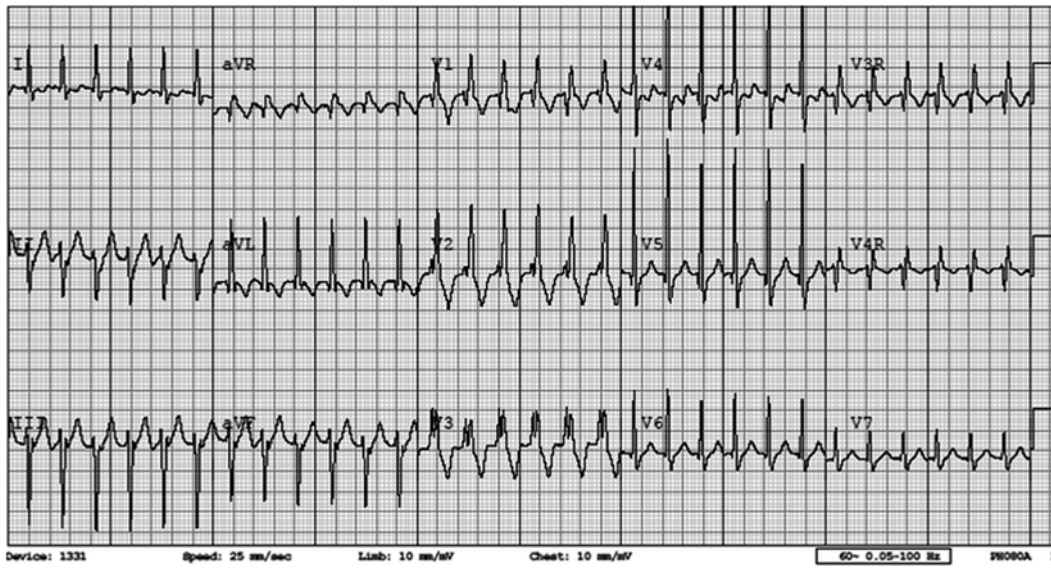


Fig. 13.13 Electrocardiogram in an 11-year-old presenting with findings stained tachycardia. This wide complex tachycardia exhibits right bundle branch block morphology and left superior axis and is narrower than the usual VT that involves mostly working myocardium. This tachycardia is highly suggestive of left posterior fascicular VT. After conversion to sinus rhythm with a calcium channel blocker this patient underwent radiofrequency ablation along the mid-low septum in the region of the left posterior fascicle permanently eliminated the VT

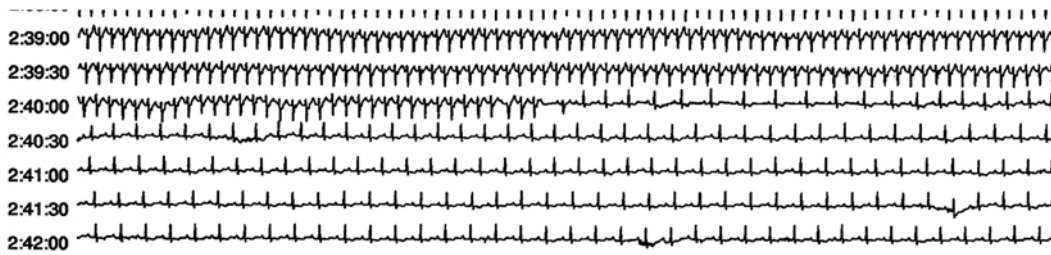


Fig. 13.14 Monitor tracing in an 8-year-old boy with left posterior fascicular ventricular tachycardia acutely and successfully treated with a verapamil bolus

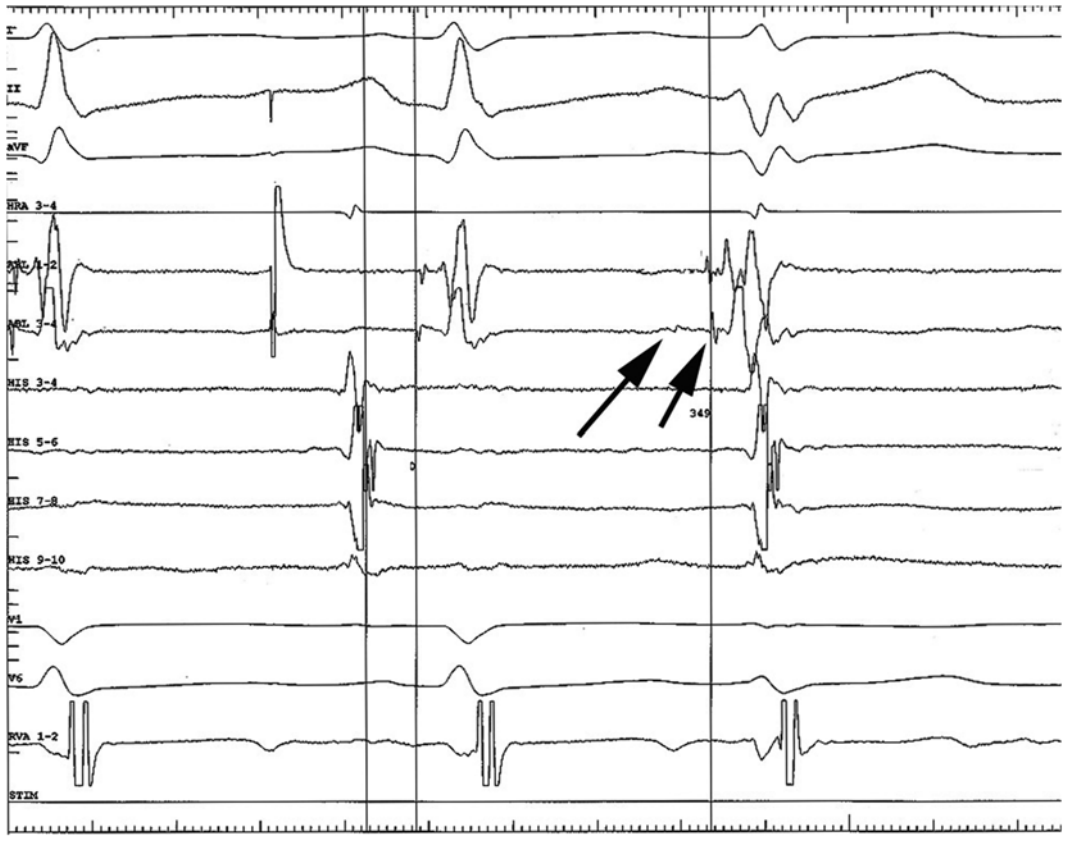


Fig. 13.15 Intracardiac electrograms demonstrating the activation sequence in the left posterior fascicle in sinus rhythm (second beat) and in the premature ventricular beat identical in morphology of the QRS complex during the left posterior fascicular tachycardia (third beat). The fifth and sixth tracings from the top are electrograms recorded through the distal (ABL 1-2) and proximal (ABL 3-4) electrode pairs on the ablation catheter. Note the proximal pair (sixth tracing) in the third beat is preceded by a prepotential (*left arrow*) before the left posterior fascicular signal (*right arrow*). Also notice the electrode pair (ABL 3-4) in the second (sinus) beat is activated before the distal electrode pair that is further (i.e., apical) along the fascicle. In contrast, the activation sequence is the reverse for the VPB indicating a change in the activation pattern for it and the VT. This VT is also amendable to successful ablation in selected patients. Entry into the left ventricle via the retrograde (larger patients) or transseptal approach provides access to the left posterior fascicle identified by a potential representing the specialized conducting left posterior fascicle

beta-blockers, but it typically exhibits a calcium channel blocker sensitivity providing both the acute and long-term treatment of this arrhythmias.

Ventricular Tachycardia in the Setting of Repaired Congenital Heart Disease

Background

Ventricular arrhythmias including VT following congenital heart disease surgery is a well known, late-term complication. Age at operation, interval from surgery, QRS duration and pulmonary regurgitation have been identified as risk factors for ventricular tachycardia and sudden cardiac death; despite these observations, the overall survival of this group remains favorable into the fourth decade and beyond. Ventricular extrastimulation at electrophysiology study may yield further risk stratification and prompt therapeutic considerations such as medication, ablation, or device therapy (Fig. 13.16).

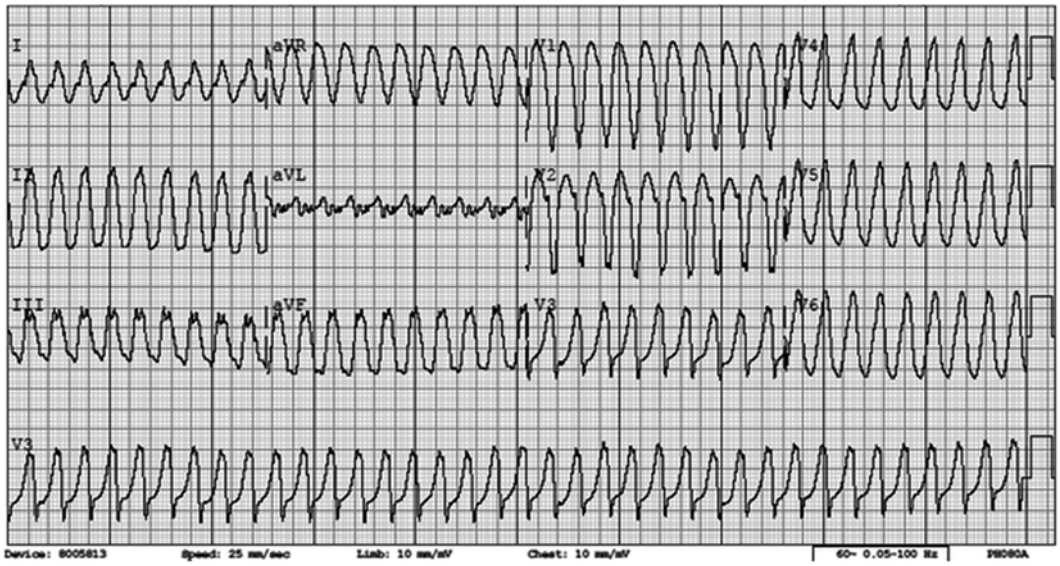


Fig. 13.16 This monomorphic VT presented in a 27-year-old late after repair of tetralogy of Fallot. The inferior axis and left bundle branch block morphology predicted origin from the right ventricle near his RVOT outflow patch. This VT was successfully ablated

Ventricular tachycardia in the setting of genetic or molecular cellular abnormalities: (see Chap. 18)

Some ventricular tachycardias are seen in the setting of genetic potassium, sodium, or calcium ion channel defects producing abnormalities in depolarization and repolarization of the sarcolemma (see Chap. 19). The most frequent is the congenital long QT syndromes due to alterations in structure and function of transmembrane potassium or sodium channels. The Brugada syndrome (sodium channel defect) has been identified as an important cause of sudden death in certain subpopulations. Some of these ventricular tachycardias are catecholamine provoked, such as in catecholaminergic polymorphic ventricular tachycardia.

Other entities are more likely to show ventricular arrhythmias after pauses in cardiac rhythm as in the pause-dependent type torsade de pointes arrhythmia or rarely, in the presence of complete heart block and profound bradycardia. However, even with advances in genetic testing there remains a number of young patients presenting with VT or sudden death in which no underlying structural, functional, electrical, or genetic abnormality has been identified.

Treatment of VT

Immediate visual and physical inspection of the patient is critical assessing heart rate, reparations, color, and perfusion. Acute treatment should follow Pediatric Advanced Life Support and Advanced Cardiovascular Life Support (PALS, ACLS algorithm: (https://www.acls.net/images/algo-arrest.pdf). In particular, if the patient has evidence of hemodynamic compromise during the VT, then cardiac pulmonary resuscitation (CPR) with compressions should be initiated followed by direct current cardioversion/defibrillation with an automatic external defibrillator (AED) if a "shockable" rhythm (VT or Ventricular fibrillation), identified by the device, is present.

Intravenous amiodarone may also be used in most patients, though has a wide side effect profile (see Chap. 21). Other medications such as esmolol or procainamide may also be considered

during an event. A procainamide slow push over 20 min (10–15 mg/kg) may be effective for VT and would also be expected to convert many other non-VT tachycardias that are dependent on the presence of an accessory pathway. Esmolol has less of a proarrhythmia effect and can also be easily titrated. Blood pressure monitoring is critical as the blood pressure will be in this group of patients and all three of these medications may further lower the blood pressure. Polypharmacy should be avoided.

If patients present without hemodynamic compromise the caregiver, often a bystander and first responder, may tailor the treatment to the history (symptoms), clinical status of the patient, and electrocardiographic findings. The ECG may reveal the more common forms of VT seen in pediatric patients without known heart disease that may pose a life-threatening risk. Left posterior fascicular VT (RBBB morphology with a superior QRS axis) often responds to calcium channel blockers; therefore, a slow verapamil push may be considered. With this arrhythmia and verapamil, caution is advised for use in neonates <6 weeks old. Though not typically used for the treatment of VT, adenosine may occasionally be useful in patients with RVOT-VT.

Arrhythmia Prevention

After initial management and conversion to sinus rhythm, chronic therapy must be considered. In patients with congenital heart disease, one should consider addressing any underlying functional hemodynamic abnormality of the heart as an improvement in function may considerably reduce the VT or reduce symptoms associated with episodes. An example would be reduction by pulmonary valve replacement of right ventricular volume overload due to unrestricted pulmonic insufficiency and subsequent progressive RV dilation in a patient with a transannular patch repair of tetralogy of Fallot.

In patients with minimal symptoms and no underlying structural or functional myocardial disease, conservative management may be appropriate while monitoring for spontaneous resolution of the arrhythmia. It has been suggested that the spontaneous resolution rate of VT may be between 30 and 70 % depending the VT location. In older patients without heart disease, conservative management is also generally appropriate for those with repetitive non-sustained VT in the absence of symptoms and in the absence of significant ventricular dysfunction.

Pharmacological therapy (see Chap. 21) can be guided by the morphology of the tachycardia and the clinical situation. Beta-blockers are one of the most commonly used medications as an initial medication for the suppression of VT, and are generally well tolerated. Beta-blockers may be very effective for patients who have no cardiac malformations, for example, patients with the long QT syndrome. Similarly, oral verapamil therapy is well tolerated and effective for patients with calcium-sensitive left posterior fascicular VT. Digitalis has no direct role in the treatment of ventricular arrhythmias but as a medication given to improve myocardial function it may have indirect benefit along with the use of low dose beta-blockers or afterload reduction therapy.

Type IA antiarrhythmic agents such as procainamide, quinidine, and disopyramide have had a diminishing role over time in the prophylactic treatment of VT primarily due to their high side effect and frequent dosing profiles and the availability of more effective antiarrhythmic medications in other classes. Likewise Type IB agents such as diphenylhydantoin and tocainide are rarely used. Thus, the use of Type IA or Type IB agents should be individualized to situations where a patient cannot benefit from catheter ablative therapy and potentially when the individual medication has been shown at electrophysiologic induction study and clinical follow-up to be beneficial in suppressing the tachycardia.

Type IC agents have been shown to be nearly equally effective in the treatment of both supraventricular and ventricular arrhythmias in the young. However, flecainide should be avoided in patients with congenital heart disease (especially in patients with slow ventricular conduction—long QRS complex, and these are not indicated for PVC suppression. Patients with ischemia-induced arrhythmias may be at increased risk for

ventricular arrhythmias soon after initiating medication; therefore, one should start these medications in a well-monitored setting if there is any underlying structural heart disease.

Type III agents may also be highly effective in the suppression of VT. Sotalol has a significant component of beta-blockade effect in addition to its Type III (block the potassium channel) action. Recently dofetilide, which has been approved for atrial arrhythmias, has been shown to be potentially effective for the treatment of ventricular tachycardia though there remains limited data on its use for ventricular arrhythmias in the pediatric population. Amiodarone can be highly effective; however, the benefit needs to be weighed against the risk of long-term side effects when a young patient is placed on chronic therapy. Amiodarone should be avoided if an electrophysiologic study is contemplated because of the long half-life.

Procedural Management

Surgical management

Transcatheter ablation has virtually replaced the surgical approach to the treatment of ventricular tachycardia. Effective antiarrhythmic medication and implantable defibrillation devices may supplant thoracotomy. The exception may be when the surgical approach may be required for management of hemodynamic lesions as well as ablation of arrhythmias. For lesions such as cardiac tumors, aneurysms, or large ventricular patches, surgical excision may be needed.

Catheter Ablation

Current guidelines for catheter ablation of VT in adults with structural heart disease, prior myocardial infarction or cardiomyopathy include patients with symptomatic monomorphic VT which is drug refractory or for the patient who does not desire medications; for patients having VT storms not due to a reversible cause; for frequent arrhythmias which are presumed to cause ventricular dysfunction; for bundle branch reentry; or for recurrent sustained polymorphic VT/VF which is drug refectory. It also can be considered in patients with VT despite antiarrhythmic therapy and in some patients post-myocardial infarction as an alternative to antiarrhythmic medication. In patients with a structurally normal heart, the procedure is indicated for patients who have symptomatic sustained or repetitive non-sustained type monomorphic VT; for patients with VT not responsive to medication therapy; or for recurrent sustained polymorphic VT/VF where it is felt the trigger can be targeted. In the pediatric population, the most successful experiences in catheter ablation of VT certainly come from patients with a structurally normal heart and a focal origin of their tachycardia.

In patients felt to have sustained monomorphic VT from the right ventricular outflow tract experience confirms that some of these tachycardias will originate from the left side of the outflow septum or within the aortic coronary cusp so the operator needs to be prepared for a possible retrograde aortic and/or transseptal-trans-mitral approach (Fig. 13.17).

In these patients, careful evaluation of the coronary arteries is important to avoid collateral damage during the ablation. Radiofrequency lesions should be at least 5 mm from the coronary arteries; alternatively, cryotherapy may be considered and has less risk of permanent damage if the lesion is halted at the first (electrocardiographic) sign of coronary injury. Another group of patients where catheter ablation can be contemplated are those with arrhythmogenic right ventricular cardiomyopathy. Caution must be exercised in this disease however since the disease process is often progressive and effect of the ablation may be short lived. In these patients, recent studies suggest ablation may be more effective if approached from the epicardium. Other disorders such as Chagas disease or a presumed epicardial VT focus has resulted in an increase in the number of epicardial ablations in adult patients with VT.

Patients with underlying structural heart disease are much more likely to have reentry circuits as the mechanism for their arrhythmia. These reentry circuits often develop around areas of scar, such as that seen after a right ventriculotomy for tetralogy of Fallot repair. In these cases, the superior aspect of the scar may define one boundary of

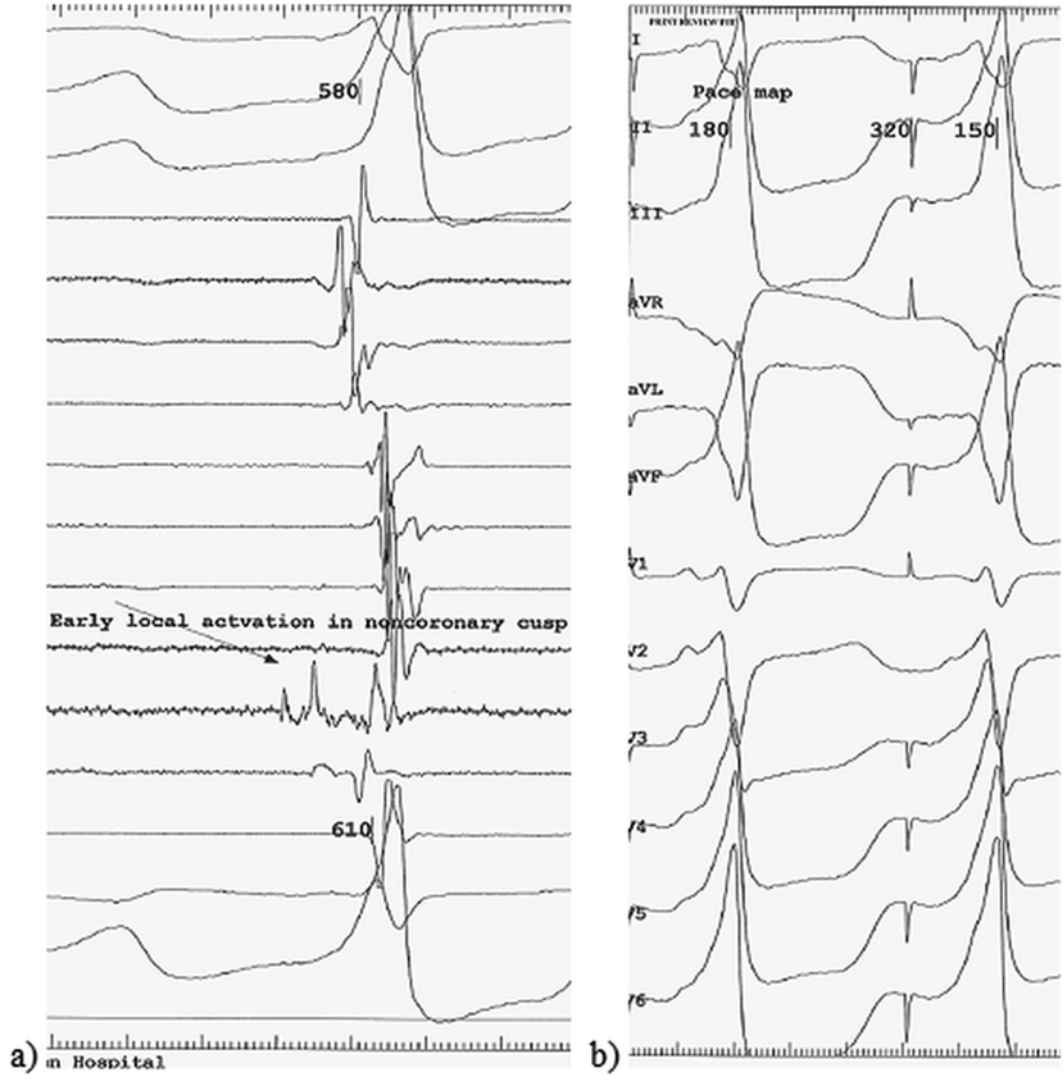


Fig. 13.17 (**a**) Intracardiac electrogram showing the earliest local activation of a focal ventricular arrhythmia within the noncoronary cusp. (**b**) Pace mapping showed 12/12 match between the ventricular arrhythmia (first beat) and the paced ventricular beat (second beat)

a portion of the circuit and the pulmonary valve annulus may define the other boundary. Having such a simple reentry circuit invites ablation across the corridor between the inert electrical barriers (such as from the scar to the pulmonary valve area), thus interrupting the possibility of reentry through the corridor in either direction. Other potential well-defined inert electrical barriers setting up potential corridors in the heart would include AV valve annuli, septal patches, or other scars. Difficulty in assessing and treating reentry VT arises when there are multiple reentrant circuits between and around a number of inert electrical barriers. Therefore, when considering catheter treatment of VT, a careful and very complete review of the underlying cardiac structure, the prior surgical techniques along with extensive mapping of the electrical circuits using computer-based electro-anatomic mapping systems are essential to detect possible reentry circuits.

Several approaches are available for mapping and ablation of VTs. Single point catheter mapping can be accomplished for focal origin tachycardia by isolating the earliest site of ventricular activation. Once found, pacing at the suspected site can be used to compare the "pace map" to the 12-lead EKG of the VT looking for a match to the clinical tachycardia. If the ECG during the VT is identical in all 12 leads to the ventricular depolarization pattern in all 12 leads of the ECG during pacing with the ablation catheter, one can infer that the ablation catheter tip electrode is located at the origin of the VT. Pace mapping techniques are useful when the inducible tachycardia is not hemodynamically stable enough to allow activation mapping during the VT. In addition, if the VT mechanism is triggered activity or automaticity at a focal site, then ablation at the best pace map site has a high likelihood of ablating the arrhythmia. Anesthesia may suppress VT, especially RVOT arrhythmias, therefore lightening or transitioning off of inhaled anesthetic may be necessary during the procedure if the arrhythmia is non-inducible.

If the tachycardia is due to a reentry circuit, an exact pace map may be found anywhere along the slowly conducting corridor (as well as a side branch of the circuit) and a focal ablation site is less likely to be successful since complete block across the slow conduction corridor of the reentry circuit is required. Therefore, lesions are typically placed across an isthmus of conductive tissue between nonconductive barriers to create block across the reentry loop. In addition, the elegant technique of concealed entrainment to establish the location of the critical slow conduction zone by observing VT behavior during and just after pacing is helpful in identifying appropriate ablation targets in reentry VT; the technique can be applied in the patient with congenital heart disease and the usual reentry arrhythmia. The advent of electro-anatomical mapping and non-contact mapping has allowed more precise delineation of early excitation sites from focal tachycardias and has allowed better definition by virtue of three-dimensional representations of the slow conduction paths between low voltage inert zones. These mapping techniques allow improved catheter localization and can reduce the need to use radiation for the procedure (Fig. 13.18). Additionally, some of these systems have the potential to delineate the reentry circuit or origin of tachycardia in a single beat so that sustained tachycardia is not required, an especially important benefit in those with hemodynamically unstable VT.

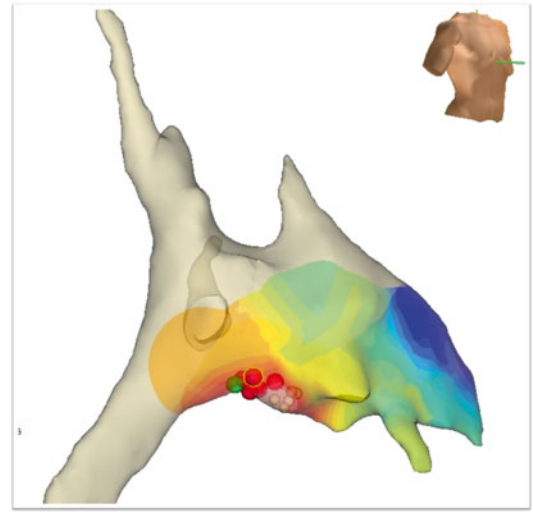


Fig. 13.18 An RAO view of the 3-D geometry (IVC, SVC, RA, and RV) and activation map in a 12-year-old female with ventricular tachycardia who underwent a radiation-free procedure. The spherical marking near the inferior base of the RV indicate the site of successful ablation of a focal tachycardia confirmed with electro-anatomic 3-D mapping and pace mapping

The ability of ablative lesions in the ventricular myocardium to be effective is still limited by the ability to create transmural lesions. Therefore, various catheter technologies have been developed to assist with transmural lesions delivery.

Device Therapy

An Implantable cardioverter-defibrillator is potentially lifesaving for patients with arrhythmias that are not amendable to ablative therapy or who remain at risk on chronic oral antiarrhythmia medication. Patients without underlying structural heart disease who may need device therapy are those who have the long QT syndrome,

CPVT, Brugada, or those who have suffered a cardiac arrest due to an unknown cause. Although less common in childhood, those with arrhythmogenic right ventricular cardiomyopathy may benefit from an ICD, as might those with dilated or hypertrophic cardiomyopathies. Among patients with congenital heart disease, the most widely represented group are those late after repair of tetralogy of Fallot. As the number of adults with congenital heart disease continues to increase, now more in number than children with heart disease, there is expected to be an emerging number of patients with more complex and evolving heart disease who may require ICD placement. Many of these, such as those who have completed the surgical staged therapy for single ventricle anatomy may present unique challenges due to concerns with vascular access, complex arrhythmias, variable anatomy, and intolerance of the arrhythmias.

Incorporation of brady and antitachycardia pacing into ICD units and combining pace/sense function into defibrillating leads has also benefited those needing ICD therapy. While the availability of transvenous ICD systems appears to be a benefit, the risk of having to use a transvenous system in a young patient incurs not only the risk of venous thrombosis limiting later access but also the need and risk of lead extraction expected over longer life span in the growing patient. Due to these concerns, epicardial leads and even leadless pacemakers and ICDs are being developed. With such varied cardiac anatomy in the pediatric and congenital heart population (especially the single ventricle group) the approaches for device placement call for creativity.

In all children with VT who require devices, the significant problem of inappropriate shock delivery due to over sensing, lead damage, sinus tachycardia entering the tachycardia detection zones, and other causes has not been fully surmounted. Also, the psychological burden of living with an ICD needs to be carefully and consistently monitored and addressed. The presence of the ICD in one's body is certainly challenging to a developing individual, but the anticipation that the device may cause a shock, or that it may not work in the intended way potentially could create a chronic psychological stress in any individual. Because of this many physicians also recommend close affiliation with a psychologist to assist with the emotional support needed by patients and their families.

Summary

Ventricular tachycardias in the young are a diverse group of arrhythmias generally considerably different in etiology and presentation than those seen in the adult with ischemic heart disease. There are a wide variety of ventricular substrates and a superimposed variety of electrophysiologic mechanisms that challenges diagnosis and treatment. The ability of many young patients to tolerate some forms of VT may allow the clinician to approach the arrhythmia in a more deliberate and conservative fashion. In many young patients with idiopathic LV or RV VT, the arrhythmia may spontaneously remit. Nonetheless VT still remains an important cause of sudden death in the young. This compels the understanding and utilization of a variety of diagnostic and treatment strategies. In patients after surgery for congenital heart disease, VT needs a comprehensive approach based on a complete analysis of the arrhythmia and cardiac malformation. For patients with cardiomyopathies and electrical heart disorders, exciting work in genetics offers the hope that further individualization of therapy and understanding of prognosis may soon be at hand. Finally, heightened awareness and increased use of newer myocardial imaging and ablation techniques offer hope for an improved ability to risk stratify and treat this important arrhythmia.

Suggested Reading

Aliot EM, et al. EHRA/HRS expert consensus on catheter ablation of ventricular arrhythmias: developed in a partnership with the European Heart Rhythm Association (EHRA), a registered branch of the European Society of Cardiology (ESC), and the Heart Rhythm Society (HRS); in collaboration with the American College of Cardiology (ACC) and the

American Heart Association (AHA). Europace. 2009; 11(6):771–817.
Annique R, Pavlovic M, Pfammatter JP. Frequency of spontaneous ventricular tachycardia in a pediatric population. Am J Cardiol. 2008;101(6):852–4.
Azaouagh A, Churzidse S, Konorza T, Erbel R. Arrhythmogenic right ventricular cardiomyopathy/dysplasia: a review and update. Clin Res Cardiol. 2011;100(5):383–94.
Batra A, J Silka M. Ventricular arrhythmias. Prog Pediatr Cardiol. 2000;11(1):39–45.
Beaufort-Krol GCM, Bink-Boelkens MTE. Oral propafenone as treatment for incessant supraventricular and ventricular tachycardia in children. Am J Cardiol. 1993;72:1213–4.
Benson Jr DW, Smith WM, Dunnigan A, Sterba R, Gallagher JJ. Mechanisms of regular, wide QRS tachycardia in infants and children. Am J Cardiol. 1982;49(7):1778–88.
Betensky BP, Park RE, Marchlinski FE, Hutchinson MD, et al. The V2 transition ratio. A new electrocardiographic criterion for distinguishing left from right ventricular outflow tract tachycardia origin. J Am Coll Cardiol. 2011;57:2255–62.
Bhandari AK, Hong RA, Rahimtoola SH. Triggered activity as a mechanism of recurrent ventricular tachycardia. Br Heart J. 1988;59(4):501–5.
Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. J Am Coll Cardiol. 1992;20:1391–6.
Callans DJ, Ren JF, Michele J, Marchlinski FE, Dillon SM. Electroanatomic left ventricular mapping in the porcine model of healed anterior myocardial infarction: correlation with intracardiac echocardiography and pathological analysis. Circulation. 1999;100: 1744–50.
Collins KK, Schaffer MS, Lieberman L, Saarel E, et al. Fascicular and nonfascicular left ventricular tachycardia in the young: an international multicenter study. J Cardiovasc Electrophysiol. 2013;24(6):640–8.
Dawson DK, et al. Prognostic role of CMR in patients presenting with ventricular arrhythmias. JACC Cardiovasc Imaging. 2013;6(3):335–44.
Dickinson DF, Scott O. Ambulatory electrocardiographic monitoring in 100 healthy teenage boys. Br Heart J. 1984;51(2):179–83.
Drew BJ, Scheinman MM. ECG criteria to distinguish between aberrantly conducted supraventricular tachycardia and ventricular tachycardia: practical aspects for the immediate care setting. Pacing Clin Electrophysiol. 1995;18(12):2194–208.
Fenrich Jr AL, Perry JC, Friedman RA. Flecainide and amiodarone: combined therapy for refractory tachyarrhythmias in infancy. J Am Coll Cardiol. 1995;25(5): 1195–8.
Gaum WE, Biancaniello T, Kaplan S. Accelerated ventricular rhythm in childhood. Am J Cardiol. 1979; 43:162–4.
Glikson M, Constantini N, Grafstein Y, et al. Familial bidirectional ventricular tachycardia. Eur Heart J. 1991;12:741–5.
Iwai S, Cantillon DJ, Kim RJ, Markowitz SM, et al. Right and left ventricular outflow tract tachycardias: evidence for a common electrophysiologic mechanism. J Cardiovasc Electrophysiol. 2006;17:1052–8.
Joshi S, Wilber D. Ablation of idiopathic right ventricular outflow tract tachycardia: current perspectives. J Cardiovasc Electrophysiol. 2005;16(s1):S52–8.
Khairy P, Landzberg MJ, Gatzoulis MA, Lucron H, et al. Value of programmed ventricular stimulation after tetralogy of fallot repair: a multicenter study. Circulation. 2004;109(16):1994–2000. Epub 2004 Mar 29.
Lawrence D, Von Bergen N, Law IH, Bradley DJ, et al. Inappropriate ICD discharges in single chamber versus dual chamber devices in the pediatric and young adult population. J Cardiovasc Electrophysiol. 2009;20(3):287–90.
Lerman BB, Stein KM, Markowitz SM. Adenosine-sensitive ventricular tachycardia: a conceptual approach. Rev J Cardiovasc Electrophysiol. 1996;7(6):559–69.
Miyake CY, Davis AM, Motonaga KS, Dubin AM, et al. Infant ventricular fibrillation after ST-segment changes and QRS widening: a new cause of sudden infant death? Circ Arrhy Electrophysiol. 2013;6: 712–8.
Moore JP, Seki A, Shannon KM, Mandapati R, et al. Characterization of anatomic ventricular tachycardia isthmus pathology after surgical repair of tetralogy of fallot. Circulation. 2013;6:905–11.
Nollert G, Fischlein T, Bouterwek S, Bohmer C, et al. Long-term survival in patients with repair of tetralogy of fallot: 36-year follow-up of 490 survivors of the first year after surgical repair. J Am Coll Cardiol. 1997;30:1374–83.
Ouyang F, Cappato R, Ernst S, Goya M, et al. Electroanatomic substrate of idiopathic left ventricular tachycardia unidirectional block and macroreentry within the Purkinje network. Circulation. 2002;105: 462–9.
Schilling RJ, Peters NS, Davies W. Feasibility of a noncontact catheter for endocardial mapping of human ventricular tachycardia. Circulation. 1999;99: 2543–52.
Sears Jr S, Burns J, Handberg E, Sotile W, Conti J. Young at heart: understanding the unique psychosocial adjustment of young implantable cardioverter defibrillator recipients. PACE. 2001;24:1113–7.
Singh B, Kaul U, Talwar KK, et al. Reversibility of "tachycardia-induced cardiomyopathy" following the cure of idiopathic left ventricular tachycardia using radiofrequency energy. PACE. 1996;19(9):1391–2.
Sosa E, Scanavacca M, D'Avila A, Pilleggi F. A new technique to perform epicardial mapping in the electrophysiology laboratory. J Cardiovasc Electrophysiol. 1996;7:531–6.
Tipple M, Sandor G. Efficacy and safety of oral sotalol in early infancy. PACE. 1991;14:2062–5.

Towbin JA, Li H, Taggart RT, et al. Evidence of genetic heterogeneity in Romano-Ward long QT syndrome. Analysis of 23 families. Circulation. 1994;90(6):2635–44.

Van Hare GF, Stanger P. Ventricular tachycardia and accelerated ventricular rhythm presenting in the first month of life. Am J Cardiol. 1991;67(1):42–5.

Villain E, Bonnet D, Kachaner J, et al. Incessant idiopathic ventricular tachycardia in infants. Arch Mal Coeur Vaiss. 1990;83(5):665–71.

Von Bergen NH, Bansal S, Gingerich J, Law IH. Nonfluoroscopic and radiation-limited ablation of ventricular arrhythmias in children and young adults: a case series. Pediatr Cardiol. 2011a;32(6):743–7.

Von Bergen NH, Atkins DL, Dick II M, Bradley DJ, et al. Multicenter study of the effectiveness of implantable cardioverter defibrillators in children and young adults with heart disease. Pediatr Cardiol. 2011b; 32(4):399–405.

Sick Sinus Syndrome

14

Ira Shetty and William A. Scott

Mechanisms

Sick sinus syndrome is a clinical entity that has been associated with a variety of arrhythmias. One of the earliest descriptions was by Lown as "… a defect in the elaboration or conduction of sinus impulses characterized by chaotic atrial activity, changing P wave contour, and bradycardia, interspersed with multiple and recurrent ectopic beats with runs of atrial and nodal tachycardia." While there are numerous etiologies described in the literature, sick sinus syndrome in pediatric patients most often occurs secondary to injury to the node itself, its arterial supply or its autonomic innervation in the course of cardiac surgical interventions. This injury is usually not limited to the sinoatrial node, and abnormalities in atrial automaticity and conduction are included in the sick sinus syndrome (Table 14.1). There is evidence that the abnormal variation in heart rate has a destabilizing effect on the atrial tissue, contributing to the progression of the disease. While not specifically part of sinus node disease, these coexisting atrial and, to a lesser degree, atrioventricular conduction disturbances support the concept that the pathology affecting the sinus node is diffuse. Frequently used similar terms include chronotropic incompetence or sinus node dysfunction.

Etiology

Conditions associated with a high prevalence of sick sinus syndrome include atrial repair of d-transposition of the great arteries, complete repair for anomalous pulmonary venous drainage, atrial septal defect, and single ventricle palliation with the Fontan operation, although almost any open heart repair may result in sinus node impairment. Sinus node malformation is associated with left atrial isomerism and sinus node dysfunction may coexist with congenital complete heart block. Congenital sinus node dysfunction due to SCN5a mutation and perhaps mutations in other cardiac genes (e.g., the MYH6 gene encoding the cardiac aloha heavy chain subunit of myosin) along with congenital central hypoventilation syndrome with sinus node dysfunction are rare but have been reported. Familial clustering has been reported in the absence of structural heart disease. Extrinsic causes of sinus node dysfunction include autonomic imbalance

I. Shetty, M.D.
Pediatric Cardiology, Advocate Children's Hospital, Oak Lawn, IL, USA

W.A. Scott, M.D. (✉)
Department of Pediatrics, UT Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390, USA
e-mail: william.scott@childrens.com

M. Dick, II (ed.), *Clinical Cardiac Electrophysiology in the Young*,
DOI 10.1007/978-1-4939-2739-5_14

Table 14.1 Sick sinus syndrome

Electrocardiographic manifestations of sick sinus syndrome
Sinus bradycardia
Extreme sinus arrhythmia
Tachycardia–bradycardia syndrome
Sinoatrial exit block
Sinus pause/sinus arrest
Sinoatrial reentrant tachycardia
Electrocardiographic findings associated with sick sinus syndrome
Intra-atrial reentrant tachycardia (IART)
Atrial fibrillation
AV nodal dysfunction

and medications. Heavily conditioned athletes, and even normal preadolescent children (4–10 years old), may have bradycardia and sinus pauses of greater than 2 s due to prominent vagal influence. Recently, sleep apnea has been related to sinus node dysfunction. Many anti-arrhythmia medications can further impair the sinus node function particularly for patients with preexisting abnormalities. Neuromuscular disorders, such as Kearns Sayre (ophthalmoplegia, pigmentary degeneration of the retina, and cardiomyopathy), Friedreich's Ataxia and myotonic dystrophy may have a predilection for the conduction system and sinus node in particular. Immunologic basis for sinus node dysfunction have been seen in patients with anti-sinus node (ASN) antibodies as well as in donor hearts after orthotopic heart transplantation. Most commonly anti-Ro/SS-A or anti-LA/SS-B antibodies are well established in the mechanism of congenital AV block in infants of mothers with Sjögren's, lupus, or other undifferentiated autoimmune syndrome, but there also have been rare reports of sinus node dysfunction. While comprehensive this list may not include every cause of sick sinus syndrome.

Symptoms

Although the designation "syndrome" usually implies symptoms as part of the clinical picture, it is often difficult to elicit in the young patient. In the more extreme cases, symptoms may include pre- or frank syncope, shortness of breath, lightheadedness with activity, fatigue, weakness, and inability to do what one used to be able to.

ECG Characteristics

The ECG characteristics of sick sinus syndrome were first fully described by Ferrer, initially in the elderly. The ECG features are variable and can change within a single patient. Not all patients will manifest all of the electrocardiographic findings outlined below. Potential sources of electrocardiographic data include standard 12–15 lead electrocardiograms, Holter monitoring, event recorders, and rhythm strips from physiologic monitors. Clear documentation is not always present in short-term recordings. Multiple leads should be recorded to detail P wave morphology.

Long-term recordings with Holter provide an overview of overall heart rate variation (Fig. 14.1) and the prevalence of abnormally slow and fast rhythms. Ideally three orthogonal leads are recorded to optimize P wave recognition (i.e., Lead I, Lead II or III, and a precordial lead). Event recorders, particularly those with continuous storage capabilities, allow for correlation of symptoms to electrocardiographic changes. Newer devices have programmable parameters for automated recording of tachycardia and bradycardia episodes. An implantable device is available for special circumstances that preclude wearing an external monitor, but because it requires anesthesia and surgery for placement, it should be reserved for the patients with a diagnostic dilemma as well as high risk. Exercise testing is useful to assess the chronotropic response. All children and adolescents should be able to attain a heart rate of 180 beats per minute (near 70 % max predicted heart rates, which needs to be teased from poor effort). Patients with sinus node dysfunction also may have rate instability with exercise or exaggerated slowing of heart rate or pauses in the recovery period.

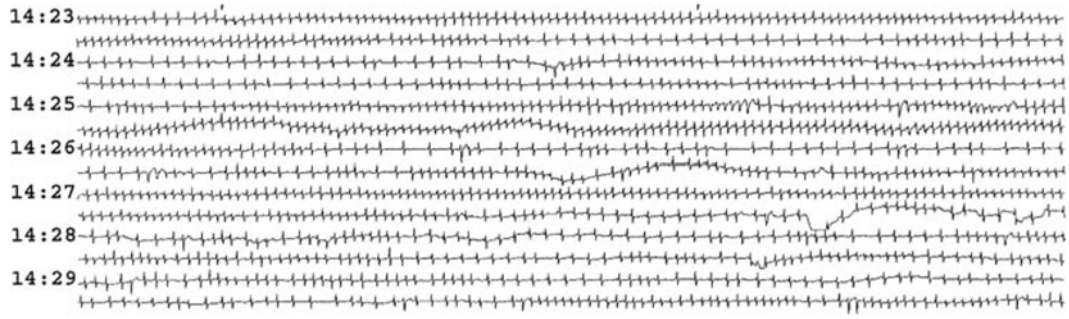


Fig. 14.1 Full disclosure printout from a Holter monitor. Individual complexes are too small for detailed evaluation, but abnormal pattern of heart rate variation is apparent

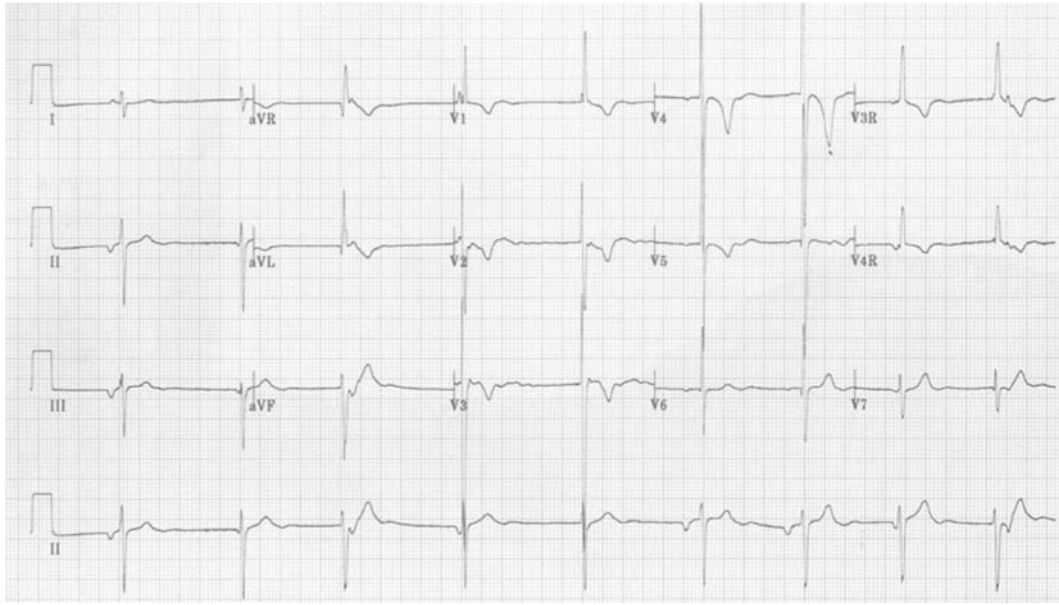


Fig. 14.2 Sinus bradycardia with alternating atrial and junctional escape rhythms in a patient 15 years after Mustard repair of d-transposition of the great arteries

Sinus Bradycardia

Bradycardia is the most common feature of sick sinus syndrome. Bradycardia may be sustained or paroxysmal. Escape rhythms (Fig. 14.2) arise from the atrium, atrioventricular node, and ventricles, but these tissues are often dysfunctional and the escape rates are frequently lower than expected for age. Healthy children may have brief periods of sinus bradycardia with atrial or junctional escape rhythm in the absence of any sinus node pathology. The normal heart rate is age dependent. The lowest values observed during Holter recording are less than those from ECG recording. Recording artifacts and other rhythm abnormalities may confound the interpretation. An abnormally low heart rate may be due to second- or third-degree atrioventricular block as well as blocked atrial and junctional extrasystoles. A sudden loss of signal may appear similar to a sinus pause. There are often clues to this type of artifact, including resump-

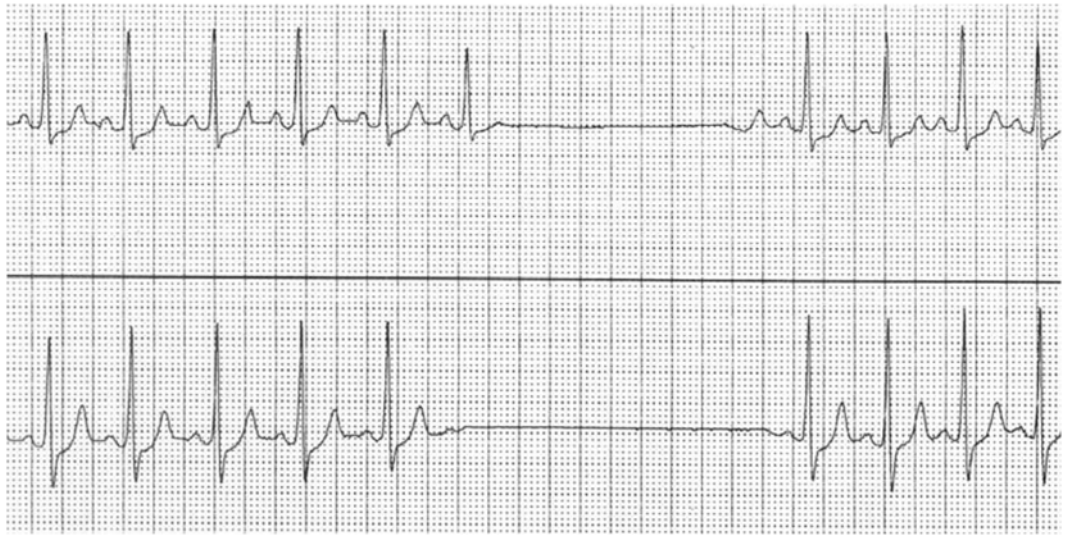


Fig. 14.3 Simultaneous lead I (*upper panel*) and lead III (*lower panel*) from Holter recording. Apparent sinus pause is actually due to artifact. Signal loss is not simultaneous on both channels and lead I resumes rhythm with a T wave which is not possible

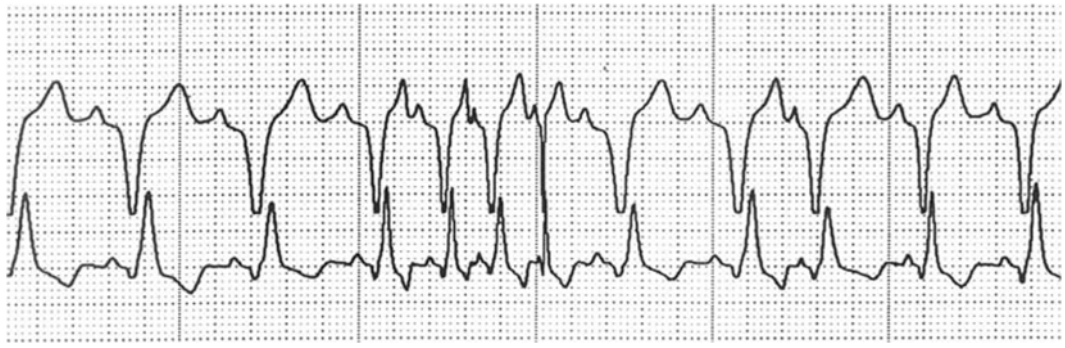


Fig. 14.4 Simultaneous lead V1 (*upper*) and V5 (*lower*) from Holter recording. Apparent bradycardia and tachycardia due to artifact from changing tape speed. Note that all components of the rhythm (P wave, QRS complex, and T wave) are compressed with tachycardia

tion of recording with a T wave or a different time of drop out on another channel (Fig. 14.3). Older Holter recorders using a tape drive mechanism can suddenly speed or slow mimicking bradycardia or tachycardia. With this type of artifact, all components of the recording are expanded or compressed (Fig. 14.4). While digitalized Holter monitors will not demonstrate this kind of artifact, one could manually manipulate the ECG paper strip that is recording the rhythm and render it abnormal.

Extreme Sinus Arrhythmia

Sinus arrhythmia is a normal pattern of heart rate acceleration and deceleration present in most children. A significant component of this variation is due to respiratory influences on the autonomic nervous system. Abnormal or extreme sinus arrhythmia is defined as greater than 100 % variation in PP intervals. Sinus node exit block may also cause variation of this magnitude.

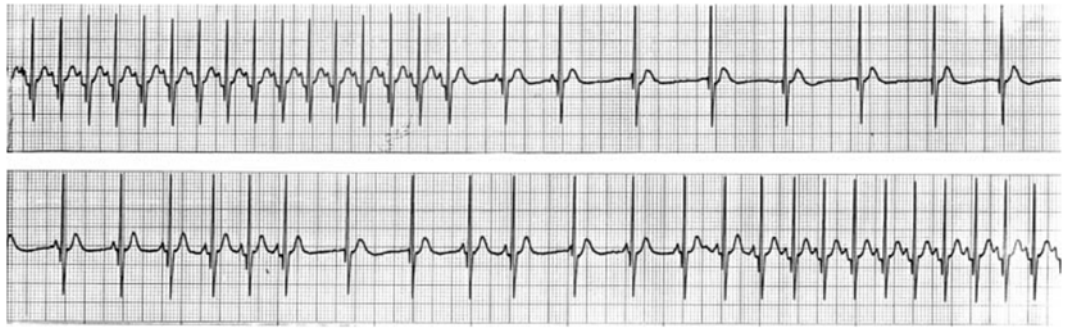


Fig. 14.5 Tachycardia–bradycardia with junctional escape in a 2-year-old

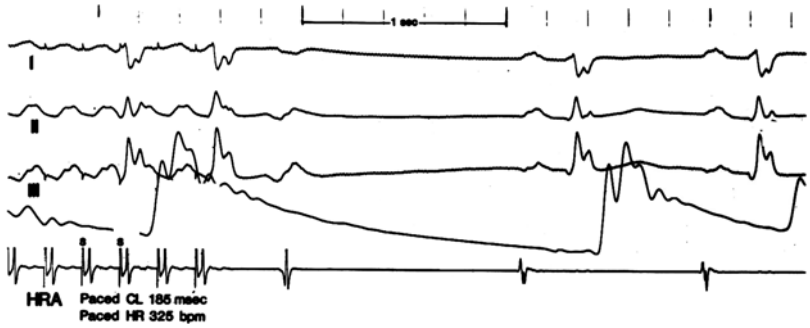


Fig. 14.6 Overdrive pacing of atrial flutter in 9-month-old girl. Note the long sinus recover time (1,300 ms) (the first beat after termination of pacing is the last reentry flutter beat) indicating suppression of the sinus node by the prolonged flutter episodes

Tachycardia–Bradycardia

The tachycardia–bradycardia syndrome is diagnosed in the presence of recurrent prolonged pauses or sustained bradycardia following paroxysms of tachycardia. The ectopic impulses of the tachycardia penetrate the sinus node and cause exaggerated overdrive suppression of already impaired automaticity, exaggerating the bradycardia (Fig. 14.5). This phenomenon is not infrequently observed acutely following overdrive pacing or DC cardioversion of atrial flutter or intra-atrial reentry tachycardia (Fig. 14.6).

Sinoatrial Exit Block

Sinoatrial exit block is failure of an impulse generated in the sinus node to propagate normally into the atrium. The degree of block is classified similar to the classification for atrioventricular node. A direct recording of the sinus node electrogram is necessary to diagnose first-degree sinoatrial block. The pattern of PP intervals prior to a pause can be used to infer second-degree block. Mobitz I sinoatrial block (Fig. 14.7) is manifest by a gradual shortening of PP intervals followed by a pause of less than two times the resting cycle length. Mobitz II is presumed to be the mechanism when a sudden pause of two times the resting cycle length is encountered (Fig. 14.8). Both of these are difficult to recognize in the presence of sinus arrhythmia and both patterns may be due to abnormal impulse formation in the sinus node. Neither of these conduction abnormalities can be absolutely proven without direct recording of the sinus node electrogram. Complete or third-degree sinoatrial block is indistinguishable from sinus node arrest on the surface electrocardiogram.

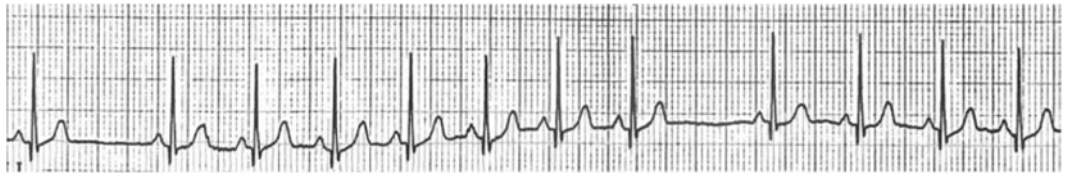


Fig. 14.7 Lead I recording suggestive of Mobitz I type sinoatrial exit block. There is a gradual shortening of PP intervals, with a consistent P wave morphology, followed by a pause of less than two times the resting cycle length. Validation of this phenomenon requires invasive recording of the sinus node electrogram

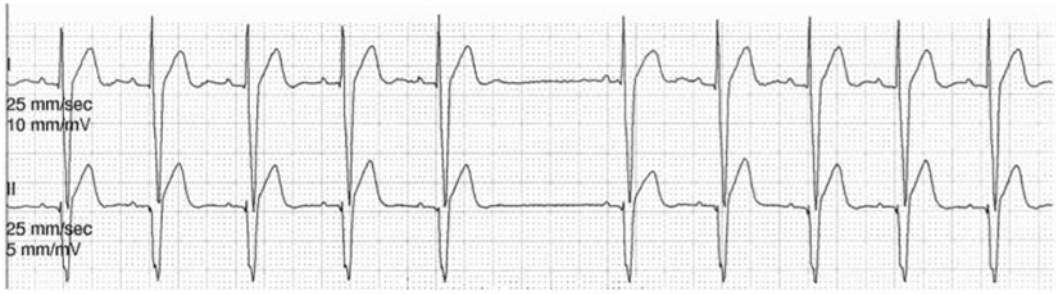


Fig. 14.8 Simultaneous lead I and II recording suggestive of Mobitz II type sinoatrial exit block. There is a pause with a PP interval that is twice the resting cycle length. Validation of this phenomenon requires invasive recording of the sinus node electrogram

Sinus Pauses and Sinus Arrest

Prolonged pauses are often present due to either sinoatrial node exit block or sinus arrest (Fig. 14.9). Sinus pauses of up to 2 s are normal in young children and adolescents. A non-sinus rhythm at a rate lower than expected for sinus rhythm is referred to as an escape rhythm and is suggestive of sinus node arrest. It too is usually normal in children without heart disease; it does not per se suggest heart disease.

Sinoatrial Node Reentrant Tachycardia

Sinoatrial reentrant tachycardia is uncommon. It results from abnormal conduction and reentry (see Chap. 7) within the sinus node or immediate perinodal tissue. The P waves are identical to those seen with sinus rhythm, but suggested by a sudden paroxysmal increase and decrease in rate. This rhythm cannot be distinguished from a focal atrial tachycardia in close proximity to the sinoatrial node.

Atypical atrial flutter or fibrillation often serves as the tachycardia component of sick sinus syndrome or tachy–brady syndrome. Typical atrial flutter is uncommon in children. More commonly atrial muscle reentry or intra-atrial reentrant tachycardia (IART) is observed (Fig. 14.10, see Chap. 8). This arrhythmia most frequently occurs following surgical interventions for congenital heart disease. The atrial rate is slower than that usually ascribed to typical atrial flutter, usually around 180–250 beats per minute rather than 300 bpm. There is an isoelectric interval between atrial activations, and the typical saw tooth pattern is not present. Unlike typical atrial flutter, 1:1 conduction to the ventricles is frequent. Most commonly 2:1 conduction is observed, but again at a rate slower than typical for atrial flutter. Variable conduction ratios may be misinterpreted as extrasystoles. Atrial fibrillation is a late finding as it heralds disease progression.

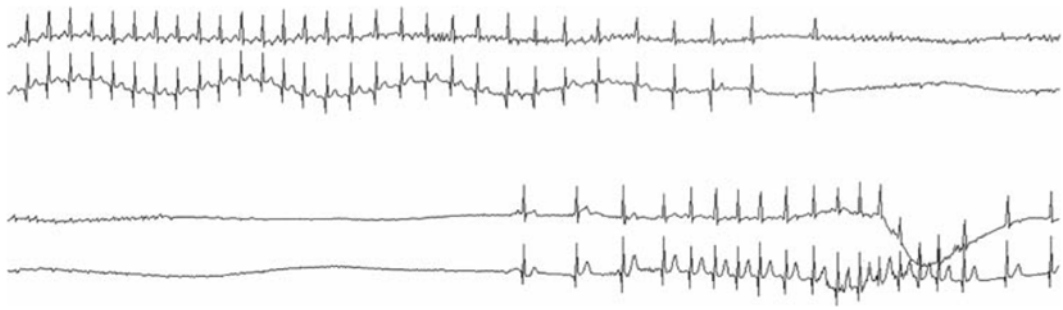


Fig. 14.9 Sinus arrest during a breath holding spell. This represents transient sinus node dysfunction due to a sudden increase in parasympathetic activity

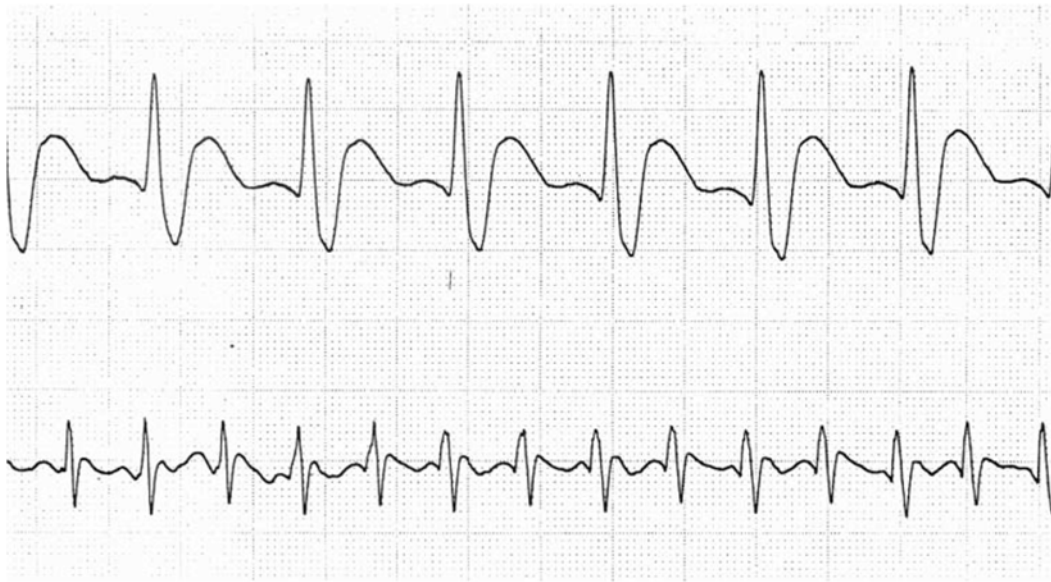


Fig. 14.10 Lead I (*upper trace*) and esophageal electrogram (*lower trace*) demonstrating intra-atrial reentrant tachycardia with 2:1 conduction. The arrhythmia is not apparent from surface ECG but esophageal recording shows atrial rate twice that of the ventricular rate

Electrophysiologic Features

Although the diagnosis of sick sinus syndrome is made through surface ECG techniques (e.g., Holter), electrophysiologic studies have contributed to the understanding of sinus node physiology. Also limited studies to assess sinus node function may be performed with temporary epicardial or transvenous pacing wires (Fig. 14.11), esophageal pacing, and with a previously implanted permanent pacemaker. Currently, clinical history and noninvasive diagnostic studies primarily guide diagnosis and management. Electrophysiologic study is not routinely performed solely for the diagnosis of sick sinus syndrome because it is invasive, has relatively low sensitivity and specificity, and noninvasive studies provide adequate information for management. Invasive electrophysiologic studies of sinus node function may be performed as an adjunct to hemodynamic study prior to surgical intervention or in association with interventional

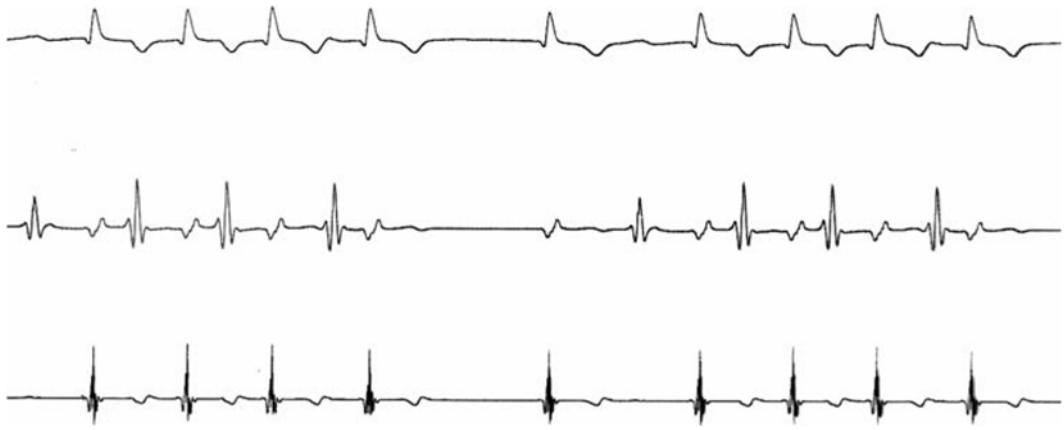


Fig. 14.11 Simultaneous recordings of lead I (*upper trace*), atrial temporary pacing wire (*middle trace*), and ventricular pacing wire (*lower trace*). Patient has low amplitude atrial activity with first-degree atrioventricular block making rhythm determination difficult. Atrial wire electrogram consistent with sinus arrest or sustained sinoatrial exit block

procedures. The primary measures of sinus node function are the sinoatrial conduction time and the corrected sinus node recovery time. However, atrial refractoriness and intra-atrial conduction times are also prolonged with surgically induced sick sinus syndrome.

Prolonged Sinoatrial Conduction Time

Total sinoatrial conduction time (TSACT) can be measured by an indirect method. The TSACT reflects conduction time into and out of the sinus node. These conduction times are not equal, thus it is more accurate to report a total sinoatrial conduction time rather than assume that the conduction velocity in both directions is equivalent and then divide the TSACT by 2. Normal values for pediatric patients are <200 ms. With this indirect method, absence of a zone of reset suggests sinoatrial node entrance block, which is abnormal as well. Sinus arrhythmia invalidates this measurement, a frequent confounder in children. Directly recorded conduction times from the sinus node electrogram reflect only conduction out of the sinus node and are usually shorter than the TSACT. As an independent measure of sinus node function, TSACT is relatively insensitive. Atropine has variable effects on TSACT as it often normalizes it, even in patients with sinus node dysfunction. Further prolongation of the TSACT is thought to be the result of depressed automaticity following enhanced conduction of the test impulse into the sinus node. This may be useful in differentiating sinoatrial exit block from sinus arrest.

Prolonged Sinus Node Recovery Time

The maximum corrected sinus node recovery time (MCSNRT) is a measure of automaticity. To perform this test one paces the atrium above the spontaneous rate in successive trials at 90, (pause for 30 s between trials) 120, 150, 180, and 210 bpm for 30 s. The sinus node recovery time (SNRT) is the interval in seconds that it takes for the first intrinsic sinus impulse to recover after the termination of 30 s of pacing. CSNRT is calculated by subtracting the SNRT from the basic sinus cycle length pre-pacing. (SNRT-intrinsic CL). The MCSNRT is the longest calculated CSNRT among the 5 pacing trials. Normal values (see Chap. 3) for MCSNRT are age related, but usually are <250–270 ms for children, <445 ms for adolescents, and <525 ms for adults. When expressed as a ratio, MCSNRT should be less than 150 % of the sinus cycle length. At high

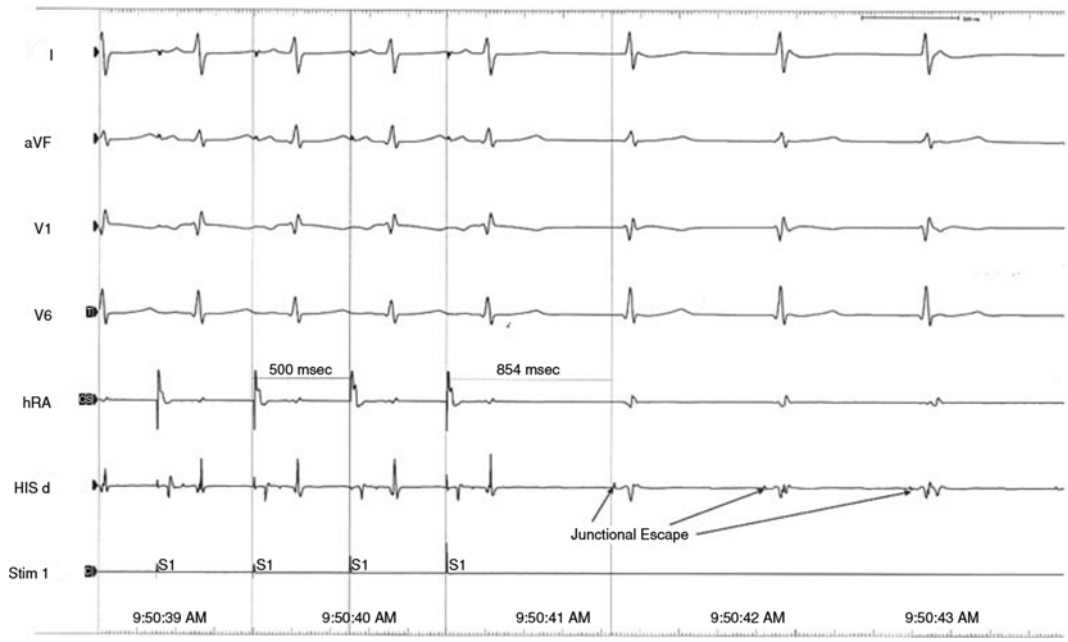


Fig. 14.12 Abnormal response to overdrive pacing. The patient had a sinus cycle length of 550 ms. The sinus node should recover in <275 ms. Here the recovery is prolonged (304 ms) and a junctional focus emerges before the sinus node. The junctional rhythm persists for 10 beats following termination of pacing

rates shortening of the return cycle may occur due to reflex responses to hypotension, sinus node entrance block, or local release of catecholamines. Abnormal results (Fig. 14.12) may be secondary to excess vagal tone and normalize following autonomic blockade in normal patients; in contrast patients with true dysfunction tend to show no improvement following autonomic blockade. The specificity of this test may be enhanced by co-administration of disopyramide or autonomic blockade, but this has not been conclusively demonstrated in children. Other findings suggestive of sinus node dysfunction include secondary pauses, and a prolonged total recovery time, defined as greater than 5–6 beats to return to the resting cycle length. MSCNRT that occurs at longer pacing cycle lengths more strongly supports the diagnosis of sinus node disease.

In practice these invasive electrophysiologic studies are rarely necessary or used to diagnose and manage sick sinus syndrome.

Treatment

Prospective, randomized clinical trials are not available to guide management in pediatric patients. The presence of sick sinus syndrome does not mandate therapy. Most patients with the subjective assessment of sick sinus syndrome are asymptomatic and there is not a risk for sudden death in the asymptomatic individual. Acute symptomatic bradycardia may be treated with atropine, isoproterenol, or transcutaneous pacing. Temporary transvenous or trans-esophageal pacing can be established until a permanent pacing system can be implanted.

There is little role for chronic drug therapy for the bradycardia associated with chronic sinus node dysfunction. Symptomatic bradycardia is treated with permanent pacing. Symptomatic bradycardia due to sinus node dysfunction is a clear indication (Class I) for pacemaker placement. Asymptomatic episodes of heart rates

under 40 bpm or pauses >3 s are less clear indications for intervention (Class IIa) in the child as well as in the adolescent (Class IIb). Consideration should be given to the patient's size, cardiac anatomy, and AV nodal function, as well as the presence of any tachyarrhythmias.

Atrial pacing has significant advantages over ventricular pacing for the treatment of sick sinus syndrome; therefore most patients receive atrial pacemakers. A rate response algorithm is programmed for those who appear to have significant chronoscopic incompetence. Rate response algorithms are adjusted by either accelerometers and/or minute ventilation. Most pacemaker manufacturers have only accelerometers. Accelerometers utilize piezoelectric components to sense physical movement or activity often requiring heel strike movement, so is less than ideal for someone swimming, cycling, or for an infant. Minute ventilation sensors measure transthoracic impedance, an indirect measurement of tidal volumes and respiratory rates which is highly correlated with breathing. Patients who are active with cycling, swimming or have lower extremity walking problems may benefit more from a combined rate response algorithm (accelerometer and minute ventilation). The rate response can be optimized with exercise testing and ambulatory Holter monitoring. Patients with any degree of AV nodal dysfunction, or for those where there is concern about the reliability of atrial pacing, receive dual chamber pacemakers. Initially the AV delay may be programmed to allow for native AV conduction to occur. Later progression of AV node dysfunction can be accommodated with adjustment of the AV interval. Patients who have had Mustard, Senning, and Fontan procedures for congenital heart disease often have scarred atria complicating epicardial lead placement. In the Fontan patient transvenous placement, while technically feasible and reported, may increase the risk of thrombosis. Achieving and maintaining adequate sensing and stimulation thresholds in the Fontan baffle may be very challenging and rate support with ventricular pacing alone may have to be accepted.

Coexisting tachycardias complicate dual chamber pacing. Rapid atrial rates that are tracked by the pacemaker may result in hemodynamic compromise from the high rate. Reducing the programmed upper rate limit is one method to avoid inappropriate tracking of tachycardia. Another is mode switching where the pacemaker automatically reverts to ventricular pacing only if the atrial rate exceeds a programmed threshold.

Symptomatic tachycardia is initially managed with pharmacologic therapy (Chaps. 8 and 21). The choice of medication must include consideration of the underlying heart disease, cardiac function, and the state of the remainder of the conduction system. Digoxin may not significantly worsen bradycardia in all patients and may help to decrease AV conduction of rapid tachycardias. ß-Blocking agents, sotalol, and amiodarone may all inhibit sinus or escape pacemaker automaticity such that permanent pacing is needed for rate support. Pharmacologic therapy should be initiated with continuous monitoring in the hospital. Catheter ablation of the tachycardia is one option but has only moderate acute success (70–80 %) and may be only transiently successful. Another option is surgical ablation with revision of the initial repair along with cryo- or radio-frequency ablation of arrhythmia substrates. Select patients with infrequent arrhythmias that are reproducibly terminated by overdrive pacing (Fig. 14.13) may be candidates for antitachycardia pacemakers.

Conclusion

In the young patient the prognosis is generally favorable. Sick sinus syndrome is a slowly progressive disease and deterioration of sinus node function continues into adulthood for survivors of surgery for congenital heart disease. More than 50 % of patients with d-transposition who underwent venous repair develop some degree of sinus node dysfunction and up to 20 % will require pacing for sinus node dysfunction during

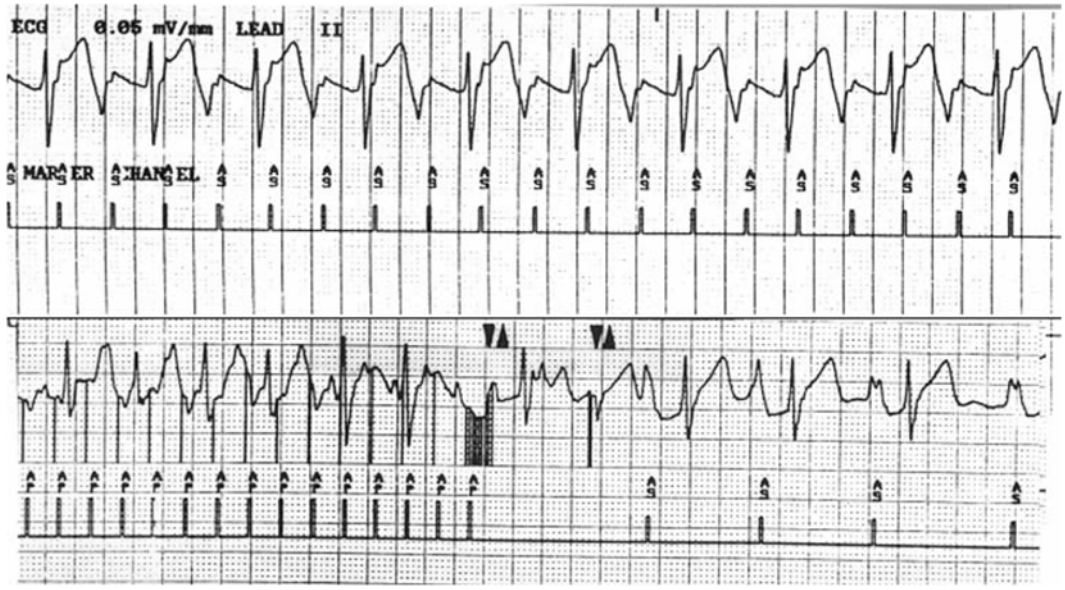


Fig. 14.13 Intra-atrial reentrant tachycardia following Fontan repair. The patient has a dual chamber pacemaker and atrial sensed events (AS) show 2:1 conduction. In the lower panel, sinus rhythm is restored following overdrive stimulation through the pacemaker

long-term follow-up. A similar pattern has been observed for the Fontan operation, but recent modifications to the procedure may substantially decrease the prevalence of sick sinus syndrome. Atrial pacing may slow the progression to atrial fibrillation. Sudden death related to bradycardia or prolonged pauses are rare. While there are no significant long-term data following adult congenital heart patients with sinus node dysfunction, adult populations with normal hearts free of cardiac malformations but known or suspected coronary heart disease and sinus node dysfunction have been studied. Few studies suggest that chronotropic incompetence is predictive of increased mortality. The development of AV nodal dysfunction is also progressive, but relatively slow in both adult and pediatric studies. In contrast over time the associated tachyarrhythmias may be increasingly difficult to control and may require additional medical, catheter, or surgical interventions and pose a larger risk for sudden death for patients following surgery for complex congenital heart disease.

Suggested Reading

Anderson JB, Benson DW. Genetics of sick sinus syndrome. Card Electrophysiol Clin. 2010;2(4):499–507.

Benson DW, Wang DW, Dyment M, Knilans TK. Congenital sick sinus syndrome caused by recessive mutations in the cardiac sodium channel gene (SCN5A). J Clin Invest. 2003;112(7):1019–28.

Calzolari V, Angelini A, Basso C, Livi U, et al. Histologic findings in the conduction system after cardiac transplantation and correlation with electrocardiographic findings. Am J Cardiol. 1999;84:756–9.

Campbell RM, Dick M, Crowley DC, Rocchini AP, et al. Atrial pacing to estimate total sinoatrial conduction time in children. Pediatr Cardiol. 1988;9:85–9.

Crawford MH, Bernstein SJ, Deedwania PC, DiMarco JP, et al. ACC/AHA guidelines for ambulatory electrocardiography. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the Guidelines for Ambulatory Electrocardiography). Developed in collaboration with the North American Society for Pacing and Electrophysiology. J Am Coll Cardiol. 1999;34:912–48.

Cuneo BF, Strasburger JF, Niksch A, Ovadia M, et al. An expanded phenotype of maternal SSA/SSB antibody-associated fetal cardiac disease. J Matern Fetal Neonatal Med. 2009;22(3):233–8.

Dilawar M, Bradley SM, Saul JP, Stroud MR, et al. Sinus node dysfunction after intraatrial lateral tunnel and extracardiac conduit fontan procedures. Pediatr Cardiol. 2003;24:284–8.

Dobrzynski H, Boyett MR, Anderson RH. New insights into pacemaker activity: promoting understanding of sick sinus syndrome. Circulation. 2007;115(14): 1921–32.

Elhendy A, Mahoney D, Khandheria B, Burger K, et al. Prognostic significance of impairment of heart rate response to exercise: impact of left ventricular function and myocardial ischemia. JACC. 2003;42(5):823–30.

Ferrer MI. The sick sinus syndrome. JAMA. 1968; 206:206–45.

Garrigue S, Bordier P, Jais P, Shah D, et al. Benefit of atrial pacing in sleep apnea syndrome. N Engl J Med. 2002;346:404–12.

Gelatt M, Hamilton RM, McCrindle BW, Connoly M, et al. Arrhythmia and mortality after the mustard procedure: a 30-year single-center experience. J Am Coll Cardiol. 1997;29:194–201.

Gregoratos G, Abrams J, Epstein AE, Freedman RA, et al. ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/NASPE Committee to Update the 1998 Pacemaker Guidelines). J Cardiovasc Electrophysiol. 2002;13: 1183–99.

Helbing WA, Hansen B, Ottenkamp J, Rohmer J, et al. Long-term results of atrial correction for transposition of the great arteries. Comparison of Mustard and Senning operations. J Thorac Cardiovasc Surg. 1994;108:363–72.

Hilma H, Gudbjartsson DF, Sulem P, et al. A rare variant in MYH6 is associated with high risk of sick sinus syndrome. Nat Genet. 2011;43:316–20.

Janousek J, Paul T, Luhmer I, Wilken M, et al. Atrial baffle procedures for complete transposition of the great arteries: natural course of sinus node dysfunction and risk factors for dysrhythmias and sudden death. Z Kardiol. 1994;83:933–8.

Kardelen F, Celiker A, Ozer S, Ozme S, et al. Sinus node dysfunction in children and adolescents: treatment by implantation of a permanent pacemaker in 26 patients. Turk J Pediatr. 2002;44:312–6.

Kavey RE, Gaum WE, Byrum CJ, Smith FC, et al. Loss of sinus rhythm after total cavopulmonary connection. Circulation. 1995;92:II304–8.

Lauer M, Okin P, Larson M, Evans J, Levy D. Impaired heart rate response to graded exercise. Circulation. 1996;93:1520–6.

Lauer M, Francis G, Okin P, Pashkow F, et al. Impaired chronotropic response to exercise stress testing as a predictor of mortality. JAMA. 1999;281(6):524–9.

Lotze U, Maisch B. Humoral immune response to cardiac conducting tissue. Springer Semin Immunopathol. 1989;11:409–22.

Meijboom F, Szatmari A, Deckers JW, Utens EM, et al. Long-term follow-up (10 to 17 years) after Mustard repair for transposition of the great arteries. J Thorac Cardiovasc Surg. 1996;111:1158–68.

Menon A, Silverman ED, Gow RM, Hamilton RM. Chronotropic competence of the sinus node in congenital complete heart block. Am J Cardiol. 1998;82:1119–21. A9.

Oberhoffer R, von Bernuth G, Lang D, Gildein HP, Weismuller P. Sinus node dysfunction in children without heart defect. Z Kardiol. 1994;83:502–6.

Ozer S, Schaffer M. Sinus node reentrant tachycardia in a neonate. Pacing Clin Electrophysiol. 2001;24:1038–40.

Paul T, Ziemer G, Luhmer L, Bertram H, et al. Early and late atrial dysrhythmias after modified Fontan operation. Pediatr Med Chir. 1998;20:9–11.

Weese-Mayer DE, Silvestri JM, Menzies LJ, Morrow-Kenny AS, et al. Congenital central hypoventilation syndrome: diagnosis, management, and long-term outcome in thirty-two children. J Pediatr. 1992;120(3): 381–7.

First- and Second-Degree Atrioventricular Block

15

Anna Kamp and William A. Scott

The primary role of the AVN is to conduct electrical action potentials from the atria to the ventricles. The AV node introduces a delay in the conduction of the electrical impulse from the atria to the ventricles to allow atrial mechanical systole to complete the filling of the ventricles before ventricular systole. The His bundle, in continuity with the AV node, provides an escape (backup) pacemaker (albeit much slower) in case of sinus node failure.

Anatomy and Electrophysiology of the AV Node

Electrical conduction through the myocardium is dependent on the individual myocyte, cell-to-cell conduction, and propagation through the whole organ. One cellular characteristic that contributes to impulse conduction velocity in the heart is the composition and density of specific ion channels that are responsible for cellular transmembrane depolarization. The more rapidly a local region of the cell membrane is able to change its potential (inside relative to the outside), the more rapid is conduction down the length of the myocyte. Therefore, cells that depend on the rapid sodium current (such as the atria, ventricular, and His–Purkinje tissue) for the upstroke of phase 0 of the action potential conduct the signals rapidly, while cells that are dependent on the slower calcium current for phase 0 conduct signals more slowly. Although the various phases of the action potential of cell membranes are generated by more than one ion current, this difference is demonstrated by comparing the slower AV node conduction velocity (dominant calcium-dependent action potentials) to the faster atrial and ventricular tissue conduction velocity (dominant sodium channel-dependent action potentials). Another property that contributes to conduction velocity is the nature of the cell-to-cell connections—the gap junctions composed of different expressions of connexin membrane proteins. Connexin proteins cluster at gap junctions and form intracellular channels between cardiac myocytes. Electrical coupling in the AV node is poor because there are few gap junctions and the gap junctions are small. There are four connexin protein isoforms expressed within the heart (C×40, C×43, C×45, and C×30.2); their distribution in the different tissues within the atria, ventricles, and AV node vary and lead to the different electrical properties in each. Conduction through the AV node is slower than through atrial

A. Kamp, M.D.
Department of Pediatrics, Pediatric Cardiology, Ohio State University, Columbus, OH, USA

W.A. Scott, M.D. (✉)
Department of Pediatrics, UT Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390, USA
e-mail: william.scott@childrens.com

M. Dick, II (ed.), *Clinical Cardiac Electrophysiology in the Young*,
DOI 10.1007/978-1-4939-2739-5_15

or ventricular myocardium for multiple reasons: lower concentration of Na+ channels in the AV node, contributing to the delay in conduction, a more complex arrangement in that they are separated by connective tissue and are also smaller in diameter, both contributing to slower conduction and the distribution of the different connexins in and around the compact AV node. In addition, the conduction through the AV node is strongly modulated by autonomic innervation to the node, a number of forms of cardiac abnormalities, as well as the patient's basal state.

The AV node is located in the atrial septum at the apex of the triangle of Koch and is connected to the His bundle; the AV node can be divided into the lower node bundle and the compact node. The AVN region comprises functionally separate fast and slow pathways. Recent studies examining the histologic and molecular structure (ion channels and connexin isoforms) of the AV node and His bundle indicate that there are different functional components of the AV node and the His bundle and that they have different conduction properties. A rightward (inferior node) extension likely corresponds to a slow (conducting) pathway; a leftward extension and the corresponding fast (conducting) pathway are less well established (see Chaps. 1 and 5).

Abnormal conduction to the ventricles can result from intrinsic AV nodal or infranodal (the His–Purkinje system) disease (all potentially, deleteriously altering the cellular structural and electrical properties of the AV conduction system) including inflammation, infection, and degenerative changes including cardiomyopathy and apoptosis, or from extrinsic causes, including abnormal autonomic tone, electrolyte imbalance, hypothermia, trauma (surgery), and medication effects. First-degree AV block is almost always due to abnormal conduction in the atrium or AV node. Up to 20 % of patients with first-degree AV block and congenital heart disease, most notably AV septal defect and Ebstein's anomaly, have, in addition, prolonged intra-atrial conduction. Transient prolongation or failure of AV conduction may result from concealed conduction of atrial, junctional, or ventricular extrasystoles (Figs. 15.1, 15.2, and 15.3). Second-degree AV block may occur within the AV node, the His–Purkinje system, or at the ventricular level.

Similar to the sinus node, the AV node is innervated by the autonomic nervous system, which consists of a complex interaction of the sympathetic and parasympathetic nervous systems.

Cardiac chronotropic and inotropy are influenced by differing sympathetic and parasympathetic effects. Sympathetic nerves descend from the brain to the stellate and paravertebral ganglia where they synapse with postganglionic neurons. The sympathetic nervous system increases heart rate and contractility by binding norepinephrine to adrenergic receptors, initiating the adenylate cyclase-cAMP cascade. Parasympathetic nerves originate in the brain stem and project from the vagus nerve to postganglionic fibers within cardiac ganglia. The parasympathetic nervous system slows heart rate and decreases contractility by binding acetylcholine to cardiac muscarinic receptors or neural nicotinic receptors. Postganglionic sympathetic nerves extend from

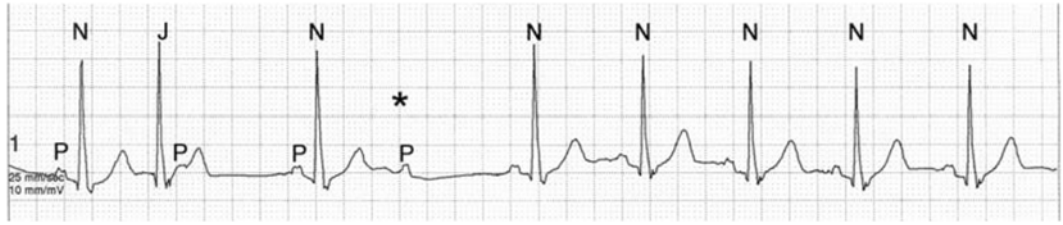


Fig. 15.1 Sinus rhythm with a junctional premature beat (J), which results in AV node refractoriness and block of the next sinus beat. *Subsequent non-conducted atrial impulse may be due to concealed junctional extrasystole, again making the AV node refractory without activating atrium or ventricle. Proof of this phenomenon requires intracardiac recordings

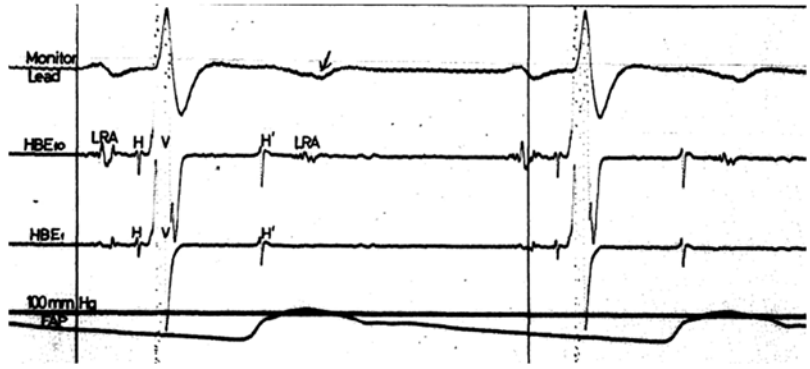


Fig. 15.2 Spontaneous His bundle extrasystoles (H′) arising at an H–H′ interval of 257 ms producing bigeminal rhythm. H′ fails to conduct to the ventricle but conducts retrograde to the atrium resulting in reversal of atrial activation from low to high atrium, associated with an inverted P wave (*arrow*). The bigeminal His bundle extrasystoles cause a marked slowing of ventricular rate. [Reprinted from Nasrallah AT, Gillette PC, Mullins CE, et al. Concealed his bundle extrasystoles in congenital heart disease. *American Journal of Cardiology*. 1975;35(2): 288–292. With permission from Elsevier.]

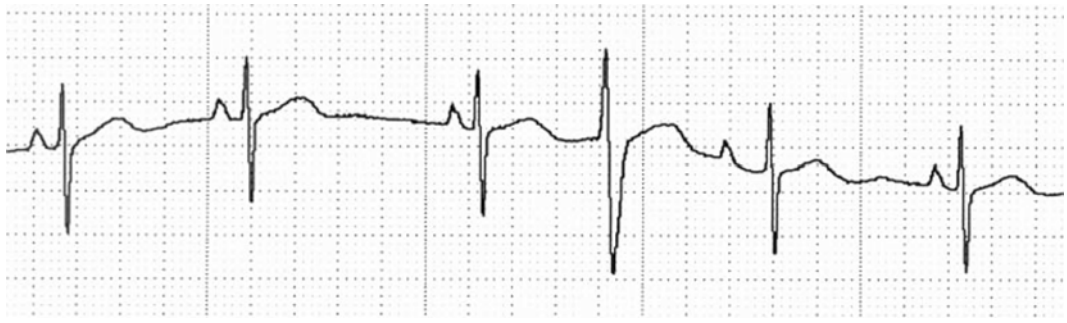


Fig. 15.3 Sinus rhythm with interpolated PVC. Concealed retrograde conduction into the AV node results in relative refractoriness and first-degree block (longer PR interval) of subsequent sinus impulse

the paravertebral ganglia to the heart where they meet with the parasympathetic nerves to form the cardiac neuronal plexus at the base of the heart.

The sympathetic innervation of the conduction system dominates in infancy but shifts to a balance of sympathetic and parasympathetic innervation in childhood and is complete in adulthood. Autonomic innervation is less prominent in the His–Purkinje system and has less influence on conduction in these areas. Bradycardia and PR interval prolongation usually reflects increased vagal tone on the sinus and AV nodes. PR interval prolongation in the presence of normal sinus rates is suggestive of AV nodal dysfunction. Functional first- and second-degree AV block can also present during rapid atrial pacing (Fig. 15.4), where, unlike sinus tachycardia, there is less sympathetic enhancement of AV nodal conduction.

ECG Characteristics

Multiple channel ECG recordings are often indispensable for detection of P wave morphology and PR intervals. Recording of atrial activity from esophageal or temporary epicardial pacing leads after surgery (Fig. 15.5) are also very useful when P waves are indistinct. Long-term recordings from Holter monitoring often reveal patterns not apparent in the 12 lead electrocardiogram.

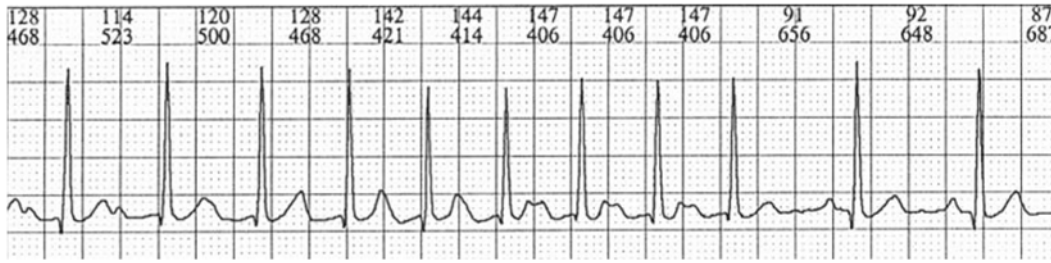


Fig. 15.4 Atrial pacing (stimulus artifact not present) producing a tachycardia that transitions to sinus rhythm. There is first-degree AV block during the tachycardia that resolves with the return of sinus rhythm

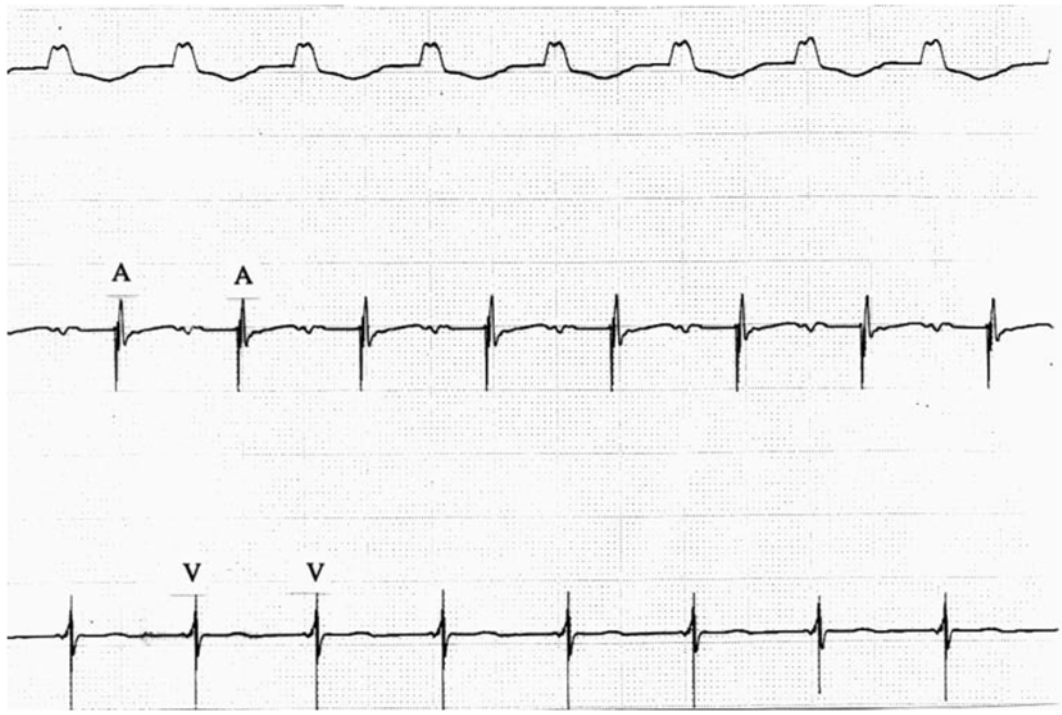


Fig. 15.5 Surface ECG (*upper signal*), atrial wire recording (*middle signal*), and ventricular wire recording in a patient with first-degree AV block following surgical repair of an atrioventricular septal defect. Atrial activity was not apparent from the surface ECG. Atrial wire recordings confirm 1:1 AV relationship with prolonged AV conduction time

First-Degree AV Block

First-degree AV block (Fig. 15.6) is defined as a PR interval above the normal range for age, but with persistent 1:1 AV conduction. The normal PR interval also decreases with increasing heart rate. Age-appropriate PR intervals are summarized in Table 15.1. The PR interval can be very long (Fig. 15.7) but usually, in the absence of heart disease, does not progress. The delay is located in the AV node mediated through excessive parasympathetic tone. Exercise, both recreational and during stress testing, induces parasympathetic withdrawal and sympathetic enhancement resulting in normalization of AV conduction and the PR interval (Fig. 15.7).

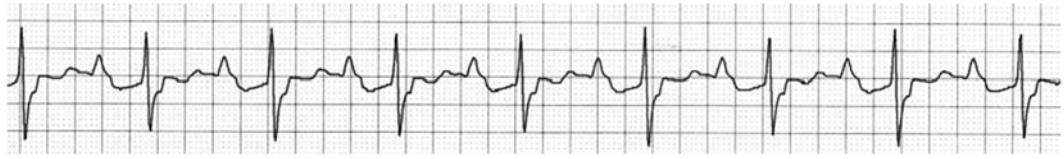


Fig. 15.6 Sinus rhythm with first-degree AV block

Table 15.1 Maximum normal PR interval

Age	PR (s)
0–3 days	0.16
4–30 days	0.14
1–3 months	0.13
4–6 months	0.15
7–12 months	0.16
1–5 years	0.16
6–12 years	0.17
>12 years	0.20

Second-Degree AV Block

Several distinct patterns of second-degree AV block can be recognized. Consistent periodicity (i.e., dropping every third, fourth, or fifth beat) is frequently present. The ratio of P-to-R waves provides a description of the pattern (i.e., 3:2, 4:3). This pattern of "grouped beats" should always suggest second-degree AV block. Regular non-conducted atrial extrasystoles may also present with this pattern and are distinguished by the irregular PP interval, as well as the different P wave morphologies (Fig. 15.8).

Mobitz I (Wenckebach)

With typical Mobitz I, or Wenckebach (Figs. 15.9 and 15.10), there is gradual prolongation of the PR interval prior to a non-conducted beat. The greatest increase in PR interval is between the first and second conducted beats of a series. The lesser increment increase of the PR interval on subsequent beats leads to a shortening of the RR interval. Following the non-conducted beat, the normal PR interval is restored resulting in an RR interval that is less than twice the sinus rate.

Atypical Wenckebach, which may be more common than the typical form, refers to other patterns of PR prolongation in association with the appearance of a dropped beat (no conduction to the ventricles)—AV block. This pattern may occur in the presence of sinus arrhythmia and with longer runs of conducted beats between block cycles.

Mobitz II

The PR interval does not vary prior to non-conducted beats with Mobitz II second-degree AV block, and, in the absence of a supraventricular arrhythmia, the RR interval is constant (Fig. 15.11). Since there is no change in PR or RR interval during the conducted beats, the RR interval following a non-conducted beat should be twice that of a conducted RR interval.

When every other beat is non-conducted in a 2:1 pattern, insufficient information is present to distinguish the pattern of Mobitz I from Mobitz II. Long-term recordings may reveal other ratios of conduction allowing discrimination of these two entities (Figs. 15.10 and 15.11). Long QT syndrome may present with 2:1 conduction as the ventricles, due to the mutated K+ ion channel (LQTS1) delaying ventricular repolarization, are refractory to successive sinus impulses; it is a poor prognostic sign.

Advanced

Advanced AV block is present when two or more impulses are not conducted in the absence of complete heart block (Fig. 15.12). Patients with advanced AV block may progress to complete heart block (Chap. 16).

Electrophysiologic Features

Electrophysiologic studies have provided invaluable insights into AV node physiology. Currently, clinical history and noninvasive diagnostic studies

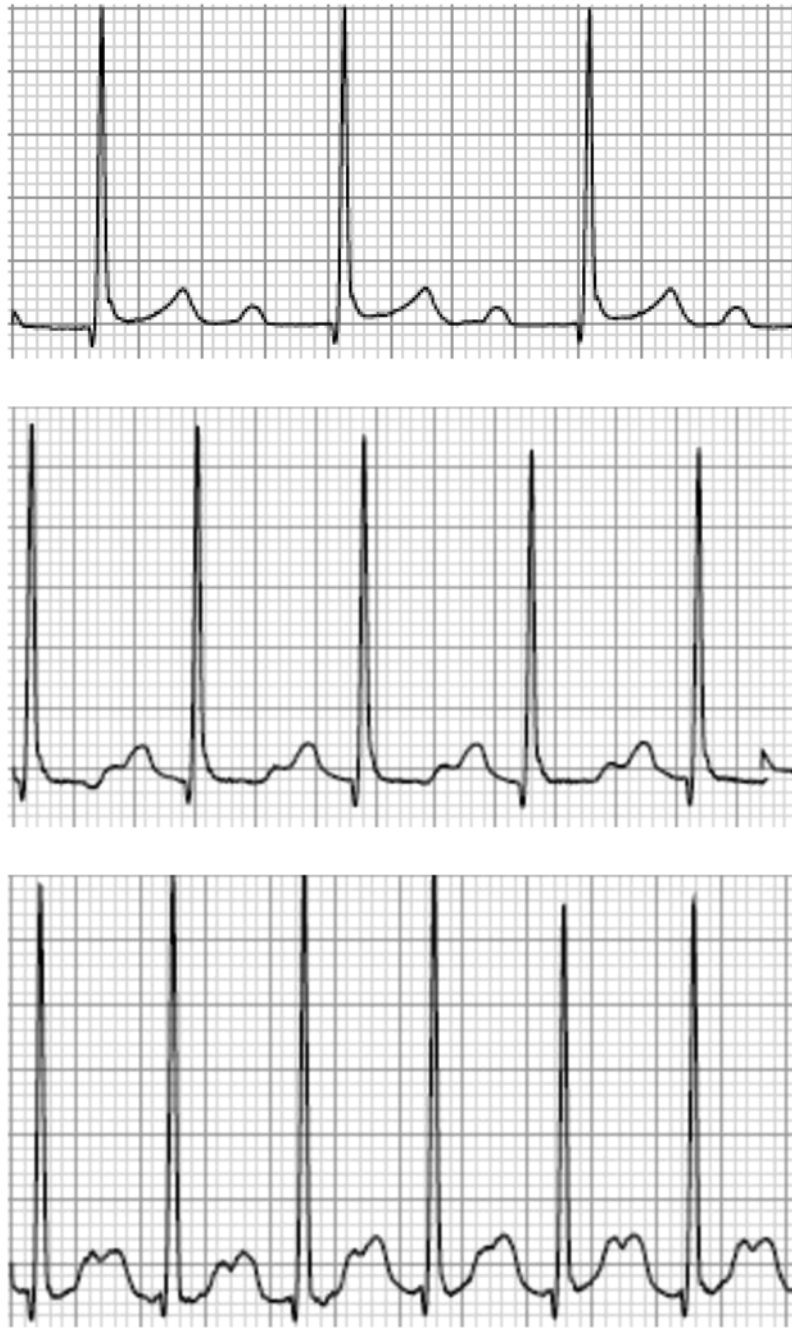


Fig. 15.7 16-year-old girl with first-degree AV block at baseline. With exercise, the PR interval shortens and there is 1:1 AV conduction

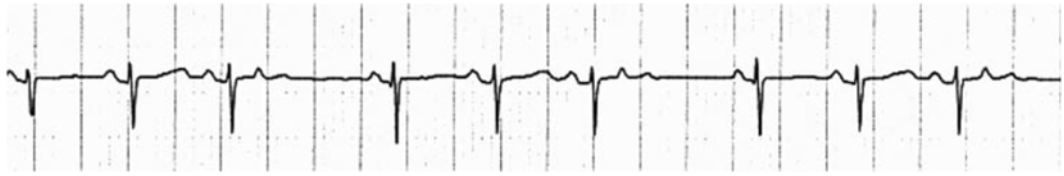


Fig. 15.8 Sinus rhythm with frequent non-conducted atrial extrasystoles in a quadrigeminal pattern. The grouped beats mimic second-degree AV block, but the variation in P wave timing and morphology are distinguishing features

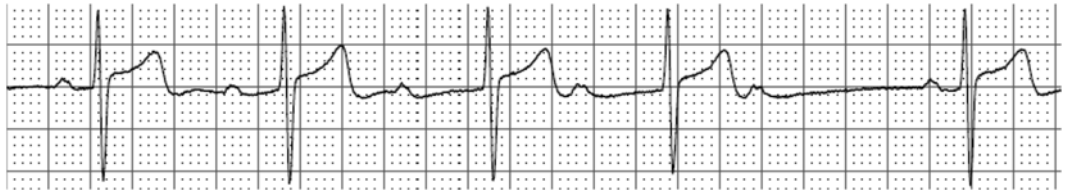


Fig. 15.9 Sinus rhythm with first-degree and Mobitz I second-degree AV block with a 5:4 conduction ratio

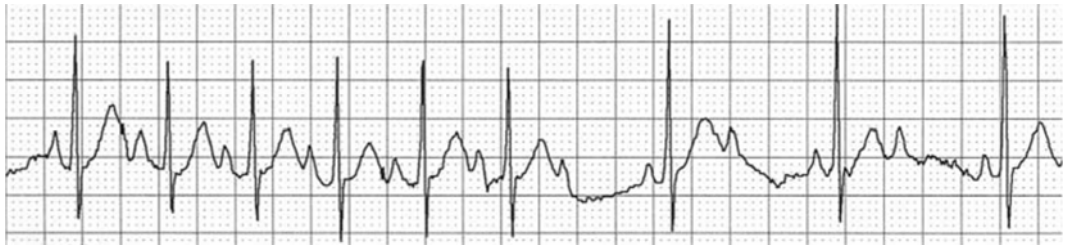


Fig. 15.10 Sinus rhythm with Mobitz I second-degree AV block that transitions to 2:1 block

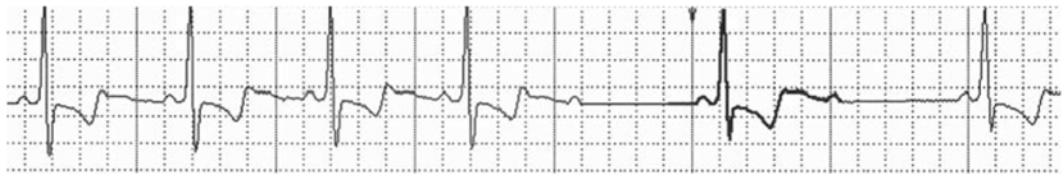


Fig. 15.11 Sinus rhythm with stable PR interval that transitions to 2:1 block. In the absence of prior PR interval prolongation, this most likely represents Mobitz II AV block

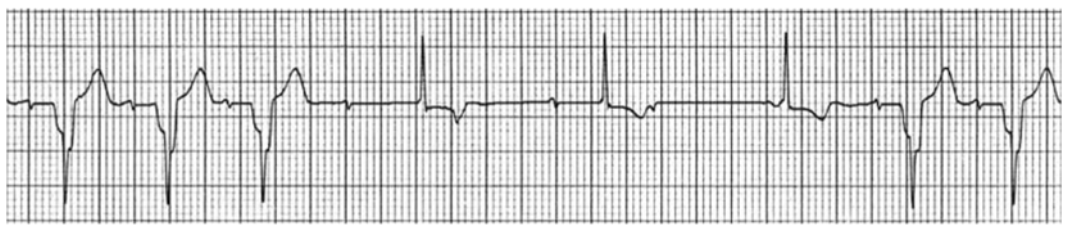


Fig. 15.12 Sinus rhythm in a patient with nodoventricular pathway. Advanced AV block associated with narrow complex escape rhythm

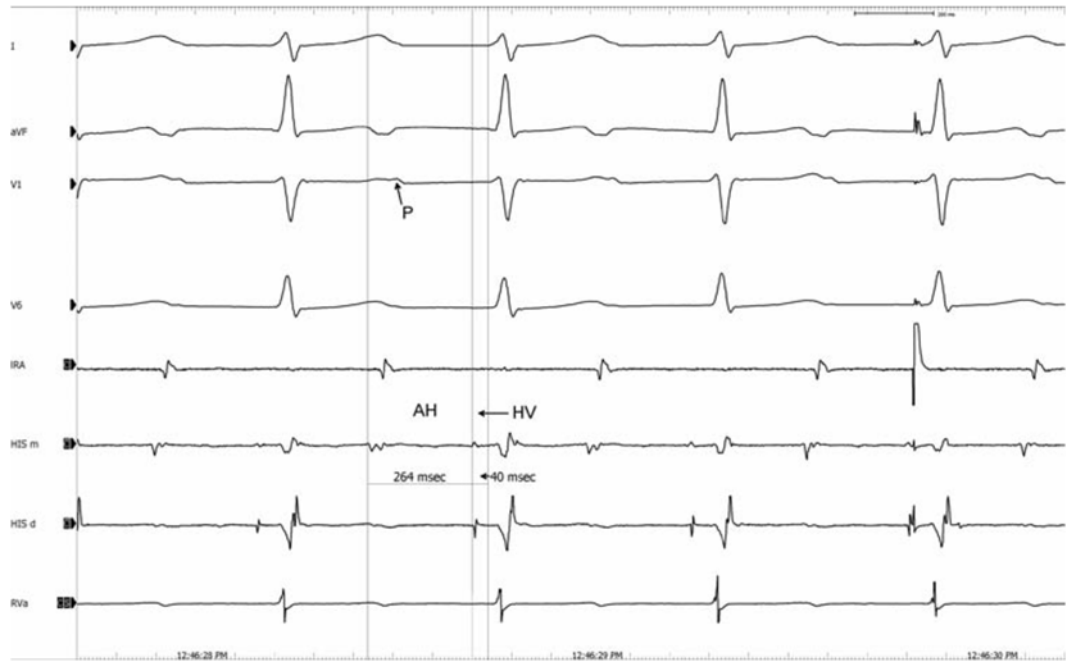


Fig. 15.13 Intracardiac study of a patient with first-degree AV block. Note prolonged AH and normal HV intervals localizing conduction delay to the AV node

primarily guide diagnosis and management of first- and second-degree AV block. Electrophysiologic study is not routinely performed solely for the assessment of first- and second-degree AV block because surface electrocardiograms provide adequate information for management. Invasive electrophysiologic studies of AV node function can be performed as an adjunct to hemodynamic study when deemed useful.

Measurements relevant to AV conduction include the intra-atrial conduction time (from the high right atrium near the sinus node to the low septal right atrium near the AV node), the AH interval, a measure of AV nodal conduction, and the HV interval, which reflects conduction through the His–Purkinje system to the ventricles (See Chap. 3). Intracardiac recordings allow distinction of the level at which block occurs (Figs. 15.13 and 15.14). Slow intra-atrial or AV nodal conduction is almost always the mechanism for first-degree AV block and is confirmed by recording a prolonged intra-atrial conduction time or AH interval. Similarly, Mobitz I block is almost always within the AV node such that the AH interval prolongs and there is no His bundle deflection with the onset of AV block. In contrast, Mobitz II block is more frequently infranodal. The AH interval typically remains constant and there is a His bundle deflection resulting in a non-conducted impulse and no ventricular activation.

Patients with first-degree or Mobitz I second-degree AV block often have prolonged effective and functional refractory periods for the atrium or the AV node. Normally, the effective refractory period of the His–Purkinje system and ventricular tissue is shorter than the functional refractory period for the AV node. Thus, block distal to the His during programmed stimulation is abnormal, though exceeding rare in the young.

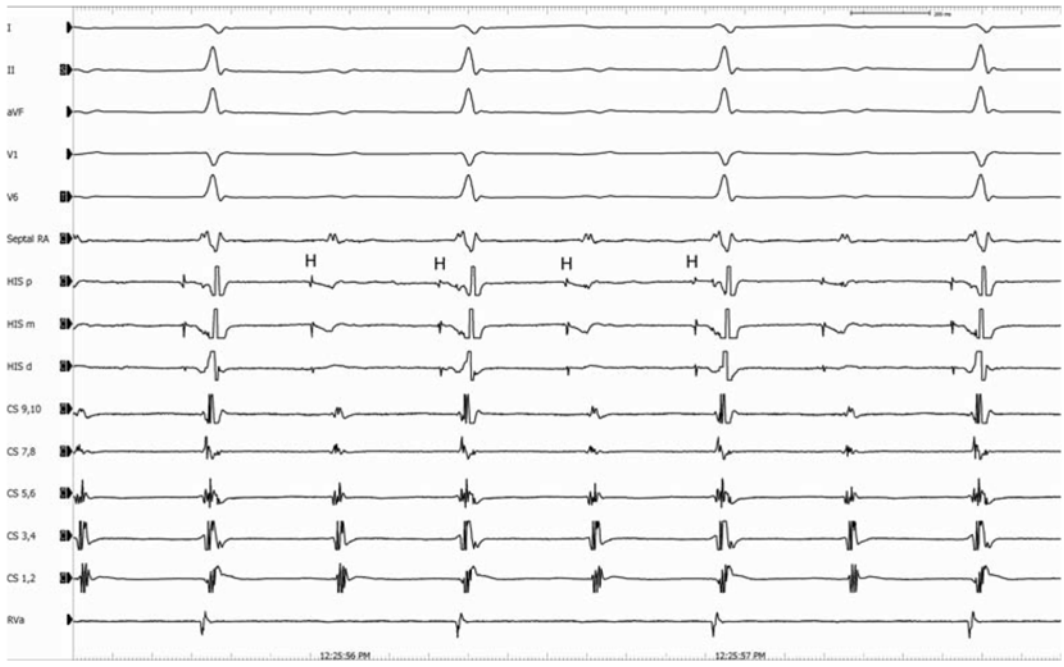


Fig. 15.14 Supraventricular tachycardia with 2:1 block. Note His depolarization (H) for conducted and blocked impulses localizing block to the distal conduction system

Prognosis and Treatment

Most children with first- and second-degree AV block do not experience progression to complete heart block and most do not require treatment. Transient first- and second-degree AV block may be observed during Holter recordings of healthy children and adolescents, particularly those who are athletes and particularly at night with predominantly sympathetic withdrawal. Avoidance of medications known to slow AV conduction is prudent, especially in those patients at risk for AV conduction system disease. For patients who are already receiving these medications, the potential benefit must be weighed against the risk of impaired conduction.

Patients who are acutely symptomatic with second-degree AV block are uncommon, but can be treated with atropine, isoproterenol, and temporary pacing. With some infectious diseases, such as Lyme carditis, the block may resolve entirely after antibiotic therapy. There are no chronic medical management options for patients with significant AV block. Consensus guidelines exist only for advanced AV block, long QT syndrome with 2:1 block or greater, and progressive AV block related to neuromuscular disease (see Chap. 16, Table 16.2). Patients with associated structural heart disease, a family history of progressive AV block or sudden death, and those known to carry the mutation of *NKX2.5* gene, require close surveillance and possibly permanent pacing as well.

Suggested Reading

Abaci A, Unlu S, Alsancak Y, et al. Short and long term complications of device closure of atrial septal defect and patent foramen ovale: meta-analysis of 28,142 patients from 203 studies. Catheter Cardiovasc Interv. 2013;82(7):1123–38.

Abe T, Tsuda E, Miyazaki A, et al. Clinical characteristics and long-term outcome of acute myocarditis in children. Heart Vessels. 2013;28:632–8.

Akin I, Kische S, Paranskaya L, et al. Predictive factors for pacemaker requirement after transcatheter aortic valve implantation. BMC Cardiovasc Disord. 2012;12:87.

Anderson J, Czosek R, Knilans T, et al. Postoperative heart block in children with common forms of congenital heart disease: results from the KID database. J Cardiovasc Electrophysiol. 2012;23: 1349–54.

Askanase AD, Friedman DM, Copel J, et al. Spectrum and progression of conduction abnormalities in infants born to mothers with anti-SSA/Ro-SSB/La antibodies. Lupus. 2002;11:145–51.

Aziz PF, Serwer GA, Bradley DJ, LaPage MJ, et al. Pattern of recovery for transient complete heart block after open heart surgery for congenital heart disease: duration alone predicts risk of late complete heart block. Pediatr Cardiol. 2013;34(4):999–1005.

Batra A, Epstein D, Silka M. The clinical course of acquired complete heart block in children with acute myocarditis. Pediatr Cardiol. 2003;24:495–7.

Benson DW. Genetics of atrioventricular conduction disease in humans. Anatomical Record Part A. 2004;280A:934–9.

Bleicher N, Elkayam U. Preventing congenital neonatal heart block in offspring of mothers with anti-SSA/Ro and SSB/La antibodies: a review of published literature and registered clinical trials. Autoimmun Rev. 2013;12:1039–45.

Brucato A, Frass M, Franceschini F, et al. Risk of congenital complete heart block in newborns of mothers with anti-Ro/SSA antibodies detected by counterimmunoelectrophoresis: a prospective study of 100 women. Arthritis Rheum. 2001;44:1832–5.

Brucato A, Jonson A, Friedman D, et al. Proposal for a new definition of congenital complete atrioventricular block. Lupus. 2003;12:427–35.

Buyon JP, Hiebert R, Copel J, et al. Autoimmune-associated congenital heart block: demographics, mortality, morbidity and recurrence rates obtained from a National Neonatal Lupus Registry. J Am Coll Cardiol. 1998;31:1658–66.

Buyon JP, Kim MY, Copel JA, Friedman DM. Anti-Ro/SSA antibodies and congenital heart block: necessary but not sufficient. Arthritis Rheum. 2001;44:1723–7.

Capone C, Buyon J, Friedman D, et al. Cardiac manifestations of neonatal lupus: a review of autoantibody associated congenital heart block and its impact in an adult population. Cardiol Rev. 2012;20(2):72–6.

Cruz RB, Viana VS, Nishioka SA, et al. Is isolated congenital heart block associated to neonatal lupus requiring pacemaker a distinct cardiac syndrome? Pacing Clin Electrophysiol. 2004;27:615–20.

Desai V, Kelton C, Czosek R, et al. Frequencies, costs, and complications of catheter ablation for tachyarrhythmias in children: 2000–2009. PACE. 2013;00:1–13.

Epstein A, DiMarco J, Ellenbogen K, et al. ACC/AHA/HRS 2008 Guidelines for device-based therapy of cardiac rhythm abnormalities. Heart Rhythm. 2008;5(6):e1–62.

Friedman D, Kim M, Copel J, et al. Utility of cardiac monitoring in fetuses at risk for congenital heart block: the PR interval and dexamethasone evaluation (PRIDE) prospective study. Circulation. 2008;117:485–93.

Glickstein JS, Buyon J, Friedman D. Pulsed Doppler echocardiographic assessment of the fetal PR interval. Am J Cardiol. 2000;86:236–9.

Groves AM, Allan LD, Rosenthal E. Outcome of isolated congenital complete heart block diagnosed in utero. Heart. 1996;75:190–4.

Izmirly P, Costedoat-Chalumeau N, Pisoni C, et al. Maternal use of hydroxychloroquine is associated with a reduced risk of recurrent anti-SSA/Ro-antibody—associated cardiac manifestations of neonatal lupus. Circulation. 2012;126:76–82.

Jaeggi ET, Hamilton RM, Silverman ED, et al. Outcome of children with fetal, neonatal or childhood diagnosis of isolated congenital atrioventricular block. J Am Coll Cardiol. 2002;39:130–7.

Karpawich PP, Gillette PC, Garson Jr A, Hesslein PS, Porter CB, McNamara DG. Congenital complete atrioventricular block: clinical and electrophysiologic predictors of need for pacemaker insertion. Am J Cardiol. 1981;48:1098–102.

Kertesz NJ, Friedman RA, Colan SD, et al. Left ventricular mechanics and geometry in patients with congenital complete heart block. Circulation. 1997;96:3430–5.

Lin A, Mahle W, Frias P, et al. Early and delayed atrioventricular conduction block after routine surgery for congenital heart disease. J Thorac Cardiovasc Surg. 2010;140:158–60.

Michaelsson M, Jonzon A, Riesenfeld T. Isolated congenital complete atrioventricular block in adult life. A prospective study. Circulation. 1995;92:442–9.

Miranda-Carus ME, Askanase AD, Clancy RM, et al. Anti-SSA/Ro and anti-SSB/La autoantibodies bind the surface of apoptotic fetal cardiocytes and promote secretion of TNF-alpha by macrophages. J Immunol. 2000;165:5345–51.

Moak JP, Barron KS, Hougen TJ, et al. Congenital heart block: development of late-onset cardiomyopathy, a previously underappreciated sequela. J Am Coll Cardiol. 2001;37:238–42.

Morquio L. Sur une maladie infantile et familiale caracterisée par des modifications permanentes du pouls, des attaques syncopales et epileptiforme et la mort subite. Arch Méd d'Enfants. 1901;4:467.

Nield LE, Silverman ED, Taylor GP, et al. Maternal anti-Ro and anti-La antibody-associated endocardial fibroelastosis. Circulation. 2002;105:843–8.

Pordon CM, Moodie DS. Adults with congenital complete heart block: 25-year follow-up. Cleve Clin J Med. 1992;59:587–90.

Schott J, Benson DW, Basson C, et al. Congenital heart disease caused by mutations in the transcription factor NKX2-5. Science. 1998;231:108–11.

Semmler D, Blank R, Rupprecht H. Complete AV block in lyme carditis: an important differential diagnosis. Clin Res Cardiol. 2010;99:519–26.

Sholler GF, Walsh EP. Congenital complete heart block in patients without anatomic cardiac defects. Am Heart J. 1989;118:1193–8.

Siehr S, Hanley F, Reddy V, et al. Incidence and risk factors of complete atrioventricular block after operative ventricular septal defect repair. Congenit Heart Dis. 2014;9(3):211–5.

Tunks R, Clowse M, Miller S, et al. Maternal autoantibody levels in congenital heart block and potential prophylaxis with anti-inflammatory agents. Am J Obstet Gynecol. 2013;208:64.e1–7.

Udink ten Cate FE, Breur JM, Cohen MI, et al. Dilated cardiomyopathy in isolated congenital complete atrioventricular block: early and long-term risk in children. J Am Coll Cardiol. 2001;37:1129–34.

Van Geldorp I, Vanagt W, Vugts G, et al. Late recovery of atrioventricular conduction after postsurgical chronic atrioventricular block is not exceptional. J Thorac Cardiovasc Surg. 2013;145:1028–32.

Waltuck J, Buyon JP. Autoantibody-associated congenital heart block: outcome in mothers and children. Ann Intern Med. 1994;120:544–51.

Weindling S, Saul J, Gamble W, et al. Duration of complete atrioventricular block after congenital heart disease surgery. Am J Cardiol. 1998;82:525–7.

White P, Eustis R. Congenital heart block. Am J Dis Child. 1921;22:299.

Winkler RB, Freed MD, Nadas AS. Exercise-induced ventricular ectopy in children and young adults with complete heart block. Am Heart J. 1980;99:87–92.

Xiao GQ, Hu K, Boutjdir M. Direct inhibition of expressed cardiac L- and T-type calcium channels by IgG from mothers whose children have congenital heart block. Circulation. 2001;103:1599–604.

Complete Atrioventricular Block Third-Degree Heart Block

16

Anna Kamp and William A. Scott

Introduction

Complete atrioventricular (AV) block is defined as interruption in the transmission of the cardiac impulse from the atria to the ventricles due to an anatomical or functional impairment in the AV conduction system (Fig. 16.1). The conduction disturbance can be transient or permanent.

The anatomy and electrophysiology of the AV node has been described in Chap. 15.

While there are various classifications regarding the age and mechanism of complete heart block (CHB) in a young person, for the purpose of this discussion, congenital CHB includes both immune-mediated and nonimmune-mediated heart block that is diagnosed in utero, at birth, or in the neonatal period (0–27 days after birth). Isolated congenital CHB occurs without coexisting structural heart disease. Acquired CHB can be a complication of surgical repair, infection, neoplasm, or other rare occurrences; it can occur later in childhood or adolescence spontaneously without identifiable cause, and persist or resolve (Table 16.1).

Congenital CHB was first described in 1901 by Morquio, who also noted a familial occurrence and an association with Stokes–Adams attacks and death. The presence of fetal bradycardia (40–80 bpm) as a manifestation of CHB was first noted in 1921. The incidence of congenital CHB in the general population varies between 1 in 15,000 and 1 in 22,000 live-born infants, the majority of which are autoimmune mediated.

Autoimmune-Mediated CHB

Neonatal Lupus

Complete heart block, hepatobiliary disease, malar rash, thrombocytopenia and, less frequently, myocarditis comprise neonatal lupus primarily presenting in utero or in the neonate. Frequently, the only manifestation of neonatal lupus, and by extension an autoimmune abnormality in the mother, is CHB in the newborn. Since skin, liver, and blood cells regenerate, the effect of passively acquired antibodies in these organs in the fetus/newborn resolves, usually in the first 6 months of life. However, cardiac cells are not regenerative and thus CHB from neonatal lupus is permanent.

In the absence of congenital heart disease, neonatal lupus is responsible for 60–90 % of cases of

A. Kamp, M.D.
Department of Pediatrics, Pediatric Cardiology, Ohio State University, Columbus, OH, USA

W.A. Scott, M.D. (✉)
Department of Pediatrics, UT Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390, USA
e-mail: william.scott@childrens.com

M. Dick, II (ed.), *Clinical Cardiac Electrophysiology in the Young*,
DOI 10.1007/978-1-4939-2739-5_16

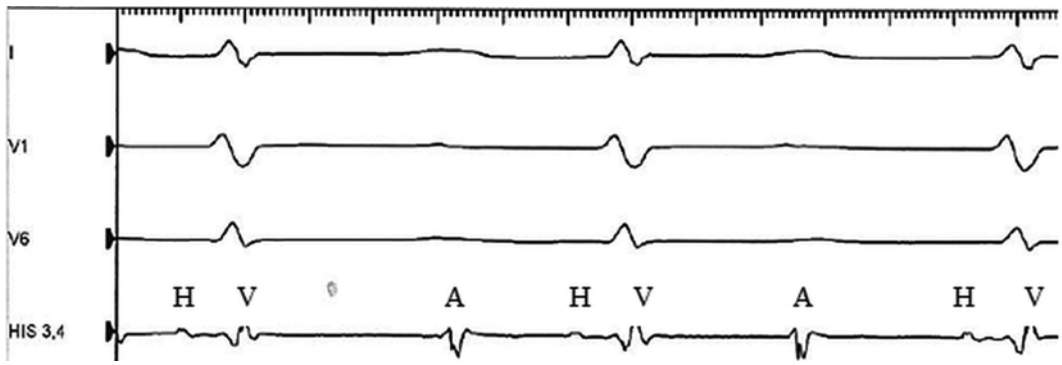


Fig. 16.1 ECG and His bundle electrogram of Complete Heart Block. Leads I, V1, V6 with an atrial (A) electrogram, a His bundle electrogram (H), and ventricular (V) electrogram demonstrating CHB with a His bundle (H) escape rhythm

Table 16.1 Etiology of complete heart block

Isolated complete heart block—No associated structural heart disease
• Congenital HB—Immune mediated
• Congenital HB—nonimmune mediated
• Cardiac manifestation of neuromuscular disease
– Emery–Dreifuss muscular dystrophy
– Kearns–Sayre syndrome
– Myotonic dystrophy
• Genetic associations
– Idiopathic AV conduction disease
– PRKAG2—ventricular preexcitation and AV block
– SCN5A
– NKX2.5
• Fibrosis and sclerosis
– Fibrosis and sclerosis of the conduction system accounts for about one-half of cases of AV block in adults
– *Lenegre's disease* is a progressive, fibrotic, sclerodegenerative disease of the conduction system in younger individuals associated with slow progression to CHB and may be hereditary
• Valvular disease: Calcification and fibrosis of the aortic or mitral valve rings can extend into the conducting system
• Cardiomyopathies
– Hypertrophic obstructive cardiomyopathy
– Infiltrative processes such as amyloidosis and sarcoidosis
• Hyperthyroidism, myxedema, and thyrotoxic periodic paralysis
• Malignancies: Such as Hodgkin's disease and other lymphomas; multiple myeloma; and cardiac tumors
• Drugs: A variety of drugs can impair conduction and cause AV block
• Ischemic heart disease
Complete heart block associated with congenital heart disease, most commonly:
• L-transposition of the great arteries
• Single ventricle
• Heterotaxy syndrome

congenital CHB. Maternal IgG auto-antibodies to SSA/Ro and/or SSB/La from a mother with an autoimmune connective tissue disorder, most frequently lupus erythematosus, cross the placenta to the fetus during the first trimester. Anti-Ro/SSA and/or anti-La/SSB antibodies bind to fetal cardiac tissue, leading to immune-mediated injury to the AV node and its surrounding tissue.

Both Ro/SSA and La/SSB antigens are abundant in fetal heart tissue between 18 and 24 weeks. Apoptosis induces translocation of Ro/SSA and La/SSB to the surface of fetal cardiomyocytes; the maternal, transplacental anti-Ro and anti-La antibodies then bind to the surface of the fetal cardiomyocytes and induce the release of tumor necrosis factor by macrophages, resulting in fibrosis. In addition to inducing tissue damage, anti-Ro/SSA and/or anti-La/SSB antibodies inhibit calcium channel activation of the cardiac L- and T-type calcium channels themselves; L-type channels allow action potential propagation and conduction in the AV node. The sinoatrial (SA) node also may be involved; sinus

bradycardia has been described in 3.8 % percent of fetuses but is usually not permanent.

Immune-mediated CHB accounts for almost all cases of CHB presenting in utero or during the neonatal period. Rarely, it may explain a few cases occurring later (approximately 5 %). Approximately 2 % of babies born to SSA/SSB + mothers, the majority of whom are often asymptomatic, have CHB; however, the recurrence rate for future offspring may be as high as 17 %.

Clinical Manifestations of Neonatal Lupus

The patients with the neonatal lupus syndrome tend to present earlier than those with CHB not due to neonatal lupus.

Congenital CHB may present with fetal bradycardia between 18 and 28 weeks of gestation. In utero detection is made by echocardiography, which can estimate the fetal PR interval. Complications of CHB in utero include hydrops fetalis, myocarditis, endocardial fibroelastosis, pericardial effusion, and spontaneous intrauterine fetal death. Advanced AV block and cardiomyopathy can occur within one week of normal fetal echo without first-degree AVB (Fig. 16.2).

Infants who present with heart block in utero, but who survive until birth, have a high neonatal mortality rate. In one report, 6 of 22 such infants (27 %) died within one week of birth. In another series, 10 of 107 (9 %) died within the first 3 months. Infants born before 34 weeks have a higher mortality rate than those born later (52 % vs. 9 %). Infants with

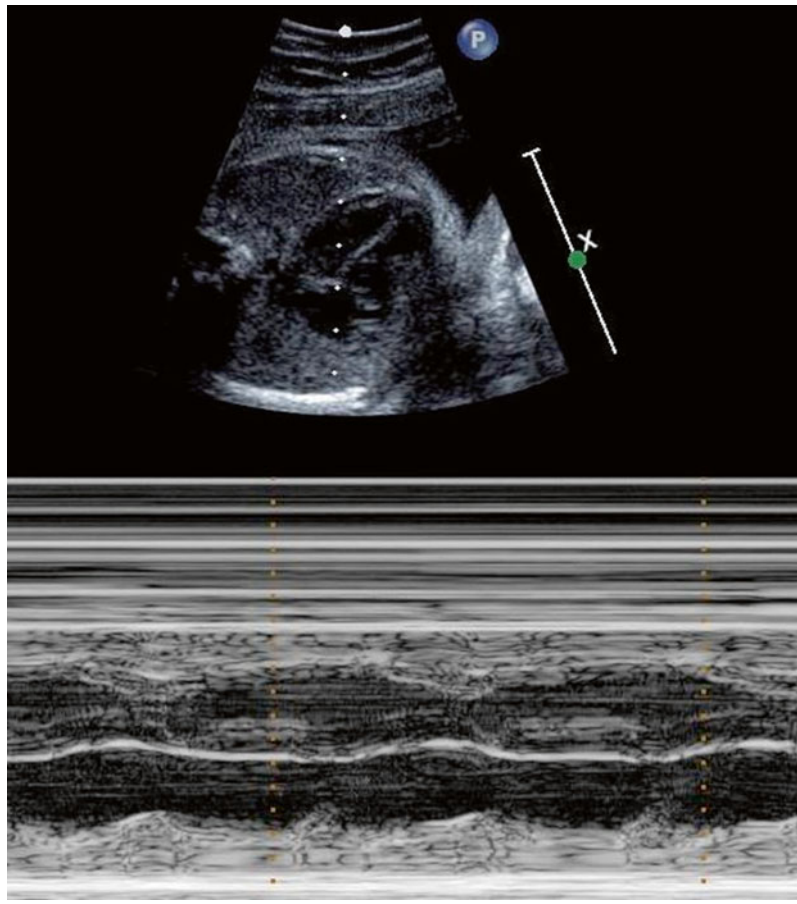


Fig. 16.2 Fetal echocardiographic diagnosis of complete AV block. M mode fetal echo demonstrating atrial (A) and ventricular contractions (V) and complete heart block

first- or second-degree heart block at birth can progress to CHB.

As in the fetus, the cardinal finding of CHB in the neonate is a slow heart rate. In addition to bradycardia, other clinical clues in the neonate include intermittent cannon waves in the neck, a first heart sound that varies in intensity, and intermittent gallops and murmurs. As with cases presenting in utero, almost all presenting in the neonatal period are immune mediated. The newborn at greatest risk has a rapid atrial rate, often 150 bpm or faster, and a ventricular rate less than 50 bpm.

Similar to acquired CHB, the ECG most commonly shows a narrow QRS complex due to a junctional escape rhythm. First- or second-degree heart block found in infants at birth can progress to CHB. The outcome for patients diagnosed as neonates is better than for those diagnosed in utero.

Outcome

In the immediate postnatal period, CHB with low escape rhythm may be supported with isoproterenol or postnatal pacemaker insertion. Overall mortality rate is 4–29 %; mortality rate before age 3 months is 15 %, and the mortality rate from cardiac complications at any age is 14 %.

Data regarding prevention of immune-mediated CHB in at-risk fetuses is not conclusive. However, recent data suggest that prophylactic use of hydroxychloroquine and/or dexamethasone therapy in mothers with known anti-Ro/SSA and anti-La/SSB autoimmune disease has been associated with a decreased incidence of fetal heart block. Dexamethasone has been demonstrated to reverse PR prolongation when started during fetal life.

Complete Heart Block, Nonimmune Mediated

Nonimmune causes of congenital CHB include various structural cardiac defects, particularly congenitally corrected transposition of the great arteries, AV discordance, or polysplenia with AV canal defect. Additionally, several genetic disorders such as familial atrial septal defect and Kearns–Sayre syndrome have been identified. In most cases, CHB is characterized pathologically by fibrous tissue that either replaces the AV node and its surrounding tissue or by an interruption between the atrial myocardium and the AV node.

Presentation in Childhood

As many as 40 % of cases of CHB do not present until childhood (mean age 5 to 6 years) (Fig. 16.3). Few of these patients have neonatal lupus. The diagnosis is usually made when detecting a slow pulse or by presentation with fatigue or syncope, though syncope can herald a more ominous course.

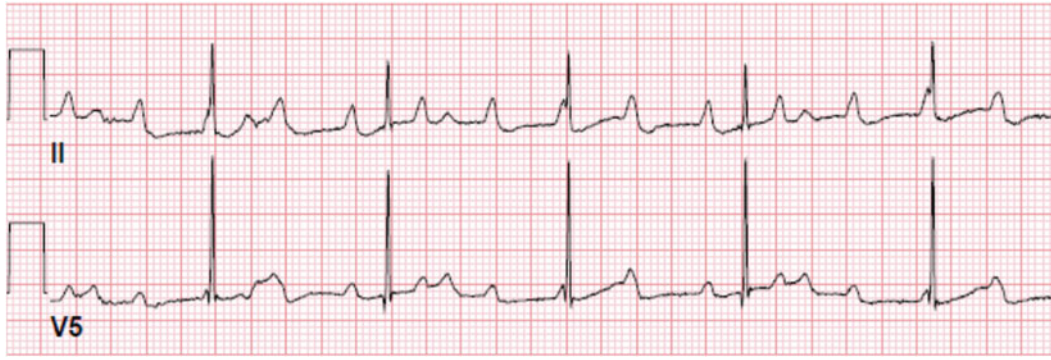


Fig. 16.3 Complete heart block with junctional escape. A 2-year-old presenting with asymptomatic bradycardia. ECG demonstrates complete heart block with junctional escape

Complete heart block may be intermittent when first detected, but usually becomes persistent in later childhood. It was once presumed that most unexplained CHB diagnosed for the first time beyond infancy was congenital in origin and has escaped notice because of a higher ventricular rate and the absence of symptoms. However, given that prenatal ultrasound is now well developed and in wide use, it appears that cases not detected in fetal life, in fact have preserved AV conduction at birth and acquire progressive AV nodal disease thereafter. Findings from different centers are consistent with the notion of progressive AV nodal disease. In one report, the number of childhood case referrals remained constant from 1980 to 1998 despite the introduction of fetal echocardiography and the wide availability of heart rate monitoring during pregnancy and labor. Second, in a series of 102 patients who were asymptomatic through age 15 and were followed for 7–30 years thereafter, a slow decline in ventricular rate was noted with increasing age. Some patients present with bradycardia-related symptoms, including reduced exercise tolerance, presyncope, or syncope. Sudden death has also been described.

AV Conduction Disease, Genetic Association

AV conduction abnormalities can be the major cardiac manifestation of neuromuscular diseases or of other genetic mutations. Emery–Dreifuss muscular dystrophy occurs as an X-linked trait or an autosomal dominant mutation; X-linked Emery–Dreifuss occurs due to emerin mutations and an autosomal dominant inheritance pattern is due to lamin A/C mutations. Conduction system abnormalities in Emery–Dreifuss muscular dystrophy are progressive and can occur throughout the conduction system. Kearns–Sayre syndrome is a mitochondrial disorder with conduction abnormalities. Myotonic dystrophy is an autosomal dominant disorder with progressive conduction abnormalities. Mutations in NKX2.5 can be associated with AV conduction disease, as well as congenital heart defects; AV block is progressive, with CHB developing usually by the third decade of life.

Acquired CHB

Acquired CHB in children most commonly occurs due to surgical repair of congenital heart disease. Infrequently, AV block can occur due to other causes, such as catheter-based interventions or infectious myocarditis. Other rare causes of AV block are listed in Table 16.1; many of these occur more commonly in adult patients and only rarely occur in children.

Surgical CHB

The incidence of early postoperative heart block associated with surgical correction or palliation of congenital heart disease is known to be between 0.7 and 3 %, depending on the cardiac lesion. However, certain surgeries or congenital defects carry a higher risk of surgical heart block. CHB after surgical repair of congenital heart disease is most associated with VSD repair. Weight under 4 kg and inlet VSD have been identified as risk factors for permanent surgical heart block requiring a pacemaker.

For some patients, early surgical complete heart block (SCHB) is temporary and AV conduction returns. Surgical AV block following surgery for congenital heart disease resolves in 2/3 of patients by the ninth postoperative day. Surgical AV block is considered permanent when persisting >7–14 days. AV conduction that recovers late (>14days) after surgery is known to occur in 12 % and has been reported to occur anywhere between 3 weeks and 7 years postoperatively. CHB can also occur late after surgical correction, including those patients with transient AV block in the immediate postoperative period. The incidence of late postoperative heart block has not been well established. Recently, it has been reported to be between 0.3 and 0.7 %. The development of late postoperative AV block has also been hypothesized to have a genetic component. Late recurrence of transient SCHB does not appear to be related to the electrophysiologic properties of the conduction system as determined by electrophysiologic studies performed following recovery of the transient SCHB.

CHB Due to Catheter-Based Intervention

Diagnostic catheter-based procedures have an extremely low incidence of CHB. Interventional catheter-based procedures have a variable risk of CHB. Temporary heart block is reported to occur in 0.4 % of interventional procedures for ASD/PFO closure. CHB requiring pacemaker implantation as a result of ASD/PFO closure is an extremely rare occurrence, reported in 1 patient of >28,000 in a meta-analysis. However, conduction abnormalities requiring pacemaker implantation are more common after transcatheter aortic valve implantation (TAVI), reported in 6–42 % of cases. CHB during interventional electrophysiology studies with ablation has been reported to be as high as 0.9 %; however, this report includes temporary AV block. Complete AV block associated with ablation procedures requiring a pacemaker is rare.

CHB Due to Infectious Myocarditis

Complete heart block can occur as an infrequent complication of myocarditis. Most cases of myocarditis with CHB present with a fulminant course. Approximately 2/3 of patients with CHB from myocarditis regained AV node function, most within 1 week; 27 % required pacemaker implantation. Lyme carditis can occur from Lyme borreliosis, the most common tick-borne disease in the northern hemisphere; Lyme carditis can present with CHB during the second stage of Lyme disease. Lyme carditis is a common etiology for acquired CHB; it is usually reversible when treated with ceftriaxone.

Management of CHB

The principal therapeutic decision at the time of diagnosis involves the need for pacemaker placement. The American College of Cardiology/American Heart Association/North American Society for Pacing and Electrophysiology Task Force on Practice Guidelines (Committee on Pacemaker Implantation) for third-degree AV block in children, adolescents, and patients with congenital heart disease are outlined in Table 16.2. Class I indications are those for which there is evidence and/or general agreement that a permanent pacemaker should be implanted. This class includes patients with advanced second- or third-degree heart block, which is permanent or intermittent (Fig. 16.4). Class II conditions are those for which permanent pacemakers are frequently used, but there is divergence of opinion with respect to their necessity. Some of these conditions reflect advanced but not CHB.

These guidelines are reasonable but should be tailored to the patient's needs. Infants with CHB but otherwise a structurally normal heart may be followed without a pacemaker even if the heart rate is as low as in the 40s when asleep; other earlier reports recommend pacemaker implantation if the infant heart rate is below 50–55 bpm at

Table 16.2 Indications for pacemaker implant in children

Class I
• Advanced second- or third-degree AV block with symptomatic bradycardia (syncope or presyncope)
• Advanced second- or third-degree AV block with ventricular dysfunction or low cardiac output
• Postoperative advanced second- or third-degree AV block that persists at least 7 days after surgery
• Congenital AV block with wide QRS escape rhythm or complex ventricular ectopy
• Congenital AV block with ventricular dysfunction
• In an infant, ventricular rates <55 bpm or <70 bpm with congenital heart disease
Class II—permanent pacemaker reasonable
• Congenital third-degree AV block beyond the first year of life with average heart rate <50 bpm
• Congenital third-degree AV block beyond the first year of life with abrupt pauses in ventricular rate 2 or 3 times the basic cycle length
• Congenital third-degree AV block beyond the first year of life with symptoms due to chronotropic incompetence
• Unexplained syncope in a patient with prior congenital heart surgery, complicated by transient complete heart block, after evaluation to exclude other causes
• Transient postoperative CHB that reverts to sinus rhythm with residual bifascicular block
• Congenital CHB in asymptomatic children with acceptable rate, narrow QRS, and normal ventricular function

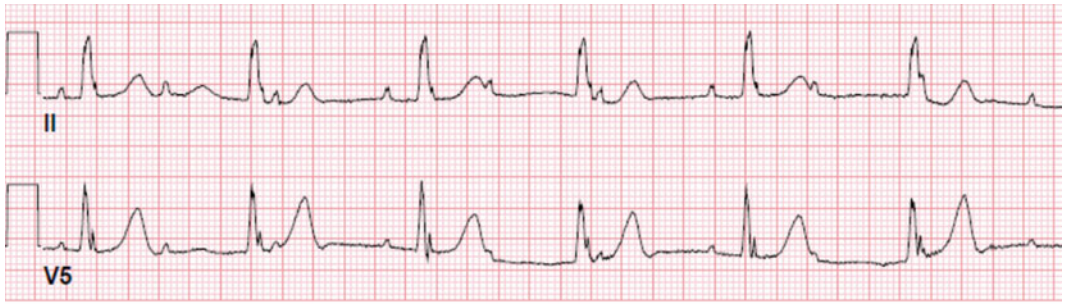


Fig. 16.4 Complete heart block with ventricular escape. A 5-year-old boy, asymptomatic, presented with fractured ventricular pacing lead. ECG demonstrates complete heart block with ventricular escape

any time. Equally important is the variation in the heart rate and the overall status of the child. In contrast, an infant with CHB (congenital or surgical) and structural heart disease should receive a pacemaker.

Long-Term Prognosis

Complete heart block presenting in utero or the neonatal period due to maternal antibodies is associated with a significant early mortality. Of 175 cases described in two reports, 29 (17 %) died either in utero or within the first three months of life. Infants and young children with CHB who are asymptomatic usually remain so until later childhood, adolescence, or adulthood. Children with a mean heart rate below 50 bpm and evidence of an unstable junctional escape rhythm may benefit from early pacemaker implant. Even patients who have been asymptomatic throughout childhood are at increased risk of sudden death as they get older. In a review of 102 patients who were without symptoms through age 15, 27 (26 %) had a subsequent syncopal episode, eight of which were fatal. Six of these eight episodes represented a first syncopal episode. It is therefore reasonable to strongly consider a pacemaker in asymptomatic adolescent or teenage patients with CHB.

Those patients who do not experience symptoms may nonetheless experience physiologic consequences of bradycardia. The ventricular rate tends to fall slowly with age. To compensate for the slow heart rate, the heart enlarges to produce a higher stroke volume; in some cases, this can lead to voltage criteria for left ventricular enlargement and nonspecific ST-T wave changes, as well as to heart failure. Therefore, assessing the asymptomatic patient with serial Holter monitors and echocardiograms is recommended.

In general, the prognosis for the majority of young patients following pacemaker implantation for isolated CHB is excellent. However, multiple single center studies have demonstrated a more severe prognosis with immune-mediated CHB, specifically, requiring pacing at an earlier age and the development of pacing-mediated cardiomyopathy. The development of cardiomyopathy in such patients may be a consequence of myocardial fibrosis associated with CHB. Immune-mediated CHB may result from a different pathologic mechanism than nonimmune-mediated CHB, therefore resulting in different outcomes. Regardless of the mechanisms of CHB, long-term consequences of right ventricular pacing are known to result in consequent ventricular asynchrony and dysfunction. An echocardiographic comparison was performed between patients with congenital CHB, each of whom had a pacemaker, and matched healthy control subjects. Echocardiography was performed before pacemaker implantation and after at least five years of right ventricular pacing in the CHB patients. The CHB patients with pacemakers, when compared to normal controls, developed asynchronous left ventricular contraction, an increase in left ventricular end-diastolic diameter, a decrease in cardiac output, and a decrease in exercise performance.

When pacemaker therapy is initially considered in infants or young children, considerations for type of pacing system are limited by patient size and lead location. However, new evidence exists regarding site of ventricular pacing and biventricular pacing, resulting in improved ventricular synchrony. Consideration of lead location, regardless of patient size may, in part, address changes in LV size and function (See Chap. 18).

Suggested Reading

Abaci A, Unlu S, Alsancak Y, et al. Short and long term complications of device closure of atrial septal defect and patent foramen ovale: meta-analysis of 28,142 patients from 203 studies. Catheter Cardiovasc Interv. 2013;82(7):1123–38.

Abe T, Tsuda E, Miyazaki A, et al. Clinical characteristics and long-term outcome of acute myocarditis in children. Heart Vessels. 2013;28:632–8.

Akin I, Kische S, Paranskaya L, et al. Predictive factors for pacemaker requirement after transcatheter aortic valve implantation. BMC Cardiovasc Disord. 2012;12:87.

Anderson J, Czosek R, Knilans T, et al. Postoperative heart block in children with common forms of congenital heart disease: results from the KID database. J Cardiovasc Electrophysiol. 2012;23:1349–54.

Askanase AD, Friedman DM, Copel J, et al. Spectrum and progression of conduction abnormalities in infants born to mothers with anti-SSA/Ro-SSB/La antibodies. Lupus. 2002;11:145–51.

Aziz PF, Serwer GA, Bradley DJ, LaPage MJ, et al. Pattern of recovery for transient complete heart block after open heart surgery for congenital heart disease: duration alone predicts risk of late complete heart block. Pediatr Cardiol. 2013;34(4):999–1005.

Batra A, Epstein D, Silka M. The clinical course of acquired complete heart block in children with acute myocarditis. Pediatr Cardiol. 2003;24:495–7.

Benson DW. Genetics of atrioventricular conduction disease in humans. Anatomical Record Part A. 2004;280A:934–9.

Bleicher N, Elkayam U. Preventing congenital neonatal heart block in offspring of mothers with anti-SSA/Ro and SSB/La antibodies: a review of published literature and registered clinical trials. Autoimmun Rev. 2013;12:1039–45.

Brucato A, Frass M, Franceschini F, et al. Risk of congenital complete heart block in newborns of mothers with anti-Ro/SSA antibodies detected by counterimmunoelectrophoresis: a prospective study of 100 women. Arthritis Rheum. 2001;44:1832–5.

Brucato A, Jonson A, Friedman D, et al. Proposal for a new definition of congenital complete atrioventricular block. Lupus. 2003;12:427–35.

Buyon JP, Hiebert R, Copel J, et al. Autoimmune-associated congenital heart block: demographics, mortality, morbidity and recurrence rates obtained from a National Neonatal Lupus Registry. J Am Coll Cardiol. 1998;31:1658–66.

Buyon JP, Kim MY, Copel JA, Friedman DM. Anti-Ro/SSA antibodies and congenital heart block: necessary but not sufficient. Arthritis Rheum. 2001;44:1723–7.

Capone C, Buyon J, Friedman D, et al. Cardiac Manifestations of Neonatal Lupus: a review of autoantibody associated congenital heart block and its impact in an adult population. Cardiol Rev. 2012;20(2):72–6.

Cruz RB, Viana VS, Nishioka SA, et al. Is isolated congenital heart block associated to neonatal lupus requiring pacemaker a distinct cardiac syndrome? Pacing Clin Electrophysiol. 2004;27:615–20.

Desai V, Kelton C, Czosek R, et al. Frequencies, costs, and complications of catheter ablation for tachyarrhythmias in children: 2000–2009. PACE. 2013;00:1–13.

Epstein A, DiMarco J, Ellenbogen K, et al. ACC/AHA/HRS 2008 Guidelines for device-based therapy of cardiac rhythm abnormalities. Heart Rhythm. 2008;5(6):e1–62.

Friedman D, Kim M, Copel J, et al. Utility of cardiac monitoring in fetuses at risk for congenital heart block: the PR interval and dexamethasone evaluation (PRIDE) prospective study. Circulation. 2008;117:485–93.

Glickstein JS, Buyon J, Friedman D. Pulsed Doppler echocardiographic assessment of the fetal PR interval. Am J Cardiol. 2000;86:236–9.

Groves AM, Allan LD, Rosenthal E. Outcome of isolated congenital complete heart block diagnosed in utero. Heart. 1996;75:190–4.

Izmirly P, Costedoat-Chalumeau N, Pisoni C, et al. Maternal use of hydroxychloroquine is associated with a reduced risk of recurrent anti-SSA/Ro-antibody—associated cardiac manifestations of neonatal lupus. Circulation. 2012;126:76–82.

Jaeggi ET, Hamilton RM, Silverman ED, et al. Outcome of children with fetal, neonatal or childhood diagnosis of isolated congenital atrioventricular block. J Am Coll Cardiol. 2002;39:130–7.

Karpawich PP, Gillette PC, Garson Jr A, Hesslein PS, Porter CB, McNamara DG. Congenital complete atrioventricular block: clinical and electrophysiologic predictors of need for pacemaker insertion. Am J Cardiol. 1981;48:1098–102.

Kertesz NJ, Friedman RA, Colan SD, et al. Left ventricular mechanics and geometry in patients with congenital complete heart block. Circulation. 1997;96:3430–5.

Lin A, Mahle W, Frias P, et al. Early and delayed atrioventricular conduction block after routine surgery for congenital heart disease. J Thorac Cardiovasc Surg. 2010;140:158–60.

Michaelsson M, Jonzon A, Riesenfeld T. Isolated congenital complete atrioventricular block in adult life. A prospective study. Circulation. 1995;92:442–9.

Miranda-Carus ME, Askanase AD, Clancy RM, et al. Anti-SSA/Ro and anti-SSB/La autoantibodies bind the surface of apoptotic fetal cardiocytes and promote

secretion of TNF-alpha by macrophages. J Immunol. 2000;165:5345–51.

Moak JP, Barron KS, Hougen TJ, et al. Congenital heart block: Development of late-onset cardiomyopathy, a previously underappreciated sequela. J Am Coll Cardiol. 2001;37:238–42.

Morquio L. Sur une maladie infantile et familiale characterisée par des modifications permanentes du pouls, des attaques syncopales et epileptiforme et la mort subite. Arch Méd d'Enfants. 1901;4:467.

Nield LE, Silverman ED, Taylor GP, et al. Maternal anti-Ro and anti-La antibody-associated endocardial fibroelastosis. Circulation. 2002;105:843–8.

Pordon CM, Moodie DS. Adults with congenital complete heart block: 25-year follow-up. Cleve Clin J Med. 1992;59:587–90.

Schott J, Benson DW, Basson C, et al. Congenital heart disease caused by mutations in the transcription factor NKX2-5. Science. 1998;231:108–11.

Semmler D, Blank R, Rupprecht H. Complete AV block in lyme carditis: an important differential diagnosis. Clin Res Cardiol. 2010;99:519–26.

Sholler GF, Walsh EP. Congenital complete heart block in patients without anatomic cardiac defects. Am Heart J. 1989;118:1193–8.

Siehr S, Hanley F, Reddy V, et al. Incidence and risk factors of complete atrioventricular block after operative ventricular septal defect repair. Congenit Heart Dis. 2014;9(3):211–5.

Tunks R, Clowse M, Miller S, et al. Maternal autoantibody levels in congenital heart block and potential prophylaxis with anti-inflammatory agents. Am J Obstet Gynecol. 2013;208:64.e1–7.

UdinktenCate FE, Breur JM, Cohen MI, et al. Dilated cardiomyopathy in isolated congenital complete atrioventricular block: early and long-term risk in children. J Am Coll Cardiol. 2001;37:1129–34.

Van Geldorp I, Vanagt W, Vugts G, et al. Late recovery of atrioventricular conduction after postsurgical chronic atrioventricular block is not exceptional. J Thorac Cardiovasc Surg. 2013;145:1028–32.

Villain E1, Coastedoat-Chalumeau N, Marijon E, Boudjemline Y, Piette JC, Bonnet D. Presentation and prognosis of complete atrioventricular block in childhood, according to maternal antibody status J Am Coll Cardiol. 2006;48(8):1682–7.

Waltuck J, Buyon JP. Autoantibody-associated congenital heart block: outcome in mothers and children. Ann Intern Med. 1994;120:544–51.

Weindling S, Saul J, Gamble W, et al. Duration of complete atrioventricular block after congenital heart disease surgery. Am J Cardiol. 1998;82:525–7.

White P, Eustis R. Congenital heart block. Am J Dis Child. 1921;22:299.

Winkler RB, Freed MD, Nadas AS. Exercise-induced ventricular ectopy in children and young adults with complete heart block. Am Heart J. 1980;99:87–92.

Xiao GQ, Hu K, Boutjdir M. Direct inhibition of expressed cardiac L- and T-type calcium channels by IgG from mothers whose children have congenital heart block. Circulation. 2001;103:1599–604.

Syncope

17

Margaret J. Strieper, Robert Campbell, and William A. Scott

Introduction

Syncope, defined as the temporary loss of consciousness and postural tone resulting from an abrupt, transient decrease in cerebral blood flow, has emerged over the last decade as one of the most common reasons for a pediatric cardiology referral. Other widely used synonyms are vasovagal syncope or "simple fainting." Although many individuals will experience syncope at least once during their lifetime (estimated 30 % lifetime risk), it is usually self-limited and benign. Rarely, it may be the first warning sign of a serious condition including arrhythmia, structural heart disease, or noncardiac disease (Table 17.1). Patients with recurrent syncopal episodes, syncope during exercise, emotion/stress-induced syncope, syncope resulting in injury, syncope in the driving-age pediatric patient, syncope in those with a family history of hypertrophic cardiomyopathy or a channelopathy, or syncope in patients with congenital heart disease require investigation. Recurrent syncope may cause a major impact on lifestyle, interfering with school and/or sports. Many states impose driving restrictions following syncope. This chapter presents a differential diagnosis (Table 17.1) of syncope in children, outlines in detail neurocardiogenic or neurally mediated syncope (NCS, NMS), and reviews different evaluation and treatment strategies.

Diagnostic Evaluation

Given the many possible causes of syncope, the diagnostic evaluation can be quite involved and expensive and the specific etiology may never be determined. Therefore, a carefully planned approach rather than a "shotgun" diagnostic strategy is important. The patient history, family history, physical examination, and an electrocardiogram are fundamental and direct the remainder of the evaluation. Table 17.2 details the components of a comprehensive syncope evaluation. The patient history is the cornerstone on which the syncope evaluation is constructed and the diagnosis depends; it is often, along with the

M.J. Strieper, D.O. (✉) • R. Campbell, M.D.
Sibley Heart Center, Children's Healthcare of Atlanta, Department of Pediatrics, Emory University School of Medicine, Atlanta, GA, USA
e-mail: strieperp@kidsheart.com; campbellr@kidsheart.com

W.A. Scott, M.D.
Department of Pediatrics, UT Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390, USA
e-mail: william.scott@childrens.com

M. Dick, II (ed.), *Clinical Cardiac Electrophysiology in the Young*,
DOI 10.1007/978-1-4939-2739-5_17

Table 17.1 Differential diagnosis of syncope

Neurocardiogenic
Cardiac—Arrhythmia
Channelopathies
Complete heart block
Sick Sinus syndrome
Tachyarrhythmias—supraventricular and ventricular tachycardia
Cardiac—Structural
Cardiomyopathy—hypertrophic/dilated
Coronary artery anomalies
Tumor
Left ventricular outflow obstruction
Primary pulmonary arterial hypertension
Eisenmenger syndrome
Mitral valve prolapse
Medication
Recreational (illegal)
Antiarrhythmic
Diuretics
Vasodilators
Producing QT prolongation
Neurologic
Seizure
Vertigo
Migraine
Tumor
Psychiatric
Conversion reaction
Panic attack
Hysteria
Hyperventilation
Metabolic
Hypoxia
Hypoglycemia

physical examination and an ECG, all that is necessary. Important historical details from the patient include: the age of the patient (syncope is rare before 10 years of age except for breath-holding spells in the toddler), time of day of the event (early morning is typical), the state of hydration and nutrition at the time of the event (when last had fluid or food intake), the environmental conditions (i.e., ambient temperature), the patient's activity or body position immediately prior to the syncopal episode, the frequency and duration of the episodes, and any aura, prodrome, or specific symptoms and signs prior to the episode. Witnesses, if available, should provide details regarding the patient's condition prior to the syncope, duration of loss of consciousness, any injuries or seizure-like movements, heart rate during episode (rarely available), and duration and nature of recovery (often patients are sleepy after neurocardiogenic syncope (NCS)). Medications (prescriptions and/or over-the-counter) used by the patient are critical historical points particularly regarding proarrhythmic agents such as QT prolonging medications. Information regarding prior diagnostic reports and/or consultations can prevent duplicate testing.

Family history is vital in the evaluation of syncope. It is not uncommon to find a history of multiple family members who experienced syncope during adolescence. Many of the older family members may also report a history of low blood pressure, and many families limit salt due to a hypertensive family member who is on a salt-restricted diet. However, if the family history is positive for recurrent syncope, it is also important to consider other familial disorders by specific questioning about the presence of hypertrophic or dilated cardiomyopathy, long QT syndrome (and other ion channelopathies), primary pulmonary hypertension, or arrhythmogenic right ventricular dysplasia. Families should be queried regarding sudden unexplained death in children or young adults (i.e., drownings, sudden cardiac death, sudden infant death syndrome, and car accidents), seizures, or familial congenital deafness (Table 17.2). Noting the person or source providing the family history and an estimate of its reliability can be of future use; it may be helpful to request further details from additional family members, particularly if a genetic disorder is suspected. A genetic counselor can be invaluable in helping to sort out the family history.

During the patient examination, orthostatic vital signs (magnitude of decrease in blood pressure relative to change from supine to erect position and heart rate changes) should be obtained. Many patients will manifest a mild (up to a 30 mmHg drop in blood pressure) but asymp-

Table 17.2 Syncope evaluation

Patient history[a]
Age at onset
Time of day
Frequency (increasing or decreasing over time)
Prodrome (see text: patient may be amnestic)
Situation (activity, place, body position)
State of hydration
Patient and witness description of event
Duration of loss of consciousness
Symptoms upon recovery (sleepy)
Medications (prescription, OTC)
Concomitant disease
Prior evaluation and results
Family history[a]
Sudden death at young age
SIDS
Syncope
Seizures
Accidental death (e.g., drowning, automobile accidents)
Pacemaker/defibrillator
Congenital deafness
Cardiomyopathy
Patient exam[a]
General condition (habitus, phenotype, hydration, nutritional state, thyroid)
Cardiac
Blood pressure—sitting, lying, standing (for orthostatic response)
Pulse—strength, rate, UE/LE difference
Heart murmurs suggesting anatomic disease
Musculoskeletal
Inherited connective tissue disorder phenotype
Neurologic
ECG[a]
Rate and rhythm
AV conduction (heart block)
Intraventricular conduction (Brugada syndrome, arrhythmogenic right ventricular dysplasia)
QTc interval (male ≤ 0.45 s; female ≤ 0.46 s)
T-wave morphology
Exercise testing[b]
Abnormal rhythm or blood pressure response.
Especially rule out LQTS, exercise-induced syncope
Noninvasive imaging[b]
Echo Doppler
Anatomic/structural assessment
Tumors
Pulmonary artery pressure estimate
Outflow track gradients
Abnormal origin left coronary artery
Coronary aneurysms
MRI
Arrhythmogenic right ventricular dysplasia
Coronary arteries
Tumors
Ambulatory monitoring
Transtelephonic ECG
Holter[b]
Implantable recorder
Head-up tilt testing (HUT)[b]
Catheterization[b]
Hemodynamic
Angiographic
Electrophysiologic study
Biopsy
Right ventricular endomyocardial biopsy

Notes: *LE* lower extremity, *UE* upper extremity, *SIDS* sudden infant death syndrome
[a]All patients
[b]As clinically indicated

tomatic orthostatic change with upright positioning. An ECG should be obtained on every patient who experiences syncope, particularly if it is recurrent, occurs with exercise, and is not associated with the characteristic symptoms of NCS. The ECG should be evaluated for heart rate, corrected QT interval (gender-related), T-wave morphologic changes (persistent so-called juvenile T waves in the older adolescent), T-wave alternans, or any ventricular arrhythmia. The ECG should also be evaluated for ventricular preexcitation syndromes, atrioventricular (AV) conduction, or features of Brugada syndrome (see Chaps. 4, 13–15, 18).

For the infrequent patient whose evaluation lacks internal consistency, other studies may be advisable, such as echocardiography to examine for cardiomyopathy, myocarditis, anomalous coronary arteries, pulmonary arterial hypertension, or arrhythmogenic right ventricular dysplasia. A rare patient may warrant cardiac catheterization, including hemodynamic, angiographic, and electrophysiologic evaluation, along

with right ventricular endomyocardial biopsy, to exclude potential structural, functional, and arrhythmic abnormalities, particularly before clearance to resume activities.

NCS: Simple Fainting, Vasovagal Syncope

Pathophysiology

The pathophysiologic mechanisms underlying NCS are complex, likely heterogeneous, and not completely understood. However, one major hypothesis invokes a cardiac-central nervous system reflex (Fig. 17.1). The most common initiating event is prolonged (or the abrupt assumption of) upright position (sitting or standing), which subjects the patient to gravitationally mediated venous pooling in the lower extremities and pelvis. This causes an abrupt central hypovolemia (compared to the immediate preexisting state), leading to a decrease in venous return and stroke volume. In addition, an emotional or physical stress (e.g., pain or fright) or a reflex mechanism related to hair grooming, glutition (swallowing), or micturation may initiate this sequence by stimulating a reflex increase in sympathetic output manifested as tachycardia and vasoconstriction along with an increase in ventricular contractility. Activation of C-fiber mechanoreceptors increases afferent neural traffic to the central nervous system (medulla), stimulating the brain-stem motor center and causing several and often combined possible responses, such as the following: (1) an increase in parasympathetic activity, causing profound bradycardia or asystole; (2) a sympathetic withdrawal resulting in peripheral vasodilatation (venous and arterial), a decrease in systemic blood pressure, and decrease in heart rate; and (3) an increase in serotonin concentration, also resulting in peripheral vasodilatation and marked decrease in the systemic blood pressure. This sequence of events is one hypothesis, but it does not account for all the observed complex and integrated interaction between the neurohumoral traffic and the cardiovascular responses, additionally confounded by age and comorbidity.

As a result of the loss of consciousness, postural tone and the upright state, the patient falls to a supine position restoring venous return and the central circulating blood volume (i.e., heart and lungs) followed by rapid normalization of blood pressure and heart rate. The loss of consciousness is usually short (generally $\leq$1–2 min). Excretory incontinence is uncommon. Seizures rarely occur as a result of the sudden prolonged decrease in cerebral perfusion. During recovery, return to sentience is rapid but post-event fatigue is common.

Clinical Presentation: NCS–NMS and Other Considerations

A prodrome lasting from several seconds to 1–2 min and consisting of nausea, epigastric discomfort, a clammy and cold sweat, pallor, dizziness, lightheadedness, tunnel vision, headache, and weakness is highly characteristic and strongly suggests simple fainting, vasovagal or neurocardiogenic syncope. If the prodrome is of sufficient duration, patients may learn to recognize their symptoms and lie down to relieve the symptoms and prevent syncope. Some patients with profound bradycardia or asystole may have little or no prodrome, causing a sudden loss of consciousness that may result in injury. Absence of a significant prodrome also raises the possibility of structural, functional, or arrhythmic causes for syncope. On the other hand, palpitations, chest discomfort, and a sudden loss of consciousness as well as a prompt recovery are more compatible with an isolated cardiac event. Other symptoms such as atypical precordial chest pain or tightness in the chest, breathlessness, acrocyanosis, tingling in the hands or feet, and a sense of alarm or anxiety are compatible with hyperventilation and a "panic attack."

If "seizures" (tonic-clonic movements) occur as a result of cerebral hypoperfusion and anoxia, the patient can be confused as having a primary neurologic abnormality. Formal neurologic consultation and neurologic testing should be considered if seizures are part of the presentation. Interestingly, longstanding complaints of intermittent

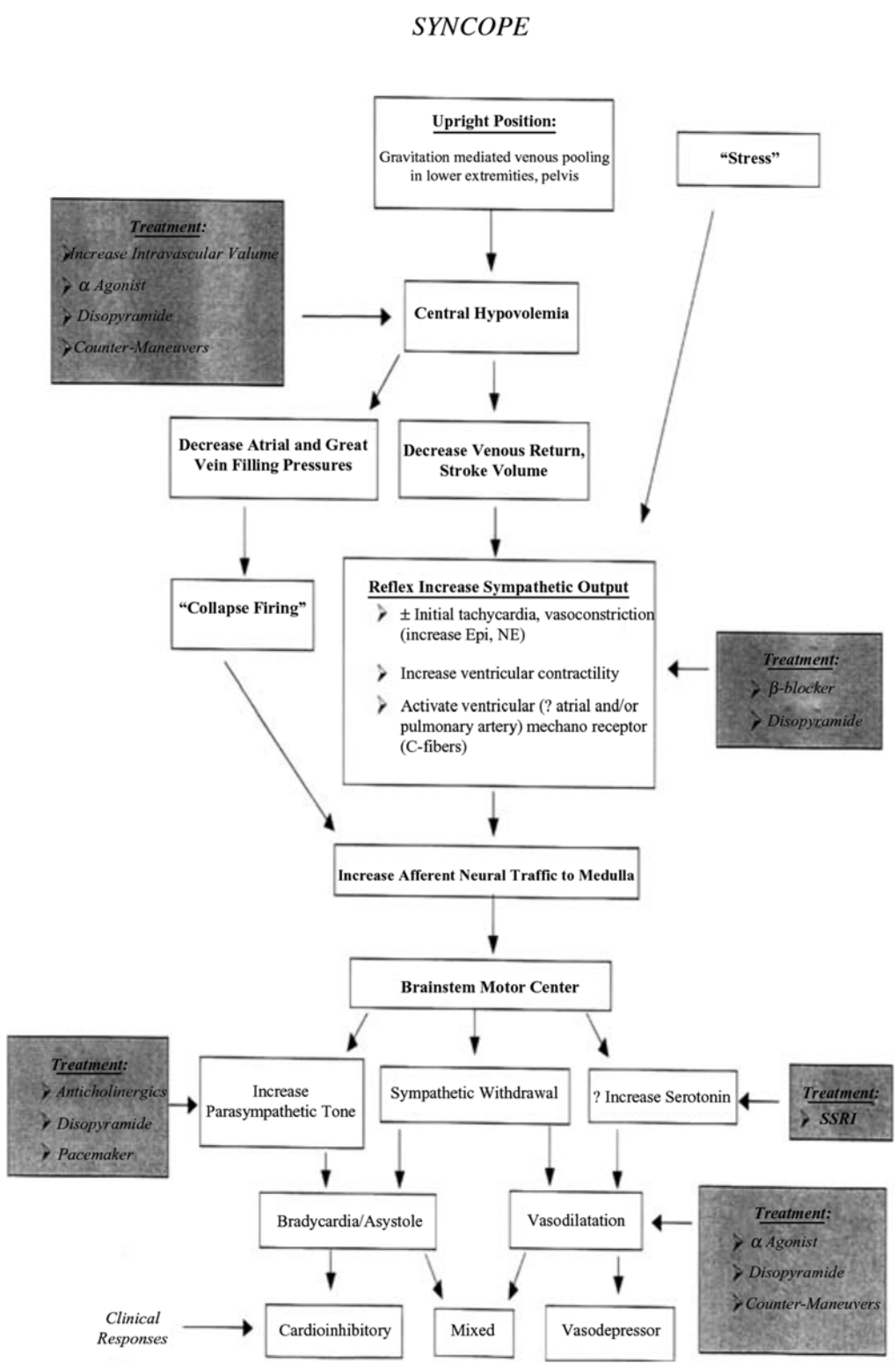


Fig. 17.1 Algorithm of one possible mechanism for neurocardiac syncope [Reprinted from Strieper MJ. Distinguishing benign syncope from life threatening cardiac causes of syncope. Semin Pediatr Neurol 2005;12:32–38. With permission from Elsevier]

abdominal pain and nausea, most likely due to a profound increase in vagal tone, constitute an unusual and rarely suspected presentation of NCS. This symptom complex, as a manifestation of NCS, may be associated with a positive head-up tilt (HUT) evaluation, and may respond favorably to NCS treatment. In addition, there may be a link between NCS and chronic fatigue syndrome, which also has findings of hypotension, headaches, and postexertional fatigue. However, it is unlikely that an otherwise healthy preadolescent child or adolescent would exhibit the chronic fatigue syndrome.

Patients who present with syncope during exercise are also a challenge. Gradual loss of consciousness, associated with a pre-syncopal prodrome and occurring as the exercise is reaching its completion and the exerciser is in an exhausted state at the finish after maximal effort suggests the possibility of exercise-induced NCS, provoked by preexisting unrecognized dehydration, exercise-induced catecholamine-enhanced ventricular contractility, a sudden decrease at the end of exercise in the peripheral blood flow from the vasodilated skeletal muscle vasculature and cerebral vasoconstriction (induced by the respiratory alkalosis of the exercise-related hyperventilation) producing a decrease in cerebral blood flow at that critical moment and syncope. On the other hand, sudden syncope during exercise and without prodrome raises the suspicion for a more serious underlying cardiac structural or functional cause, including arrhythmias, and warrants further investigation.

Postural orthostatic tachycardia syndrome (POTS) has been described as a specific variation of NCS, usually in older adolescents and adults but may occur in children as well. Most of these patients present with symptoms of rapid palpitations suggesting a primary tachycardia, but on further questioning, also have associated symptoms suggesting low blood pressure (BP) including dizziness and lightheadedness. Hyperthyroidism can present in this manner. When this clinical situation presents, ECG and BP monitoring should be performed to evaluate for primary tachycardia. Sinus tachycardia (130–160 bpm) during a symptomatic hypotensive phase strongly supports the diagnosis of POTS and helps to exclude primary tachycardia. Treatment is directed towards prevention of venous pooling and intravascular volume depletion.

Breath-holding spells most likely represent a variation of NCS in the small child. These spells generally occur in young children between the ages of 12 months and 4 years of age. As a result of painful stimuli or emotional upset, these episodes usually begin with crying which escalates. Breath holding generally occurs during expiration which can cause hypoxemia (inducing hypoxemic syncope) and a decrease in venous return (provoking the NCS reflex). Evaluation with continuous ECG monitoring generally reveals significant bradycardia or prolonged asystole (10–15 s) (Fig. 17.2). With loss of consciousness, spontaneous respirations resume and the patient generally shows a rapid return to full consciousness with normalization of heart rate. Although there is no proven treatment for breath-holding spells, which generally resolve spontaneously with age, a trial of anticholinergic agents (belladonna) along with parental counseling may reduce their recurrence.

Another clinical entity, usually occurring in the toddler, is the reflex anoxic seizures, caused by sudden asystole, without breath holding. Detection is difficult because of the abrupt onset and immediate recovery; the event may be limited to a sudden "face plant" followed by prompt recovery. An implanted loop recorder can be diagnostic. These patients may respond to permanent pacing or vagolytic therapy.

Vocal cord dysfunction, often associated with and mistaken for asthma attack, can present with shortness of breath dyspnea, wheezing, coughing, tightness in the throat, skin discoloration due to oxygen deprivation, noise during inhalation stridor, and in severe cases, loss of consciousness. Due to the difficulty and delay in diagnosis, considerable anxiety often accompanies the patient's symptom complex further confounding the origin of the syncope. Diagnosis is dependent upon laryngoscopic exam during an episode.

Other clinical triggers highly consistent with NCS are syncope during hair combing, micturition,

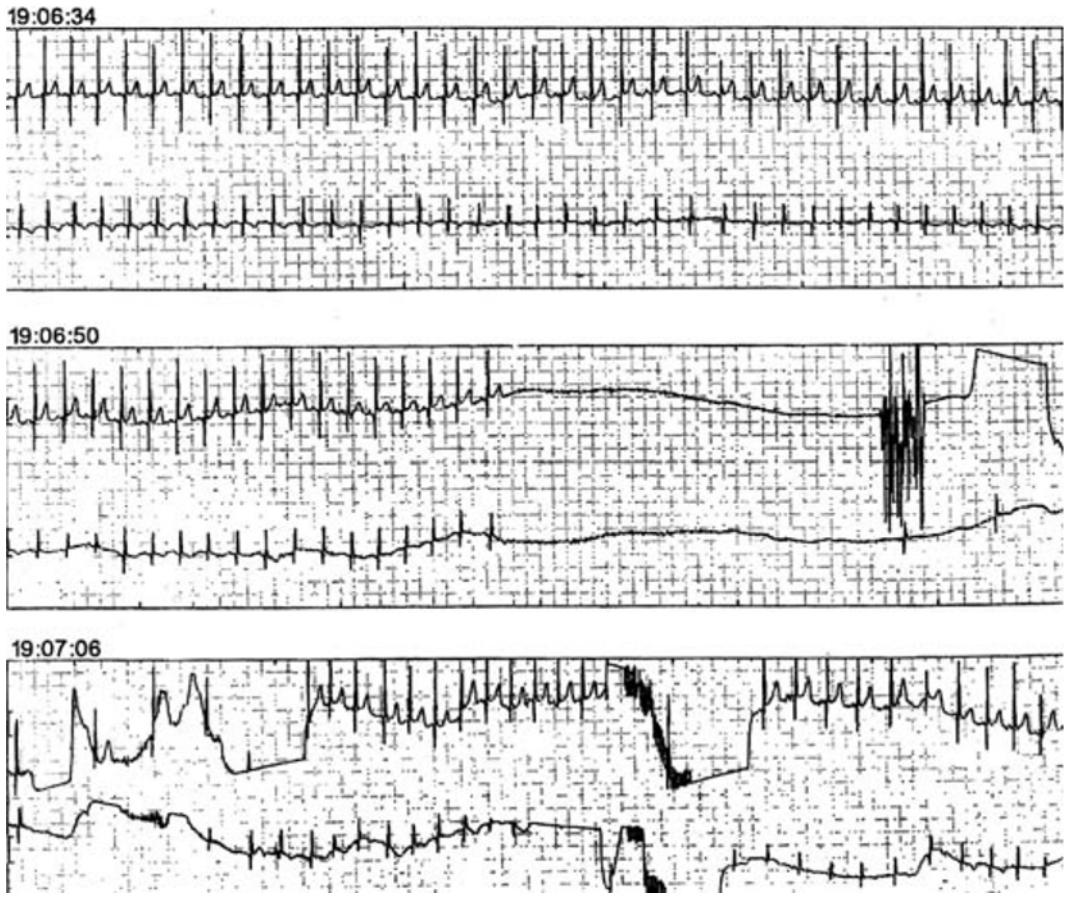


Fig. 17.2 Breath-holding spell in 11-month-old boy. Note tachycardia followed by abrupt asystole

deglutition, Valsalva maneuvers, hot morning showers, or blood drawing or donation (even if lying horizontal). Even a cough and laughter have been identified as triggers for NCS.

A "stressful" milieu is often in the background of 20–25 % patients with recurrent syncope. It is often prudent to introduce the notion of stress-related factors early in the patient evaluation, thereby introducing the possibility that psychiatric issues may be involved. Several findings may suggest the presence of a psychiatric role in the genesis of "syncope." First, patients who experience the onset of syncope in the supine position [excluding a strong physical provocative stress (phlebotomy, donating blood, dental tooth extraction, or simple suturing of a laceration) or an arrhythmia] may have a psychiatric cause. Second, patients with psychiatric issues do not often rapidly recover from their loss of consciousness even after resuming the supine position. Third, the syncope is frequently prolonged with waxing and waning levels of consciousness and by witnessed accounts often up to several hours. Finally, there is a marked indifference to syncope and its ramifications. These patients often experience a conversion reaction, "lose consciousness" but maintain blood pressure and heart rate during the HUT table test. This HUT finding is important, since the patient-specific diagnosis directs the appropriate recommendations.

A variant of NCS may result in an extensive multisystem (presumably mediated through the autonomic nervous system) symptom complex of repeated vague, "blacking out" episodes (often brief and not associated with a total loss of consciousness), nausea (even vomiting), alarm,

profound fatigue, and clinical depression. The patient, usually an adolescent, is often described as a high achiever in school, athletics, or the arts who suddenly becomes dysfunctional with the full spectrum of profound dysautonomia. This broad array of symptoms suggests the possibility of a generalized "autonomic instability" in some patients expressed through a number of organ systems and may benefit from consultation with a mental health provider. It may be related to the chronic fatigue syndrome.

HUT Table Test: Indications

Current indications for a HUT table test include: (1) recurrent unexplained syncope with no evidence by exam, or ECG, for a structural or arrhythmia abnormality; (2) syncope resulting in injury; (3) exercise-induced syncope if atypical; (4) syncope in the driving-age patient; (5) recurrent troublesome pre-syncope causing severe patient incapacitation that interferes with the events of daily living; or (6) failed empiric treatment for NCS. Syncope that is characterized by a typical history, is infrequent, and is not associated with injury or a potentially adverse event (driving a car, exercise) does not require confirmation by a HUT test.

HUT Protocol

A number of HUT protocols have been advanced. The basic principle in HUT is a passive head-up tilt at an angle of 60–80° for 20–60 min or until hypotension, bradycardia, pre-syncope, syncope, or clinical symptoms are reproduced or the time has ended (Fig. 17.3). A continuous noninvasive digital arterial pulse waveform is useful to allow uninterrupted recording of noninvasive beat-to-beat representation of the arterial pressure during the HUT test (Fig. 17.3a). The use of automated or manual blood pressure recordings is less optimal during the presence of HUT-induced hypotension.

If this baseline HUT is negative (no symptoms, no hypotension or bradycardia), various medications including isoproterenol, sublingual

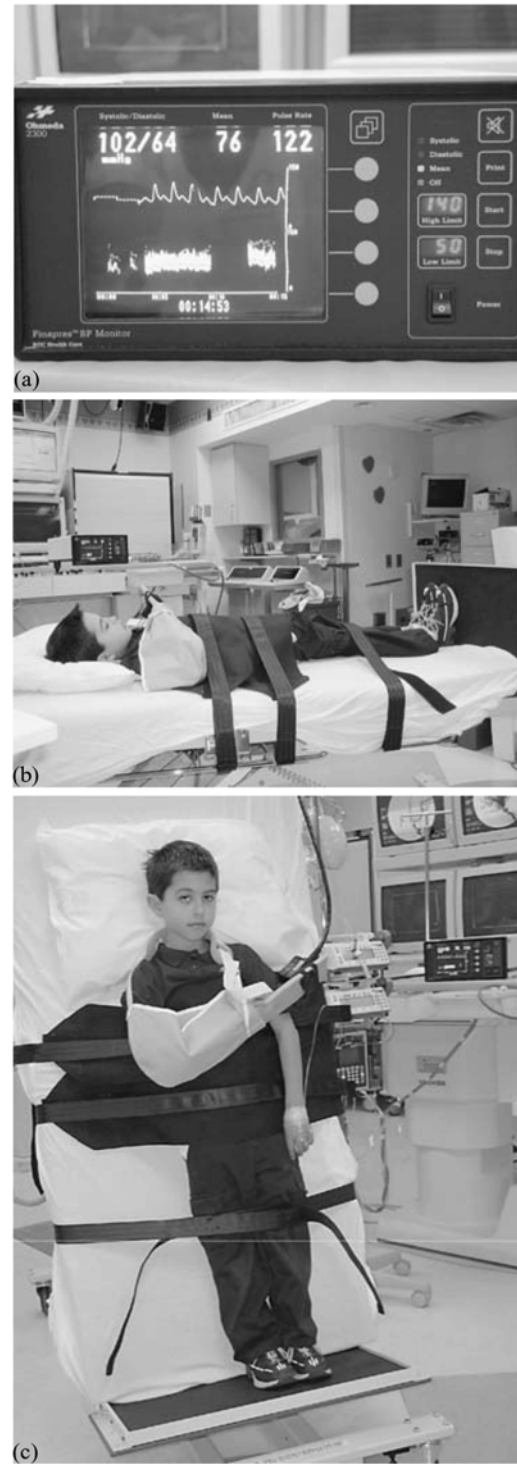


Fig. 17.3 (**a**) Finapres monitor for continuous heart rate and noninvasive blood pressure measurement. (**b**) The patient positioned supine on the tilt table with EKG and blood pressure monitor. (**c**) Tilt to 80° upright position, with "seat belt" restraint

Type		Definition
Type 1	Mixed	Heart rate falls at the time otf syncope but the ventricular rate does not fall to less than 40 beats/min or falls less than 40 beats/min for less than 10 seconds with or without asystole of less than 3 seconds. Blood pressure falls before the heart rate falls.
Type 2A	Cardioinhibition without asystole	Heart rate falls to a ventricular rate less than 40 beats/min for more than 10 seconds, but asystole of more than 3 seconds does not occur. Blood Pressure falls before the heart rate falls.
Type 2B	Cardioinhibition with asystole	Asystole occurs for more than 3 seconds. Blood pressure fall coincides with or occurs before the heart rate falls.
Type 3	Vasodepressor	At the time of syncope, heart rate does not fall more than 10% from its peak.

Fig. 17.4 Classification of positive responses to title-test [Reprinted from Nowak L, et.al. Investigation of various types of neurocardiogenic response to head-up tilting by extended hemodynamic and neurohumoral monitoring. Pacing and Clinical Electrophysiology 2007;30(5): 623–630. With permission from John Wiley & Sons]

nitrates, or intravenous clomipramine can be used to induce an end point during a repeat HUT. Once medication is administered the patient is again tilted for the defined time or until a positive HUT response occurs.

There are three positive HUT NCS clinical responses (Fig. 17.4). The first clinical response is the patients with a *mixed* hypotensive and bradycardic response, defined as a ≥50 % decrease in mean arterial pressure and a ≥50 % decrease from the maximum heart rate during HUT testing. This represents approximately 50 % of the positive HUT responses. Second, a *cardioinhibitory* response is defined as sudden severe bradycardia or asystole, which occurs in approximately 5–10 % of HUT positive patients; a widely used classification system divides this group into two forms, based on length of impulse pause (Figs. 17.4 and 17.5). Finally, *vasodepressor* response, defined as a ≥50 % decrease in mean arterial blood pressure, often with preservation of the heart rate or only a mild increase in heart rate. This represents approximately 40 % of positive tilt table responses.

These clinical responses are not necessarily patient specific nor are they necessarily reproducible; there could be considerable variation day-to-day and HUT-to-HUT, with different responses expressed at different times.

Although the HUT test is regarded in some quarters as the "gold standard" for NCS diagnosis, it should be noted that it is only a supportive test, confirming the clinical history. HUT engages a complex physiologic neural-humoral-cardiovascular reflex response with a highly provocative and exaggerated physiologic stress in individuals who may or may not be particularly vulnerable to this stress. HUT is most useful when clinical symptoms and significant hypotension and/or bradycardia are reproduced during the episode. Only then can this test be interpreted as truly positive. False positive HUT responses can occur, when patients experience hypotension or bradycardia but the clinical symptoms are not exactly reproduced. Negative HUT responses may represent either a true negative (patient does not suffer from NCS) or a false negative (patient is NCS positive, but HUT negative). It is not possible at this time to distinguish clinically false negative results from true negative HUT results**.** There is no widely accepted standard HUT protocol. Considerable variation in tilt angle, duration of tilt, and monitoring exists between centers. This lack of a standard protocol confounds the interpretation of HUT responses between centers. Sensitivity and specificity for HUT test parameters is by report variable and limited data regarding sensitivity and specificity in pediatric patients are available.

Implantable Loop Recorders

Patients that present a diagnostic dilemma with infrequent episodes may benefit from having an implantable loop recorder (ILR) placed. The ILR can correlate EKG findings with the symptoms.

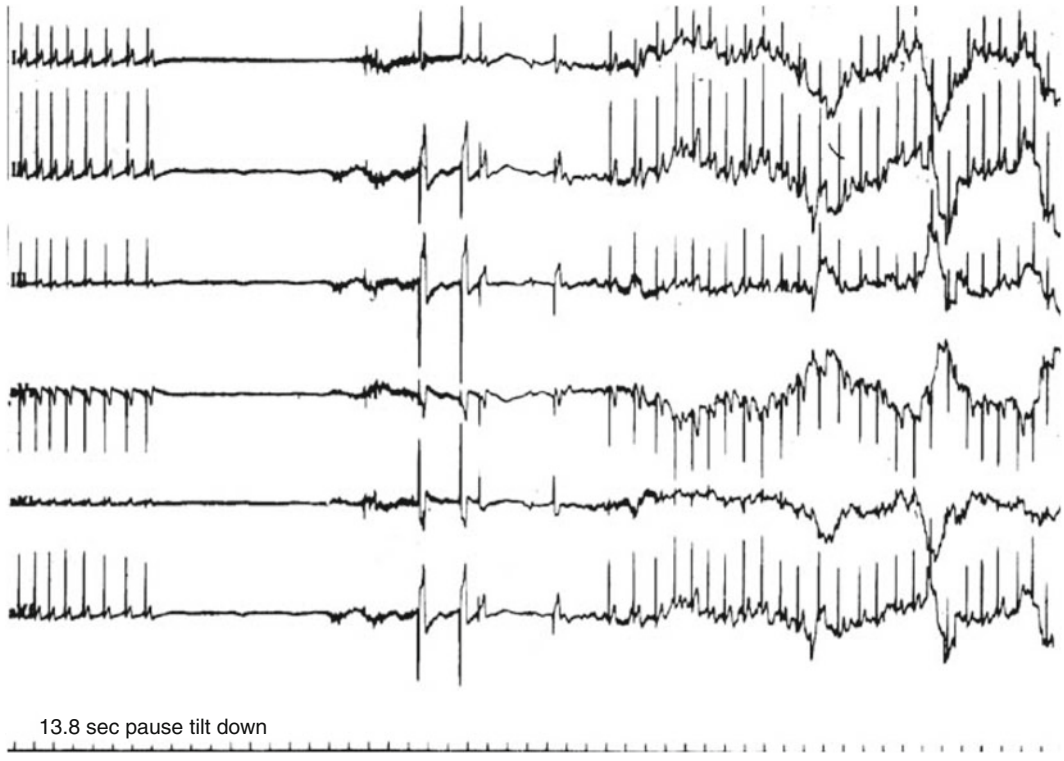


Fig. 17.5 Cardioinhibitory response in 15-year-old girl after 4 min of HUT—13 s asystole. Note the slowing of the heart rate before asystole (paper speed 12.5 mm/s)

ILRs have not been studied systematically in the pediatric population; however, the adult literature reports that after 2 years there was a probability of diagnosis in about 50 % of adults that had ILRs implanted with most diagnoses being bradycardia. Newer (2014) ILRs have increased miniaturization and longer implanted life (3 years) and thus increase their usefulness in ambiguous cases. However, because of the required surgery and resultant permanent scar, placement of an ILR in a child should be limited to patients in whom a life-threatening outcome is a valid possibility.

NCS Treatment

The purpose of treatment for NCS is to prevent recurrent syncope. Additionally, pre-syncopal symptoms may also be eliminated. However efforts to eliminate all pre-syncopal symptoms are often associated with drug side effects and the use of multiple medications. There are only limited randomized treatment trials for pediatric patients. The opinion that any treatment for pediatric syncope patients is better than no treatment has not been established. Additionally, NCS in the young almost always resolves spontaneously within several months to years after onset. Apparent therapeutic drug efficacy may simply represent spontaneous resolution of NCS. Occurrences of syncopal episodes are unpredictable and some patients may be event free for months to years or longer. Therefore, duration of treatment and assessment of drug effect is further confounded. A daily diary to record syncope and pre-syncopal episodes may help when evaluating symptoms both before and after treatment.

Volume Expansion

Maintaining adequate intravascular volume is the foundation for the treatment of NCS. Patients are instructed to avoid caffeinated beverages (due to the renal diuretic effect), but any and all other fluids are encouraged. Specially, liquid such as "sport drinks" with additional sodium are preferable for maintaining hydration. Up to 60–120 oz a day are recommended for adolescents. Reusable plastic 16 oz. bottles should be part of the young person's backpack; he or she be allowed access to it at all times including school. Frequent "swigs" each hour from the bottle are encouraged. Salt tablets may be prescribed, but they are relatively large, difficult to swallow, and will frequently cause nausea. Alternatively, patients are encouraged to liberally use salt with meals and eat non-fatty salted snacks (i.e., pretzels, salted nuts, and salted popcorn without butter).

Although fluid administration alone helps to alleviate symptoms, it may not alone be adequate to prevent most patient symptoms or recurrent syncope. However, drug therapy alone, in the absence of adequate of intravascular volume, is rarely as effective as when combined with good hydration.

Counter Maneuvers

Some simple patient physical maneuvers may help to ameliorate or abort pre-syncopal symptoms or syncope. These maneuvers generally involve exercising the muscles of the leg (leg pumping and tensioning, leg crossing, squatting, elevation of the legs above the level of the heart). A recent study demonstrated a therapeutic effect with isometric handgrip to abort impending NCS by increasing systemic blood pressure. These simple maneuvers can be taught to even young children. However, it is important that these patients have an adequate prodrome to allow them time to perform the maneuvers prior to the onset of true syncope. The possible beneficial effects of conditioning by using prolonged exposure to the upright position in pediatric NCS patients are often stymied by lack of patient compliance due to the time required for appropriate conditioning.

Medications

Fludrocortisone

Florinef (fludrocortisone) has several effects. It increases intravascular volume and sodium, often at the expense of an increased urinary loss of potassium. It also may augment the peripheral effects of catecholamines, leading to both venous and/or arterial vasoconstriction. Together with adequate intravascular volume through the use of oral hydration, significant decrease in venous return may not occur and NCS may be prevented. Florinef has been demonstrated to produce a positive therapeutic response in a non-blinded pediatric population, and fludrocortisone acetate and beta-blocker treatment (for pediatric NCS) have been found to be equally effective. Florinef is generally well tolerated with a low incidence of side effects. Monitoring for hypokalemia, as a result of increased urinary loss, is important. When receiving Florinef and alpha agonist medications, patients must be monitored for the onset of hypertension, due to the combined vasoconstrictive effects.

Alpha Agonist Agents

Alpha agonist agents work through their vasoconstrictor effects; venoconstriction helps to maintain ventricular volume, while arterial constriction offsets the hypotensive response. Acute intravenous phenylephrine hydrochloride is effective in pediatric patients for blocking NCS responses on follow-up HUT, after an initial positive HUT. Midodrine stimulates the alpha-1-adrenergic receptors and together with adequate hydration strategies, is often an effective treatment for NCS. Up to 75–80 % of HUT positive patients may respond to this treatment, with complete elimination of recurrent syncope and either improvement in or elimination of pre-syncopal symptoms. Patients who fail with this treatment are treated concomitantly with Florinef. Together these two medications may provide up to 85–90 % control for tilt positive pediatric patients. Patients on Midodrine should be monitored for supine hypertension. The med-

ication is usually given three times during the day at q 6 h intervals; it should be taken in the early morning, noon, and early evening to prevent the occurrence of supine hypertension. Compliance is an issue with a medication needing frequent dosing.

Beta-Blockers

Beta-blockers were one of the first drug treatment options described for NCS. These medications operate through several mechanisms, including block of sympathetically mediated increase in ventricular contractility and activation of the C-fibers, and also by prevention of sympathetically mediated arterial vasodilatation. Some patients may manifest side effects, which may mask the therapeutic benefits or aggravate the pre-syncopal symptoms. Care should be taken when using this agent with patients who suffer from POTS, since block of the compensatory sinus tachycardia may actually worsen the patient's clinical status, causing syncope. They should be prescribed in low doses and titrated to an effective dose as necessary.

Disopyramide

Disopyramide, an antiarrhythmic agent, has been employed as a third-line NCS treatment. Data suggest several mechanistic actions, including peripheral anticholinergic effect (to combat bradycardia), negative inotropic properties (preventing activation of the C-fibers), and smooth muscle vasoconstriction, preventing both venous and arterial vasodilatation. Despite the concern for possible drug side effects, specifically proarrhythmia, this drug is generally tolerated quite well by pediatric patients and may prove effective when other agents fail.

Anticholinergic Agents

This drug group may be most effective for patients who manifest profound parasympathetic-driven bradycardia or asystole or a parasympathetic component to peripheral arterial vasodilatation leading to hypotension. Even when effective, pronounced drug side effects including dry mouth, urinary retention, constipation, and visual blurring often make long-term treatment with these drugs intolerable. A recent study has demonstrated a possible therapeutic benefit with the use of glycopyrrolate for breath-holding spells in young infants.

Serotonin Reuptake Inhibitors

Because serotonin may lead to vasodilatation, promoting a vasodepressor or mixed NCS clinical response, serotonin reuptake inhibitors (SSRIs) have been advocated by some for the treatment of drug refractory NCS. The mechanism of action is still uncertain, although it has been speculated that these agents may desensitize central serotonin receptors or decrease serotonin release to the peripheral circulation. These drugs may also be applicable for patient subsets when anxiety or emotional upset triggers the NCS episode or in whom the emotional response to recurrent syncope is also problematic clinically. They also may be useful for the individual who expresses the severe form with profound fatigue and clinical depression. Patients with this degree of disability are best managed in consultation with a physician (psychiatrist) with experience with these medications.

Pacemaker Therapy

While initially thought to be an ideal therapy for patients with predominant bradycardia or asystole, many centers have learned that pacing alone is often ineffective in preventing all episodes of NCS. Many patients, although adequately paced, will still be symptomatic as a result of vasodepression and hypotension. Patients with asystolic HUT responses can often be managed effectively with medications, obviating the need for pacemaker therapy. Since medical therapy generally will prevent recurrent syncope, and NCS is often

self-limited, the decision to implant a permanent pacemaker should be the last resort, especially in a young person.

Prognosis

Most patients have spontaneous resolution of their NCS syncope and pre-syncope in 6–12 months following onset of episodes. Based on our experience, 5–10 % of NCS patients will have symptoms over an extended period of time, often 3–5 years. The reasons for these differing clinical courses are unknown.

A special concern with NCS is the driving-age patient. Even following diagnosis of NCS as the definite cause of the patient's syncope, and the institution of effective therapy, these patients should be restricted from driving for at least 2–4 months. Different states have guidelines about restrictions from driving for patients with different medical issues, including seizure disorders, life-threatening arrhythmias, and syncope. It is important to be certain that a definite diagnosis has been made and that treatment has proven effective before the patient can safely return to driving. Physicians involved in care of these patients should give written instructions regarding driving restrictions, and specifically document these restrictions in detail in the patient's chart.

Conclusion

Syncope is a common clinical event. An organized, detailed approach to diagnosis, with particularly close attention paid to the details of the history, is most likely to result in a time and cost-effective evaluation. To optimally define treatment, restrictions, and prognosis, patient-specific diagnosis is important. Although NCS is the most common cause of pediatric syncope, potentially life-threatening etiologies must not be overlooked.

Suggested Reading

Anderson JB, Czosek RJ, et al. The effect of paediatric syncope on health-related quality of life. Cardiol Young. 2012;22(5):583–8.

Benditt DG, Detloff BL, et al. Age-dependence of relative change in circulating epinephrine and norepinephrine concentrations during tilt-induced vasovagal syncope. Heart Rhythm. 2012;9(11):1847–52.

Berkowitz JB, Auld D, Hulse JE, Campbell RM. Tilt table evaluation for control pediatric patients: comparison to symptomatic patients. Clin Cardiol. 1995;18: 521–5.

Bou-Holaigh I, Rowe P, Kan J, Calkins H. The relationship between neurally-mediated hypotension and the chronic fatigue syndrome. JAMA. 1995;274:961–7.

Brignole M, Croci F, Menozzi C, et al. Isometric arm counter-pressure maneuvers to abort impending vasovagal syncope. J Am Coll Cardiol. 2002;40:2053–9.

Calkins H, Byrne M, El-Atassi R, et al. The economic burden of unrecognized vasodepressor syncope. Am J Med. 1993;95:473–9.

Cox MM, Perlman B, Mayor MR, et al. Acute and long-term b-adrenergic blockade for patients with neurocardiogenic syncope. J Am Coll Cardiol. 1995;26: 1293–8.

Deal B, Strieper M, Scagliotti D, Hulse E, Auld D, Campbell RM, Strasburger J, Benson W. The medical therapy of cardioinhibitory syncope in pediatric patients. Pacing Clin Electrophysiol. 1997;20: 1759–61.

Dickinson CJ. Fainting precipitated by collapse firing of venous baroreceptors. Lancet. 1993;342:970–2.

Grubb BP, Kosinski D. Serotonin and syncope: an emerging connection? Eur J Cardiac Pacing Electrophysiol. 1996;5:306–14.

Grubb BP, Olshansky B, editors. Syncope: mechanisms and management. Armonk: Futura Publishing Company; 1998.

Grubb BP, Kosinski DJ, Boehm K, Kip K. The postural orthostatic tachycardia syndrome: a neurocardiogenic variant identified during head-up tilt table testing. Pacing Clin Electrophysiol. 1997;20:2205–12.

Hulse JE, Strieper MJ, Auld D, Campbell RM. Pseudoephedrine therapy for pediatric neurocardiogenic syncope. Ped Cardiol. 1994;15:259.

Hyphantis TN, Pappas AI, et al. Depressive symptoms and neurocardiogenic syncope in children: a 2-year prospective study. Pediatrics. 2012;130(5):906–13.

Jankovic J, Golden JL, Hiner BC, et al. Neurogenic orthostatic hypotension: a double blind, placebo-controlled study with midodrine. Am J Med. 1993;95:38–48.

Kapoor WN, Fortunato M, Hanusa BH, Schulberg HC. Psychiatric illnesses in patients with syncope. Am J Med. 1995;99:505–12.

Kosinski D, Grubb BP, Temesy-Armos P. Pathophysiological aspects of neurocardiogenic syncope. Pacing Clin Electrophysiol. 1995;18:716–21.

Linzer M, Felder A, Hacket A, et al. Psychiatric syncope. Psychosomatics. 1990;31:181–8.

Lombroso CT, Lerman P. Breath holding spells (cyanotic and pallid infantile syncope). Pediatrics. 1967;39:563–7.

Low P, Sanroni P, Joyner M, Shen W. Postural tachycardia syndrome (POTS). J Cardiovasc Electrophysiol. 2009;20(3):352–8.

Milstein S, Buetikofer J, Durmigran A, et al. Usefulness of disopyramide for prevention of upright tilt-induced hypotension bradycardia. Am J Cardiol. 1990;65: 1334–44.

Mosqueda-Garcia R, Furlan R, et al. The elusive pathophysiology of neurally mediated syncope. Circulation. 2000;102(23):2898–906.

Nowak L, Nowak FG, et al. Investigation of various types of neurocardiogenic response to head-up tilting by extended hemodynamic and neurohumoral monitoring. Pacing Clin Electrophysiol. 2007;30(5):623–30.

Ross B, Hughes S, Kolm P. Efficacy of fludrocortisone and salt for treatment of neurally-mediated syncope in children and adolescents. Pacing Clin Electrophysiol. 1992;15:506.

Rossano J, Bloemers B, Sreeram N, Balaji S, Shah MJ. Efficacy of implantable loop recorders in establishing symptom-rhythm correlation in young patients with syncope and palpitations. Pediatrics. 2003;112(3 pt 1):e228–33.

Santini L, Capria A, et al. An increased endothelial-independent vasodilation is the hallmark of the neurally mediated syncope. Clin Cardiol. 2012;35(2): 107–10.

Scott WA, Pongiglione G, Bromberg BI, et al. Randomized comparison of atenolol and fludrocortisone acetate in the treatment of pediatric neurally-mediated syncope. Am J Cardiol. 1995;76:400–2.

Sheldon R. Tilt table testing and implantable loop recorders for syncope. Cardiol Clin. 2013;31:67–74.

Sheldon R, Rose S, Ritchie D, et al. Historical criteria that distinguish syncope from seizures. J Am Coll Cardiol. 2002;40:142–8.

Stewart JM. Midodrine for the treatment of vasovagal syncope (simple faint). J Pediatr. 2006;149:740–2.

Strieper MJ, Campbell RM. Efficacy of alpha-adrenergic agonist therapy for prevention of pediatric neurocardiogenic syncope. J Am Coll Cardiol. 1993;22: 594–7.

Strieper MJ, Auld D, Hulse JE, Campbell RM. Evaluation of recurrent pediatric syncope: role of tilt table testing. Pediatrics. 1994;93:660–2.

Vaddadi G, Esler MD, et al. Persistence of muscle sympathetic nerve activity during vasovagal syncope. Eur Heart J. 2010;31(16):2027–33.

Van Dijk N, Quartieri F, Blanc JJ, et al.; PC-Trial Investigators. Effectiveness of physical counterpressure maneuvers in preventing vasovagal syncope: the Physical Counterpressure Maneuvers Trial (PC-Trial). J Am Coll Cardiol. 2002;40(11):2063–9.

Yao Y, Shi R, et al. Endocardial autonomic denervation of the left atrium to treat vasovagal syncope: an early experience in humans. Circ Arrhythm Electrophysiol. 2012;5(2):279–86.

18 Cardiac Pacemakers and Implantable Cardiovascular-Defibrillators

Gerald A. Serwer and Ian H. Law

For 50 years, cardiac pacing has been the treatment for bradyarrhythmias for both adults and children. While this continues to be the main reason for permanent cardiac pacing, implantable devices to manage tachyarrhythmias have increased over the past decade. In addition, the use of resynchronization (biventricular) pacing has found a role to treat dyssynchronous cardiac function and congestive heart failure for all ages. This chapter reviews the current indications for cardiac pacing, particularly in reference to the treatment of tachyarrhythmias, current pacemaker technology, the variety of available devices and electrodes, implantation techniques, and chronic device and electrode testing and follow-up, particularly with relevance to optimal long-term management of the child who requires device implantation.

G.A. Serwer, M.D. (✉)
Pediatric Cardiology, The University of Michigan Congenital Heart Center, Department of Pediatrics and Communicable Diseases, University of Michigan, Ann Arbor, MI, USA
e-mail: gserwer@med.umich.edu

I.H. Law, B.S.E., M.D.
Division of Cardiology, Department of Pediatrics, University of Iowa Children's Hospital, University of Iowa Carver College of Medicine, Iowa City, IA, USA
e-mail: ian-law@uiowa.edu

Indications

Indications for device placement can be divided into three categories: bradyarrhythmias, tachyarrhythmias, and heart failure.

Bradyarrhythmias

Recommended guidelines have been published, but the need for a pacemaker must be weighed for each patient. In our practices indications for pacemakers include complete heart block, sick sinus syndrome, and control of tachyarrhythmias (Fig. 18.1). The presence of second- or third-degree atrioventricular (AV) block with associated symptomatology, suggestive of chronic or intermittent low cardiac output such as syncopal or pre-syncopal events, or chronic exercise intolerance is also an indication for pacemaker placement. In patients with complete heart block, the presence of an increasing cardiac size by chest X-ray or echocardiogram, the presence of decreased ventricular function, a prolonged QT interval, and the appearance of wide QRS tachycardias intermixed with a narrow QRS rhythm would lead to the recommendation for device implantation. In our experience, a heart rate below a specific level has not been used as the sole indication for device placement. While some have recommended a rate of 50 bpm as the lowest

M. Dick, II (ed.), *Clinical Cardiac Electrophysiology in the Young*,
DOI 10.1007/978-1-4939-2739-5_18

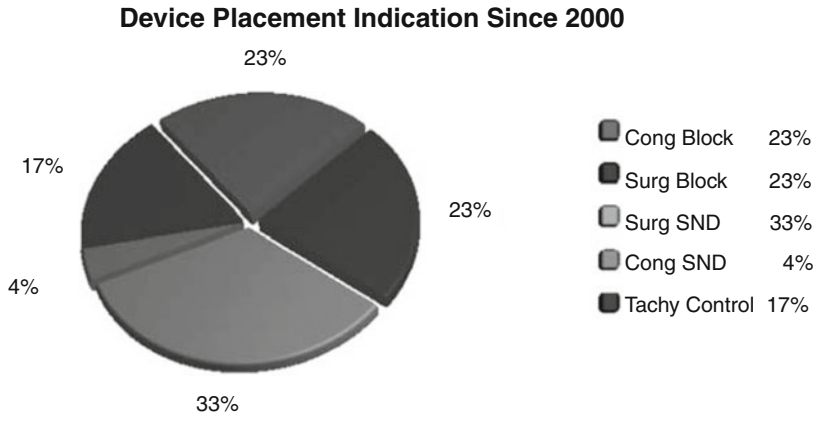


Fig. 18.1 Percentage of patients with each indication for device implantation. All are new implants since 2000. Cong Block = nonsurgically related heart block; Surg Block = surgically related heart block; Surg SND = surgically related sinus node dysfunction; Cong SND = nonsurgically related sinus node dysfunction; Tachy Control = device placed for control of tachyarrhythmia

acceptable rate, many children do well without symptoms for many years with such heart rates.

Pacemaker implantation is mandatory for all patients with surgically induced and permanent (≥7 days) complete heart block. Escape heart rate mechanisms are slow and tend to be unstable with a high incidence of sudden asystole. No patient is discharged following cardiac surgery without pacemaker implantation unless there is 100 % intact atrioventricular conduction. While later recovery of conduction can occur, it is unlikely to have complete return of conduction. Pacemaker placement is usually performed 7–14 days post-op. For patients with return of AV conduction, they must have documented 100 % AV conduction by 24-h Holter monitoring to avert pacemaker implantation.

For patients with late onset complete heart block following cardiac surgery, pacemaker placement is also recommended without requiring associated symptomatology. For these patients, the heart block is usually not persistent but intermittent. The risk of sudden syncopal episodes is considered to be elevated and thus pacemaker implantation is recommended. In addition, late resolution of postsurgical heart block (beyond 7–10 days) appears to increase the development of late onset complete heart block, hence the recommendation for pacemaker implant and follow-up.

The second largest and the most rapidly expanding group of patients that require device implantation are those with sinus node dysfunction. While most of these patients have undergone previous cardiac surgery, some have no other cardiac disease. Documented low atrial rates with or without junctional escape rhythms, along with symptoms of intermittent or chronic low cardiac output, tend to worsen with time and warrant pacemaker implantation. The younger patients with sinus node dysfunction following cardiac surgery may not require pacing, whereas patients in their late teenage and early adult years often require device implantation. Patients who have undergone extensive atrial surgery such as the Fontan procedure or the atrial switch repair of transposition of the great arteries are not only at high risk for developing sinus node disease but also for atrial tachycardias, that may in part be unmasked by low atrial rates. Control of atrial tachycardias can be greatly aided by maintenance of a minimal atrial rate of 70–80 bpm.

Tachyarrhythmias

Children who require treatment with antiarrhythmic agents for control of tachyarrhythmias that result in resting bradycardia may often benefit from pacemaker implantation. However, these

children are often candidates for implantation of an anti-tachycardia device with bradycardia pacing support. Children with hypertrophic obstructive cardiomyopathy and significant left ventricular outflow tract gradients have been shown in some studies to benefit from dual-chamber pacing to asynchronously activate the ventricles, potentially relieving intracavitary obstruction. However, this is a very controversial recommendation and has been rarely employed in our practices. If they become symptomatic (with syncope) or have complex ventricular ectopy, these children may require a combination of bradycardia pacing and an implantable defibrillator.

Indications for placement of an anti-tachycardia device in children are imprecise. Anti-tachycardia devices can be divided into two types. The first type is capable of delivering anti-tachycardia pacing and defibrillator shocks and the second type can perform only anti-tachycardia pacing. A patient who has been resuscitated from a sudden cardiac death event or has been pre-syncopal with documented ventricular tachycardia requires placement of an Implantable cardioverter-defibrillator (ICD)—i.e., secondary prevention. However, primary prevention for those children that are felt to be at risk of sudden cardiac arrest has become more prevalent, paralleling the increase in genetic testing. Children who have cardiac conditions which have a high incidence of ventricular arrhythmia, such as tetralogy of Fallot or cardiomyopathy, and who also have had documented significant ventricular ectopy are increasingly undergoing ICD placement. A long QRS duration in a patient following tetralogy of Fallot repair has also been reported as a risk factor for ventricular arrhythmia and an indication for ICD placement. However, this proposal is very controversial and is currently not used in our practices as a sole criterion for ICD placement.

Patients with atrial flutter are also being considered in specific situations for cardiac pacing. By keeping the base atrial rate above a predefined number, usually 70–85 bpm, and/or preferentially pacing slightly above the sinus rate, the burden of atrial flutter may be decreased. In addition, when this practice is coupled with anti-tachycardia pacing, control of atrial flutter may be significantly improved. The increased use of an anti-tachycardia dual-chamber rate responsive pacemaker may lead to an increase in this therapy for atrial tachyarrhythmias in children with sinus node dysfunction. Pacing algorithms for prevention of atrial flutter have been proposed but to date have not been shown to be universally effective.

Heart Failure

For patients with heart failure, cardiac resynchronization is based on the concept that the difference in activation between the right and left ventricles due to intraventricular conduction disturbances, as in left and right bundle branch block or ventricular pacing, leads to decreased ventricular performance. Pacing both ventricles in a coupled manner may lead to more normal biventricular excitation (i.e., resynchronization) and thus improve ventricular function. This technology is an established technique to improve cardiac function and quality of life in adults with significant congestive heart failure and ventricular dysynchrony manifested by a decreased left ventricular ejection fraction and a wide QRS complex. The treatment of children with biventricular pacing for improvement of ventricular performance and increased cardiac output is evolving and becoming more widely employed. A number of short- and mid-term results from single- and multi-center studies indicate that cardiac resynchronization is feasible and effective in children and young adults with congenital heart disease and heart failure. However, the indications for biventricular pacing and a candidate population of young patients have not been fully defined.

Implantation Choices

When it has been decided that a child will benefit from cardiac pacing, several decisions must be reached to provide the most optimal therapy. The first decision is whether or not

epicardial or endocardial electrode implantation is optimal. The second decision is whether dual-chamber or single-chamber pacing is in the child's best interest. Once these decisions have been reached, attention can be turned towards the choice of appropriate electrodes and, finally, the implantable device itself. One must consider not only what is in the child's immediate best interest and clinical situation, but also how the clinical state may change over time. Such decisions must take into consideration the potential for future adverse events that might be avoided or better treated with more appropriate initial choices of implantation route and devices.

Epicardial Versus Endocardial Placement

The first decision to be made following the recommendation for pacemaker implantation is whether the electrodes are to be implanted on the epicardial or endocardial surface. This decision clearly depends on the availability of venous access to the atrium and the pulmonary ventricle, as well as patient size and the presence or absence of any other conditions considered as contraindications for endocardial electrode placement (e.g., intracardiac right to left shunt). Patients in whom there is no venous route to the ventricle and atrium must undergo an epicardial implant. Often superior vena caval obstruction can often be opened by balloon dilatation and stent placement to permit passage of endocardial pacemaker leads. While there have been isolated reports of inferior vena caval passage with introduction of the electrodes in the femoral region and generator implantation in the abdomen, this is not considered optimal, due to the problems encountered with growth and the fact that such implantation may prohibit any further use of the femoral vessels for central venous access.

Patients in whom there is no pulmonary ventricle (e.g., patients with single ventricles following the Fontan procedure) are in general not candidates for transvenous pacing; in rare circumstances, transvenous ventricular pacing can be performed via the coronary sinus. Implantation of a transvenous atrial pacemaker lead in the Fontan circuit has been reported but is controversial. With the low flow state and the potential for clot formation, the possibility of right to left shunting through either a fenestration in the Fontan baffle or baffle leaks, any thrombi have the potential for systemic embolization. Another problem is the risk of pulmonary embolization and if the thrombus is large, dire consequences. In our practices such an approach is seldom used, and when used, long-term anticoagulation therapy is recommended.

There have been reports of pacemaker electrode placement within the systemic ventricle, but this approach can be associated with embolization and CNS injury. Even patients who have been maintained on Coumadin at adequate levels may still experience micro-emboli from the pacing lead. For this reason, lead placement in the systemic ventricle is not performed in our practices.

Patient size has long been debated as to its effects on the choice of electrode route. While reports of infants undergoing transvenous implantation abound, the long-term sequelae have not been well studied. With the recently developed smaller caliber transvenous leads, great vein obstruction becomes less of an issue. However, the development of significant SVC or innominate vein obstruction in a young child would severely jeopardize future electrode placement. Also the effects on tricuspid valve function in the presence of multiple electrode leads are also a concern. While electrode extraction is a possible solution, it carries a significant risk. At the current time in our practices, the transvenous approach is not used for children less than 15 kg in weight for a single lead and less than 25 kg for those requiring a dual lead system. An obvious advantage of the epicardial approach is the increase in the potential sites for pacing in an individual who will require lifelong pacing and multiple revisions as pacing leads fail. As electrodes become smaller and electrode extraction becomes safer, this consideration may change.

Contraindications to endocardial electrode placement are the presence of right to left intracardiac shunting, a hypercoagulability state, and pulmonary vascular obstructive disease.

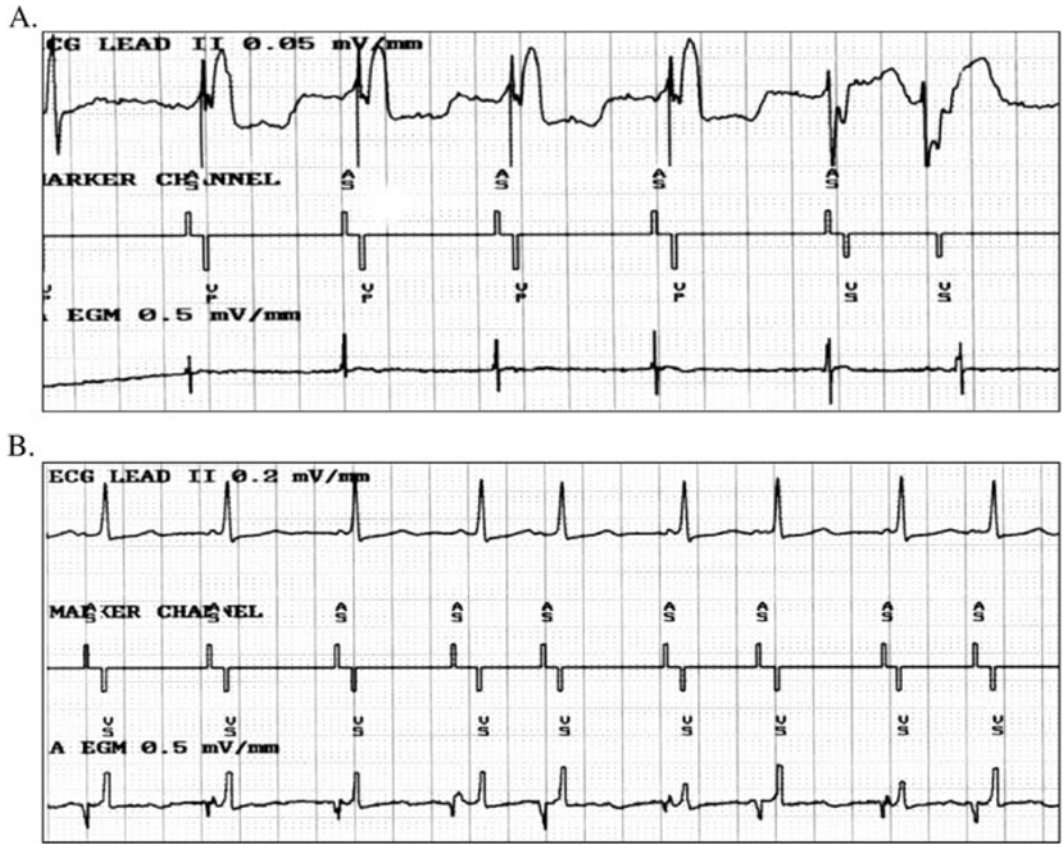


Fig. 18.2 Atrial electrograms from a patient with a bipolar electrode (**a**) versus a unipolar electrode (**b**). *Top tracing* is the body surface EKG; *middle tracing* is the pacemaker marker channel; *third tracing* is the atrial electrogram. Note the lack of a far-field R-wave in Panel (**a**) even with ventricular pacing compared to the large far-field R-wave in panel (**b**) that exceeds the atrial amplitude

Transvenous leads must be avoided in patients in whom any small emboli to the lungs would further increase pulmonary resistance.

Bipolar Versus Unipolar Electrode Usage

The next issue that must be decided is whether one will utilize bipolar or unipolar electrodes. Initially, epicardial implantation always required unipolar electrodes, as this was the only type of electrode that was available. The introduction of several types of bipolar electrodes has eliminated this issue. Bipolar implantation, in both transvenous and epicardial settings, has the advantage of creating less extracardiac stimulation and less difficulty with myo-potential extracardiac sensing. When bipolar atrial electrodes are used, there is less difficulty with far-field R-wave over-sensing, which can be a major issue if one is using an anti-tachycardia device (Fig. 18.2). In addition, bipolar electrodes tend to have higher impedance than do unipolar electrodes, thus decreasing current drain for similar output settings with subsequent increased generator longevity. This is a consequence of a smaller surface area in the bipolar pair, as the second electrode in a unipolar system is the device casing ("can") with a large surface area.

Epicardial Electrodes

Two types of epicardial electrodes are available (Fig. 18.3). The first type, the intramyocardial

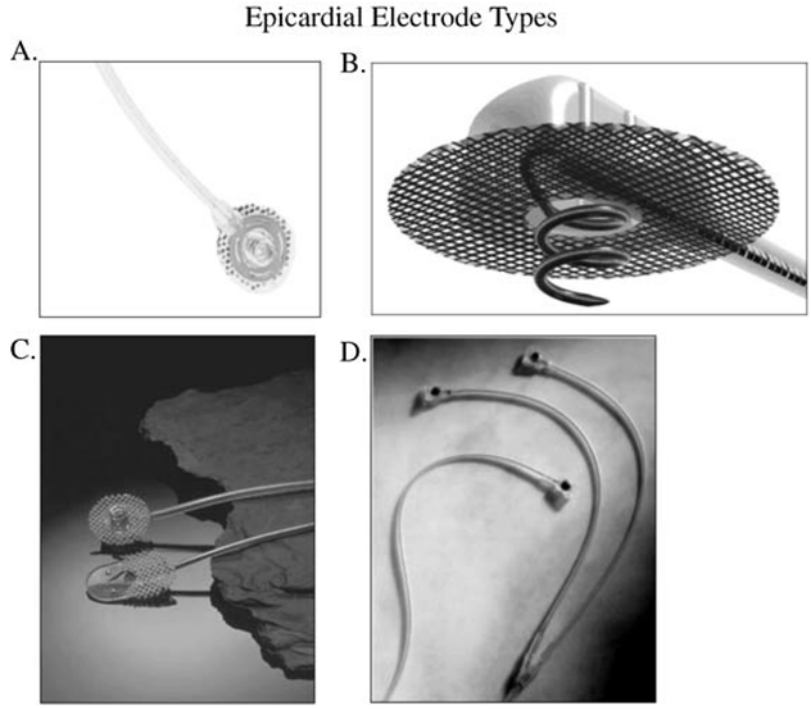


Fig. 18.3 Examples of both bipolar and unipolar epicardial electrodes. (**a**) Guidant helical bipolar intramyocardial electrode. (**b**) Medtronic 5071 unipolar helical intramyocardial electrode. (**c**) Medtronic 4951 intramyocardial barbed electrode (lower electrode) compared with the 5071 electrode (upper electrode). (**d**) Medtronic 4965 steroid eluting epimyocardial unipolar electrode (*left*) and the 4968 bipolar steroid eluting epimyocardial electrode (*right*). (**a**) [Image provided courtesy of Boston Scientific. © 2015 Boston Scientific Corporation or its affiliates. All rights reserved.] (**b–d**) [Reproduced with permission of Medtronic, Inc.]

electrode, penetrates the epicardial surface (Fig. 18.3a–c) and the second type, the epimyocardial electrode (Fig. 18.3d) has a flat plate design and rests on the epicardial surface. Both of these work adequately, but cautions must be observed. Both types of electrodes must be fixed to the epicardial surface with sutures. Failure to suture the electrode to the epicardial surface results in excessive motion of the electrode, which can result in fracture of the electrode or increased fibrosis around the electrode due to excessive irritation. Both events result in loss of pacing.

The intramyocardial bipolar electrode has a central helix surrounded by a circular plate that sits on the epicardial surface. This electrode has the advantage of being able to penetrate surface scarring or fat but the ground portion of the electrode that sits on the surface is still prone to being affected by the scarring and epicardial fat. Furthermore, it is not steroid eluting. Care must also be taken with the corkscrew electrodes because only the distal portion of the electrode of both types is active. The electrode should not be placed completely transmural with the tip of the electrode sitting within the blood pool of the ventricular cavity. This results in a low impedance circuit preventing myocardial stimulation. The proximal portion of the electrode has an insulating coating to decrease the surface area and increase the electrode impedance but limits the electrode surface area that is in contact with the myocardium. For this reason, helical electrodes cannot be used in the atrium. Due to these limitations, we have reserved the use of the intramyocardial electrode to those patients in whom the use of the epimyocardial electrode is precluded due to extensive epicardial scarring.

The second type of epicardial electrode is a flat epimyocardial electrode plate that sits on the

epicardial surface. It is available in both a unipolar and a bipolar form. The epimyocardial bipolar electrode has two separate heads, each of which must be sutured to the epicardium individually, which increases implant time and requires two separate areas of viable myocardium (Fig. 18.3d). However, its sensing vector can be optimally chosen to avoid far-field R-wave sensing in the atrium and maximize R-wave amplitude in the ventricle. It is also steroid eluting. These electrodes do not penetrate into the myocardium and therefore do not cause as much irritation and subsequent fibrosis as the intramyocardial type of electrodes. In addition, they are steroid eluting, further decreasing the fibrosis around the tip. However, if there is significant scar tissue or epicardial fat present, it can be difficult to find a section of heart muscle that can be stimulated. Thus, surgical implant times may be increased. Yet the improved thresholds and higher impedances make this electrode the epicardial implant of choice in our practice for both the atrium and ventricle.

Endocardial Electrodes

Endocardial electrodes can also be either unipolar or bipolar. Early unipolar electrodes were smaller than their bipolar equivalents and thus were preferred in children. With advances in electrode technology, this size difference has disappeared, leaving almost no advantages to using unipolar transvenous electrodes. The transvenous bipolar electrode has a relatively long rigid tip compared to the unipolar equivalent. In small atrial chambers such as those following the atrial switch repair of transposition of the great arteries, the unipolar electrode may be advantageous. However, only bipolar electrodes can be used with the anti-tachycardia devices.

The major decision to be made for transvenous implantation is between the methods of electrode fixation to the endocardial surface. Electrodes can either lodge in the trabecular recesses held in place by tines (passive fixation) or can penetrate the endocardial surface via a helix that serves not only as the active electrode but also to hold the electrode in place (active fixation). The cross-sectional surface areas of the two electrode types are comparable and the time needed to implant them is similar. For atrial electrodes and ventricular electrodes implanted in the morphologic left ventricle in patients with L-transposition of the great arteries or in patients with D-transposition of the great arteries and the atrial switch operation, active fixation electrodes are much more widely used. When right ventricular pacing at sites other that the apex is needed, active fixation electrodes are required. Active fixation electrodes may also be easier to extract.

In our practices, bipolar electrodes are used for both epicardial and endocardial approaches. The choice between passive and active fixation is more open; while both are available, active fixation types are preferred. Because extracardiac pacing and far-field R-wave sensing is less and both the acute and chronic thresholds are as good as or better than the intramyocardial electrodes, for epicardial implants bipolar epimyocardial electrodes are used. There are times, however, when this electrode type cannot be used due to excessive myocardial scar formation from prior cardiac surgical procedures; intramyocardial electrodes are then required.

In some instances, both transvenous and epicardial leads are used within the same system, a hybrid approach. This is most often employed in cardiac resynchronization therapy when the coronary sinus anatomy is suboptimal for appropriate left ventricular lead placement, when there is no transvenous access for multisite pacing, when necessitated by the cardiac anatomy (single ventricle), or when faced with small patient size.

Dual- Versus Single-Chamber Pacemakers

The next major decision that must be made is whether to use a single- or dual-chamber pacemaker. Pacemakers are classified according to the nomenclature schema devised by the Heart Rhythm Society (HRS) and the British Pacing and Electrophysiology Group (BPEG) (Fig. 18.4a). This scheme has a five-character descriptor for each device. The first column refers to the chamber or chambers being paced, the second to the chamber(s) being sensed, the third to the action taken upon a spontaneous

a HRS/BPEG Pacemaker Classification

Chamber Paced	Chamber Sensed	Response to Sensing	Rate Modulation	Multisitie Pacing
V	V	T	R	A
A	A	I	O	V
D	D	D	-----	D
O	O	O	-----	O

b HRS/BPEG Defibrillator Code

Chamber Shocked	Antitach Pacing Chamber	Tachy Detection	Antibrady Pacing Chamber
A	A	E	A
V	V	H	V
D	D	-------	D
O	O	-------	O

Fig. 18.4 (**a**) HRS/BPEG schema for pacemaker classification. (**b**) HRS/BPEG schema for defibrillator classification. See text for details. (**a**) [Reprinted from Bernstein AD, Daubert J-C, Fletcher RD, et al. The Revised NASPE/BPEG Generic Code for Antibradycardia, Adaptive-Rate, and Multisite Pacing. PACE 2003;25:260–264. With permission from John Wiley & Sons.] (**b**) [Reprinted from Bernstein AD, Camm J, Fisher JD, et al. The NASPE*/BPEG** Defibrillator Code. PACE 2006;16:1776–1780. With permission from John Wiley & Sons.]

beat occurring, the fourth to the presence or absence of activity sensing, and the fifth to the action taken when a tachycardia occurs. A similar schema has also been proposed for implantable cardioverter-defibrillators (Fig. 18.4b). For the purposes of this discussion, single-chamber pacemakers are defined as those that only have a single lead with no capability of accommodating a second electrode. On the other hand, a dual-chamber unit that has only a single lead with the other port plugged is considered a dual-chamber unit even though it is used in a single-chamber mode, a distinction that will be addressed later.

For patients that have intact atrioventricular conduction but require pacing due to sinus node dysfunction, atrial pacing, while technically single-chamber pacing, produces the same advantages as dual-chamber pacing. It is acceptable to utilize single-chamber atrial pacing in those patients who have documented reliable atrioventricular conduction and in whom ventricular pacing is unlikely to be needed in the future. The only exception to this is for patients who require anti-tachycardia devices. These pacemakers, even when programmed in the single chamber mode for atrial bradycardia pacing, require a ventricular electrode for accurate detection of atrial tachyarrhythmias.

Single-chamber ventricular pacing can often be used in the young, small patient with congenital complete heart block and an otherwise structurally normal heart. These patients tend to have good myocardial function and placement of only a ventricular epicardial electrode requires a much smaller surgical procedure. However, whenever there is a question of the adequacy of myocardial function, dual-chamber pacing with preservation of atrioventricular synchrony is preferred. Numerous studies have shown the superiority of dual-chamber versus single-chamber pacing for maintenance of cardiac output in the patient with structural cardiac disease. In addition, heart rate variability is improved when one utilizes the patient's sinus node to set the heart rate rather than an activity sensor. While activity sensors do provide some heart rate variability in older ambulatory patients, they do not provide as physiologic a heart rate response as the patient's sinus node does. In the nonambulatory neonate, the sensor is incapable of detecting the type of activity needed to vary the heart rate because activity sensors are not reliable and are of no benefit. Even minute ventilation respiratory sensors are of limited use.

Dual-chamber pacemakers are slightly larger than single-chamber devices due to the need for the pacemaker to accept two electrodes, but usually the difference is not clinically significant. Size differences are usually more a function of battery size rather than connector size. Standard single- and dual-chamber pacemakers can be implanted in the smallest neonate (with epicardial leads). Device longevity is not significantly affected by the added burden of atrial sensing. If atrial pacing is needed, then a dual-chamber device is a better choice.

One caution must be considered. When a dual-chamber pacemaker reaches elective replacement time (ERT), it reverts to VVI pac-

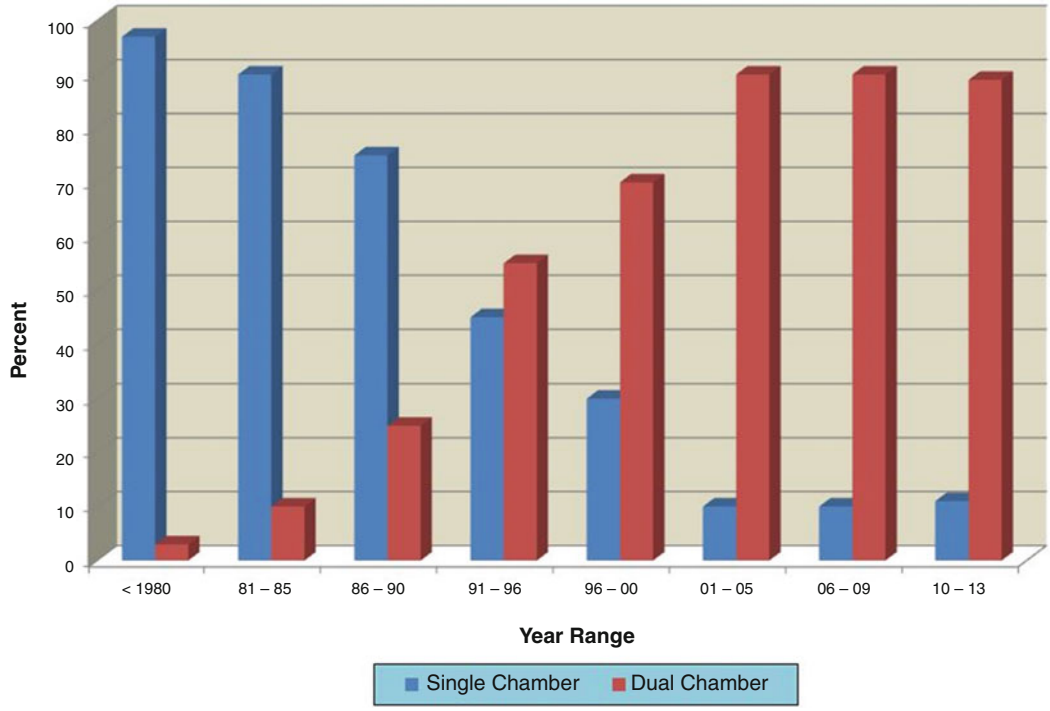


Fig. 18.5 Percentage of patients undergoing dual- versus single-chamber pacemaker implants at the University of Michigan Congenital Heart Center versus the year of implant. Overall about 75 % of implants are dual-chamber devices

ing irrespective of the programmed mode. If a dual-chamber unit is programmed AAI and there is no functional ventricular electrode, it is possible the device will essentially immediately stop pacing without warning. This must be considered for a dual-chamber device in a patient with a nonfunctional ventricular electrode. Newer devices are addressing this concern and can maintain atrial pacing even when it reaches ERT.

Dual-chamber pacing is preferred in most cases. In our experience since 2001, less than 10 % of implanted pacemakers are single-chamber units (Fig. 18.5). Single-chamber ventricular devices are used in some neonates with congenital complete heart block and normal cardiac structure and function, in patients who rarely require pacing but have a "rescue" device to prevent acute bradycardia secondary to drug therapy or intrinsic electrical system disease, and in the rare situation when an atrial electrode cannot be implanted.

Implantable Cardioverter-Defibrillators

The use of an implantable cardioverter-defibrillator (ICD) in children has become an increasingly employed therapy for those with life-threatening arrhythmias. The appropriate selection is similar to that for pacemakers, involving a choice between a dual-chamber or single-chamber device, as well as a transvenous endocardial versus epicardial approach. Similar to pacemakers, a dual-chamber ICD requires an additional electrode, but the size difference of the device is not significant. If the patient's status calls for dual-chamber pacing, then a dual-chamber ICD is necessary. For patients that do not require pacing except potentially following defibrillation, then single-chamber devices may be acceptable. However, a single-chamber device does not have the ability to discriminate sinus tachycardia from slow ventricular tachycardia or to treat atrial tachyarrhythmias should one develop. If there

have been documented atrial tachyarrhythmias in addition to ventricular tachyarrhythmias, a dual-chamber device is strongly preferred.

For patients that do not have venous access to the ventricle or are already undergoing a median sternotomy for cardiac surgery, an epicardial approach can be used. Epicardial placement of the defibrillatory patches (Fig. 18.6) can be performed with adequate defibrillatory thresholds (DFTs) obtained; however, bipolar epicardial sensing electrodes are required. In the rare, very small patient, coil electrodes designed for SVC placement can be placed around the heart in the mediastinum to serve as defibrillatory electrodes rather than patch electrodes. It is also possible to place subcutaneous coils in an infrascapular position and the ICD generator in a right upper quadrant abdominal position, creating a defibrillation vector through the heart (Fig. 18.7). While feasible, these hybrid systems are more susceptible to lead failure and should be reserved for those patients in which transvenous access is contraindicated.

A recent introduction is the subcutaneous ICD, which does not require either transvenous or epicardial electrode placement. While there has been some use in adolescents, its use remains very limited due to the size of the usual pediatric patient and programming limitations. As this approach matures, it may become a viable option in selected children.

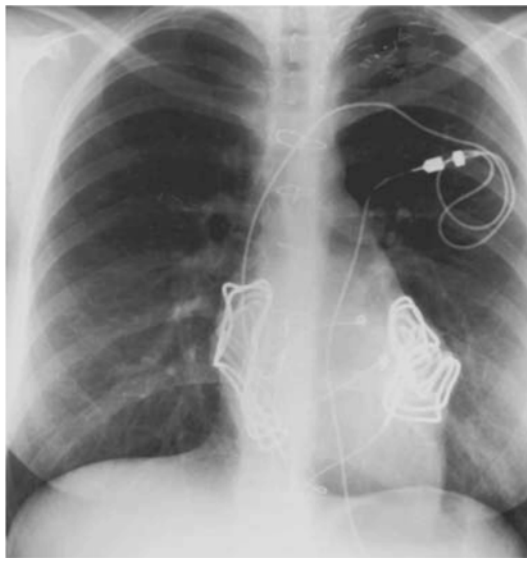


Fig. 18.6 Chest X-ray of a patient with epicardial defibrillatory electrodes and transvenous sensing and pacing electrodes. Note the use of an electrode extender to tunnel the transvenous electrode to the abdominally placed ICD (not shown) [Reprinted from Serwer GA, Leroy SS. Pediatric Pacing and Defibrillator Use. In: Ellenbogen KA, Kay GN, La C-Pu, Wilkoff BL (eds). *Clinical Cardiac Pacing, Defibrillation and Resynchronization Therapy*, 3rd edition. Philadelphia: WB Saunders; 2007: 1177–1216. With permission from Elsevier.]

Cardiac Resynchronization Devices

Cardiac resynchronization is an option for patients with heart failure or impaired ventricular function undergoing placement of a dual-chamber pacemaker or ICD. As this patient population by definition has impaired ventricular function, tracking the atrial activity can enhance ventricular filling and enable programming options, such as varying the atrioventricular delay to optimize cardiac output. In smaller chil-

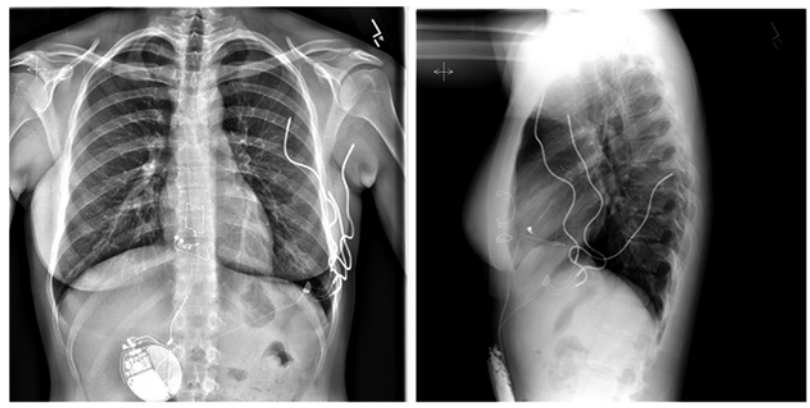


Fig. 18.7 AP (*left panel*) and lateral (*right panel*) hybrid ICD system in a young woman. The ICD generator is placed in the right upper quadrant and the subcutaneous coils are placed around the left lateral chest to create a defibrillation vector through the heart. A bipolar epicardial lead can be seen on the right ventricle

dren and patients with congenital heart disease whose anatomy limits access to the coronary sinus, an epicardial lead may be required to pace the left ventricle. However, advances in transvenous lead technology, including smaller lead shafts along with a variety of lead placement and fixation techniques, have expanded the number of young candidates for transvenous cardiac resynchronization systems. At times, a hybrid approach using both transvenous and epicardial leads may be employed.

Implantation Techniques

It is recognized that there are many ways to implant both epicardial and transvenous or endocardial electrodes. The general methodology utilized in our practices and the deviations from the standard techniques that have been found useful in selected settings are outlined. While there may be different techniques that work equally well, those described below have proved successful in our hands.

Epicardial Implant Techniques

For epicardial pacing, a suitable site on the epicardial surface, free of scar tissue, is ideal. The location of this site is often governed more by the suitability of the tissue than by consideration for location. However, studies would suggest that the pacing site could affect long-term cardiac function; a site near the LV apex or midlateral wall is preferred. Sites on the anterior RV-free wall, on the RV infundibulum, and near the LV base should be avoided due to their potential adverse effect on long-term function. For intramyocardial electrodes, a site is chosen where the myocardium is thick enough to accommodate the intramyocardial electrode. The helical fixation electrode should be sutured to the myocardial surface even though the intramyocardial portion of the electrode itself will provide fixation. Without suture fixation, the electrode will be subject to more stress and motion with each cardiac contraction, potentially resulting in premature electrode fracture and/or increased fibrosis around the electrode, resulting in threshold elevation. For epimyocardial electrodes, the choice of the site is governed by access for the surgeon and the potential for viability of the underlying myocardium.

For atrial epicardial electrodes, a right atrial site is preferential to avoid a delay in atrial sensing of the sinus node impulse. If a left atrial implant site is required, programming of a shorter AV delay may be necessary to maintain optimal atrioventricular synchrony (Fig. 18.8).

For epicardial bipolar pacing, the same considerations apply. However, the placement of the second electrode or anode becomes more critical. The second electrode needs to be positioned approximately two centimeters from the cathodal electrode. Furthermore, the axis between the two ventricular electrodes should be parallel to the long axis of the ventricle; in contrast, the axis between the atrial electrodes should be perpendicular to the long axis of the ventricle (Fig. 18.9). This configuration tends to minimize far-field R-wave sensing, which is particularly important for atrial tachycardia sensing when anti-tachycardia devices are used (Fig. 18.9). Placing the electrodes distant from the atrioventricular groove will also minimize far-field R-wave sensing.

When applying epimyocardial electrodes, care must be taken to wet the electrode prior to its application to the epimyocardial surface. These electrodes tend to have a small surface area and any intervening material that is adherent to the surface, including air, tends to insulate the surface causing high acute thresholds. If acute high thresholds are found, it is often worth waiting for a brief period to see if the thresholds will decrease as the electrode settles into its location. Care must also be taken when suturing the epimyocardial electrode to the surface so that the underlying myocardium is not buckled, which separates the active part of the electrode itself from the underlying myocardium. Often initial thresholds in excess of 2 V at 0.5 ms pulse duration will decrease to less than 1 V 24 h after implantation. Thus, if it is felt that the underlying myocardium appears quite viable and the electrode appears to be in good contact with the underlying myocardial

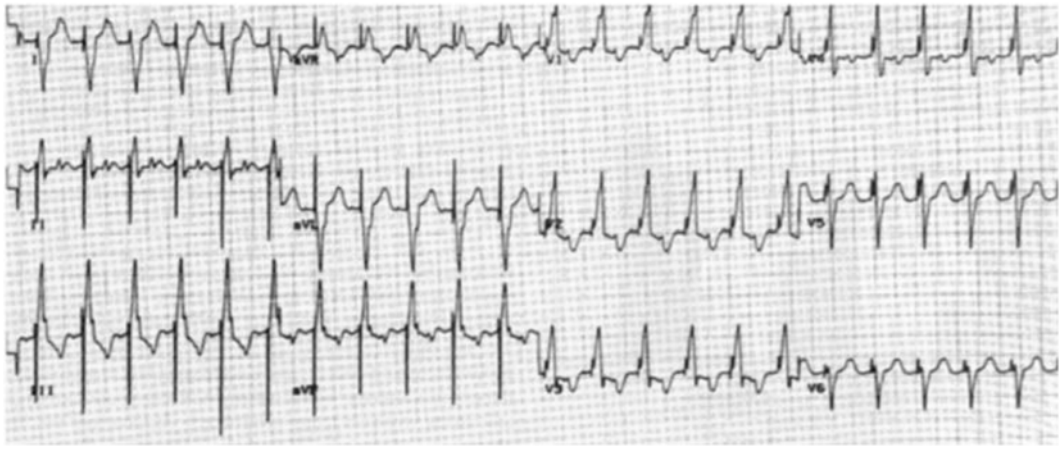


Fig. 18.8 Twelve lead EKG from a patient with left atrial electrode placement showing atrial sensing with ventricular pacing. Note the P to ventricular pace time is 220 ms even though the programmed AV interval is 150 ms. This is due to the time necessary for the sinus node impulse to propagate from the right atrium to the left atrial electrode and be sensed. Thus, to maintain an appropriate AV interval, the programmed AVI must be shorter than usual [Reprinted from Serwer GA, Leroy SS. Pediatric Pacing and Defibrillator Use. In: Ellenbogen KA, Kay GN, La C-Pu, Wilkoff BL (eds). *Clinical Cardiac Pacing, Defibrillation and Resynchronization Therapy*, 3rd edition. Philadelphia: WB Saunders; 2007: 1177–1216. With permission from Elsevier.]

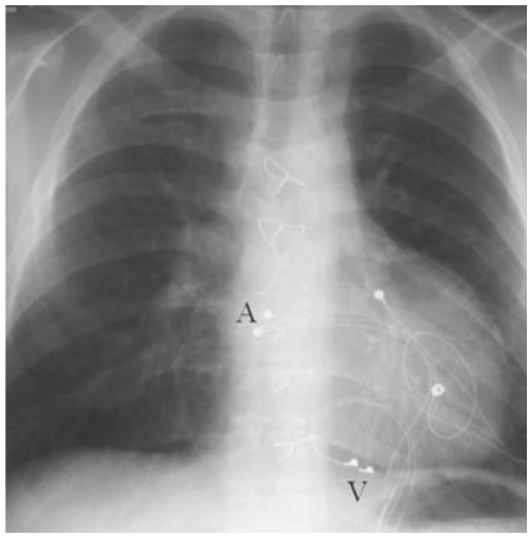


Fig. 18.9 Chest X-ray showing appropriate placement of atrial (*A*) and ventricular (*V*) bipolar epicardial electrodes. Older unipolar electrodes are also seen. A line connecting the two poles of the atrial electrodes (*A*) would be perpendicular to the long axis of the heart while such a line for the ventricular electrodes (*V*) would be parallel to it

surface, then thresholds of up to 2.5–3.0 V can easily be accepted with the expectation that these will improve quickly and provide reliable and stable long-term pacing.

Endocardial Electrode Placement

Prior to electrode insertion, a venous angiogram is performed to evaluate the anatomy, patency, and size of the innominate vein. The innominate vein can then be accessed percutaneously using the Seldinger technique, or a pocket can be created and the vein accessed through the pocket. After the vein is entered, the guidewire is advanced into the right atrium. To avoid entrapment of the electrode between the clavicle and first rib, which can lead to electrode crush and subsequent failure, the subclavian vein should be entered as far laterally as possible. In larger patients the axillary vein may be utilized, using the venogram as a road map for access. If two electrodes are needed, a second guidewire is placed via a separate puncture of the vein. After placement of the guidewires percutaneously the incision for the pacemaker pocket can be made utilizing the entry point of the wire(s) as the most proximal end of the incision. Dissection of the pocket should be carried deep enough to allow adequate tissue to cover the pacemaker. A pocket that is too shallow will result in the potential for skin breakdown or a pocket that is cosmetically

unappealing. This can be of major concern to the patient, especially children. Due to the lack of subcutaneous tissue in many children, many pacemaker pockets are created under the pectoral muscle. A more cosmetic incision, particularly important in girls and young women, is one placed laterally and more vertically in the anterior axillary line. With increased use of bipolar pacing, extracardiac stimulation of the pectoral muscle is rarely an issue. In addition, with the use of high impedance electrodes and the elimination of the insulated coating around the pacemaker can, current flows are low and diffuse enough at the level of the pectoral muscle to often avoid pectoral muscle stimulation even with unipolar electrodes.

Once the pocket has been created, the previously placed wire is dissected so that it is now contained within the pacemaker pocket and the tissue surrounding the wire is gently dissected to open a passage for the placement of the electrode introducer. To avoid blood loss even when inserting the pacing lead, the peel-away introducer (sheath) should have a hemostatic valve. The dilator and sheath are then placed over the wire and positioned in the superior vena cava. The final position of the end of the introducer must be carefully assessed. The end must either lie within the innominate vein prior to it joining the superior vena cava or must have already turned inferiorly and have entered the superior vena cava. Positioning the tip of the introducer at the innominate vein/superior vena caval junction creates a sharp angle, increasing the difficulty in introducing the electrode into the right atrium and the risk of superior vena caval perforation by the pacing electrode. In addition, if the electrode proves unsatisfactory, it can be easily replaced without again percutaneously entering the subclavian vein.

When placing a dual-chamber system, the ventricular electrode is usually placed first. While apical right ventricular pacing has been widely used, the interventricular septum appears to afford improved ventricular long-term function. However, the first priority must be to find a position within the right ventricle with low pacing thresholds, adequate, spontaneous R-wave amplitude, and a highly stable position. Once in position, the electrode is thoroughly tested (see below).

The atrial lead is introduced using the second previously placed guidewire. A second introducer is then advanced over the guidewire, but only after the ventricular lead has been positioned. This sequence must not result in the ventricular lead's dislodgement. Following placement of the second sheath, the atrial electrode is introduced into the atrium and its electrode tip is positioned on either the atrial septum or in the right atrial appendage. The J-shaped stylets are often useful in larger children, but the size of the curve is often too large for the smaller child. For smaller children, a J-shaped stylet with a smaller curve is fashioned from a straight stylet. Steerable stylets have recently been introduced that are useful for positioning of the atrial electrode, particularly in the child with abnormal atrial anatomy. If a more lateral right atrial position is chosen, high output pacing should be performed to ensure that phrenic nerve stimulation is absent.

Following electrode testing, the introducer is removed and the electrode positions of both atrial and ventricular electrodes are verified with fluoroscopy. Adequate lead lengths must be left to be sure the lead will not be dislodged when a deep breath is taken and the heart moves downward or when the heart is displaced inferiorly with standing. Placement of a large loop within the atrium to accommodate growth has been suggested, but has been met with variable success. Alternatively, slack may be introduced by advancing a "heel" into the inferior vena cava. Too often the loop adheres to the endocardial surface and the advantage of having a loop within the atrium is negated. If a loop that is too large remains, it may move within the atrium causing atrial arrhythmias, and, in some cases, may prolapse across the tricuspid valve, resulting in significant tricuspid regurgitation. Care also must be taken to ensure that excessive slack does not enable the lead body to migrate out the right ventricular outflow tract across the pulmonary valve. A generous curve is all that is usually necessary.

A relatively new bipolar lead with a 4.1 French bipolar fixed helix lead has been introduced and has found increasing acceptance for use in children. It has no lumen and, therefore, must be introduced with a guiding catheter (long sheath). The guiding catheter is introduced over

the existing guidewire and positioned within the chamber to be paced. Two types of the guiding catheters are available. One is steerable but is somewhat large (9 French), and the other is smaller (7 French) with a preformed shape. The guiding catheter is positioned next to the wall on which the electrode is to be implanted. The guidewire is removed and the pacing catheter is introduced through the guiding catheter. It is extended out the end of the guiding catheter to abut the wall. It is then carefully rotated to affix the helix to the wall. Once the lead has been fixed to the wall, the guiding catheter is pulled back to expose the proximal ring electrode. The electrode can then be tested. If adequate performance is achieved, the lead is then pushed into the chamber and the guiding catheter (designed for this purpose) is split away as it is withdrawn. Once the guiding catheter has been removed, the lead can no longer be advanced any further into the atrium due its very flexible nature. It can be pulled back but not advanced. Therefore, care must be taken to be sure that the electrode catheter is far enough into the heart to allow adequate positioning before the guiding catheter is removed.

Coronary Sinus Lead Placement

When cardiac resynchronization is performed, a transvenous lead is placed in the coronary sinus to pace the left ventricle. At first, coronary sinus leads were stylet driven, limiting access to distal coronary veins. The introduction of smaller leads that can be advanced over angiographic wires has greatly simplified access to smaller, distal, and more tortuous veins.

Prior to placing a coronary sinus lead, the coronary sinus anatomy must be determined. Congenital heart disease with associated coronary venous anomalies as well as smaller patient size may preclude transvenous cardiac resynchronization. Current coronary sinus lead placement systems use a long 8 French sheath. A variety of curves are available to suit the right atrial size and coronary sinus location. Advancing the 8 French sheath into the coronary sinus can be aided by using a steerable catheter or curved catheters and guidewires. Once the 8 French sheath has been advanced into the proximal coronary sinus, a venous angiogram is obtained using a balloon with an end-hole catheter. The distal veins are best visualized if the initial contrast injection is performed with the balloon inflated but not over inflated. To identify branching veins that are on the posterolateral aspect of the left ventricle, images are taken in both the AP and LAO projections. In general, suitable venous sites for left ventricular electrode lead placement are approximately halfway out the coronary sinus, and half the distance between the atrioventricular groove and the apex of the left ventricle (Fig. 18.10). Ideal sites are not always available and alternate sites more distal in the coronary sinus are often adequate.

Once a suitable vein has been identified, the lead is placed. Because the venogram serves as a road map for lead placement, maintaining the same fluoroscopic camera angle is extremely important. The lead may be advanced into the coronary vein by either first advancing the lead through the 8 French sheath into the coronary sinus, then back loading the angiographic wire, or conversely, guiding the angiographic wire into the desired position, then advancing the coronary sinus lead over the wire. Techniques may depend on lead type and manufacturer guidelines. Angiographic wires of variable sizes and stiffness are available to aid in negotiating the venous anatomy. While advancing the lead over the wire, the angiographic wire should be advanced well into the desired vein to insure stability of position. Lead position is maintained by passive fixation of soft tines at the tip of the lead, or by a fixed curve on the lead. If the final position of the lead is in a large vein, the probability of subsequent dislodgement is much greater.

Prior to sheath removal, sensing and pacing threshold testing is performed to assure appropriate lead function. The likelihood of phrenic nerve capture is much greater than that seen in right atrial and right ventricular leads, so high output pacing to test for phrenic nerve capture and diaphragmatic pacing is essential. The left ventricular pacing threshold can be established in a

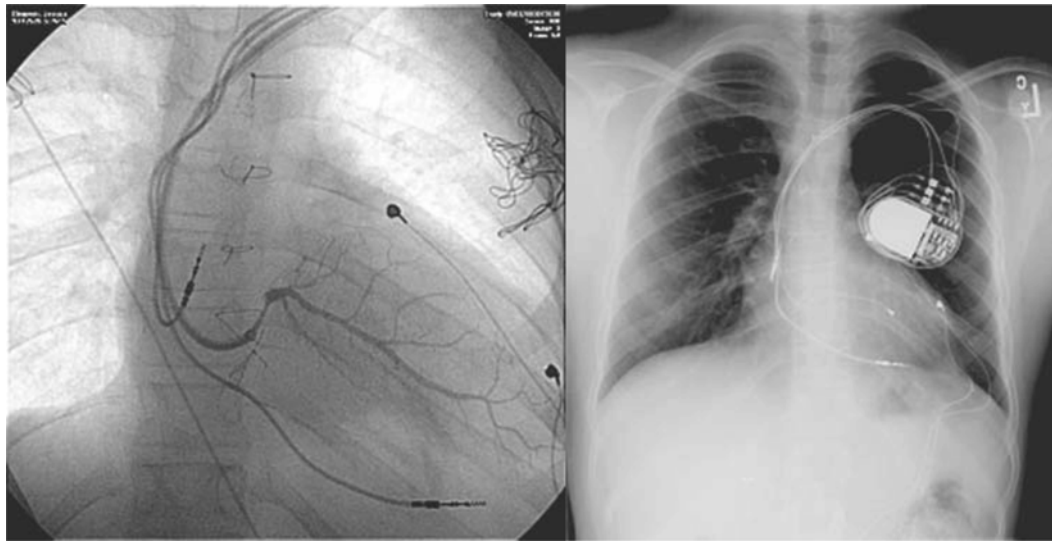


Fig. 18.10 Ten-year-old trisomy 21 girl following repair of atrioventricular septal defect and biventricular pacemaker implant for complete heart block and cardiac resynchronization. *Left panel*: Coronary sinus angiogram showing large branching vein approximately one-third of the distance along the coronary sinus with no significant continuation. *Right panel*: PA chest X-ray demonstrating final position of the left ventricular lead (white mark in middle of cardiac silhouette) one-half the distance to the apex

unipolar mode using an indifferent electrode within the dissected pocket or the cathode of the right ventricular lead. The original coronary sinus leads were unipolar, limiting pacing options. Bipolar leads are now available and newer generators can be programmed to pace the LV unipolar or bipolar. Other pacing vectors can also be utilized to optimize pacing thresholds and eliminate or greatly reduce phrenic nerve stimulation.

Once adequate electrode lead placement has been assured, the leads are then secured to the floor of the pacemaker pocket using the collar on the lead. The connectors are inserted into the generator. The generator is then placed in the pocket with the electrodes coiled beneath the pacemaker generator. Placement of the electrodes under the generator facilitates future generator replacement and minimizes the risk of electrode damage when generator replacement is necessary.

Acute Electrode Testing

At the time of initial placement, all electrodes must be tested to assure adequate performance. Thresholds are determined as the minimum voltage necessary to achieve 100 % capture at a given pulse width. Typically, in our laboratories, voltage thresholds are determined at pulse widths of 1.0, 0.5, 0.3, and 0.1 ms. Electrode impedance is also measured at pulse amplitude of 5 V and a pulse width of 0.5 ms. When spontaneous activity is present, the maximal R and P amplitudes and the slew rates are directly measured from the recorded spontaneous electrogram. In addition, the atrial electrogram also provides information concerning the degree of far-field R-wave sensing (Fig. 18.11).

Appropriate thresholds (i.e., the minimal voltage at 0.5 ms pulse duration that achieves 100 % capture) are individualized. Ideally, one should see voltages less than 1 V at 0.5 ms. However, there are some patients in whom higher thresholds must be accepted either because of a limited number of places to position the electrode or the presence of intrinsic myocardial disease that creates threshold elevation. In all instances, it must be determined that the threshold will reliably pace the heart given the maximal output of the device chosen. When a biventricular pacing system is implanted, both right and left ventricular pacing thresholds

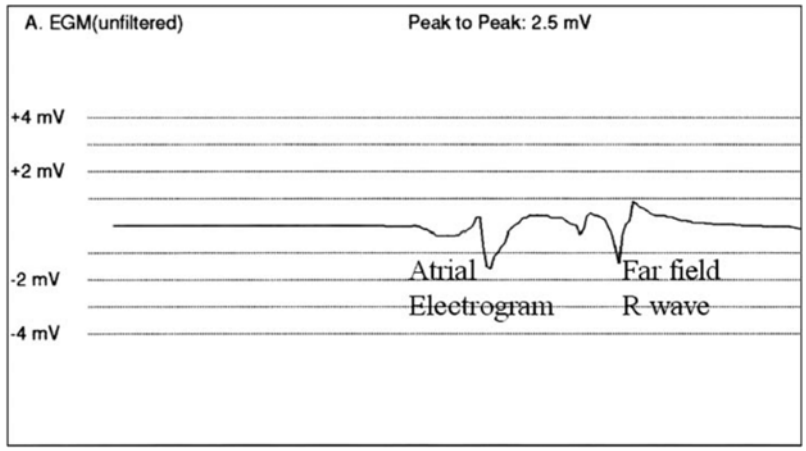


Fig. 18.11 Atrial electrogram from an atrial electrode obtained at the time of electrode placement showing the electrogram amplitude and the amplitude of the far-field R-wave

need to be established separately, as well as a biventricular pacing threshold. Criteria for ideal left ventricular lead placement in the acute setting have not been established. Proposed predictors of long-term success have included narrowing the QRS, improvement in cardiac output by Fick or thermodilution measurement, or improvement in regional ventricular wall motion by echocardiography.

Acceptable values for electrode impedance are determined by the design of the electrode and are outlined by the manufacturer.

ICD Placement

Similar to bradycardia devices, ICDs can be placed either on the epicardium, endocardium, or subcutaneously; the placement of ICDs follows close placement of bradycardia devices. The placement of an epicardial ICD involves placement of the epicardial patch electrodes or, in small children, mediastinal coil electrodes. The optimal placement for patch electrodes varies, but usually they are placed in an anterior/posterior position and are sutured to the pericardial sac rather than to the myocardial surface. However, significant scarring can result, making subsequent removal of the patches extremely difficult. Two patches are not always required if the device "can" is used as the second electrode. Placement of the one patch must then take into account the ultimate position of the device to obtain a vector that maximizes current flow through the heart. Similarly, a subcutaneous coil can be placed around the lateral aspect of the chest and back to create an appropriate defibrillation vector.

Placement of coil electrodes intended to be placed transvenously in the SVC consists of a loop made from one coil electrode that is positioned in the pericardial sac posterior to the heart. A second electrode can then be laid along the right side of the heart. In some cases, two coil electrodes can be laid in a vertical direction, one to the right side of the heart and one to the left side.

Endocardial placement requires that the ventricular coil be positioned wholly within the right ventricle. If it extends through the tricuspid valve into the right atrium, the DFT tends to be elevated and the defibrillatory efficiency is poor. In smaller children, this problem can be addressed either by attaching the electrode tip to the ventricular septum and looping the coil at the right ventricular apex or by placing the electrode tip in the right ventricular apex and then pushing the lead to position the coil along the right ventricular septal surface. The key to obtaining low DFTs is to maximize the area of contact between the coil and the ventricular myocardium.

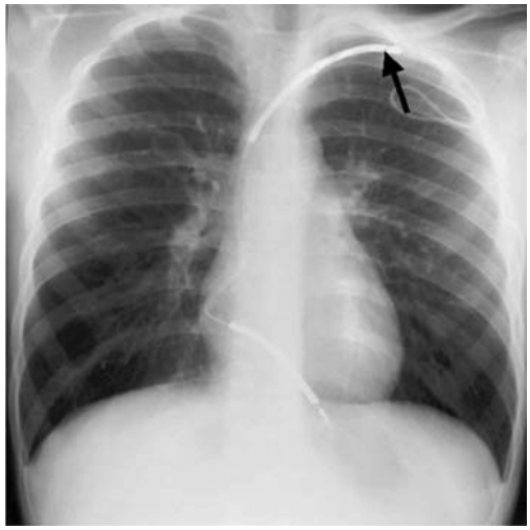


Fig. 18.12 Chest X-ray showing fracture (*arrow*) of the SVC coil of the defibrillatory electrode due to being crushed between the clavicle and first rib

The next choice that must be made is whether to use a dual-coil electrode with the second coil positioned in the superior vena cava or a single-coil electrode with the can of the ICD being the second electrode. For smaller children, the inter-coil distance is often too long and results in placement of the superior vena cava coil within the innominate vein and, in some cases, outside of the vascular space, placing the coil at risk of being crushed between the clavicle and the first rib (Fig. 18.12). Thus, in small children, a single-coil electrode lead is often used. Because of their versatility, when choosing a defibrillatory vector between the right ventricular coil and either the superior vena cava coil, ICD can, or both, dual-coil leads provide additional options to lower the DFTs. However, dual-coil leads may be more difficult to extract; therefore, the benefit of a dual-coil lead must be weighed against the risk associated with extraction.

Once the electrode leads have been positioned, DFTs can be determined. Because there is risk in inducing ventricular fibrillation, some centers choose to set the ICD at maximum output and forgo defibrillation testing. If a patient is deemed to be particularly high risk (i.e., very depressed ventricular function, extreme ventricular hypertrophy), the risk of DFT testing is not insignificant. In the majority of patients, our practice has been to test the defibrillatory capability of the device utilizing a 10-J output. If the 10-J shock is successful in converting the patient from ventricular defibrillation on two separate trials (at least 5 min apart), testing at lower energy settings is not performed. Given the output of the current devices, acute DFTs of less than 15 J are considered adequate and do not require replacement or repositioning of the electrodes. DFTs between 15 and 20 J are considered marginal and the decision as to electrode repositioning is based on the difficulty in achieving the original position. Thresholds greater than 20 J are usually considered inadequate and potentially place the patient at risk for the failure of the device to convert ventricular fibrillation. If the initial DFTs are elevated, the polarity of the shocking pulse is first reversed in an effort to lower the thresholds or to alter the shocking vector. If that is unsuccessful, the leads are then repositioned or a subcutaneous array is considered. In our experience, it is rarely necessary in children to utilize a subcutaneous array. In older patients who have had multiple cardiac procedures, the need for a subcutaneous array, while still low, is increased.

An alternative to DFT testing is the upper limit of vulnerability testing. This technique has been utilized in adults and has been proposed in pediatrics but has not gained wide acceptance.

Our practice is not to repeat DFT determination following initial placement and initial determination of thresholds unless there has been some clinical change in the patient. DFT testing rarely significantly changes from that determined at the initial placement unless there had been some change in measured defibrillatory electrode impedance, electrode position on chest X-ray, or a failed defibrillatory attempt.

Device Follow-up

Proper follow-up testing of the pacemaker and electrodes is critical to ensure continued appropriate function. Of all follow-up problems, lead malfunction is most common; generator

malfunction, and, in time, battery depletion can also occur, and all must be equally and thoroughly assessed at the time of each follow-up visit. Our schedule is to evaluate the incision using a handheld device (e.g., smart phone) picture emailed to us 2 weeks following implantation to make certain that the incision is healing well. An in-office examination is scheduled at 6 weeks and at that time chronic, long-term settings are programmed. Subsequent visits are scheduled at 3 months, 6 months, and 1 year. Patients with congenital complete heart block and a structurally normal heart are seen approximately once per year until the pacemaker is 5 years postimplantation at which time the follow-up period is decreased to 6 months. Patients with structural cardiac disease are seen as dictated by their underlying disease. Between clinic visits trans-telephonic pacemaker evaluation is performed every 3 months during the first 5 years and once per month thereafter. The development of manufacturer web-based home pacemaker interrogation systems has undoubtedly influenced this follow-up schedule. The nature of the follow-up evaluation in both the clinic and by trans-telephonic evaluation may be altered based on patient needs and characteristics.

Clinic Evaluation

When a patient returns for a clinic visit, a thorough history and physical examination is obtained, followed by an evaluation of both the pacemaker and all electrodes. Additional testing is dependent on the patient's underlying cardiac disease.

Long-term cardiac function, although unpredictable, can deteriorate over time. Whether the cause is the pacing itself or the long-term effects of the underlying cardiac disease necessitating pacing initially are unclear. Since cardiac function can deteriorate with long-term pacing, we obtain an echocardiogram to assess LV systolic function as well as tissue Doppler imaging (TDI) to assess diastolic function in all patients every few years, even in the absence of symptomatology. TDI has been shown to be more sensitive to early changes as compared with systolic indicators, such as ejection fraction and BNP levels. When cardiac function is beginning to show a decline, conversion to a different pacing site or to biventricular pacing should be considered.

Device interrogation specifically interrogates battery impedance and battery voltage. Telemetry measurement of battery voltage can be somewhat variable from reading to reading, and it can be difficult to ascertain true changes in battery voltage from one interrogation to the next. Battery impedance, however, is more reproducible and gives one a better indication of battery depletion. As the battery is depleted, the impedance rises to values usually in excess of 3,000 Ω; however, this depends on the properties of each device. Some devices will make projections based on prior usage history and battery measures. These projections are helpful as a guide but can change from visit to visit.

Electrode evaluation consists of noting the lead impedances. A significant change suggests fibrosis around the electrode tip, lead filar fracture, or lead insulation fracture. Increased impedance can be caused by fracture of some of the filars within the lead, yet capture can be maintained. These fractures can also result in oversensing and inappropriate pacing inhibition (Fig. 18.13). Normal variation in impedance can be noted from visit to visit, not to exceed 200–300 Ω. Some pacemakers monitor electrode impedance variability on a day-to-day basis, which provides useful information when there is concern about electrode tip fibrosis. Large changes in electrode impedance is insufficient as the sole indicator for electrode replacement, but this information together with changes in electrode thresholds is useful in detecting pending electrode lead problems.

Electrode threshold testing—the minimal voltage at 0.5 ms pulse duration that achieves 100 % capture—is next performed. Threshold values are typically determined for at least two and preferably three different pulse amplitudes. Some pacemakers permit determination of the minimum pulse width needed to pace at a given voltage as well. Some devices will automatically generate

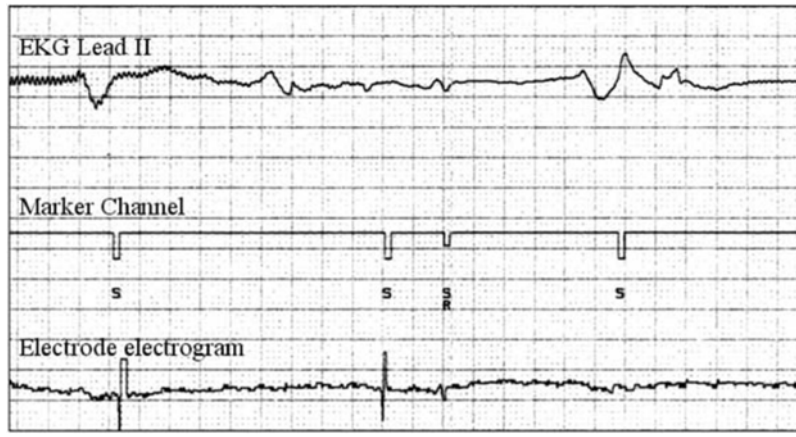


Fig. 18.13 Surface ECG with simultaneous Marker Channel and electrogram showing ventricular sensing to be occurring with no ventricular activity evident on the surface ECG indicative of electrode fracture. Elevated electrode impedance was present on device interrogation

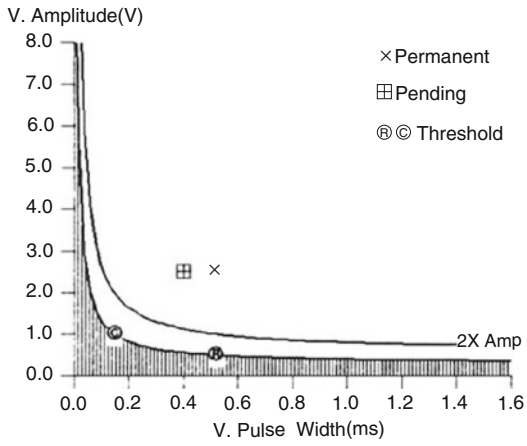


Fig. 18.14 Example of a strength–duration curve obtained at clinic follow-up, as well the appropriate output settings selected based upon it

the strength duration curve and suggest appropriate settings (Fig. 18.14). Whatever method is used is acceptable as long as it allows one to compare changes in thresholds from visit to visit.

Automatic threshold measurements can also be performed by the device and, if desired by the physician, can automatically alter device amplitude in both A and V channels. This allows for closer matching of the minimal device output needed to the programmed values, conserving battery energy and at the same time providing for patient safety. Even if the automatic programming feature is disabled, the recorded threshold values can be useful in following changes in electrode function.

The diagnostic data from the pacemaker is then reviewed, specifically evaluating the percentage of beats in each chamber that are spontaneous versus paced and the heart rate variability that is present. This is particularly important when one relies on the activity sensor for heart rate variability. The lack of variability would indicate inappropriate sensor programming. In addition, if a large percentage of time is spent at higher heart rates, then it is likely that an inappropriate sensor programming is in use.

The presence of high rate episodes may indicate the development of tachyarrhythmias in either chamber. This is particularly relevant to patients who have undergone cardiac surgical procedures that are known to predispose one to tachyarrhythmias. The presence of high rate episodes or very high rates being detected in either chamber would be an indication for further investigation. One must also be sure that the high rate criteria are not set too high or too low.

Finally, based on the data collected, the programming parameters are reviewed. Some changes are generally required within 1–3 months of device implantation as the device is "fine-tuned."

However, beyond this initial adjustment, changes are often not needed. The most common change is alterations in generator output in order to maintain an adequate pacing safety margin to guarantee 100 % capture, but, at the same time, minimize battery current drain. It is our practice to set voltage and pulse width settings high for the first 6–8 weeks following new electrode implantation as the electrodes undergo acute changes associated with initial implantation. After 6 weeks, the settings can often be lowered, which reflects the threshold values determined at the time of the clinic visit. Our general guidelines are to set the output voltage at least 1.7–2 times the threshold value for the chosen pulse duration, while making certain that the chosen pulse duration is at least twice the threshold value for the chosen pulse amplitude. To make certain both of these criteria are met, a strength duration curve is constructed evaluating the pacing threshold at different pulse amplitudes and pulse durations (Fig. 18.14).

CRT Follow-up

Follow-up of the patient with a cardiac resynchronization device requires additional testing of the left ventricular threshold and may include programming changes to optimize cardiac output. Current devices not only allow varying the atrioventricular delay, but also the interventricular delay. Techniques to optimize the atrioventricular delay include shortening the atrioventricular delay to minimize the QRS duration, and monitoring the “a” and “v” waves in the echocardiogram while adjusting the atrioventricular interval to obtain a non-fused “a-v” complex with optimal “a:v” amplitude ratio. Techniques to optimize the interventricular delay include altering the delay to narrow the QRS duration, or monitoring ventricular wall motion by echocardiogram while adjusting the RV–LV delay to achieve maximal synchronization of left ventricular contraction. The percent of LV sensing should be minimized to maximize resynchronization benefit. Other noninvasive ways to monitor the effectiveness of cardiac resynchronization are under development.

Remote Monitoring

Between visits to the pacemaker clinic, patients are monitored by either trans-telephonic of more recently remote monitoring. Trans-telephonic monitoring consists of transmission of a single lead ECG via the phone landline. Remote monitoring is a more thorough device interrogation similar to that performed at an in-office pacemaker check but sent from a remote location via a telephone connection. Patients are encouraged to send transmissions on a fixed schedule and whenever there is a concern about improper pacemaker function or rhythm status.

Device longevity, electrode performance over time (impedance and thresholds), percent paced, and high rate occurrences are recorder, stored at a remote server, and accessible through a website interface. Many manufacturers are now adhering to a specific protocol (IDCO protocol published by the Integrating Healthcare Environment (IHE) organization) to allow more uniformity and better data interchange.

Recording of such transmissions can be difficult in uncooperative children. A wireless system that does not require a wand be placed over the device is becoming more prevalent, making this less of a problem. When the device is interrogated automatically, better compliance is also achieved. If immediate viewing of the transmission is needed, it can be quickly retrieved and viewed via a web interface from any location. This can even be done today using handheld devices.

While electrode malfunction cannot necessarily be anticipated, battery depletion can. Since scheduled clinic visits are routine, semi-elective, rather than emergent, pacemaker replacement can be scheduled, avoiding many patients from presenting with unexpected pacemaker malfunction.

ICD Follow-up

In many instances, ICD follow-up is similar to pacemaker follow-up, particularly for the bradycardia pacing functions of the device.

All new episodes of device discharge should be examined to be certain that the discharge was appropriate and successful in terminating the tachyarrhythmia. In addition to pacing electrode impedances, impedance of the high voltage circuit is also available, assuring the intactness of the defibrillatory electrodes. For patients in whom high voltage impedances cannot be obtained, periodic chest X-rays are used to look for intactness of the high voltage electrodes. Periodic determination of DFTs are not routinely performed as, in our experience, such thresholds do not change unless accompanied by other indicators such as a failed defibrillatory attempt, changes in pacing, and/or high voltage electrode impedances, or changes in electrode position on chest X-ray.

Electrograms recorded from both pacing and high voltage electrodes should routinely be obtained and compared to those obtained at prior visits. Tracings for inappropriate sensing of either far-field R-wave by the atrial lead or T-waves by the ventricular lead that would lead to inappropriate tachycardia detection and inappropriate therapy should be particularly scrutinized. Careful examination of all tachyarrhythmia episodes should also be performed to make certain that the tachyarrhythmia waveforms were appropriately sensed. If there is any question concerning the adequacy of device sensing or the ability to terminate a tachyarrhythmia, then DFT testing may be needed.

Summary

Patients requiring device implantation need lifelong care. However, with appropriate selection of the device and appropriate follow-up, lifestyle changes attributed to the device can be minimized. Exercise limitations, beyond those needed to protect the device and the overlying skin, are often not necessary beyond those due to the underlying cardiac status. As new technologies are developed that minimize battery drain and increase the time between invasive procedures, device longevity is now reaching 7–10 years. Electrode lead longevity, however, can also be accurately estimated. In our experience, electrode lead longevity is between 10–12 years for transvenous leads and 5–8 years for epicardial ones. Limited data is available for ICD electrodes.

The goals of all pacemaker or ICD management are to improve cardiac performance to minimize any negative effect of the device on the patient's lifestyle and thus to enable the patient to lead an active and normal life. As new indications for device therapy become evident and new generations of devices emerge, the number of patients requiring device implantation will likely increase, underscoring the importance of these goals.

Suggested Reading

Atallah J, Erickson CC, Cecchin F, Dubin AM, et al. Multi-institutional study of implantable defibrillator lead performance in children and young adults; results of the pediatric lead extractability and survival evaluation (PLEASE) study. Circulation. 2013;127:2393–402.

Aziz PF, Serwer GA, Bradley DJ, LaPage MJ, Romano-Hirsch JC, Bove EL, Ohye RG, Dick II M. Pattern of recovery of transient complete heart block following open heart surgery for congenital heart disease: duration alone predicts risk of late complete heart block. Pediatr Cardiol. 2013;34:99–1005.

Bauersfeld U, Schonbeck M, Candinas R, et al. Initial experiences with a new steroid-eluting bipolar epicardial pacing lead. Eur J Card Pacing Electro. 1996;6:222.

Blom NA, et al. Transvenous biventricular pacing in a child after congenital heart surgery as an alternative therapy for congestive heart failure. J Cardiovas Electrophysiol. 2003;14(10):1110–2.

Cohen MI, Bush DM, Vetter VL, et al. Permanent epicardial pacing in pediatric patients. Circulation. 2001;103:2585–90.

Cohen MI, Buck K, Tanel RE, et al. Capture management efficacy in children and young adults with endocardial and unipolar epicardial systems. Europace. 2004;6:248–55.

Crossley GH, Chen J, Choucair W, et al. Clinical benefits of remote versus transtelephonic monitoring of implanted pacemakers. J Am Coll Cardiol. 2009;54(22):2012–9.

Fischbach PS, Law IH, Dick II M, et al. Use of a single coil transvenous electrode with an abdominally placed implantable cardioverter defibrillator in children. Pacing Clin Electrophysiol. 2000;23:884.

Gregoratos G, Abrams J, Epstein AE, et al. Guideline update for implantation of pacemakers and antiarrhythmic devices: summary article. Circulation. 2002;106:2145–61.

Hwang C, Swerdlow CD, Kass RM, Gang ES, et al. Upper limit of vulnerability reliably predicts the defibrillation threshold in humans. Circulation. 1994;90: 2308–14.

Janousek J, et al. Resynchronization pacing is a useful adjunct to the management of acute heart failure after surgery for congenital heart defects. Am J Cardiol. 2001;88(2):145–52.

Janoušek J, van Geldorp IE, Krupicková S, et al. Permanent cardiac pacing in children: choosing the optimal pacing site. A multicenter study. Circulation. 2013;127:613–23.

Johns JA, Fuh FA, Burger JD, Hammon Jr JW. Steroid-eluting epicardial pacing leads in pediatric patients: encouraging early results. J Am Coll Cardiol. 1992;20:395–401.

Karpawich PP, Horenstein MS, Webster P. Site specific right ventricular implant pacing to optimize paced left ventricular function in the young without and without congenital heart disease. Pacing Clin Electrophysiol. 2002;25:566.

Kristensen L, Nielsen JC, Pedersen AK, et al. AV block and changes in pacing mode during long-term follow-up of 399 consecutive patients with sick sinus syndrome treated with an AAI/AAIR pacemaker. Pacing Clin Electrophysiol. 2001;24:358–65.

Lee JC, Shannon K, Boyle NG, et al. Evaluation of safety and efficacy of pacemaker and defibrillator implantation by axillary incision in pediatric patients. Pacing Clin Electrophysiol. 2004;27(3):304–7.

Rishi F, Hulse JE, Auld DO, et al. Effects of dual-chamber pacing for pediatric patients with hypertrophic obstructive cardiomyopathy. J Am Coll Cardiol. 1997;29:734–40.

Ro PS, Chan DP, Ackley T, et al. Tissue doppler changes in pediatric complete heart block patients who are chronically paced. Congenit Heart Dis. 2009;4: 448–53.

Serwer GA, Mericle JM, Armstrong BE. Epicardial ventricular pacemaker electrode longevity in children. Am J Cardiol. 1988;61:104–6.

Serwer GA, Uzark K, Dick II M. Endocardial pacing electrode longevity in children. J Am Coll Cardiol. 1990;15:212A.

Serwer GA, Dorostkar PC, LeRoy SS. Pediatric pacing and defibrillator usage. In: Kay GN, Wilkoff BL, Ellenbogen KA, editors. Clinical cardiac pacing and defibrillation. Philadelphia: W.B. Saunders; 2000.

Stefanelli CB, Bradley DJ, Leroy S, et al. Implantable cardioverter defibrillator therapy for life-threatening arrhythmias in young patients. J Interv Card Electrophysiol. 2002;6:235–44.

Stephenson EA, Casavant D, Tuzi J, et al.; on behalf of the ATTEST investigators. Efficacy of atrial antitachycardia pacing using the Medtronic AT500 pacemaker in patients with congenital heart disease. Am J Cardiol. 2003;92:871–6.

Stephenson EA, Batra AS, Knilins TK, et al. A multicenter experience with novel implantable cardioverter-defibrillator configurations in the pediatric and congenital heart disease populations. J Cardiovasc Electrophysiol. 2006;17(1):41–6.

Strieper M, Karpawich P, Frias P, et al. Initial experience with cardiac resynchronization therapy for ventricular dysfunction in young patients with surgically operated congenital heart disease. Am J Cardiol. 2004;94: 1352–4.

Walker F, et al. Long-term outcomes of cardiac pacing in adults with congenital heart disease. J Am Coll Cardiol. 2004;43(10):1894–901.

Weindling SN, Saul JP, Gamble WJ, et al. Duration of complete atrioventricular block after congenital heart disease surgery. Am J Cardiol. 1998;82:525–7.

Zimmerman FJ, et al. Acute hemodynamic benefit of multisite ventricular pacing after congenital heart surgery. Ann Thorac Surg. 2003;75(6):1775–80.

Genetic Disorders of the Cardiac Impulse

19

Adam S. Helms, Patricia L. Arscott,
Stephanie Wechsler, and Mark W. Russell

Introduction

Heritable cardiac arrhythmias and cardiac conduction disorders are rare yet potentially fatal disorders that may involve any phase of cardiac impulse generation, propagation, or electrochemical recovery. To date, they include long QT syndrome (LQTS), short QT syndrome, Brugada syndrome, Andersen syndrome, catecholaminergic polymorphic ventricular tachycardia (CPVT), familial heart block (often with atrial septal defects), arrhythmogenic right ventricular cardiomyopathy (ARVC), hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), and familial atrial fibrillation (FAF). Molecular genetic characterization of patients and families with these disorders has led to important advances in the understanding of arrhythmia generation and improved prospects for diagnosis and treatment.

These disorders can be grouped into several main categories as follows: ion channel disorders or channelopathies, conduction system abnormalities, and cardiomyopathies.

Ion Channelopathies and Disorders of Ion Channel Regulation

Long QT Syndrome

Heritable prolongation of the QT interval as a cause for *torsades de pointes* and sudden death was first reported in the late 1950s and early 1960s in clinical studies by Jervell and Lange-Nielsen [1] (Fig. 19.1), Romano et al. [2] and Ward [3]. Patients with LQTS were characterized by abnormal prolongation of the QT interval on their 12 lead electrocardiogram and by a predisposition to ventricular arrhythmias and sudden death. The inheritance pattern was described as autosomal dominant by both Ward and Romano but as autosomal recessive by Jervell and Lange-Nielsen who also noted in their patients an association with sensorineural deafness. Genetic

A.S. Helms, M.D., M.S.
Department of Internal Medicine, University of Michigan Health Systems, 7301A MSRBIII, 1150W. Medical Center Dr., SPC 5644, Ann Arbor, MI 48103, USA
e-mail: adamhelm@med.umich.edu

P.L. Arscott, M.S. • M.W. Russell, M.D.
Pediatric Cardiology, The University of Michigan Congenital Heart Center, Department of Pediatrics and Communicable Diseases, University of Michigan, Ann Arbor, MI, USA
e-mail: parscott@med.umich.edu

S. Wechsler, M.D. (✉)
Department of Pediatric Cardiology, DUMC 3090, Durham, NC 27710, USA
e-mail: stephanie.wechsler@duke.edu

M. Dick, II (ed.), *Clinical Cardiac Electrophysiology in the Young*,
DOI 10.1007/978-1-4939-2739-5_19

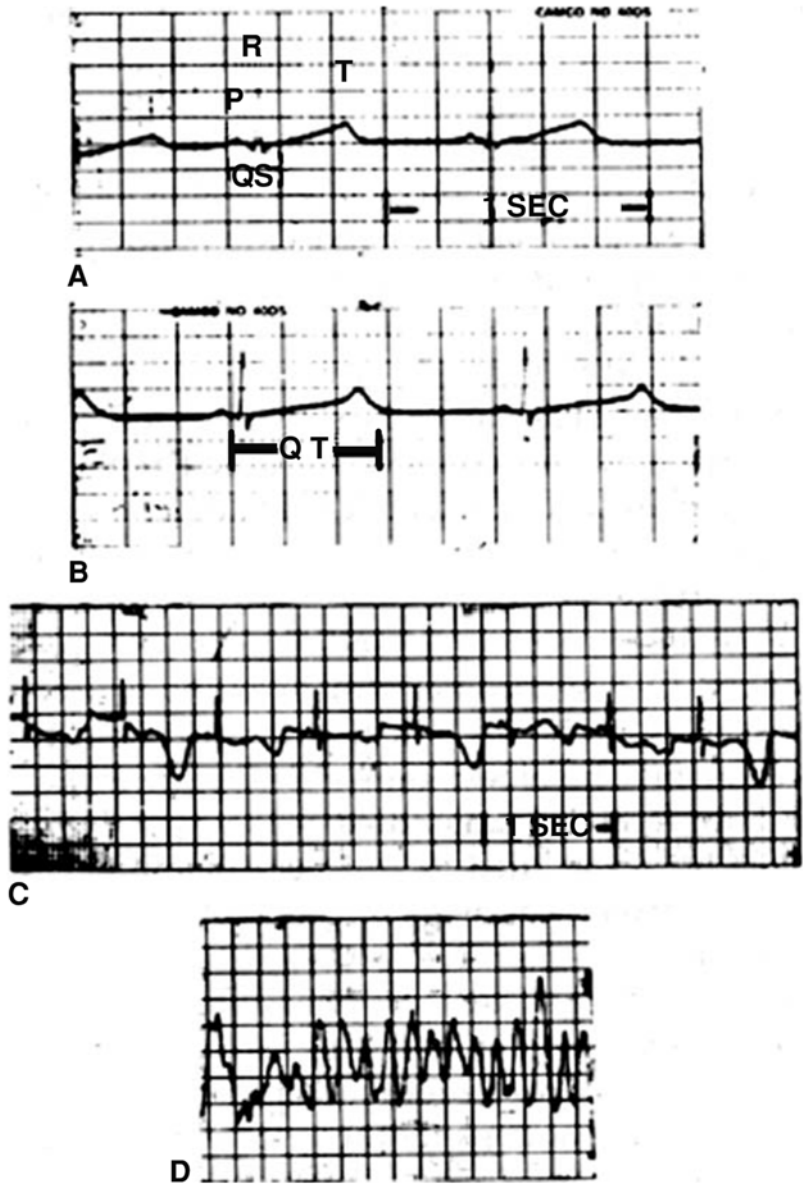


Fig. 19.1 Panels (**a**) and (**b**): Demonstrating long QTc 0.54 s in an 18-month-old boy with sensorineural deafness. Panel (**c**): Marked T-wave alternans. Panel (**d**): Spontaneous ventricular fibrillation, which self-terminated. No genetic testing was available

characterization of patients with the autosomal dominant and autosomal recessive forms of LQTS has led to the discovery that they are often manifestations of the same underlying condition; even patients with the autosomal dominant form can have subtle hearing deficits and the parents of patients with the autosomal recessive form have mild QT prolongation.

Extensive molecular genetic studies in families and in isolated patients with LQTS have determined that mutations in at least 13 different genes may be responsible for causing this disorder (Table 19.1). Electrophysiologic and genetic characterization of LQTS patients has demonstrated that mutations in these different genes cause distinct manifestations of the LQTS, each

Table 19.1 Genes in which mutations result in the long QT syndrome

Long QT locus	Gene	Gene function	Features
LQT1	*KCNQ1*	Potassium channel; *I*(Ks) current	Sudden death with stress/exercise
LQT2	*KCNH2 (HERG)*	Potassium channel; *I*(Kr) current	Worse with hypokalemia
LQT3	*SCN5A*	Sodium channel	Sudden death during sleep; bradycardia
LQT4	*ANK2*	Ankyrin-2; modifies sodium current	Sinus node dysfunction; atrial fibrillation
LQT5	*KCNE1*	Potassium channel; *I*(Ks) current	Sudden death with stress/exercise
LQT6	*KCNE2*	Potassium channel; *I*(Kr) current	
LQT7	*KCNJ2*	Potassium channel; *I*(Kr) current	Andersen syndrome; periodic paralysis
LQT8	*CACNA1C*	L-type calcium channel	Timothy syndrome: syndactyly; 2:1 AV block; cognitive deficits
LQT9	*CAV3*	Calveolin-3; modifies sodium current	Sudden death during sleep; bradycardia; SIDS
LQT10	*SCNA4B*	Sodium channel, beta subunit	Bradycardia; 2:1 AV block
LQT11	*AKAP9*	Modifies KCNQ1 function	
LQT12	*SNTA1*	Syntrophin; modifies sodium current	
LQT13	*KCNJ5*	Potassium channel; *I*(Kr) current	Atrial fibrillation

with unique risks and different responses to therapy. The traditional concept that LQTS causes cardiac arrhythmias only at times of adrenaline excess has been replaced by a more precise view, in which the molecular subtype of LQTS strongly influences both the triggers for arrhythmia and the prognosis with treatment. However, as clinical genetic testing has become increasingly integrated into clinical care, a more complex understanding of the variability in clinical expression of LQTS has also emerged. Individuals with the same mutation can exhibit very different disease severity due to unknown background genetic influence, and up to 10 % of LQTS patients may carry multiple mutations in LQTS gene(s) [4].

I_{Ks} Defects

Defects of *KCNQ1* and *KCNE1*, the alpha and beta subunits of the potassium channel responsible for the I_{Ks} current (Fig. 19.2), cause LQT1 and LQT5, respectively. Mutation of a single copy of either of these genes may cause autosomal dominant LQTS. However, mutations in both copies of one of these genes can result in severely symptomatic LQTS that is characterized by sensorineural deafness, as initially described by Jervell and Lange-Nielsen. Recently, a mutation of *AKAP9*, which encodes for part of a protein complex that regulates KCNQ1 function, has also been demonstrated to result in LQTS, now designated as LQT11. The I_{Ks} current is responsible for the slowly activating outward potassium current that contributes to the return of the myocyte to its resting potential following a depolarization (Chap. 2). LQTS-causing mutations may occur anywhere in the genes that encode these two channels, but the more severe defects appear to be those that result in the production of an ion channel subunit with abnormal potassium conduction properties. These abnormal subunits can complex with normal subunits so that the vast majority of I_{Ks} channels within the myocyte are either nonfunctional or function abnormally. Mutations that do not produce an abnormal protein product result in approximately half the number of fully functional I_{Ks} channels, causing less severe manifestation of the LQTS. With some of the mutations, no abnormalities are noted when a patient inherits only one defective copy of the gene and the LQTS only becomes apparent when two altered copies of the gene are inherited as is noted in the

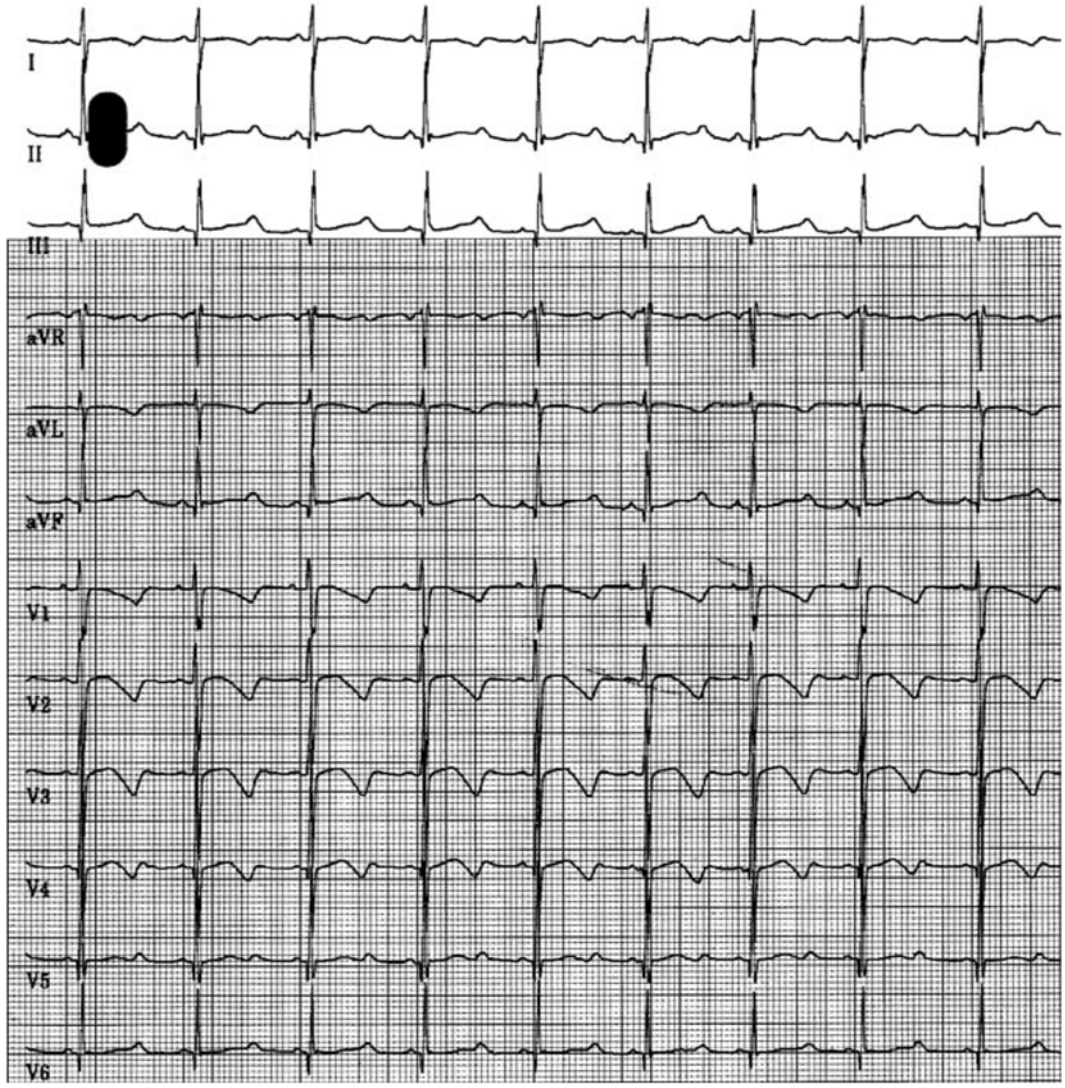


Fig. 19.2 12 Lead ECG in a 8-year-old boy with sudden loss of consciousness for 10 s. Note the QTc of 0.48 s in Lead 2 and V_5

Jervell and Lange-Nielsen syndrome. However, in general, the location of the mutation within the gene has not been demonstrated to reliably predict prognosis. This analysis has been most thoroughly examined in LQT1 [5]. An exception is the C-loop of KCNQ1 which is associated with a high rate of cardiac events in LQT1 [6].

I_{Kr} Defects

Defects of *KCNH2* and *KCNE2*, the alpha and beta subunits of the potassium channel responsible for the rapid potassium (I_{Kr}) current, cause LQT2 and LQT6, respectively. Mutations in these genes have primarily been associated with autosomal dominant LQTS. I_{Kr}, the current responsible for the initiation of cardiac repolarization following excitation-contraction, has some unique properties that affect the clinical manifestations of the LQTS in these patients. The potassium conductivity of the I_{Kr} channel is very sensitive to extracellular concentrations of potassium [7]. Independent of the transmembrane

electrochemical gradient, which, in large part, is maintained by the difference between the intracellular and extracellular potassium concentrations, the capacity of the channel to conduct an outward potassium current (i.e., I_{Kr}) varies directly with the extracellular potassium concentration. As the extracellular potassium rises, the outward potassium current through the channel increases, and conversely, a low extracellular potassium concentration inhibits the channel's function. Therefore, patients that have *KCNH2* or *KCNE2* mutations that inhibit the function of the I_{Kr} channel are particularly sensitive to low extracellular potassium concentrations that further reduce the conductance of the channel.

Mutations involving other inward rectifier potassium channels have recently been determined to cause a long QT phenotype and ventricular arrhythmias. Some mutations of *KCNJ2*, which has been implicated as the gene responsible for Andersen syndrome (see below) and encodes the channel responsible for the $K_{ir}2.1$ current, have been determined to cause significant QT prolongation. A mutation of *KCNJ5*, which encodes for a G protein-regulated inward rectifier potassium channel, was detected in a 4-generation family with LQTS. The mutation showed incomplete penetrance within the family suggesting the presence of disease modifiers in determining disease expression [8].

Mutations Affecting Sodium Conductance

Patients with defects of the cardiac sodium channel, *SCN5A*, which account for less than 10 % of the reported LQTS cases, are more susceptible to arrhythmias and sudden death during times of bradycardia and may die in their sleep. In general, they appear less likely to have an arrhythmia than patients with potassium channel defects but their arrhythmias are more likely to be fatal since they are often not observed. The LQTS-causing *SCN5A* defects described to date appear to impair the ability of the channel to completely inactivate after depolarization, allowing persistent inward leak of Na+ ions. This may lead to prolongation of the plateau phase of cardiac depolarization, thereby delaying the onset of repolarization and resulting in excess calcium loading of the myocyte. The increased intracellular calcium may allow the development of early afterdepolarizations and the generation of ventricular arrhythmias, particularly at slower heart rates. Interestingly, only a subset of *SCN5A* mutations is capable of causing LQTS. As opposed to the gain-of-function type of mutations described above for *SCN5A*-associated LQTS, other mutations in *SCN5A* result in inhibition of inward sodium current or result in a nonfunctional channel [9]. These mutations have been associated with a wide range of distinct clinical phenotypes, including Brugada syndrome, idiopathic ventricular fibrillation, FAF, sick sinus syndrome, and cardiac conduction defects.

More recently, mutations have been identified in proteins that regulate the function of the SCN5A channel, causing QT prolongation, ventricular arrhythmias, and sudden death. Mutations have been identified in *SCN4B* (the beta subunit of the sodium channel), syntrophin and ankyrin-2 (membrane-bound cytoskeletal proteins), and *CAV3* (a membrane protein that regulates the formation and recycling of specialized membrane compartments). In each case, the LQTS-causing mutation results in enhanced late sodium current and leads to sinus bradycardia, ventricular arrhythmias, and sudden death, predominantly during sleep. In addition, since these proteins link the cellular cytoskeleton to membrane-bound multi-protein complexes, mutations in these proteins can result in a spectrum of disorders, including cardiomyopathies (*SCN5A*, *CAV3*) and skeletal muscular dystrophies (*CAV3*).

Calcium Handling Abnormalities

To date, only one of the subtypes of LQTS has been determined to be due to a primary abnormality of calcium handling. Mutations of *CACNA1C*, the alpha subunit of the L-type calcium channel cause Timothy Syndrome, which is characterized by lethal ventricular arrhythmias, severe QT prolongation, webbing, or syndactyly

of the fingers and toes, and cognitive deficits [10]. Not unlike other LQTS-causing genes, mutations of *CACNA1C* can result in a range of phenotypes depending on the domain affected and the nature of the amino acid substitution. As with *SCN5A*, some mutations can result in a Brugada syndrome phenotype.

Drug-Induced LQTS

It has long been known that some patients with normal QT intervals could have marked QT lengthening and *torsades de pointes* in response to certain medications (for more complete list, see http://www.sads.org/ and http://crediblemeds.org/pdftemp/pdf/US-DrugsToAvoidList.pdf). These medications typically interact with function of the potassium channel encoded by the *KCNH2* gene, associated with congenital LQT2. These apparently "idiosyncratic" reactions have now been attributed in many cases to inherited, subclinical LQTS mutations that only become clinically apparent when there is another compromise to cardiac repolarization as occurs with certain medications that block sodium or potassium channels. The effect of these medicines on the cardiac repolarization may be particularly dramatic when they are combined with other agents such as that delay their metabolic degradation by inhibiting the P450 system or when they occur in a patient with hypokalemia, an additional inhibitor of the I_{Kr} current.

Diagnosis of LQTS

The diagnosis of the LQTS is based on the measurement of the QT interval on the 12-lead electrocardiogram and corrected for heart rate using Bazett's formula $[QT/(R-R)^{1/2}]$. Corrected QT intervals of 0.47 in males and 0.48 in females were the initial threshold values for identifying patients with LQTS. However, as genetic testing has become increasingly utilized, a major clinical challenge has emerged. Up to 30 % of individuals with known LQT-associated mutations identified through family screening may have normal QT intervals. This observation is likely due to the presence of multiple other influences on the QT interval that are yet to be defined. Moreover, the QT interval in the normal population exhibits a broad distribution. As a consequence, the QT interval thresholds above will have a low sensitivity for diagnosis of LQTS in individuals with clearly positive family histories for the disorder. On the contrary, lower thresholds would have exceedingly high false positive rates if applied to the general population. A scoring system was devised to improve the sensitivity and specificity of the diagnostic criteria for the LQTS. The scoring system categorizes each patient as high or low risk for having clinical LQTS based on their symptoms, their family history, their measured corrected QT interval and their T wave morphology [11, 12] (Table 19.2). While this appears to be a significant improvement in establishing the clinical diagnosis of LQTS, it has been developed using the most common types of LQTS, LQT1, and LQT2, as a model and may be less helpful for the less common subtypes.

When available, genetic testing is often the best screening approach for individuals with a family history of LQTS, provided that a mutation is identified in the family member (see below). Genetic testing has, however, presented a treatment dilemma in the form of the genotype positive/phenotype negative patient. These are patients who have been identified as carriers of the LQTS (they have one copy of a defective LQTS gene), but they have never had symptoms and their electrocardiogram appears entirely normal. These patients and all first-degree relatives of patients with LQTS who have not had genetic testing should avoid medications on the list of those known to prolong the QT interval (http://www.sads.org/; www.qtdrugs.org).

Beyond careful ECG QT measurements, genetic testing and the clinical scoring system described above, adjunctive testing has proven to be of little benefit. Noninvasive electrophysiologic testing may have a role in diagnosis or prognosis of LQTS. Provocative testing with epinephrine infusion has been used to diagnose LQTS not evident on a resting electrocardiogram. However, this test should be used with caution,

Table 19.2 Long QT syndrome (LQTS) diagnostic criteria

	Points
Electrocardiographic findings[a]	
QTc[b]	
≥480 ms	3
460–479 ms	2
450–459 ms (males only)	1
QTc[b] at the fourth minute of recovery from an exercise stress test ≥480 ms	1
Torsades des pointes[c]	2
T wave alternans	1
Notched T wave in 3 leads	1
Heart rate less than the second percentile for age	0.5
Clinical history	
Syncope[c]	
With stress	2
Without stress	1
Congenital deafness	0.5
Family history	
Family members with diagnosed LQTS	1
Unexplained sudden cardiac death under the age of 50 years in immediate family member (not diagnosed with known or suspected LQTS)	0.5
Probability of LQTS	*Total score*
Low	≤1
Intermediate	1.5–3.0
High	≥3.5

Reprinted from Schwartz PJ, Moss AJ, Vincent GM, Crampton RS. Diagnostic criteria for the long qt syndrome. An update. Circulation. 1993;88:782–784. With permission from Wolter Kluwers Health

[a]In the absence of medications or conditions known to affect the QT interval

[b]QTc calculated using Bazett's formula

[c]Mutually exclusive

since the false positive rate is unknown. Holter monitoring may be of benefit to determine QT intervals at various times during the day, since the QT interval at one single moment in time may not always be reflective of an individual's arrhythmic risk. In addition, exercise ECG may be helpful in determining a lack of rate adaptation of the QT interval, which occurs specifically in LQT1. Thus, a negative exercise ECG test would not exclude other forms of LQTS. In addition, measurements of the QT interval should be focused during early exercise, before the heart rate exceeds the threshold of accurate estimation with the Bazett calculation.

Treatment of LQTS

All patients with LQTS should avoid competitive athletics and all medications known to prolong the QT interval (as well as any alternative therapies that have unknown effects on the QT interval). Further recommendations and treatment choices are tailored to the individual patient. For each patient, the clinical presentation and genetic diagnosis significantly impact risk and therapeutic options in LQTS. The molecular genetic diagnosis is now an efficient starting point for clinical decision making in LQTS and is endorsed by the Heart Rhythm Society/European Heart Rhythm Expert Consensus Statement on the State of Genetic Testing for the Channelopathies and Cardiomyopathies [13]. Once a specific mutation is identified, a treatment plan (which may include pharmacotherapy, device therapy, and/or activity recommendations) can be refined based on the characteristics of the identified subtype of LQTS.

Patients with I_{Ks} defects [who have mutations of *KCNQ1* (LQT1), *KCNE1* (LQT5), and potentially *AKAP9* (LQT11)] are at greatest risk of arrhythmias and sudden death during adrenergic surges that occur during fright or anger, the "flight or fight response." Beta blockade treatment has now been well proven to improve survival in LQT1, which represents the largest genetic subgroup of patients with LQTS. It may follow that patients with LQT5, also characterized by a reduction in I_{Ks} current, may derive a similar benefit from beta blocker therapy, though clinical data on this much smaller subgroup has not yet verified. Previous studies have demonstrated that LQT1 patients who are strictly compliant to adequately dosed beta blocker therapy generally have a good prognosis. The choice of beta blocker is important as treatment with either nadolol or propranolol is superior to metoprolol [14]. All patients with LQTS are recommended to avoid competitive athletics, though the greatest

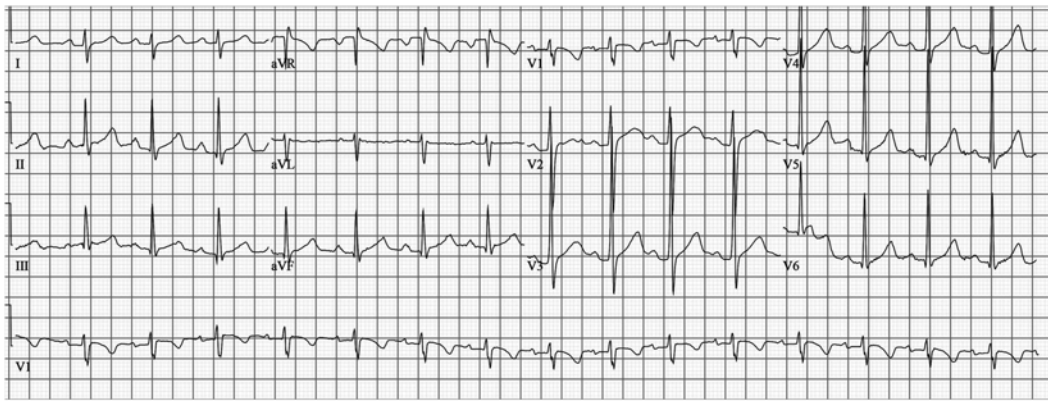


Fig. 19.3 7-Year-old boy with frequent syncope episodes; he was genotype positive for LQT3. He has a normal QTc

risk of adrenergic-mediated events is in LQT1. Interestingly, studies have also demonstrated that patients with *KCNQ1* defects, and presumably with *KCNE1* defects as well, are particularly susceptible to arrhythmias while swimming. This observation has led to the recommendation that all patients with the LQTS should not swim alone or without flotation gear. Additional studies may indicate that only those patients with I_{Ks} defects need to avoid swimming.

Patients with I_{Kr} defects [who have mutations of *KCNH2* (LQT2) and *KCNE2* (LQT6)] are uniquely predisposed to arrhythmias triggered by sudden loud noises and should remove loud alarm clocks and bedside phones. Postpartum arrhythmias are also particularly common in LQT2, likely worsened in the setting of sleep deprivation and stress, and these women should be counseled appropriately. Patients with LQT2-type LQTS have an intermediate response to beta blockade therapy so alternative and supplementary therapies have been investigated.

Hypokalemia should be avoided, and dietary intake of potassium-rich foods would theoretically be of benefit for LQT2 since extracellular potassium impacts the function of KCNH2 channels. Some clinical data has supported the use of potassium supplements or spironolactone to shorten the QT interval in LQT2, though no trial data has demonstrated a reduction in cardiac events.

LQT3, which is due to sodium channel mutations, follows a distinct clinical course from the more common LQTS subtypes which are due to abnormalities of potassium conductance (Figs. 19.3 and 19.4). Ventricular arrhythmias in LQT3 patients are unpredictable and often occur during sleep. Beta blockers have shown a lower success rate in LQT3, although newer data, primarily from a mouse model of LQT3, suggests there may be some benefit, particularly with propranolol which has a sodium channel blocking effect not demonstrated by other beta blockers [15]. The incomplete protection provided by beta blockers has prompted study of specific sodium channel blockade in LQT3. Mexiletine showed early promise as a therapy for LQT3 based on cellular models, and on observations in a subset of patients [16]. However, a more complex view has emerged, since some *SCN5A* mutations appear to cause an overlap syndrome with features of both LQT3 and Brugada. In these patients, treatment with mexiletine may not improve the sodium channel defect and may even be harmful. Therefore, further study will be required to determine if mexiletine is appropriate for a subset of LQT3 patients. Cardiac pacing has been suggested to have a potential benefit in preventing bradycardia-associated events in LQT3 but has not been prospectively studied.

LQTS is largely a medically treated disease. However, a minority of patients will have a high enough risk to warrant an implantable cardioverter-defibrillator (ICD), and, in these patients, an ICD can be life-saving. Patients who continue

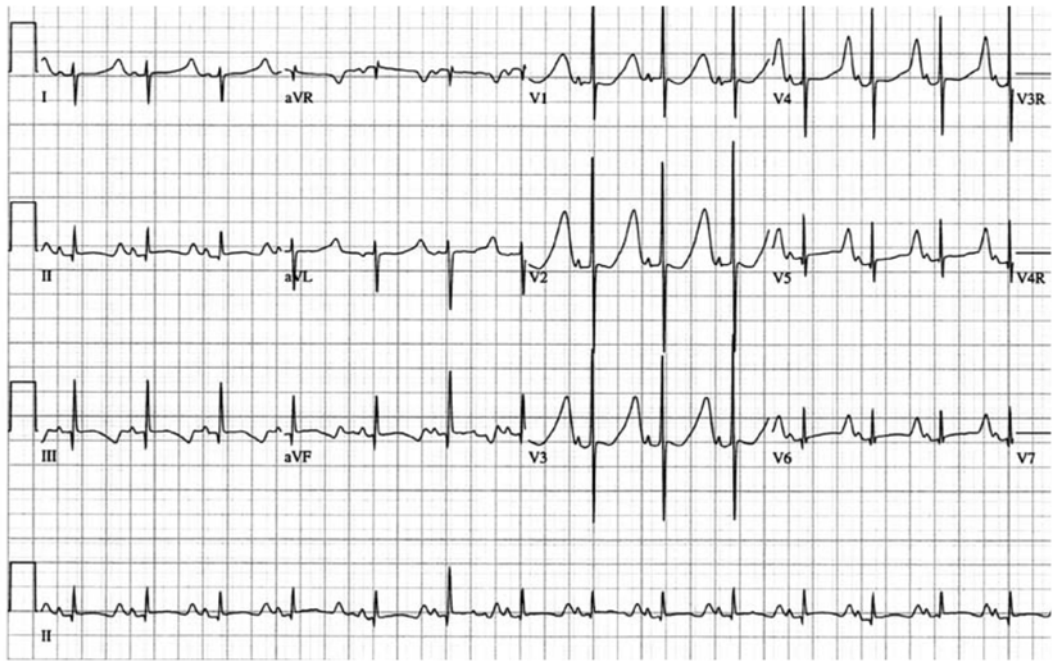


Fig. 19.4 12-Lead electrocardiogram in 2-day-old infant. Note the long flat ST segment and relatively symmetrical T-wave typical of LQTS3 and in contrast to the ECG phenotype in Fig. 19.3

to be symptomatic on therapy, have had a cardiac arrest, or have marked QT prolongation (>500 ms) are potential candidates for an ICD.

Brugada Syndrome

The Brugada syndrome (BS) is characterized by ST segment elevation in the right precordial leads (V_1–V_3) unrelated to other factors such as ischemia, electrolyte abnormalities, or structural cardiopulmonary disease [17] (Fig. 19.5). Patients with Brugada syndrome are predisposed to sudden cardiac death due to polymorphic ventricular tachycardia that degenerates to ventricular fibrillation. It is inherited as an autosomal dominant disorder with an incidence of 5–66 per 10,000 individuals. There is a much higher incidence occurring in areas of Southeast Asia, and a male predominance (8:1). The symptoms, typically syncope or cardiac arrest, usually do not appear until the third to fourth decade of life.

Genetic studies have determined that more than one gene is capable of causing the Brugada syndrome. The first gene identified as responsible for causing BS in some patients was the *SCN5A* cardiac sodium channel. Unlike *SCN5A* mutations that cause LQTS, BS-causing *SCN5A* mutations reduce the sodium channel current, either through a reduction in the number of channels and/or the diminished function of nearly half of the channels. Many of these mutations introduce a premature truncation codon, resulting in an unstable mRNA transcript and a consequent shortage of the protein product. However, the distinction electrophysiologically between Brugada syndrome and LQT3 may not always be clear, since an overlap syndrome containing features of both may arise from certain mutations, as discussed above. The diminished inward sodium current in Brugada syndrome due to SCN5A mutations is thought to allow a prominent transient outward potassium current (I_{to}) in the right ventricular epicardium, leading to an epicardial to endocardial voltage gradient. This produces

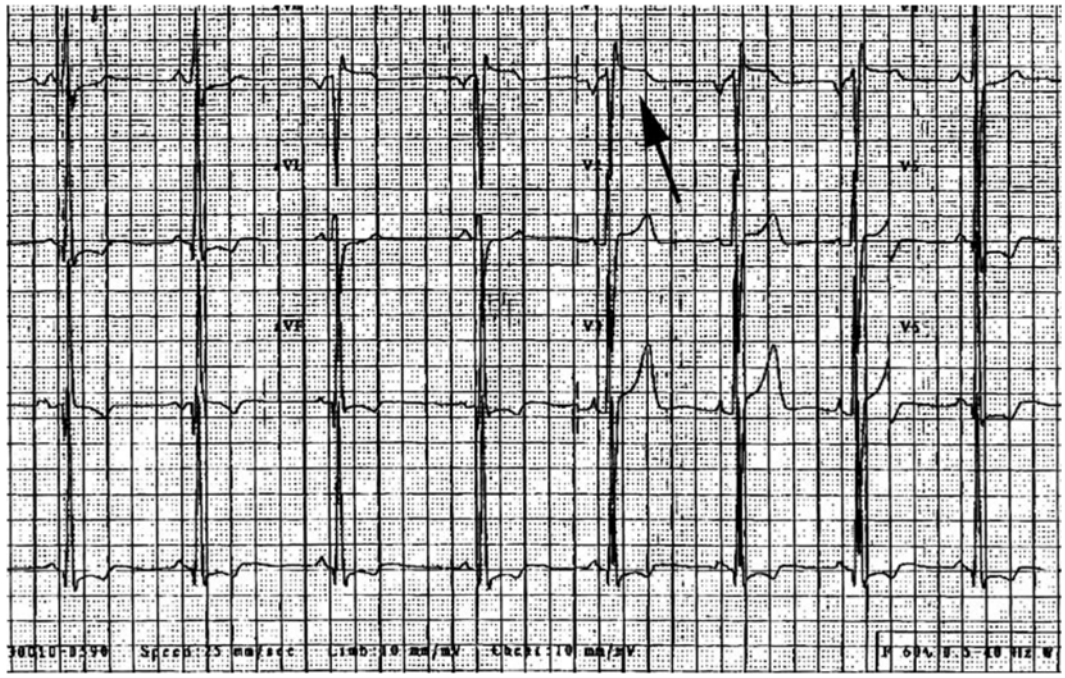


Fig. 19.5 Elevation of ST segment in V_1 (*arrow*) in a 15-year-old boy with family history of Brugada syndrome

the ST elevation that is characteristic of the disorder seen prominently in the right ventricular ECG leads (V_1–V_2) and may lead to re-excitation (phase 2 re-entry) in the ventricular epicardium, triggering ventricular arrhythmias.

BS-causing mutations have also been identified in *GPD1L* (a presumed phosphate dehydrogenase that regulates the sodium current), *CACNA1C* (the alpha subunit of the L-type calcium channel), *SCN1B* (a beta subunit of the cardiac sodium channel), *SCN3B* (a beta subunit of the cardiac sodium channel), *KCNE3* (a beta subunit of the KCNQ1 potassium channel), and *HCN4* (a hyperpolarization-activated and cyclic-nucleotide-gated cation channel that controls pacemaker activity in the sinus node). Collectively, these remain very rare causes of BS and only *SCN5A*, *GPD1L*, and *CACNA1C* mutations have been noted in more than a single family.

Diagnosis

Like LQTS, the diagnosis of BS has relied upon the characteristics of the 12 lead electrocardiogram, but also with less than optimal sensitivity and specificity. Three distinct right precordial ST wave morphologies have been described (Fig. 19.6) In Type 1 BS, there is prominent "coved" J point peak with an ST elevation of >0.2 mV followed by a negative T wave with essentially no intervening isoelectric phase. In Type II, there is a prominent J point peak (>0.2 mV) followed by a positive or biphasic T wave resulting in a saddleback appearance. In Type III, the J point elevation is less pronounced (>0.1 mV) and may be of either the "cove" or "saddleback" type. The ECG abnormalities may mimic RBBB, especially in patients with Type I BS. The BS pattern can be differentiated from RBBB by the absence of a wide S wave in lead I and in the left lateral precordial leads.

The typical ECG appearance may not always be present but may be unmasked by intravenous infusion of sodium channel blockers such as ajmaline (1 mg/kg at 10 mg/min), flecainide [2 mg/kg (maximum 150 mg) over 10 min], or procainamide (10–15 mg/kg; 100 mg/min, the only medication FDA approved in the United States). However, sensitivity and specificity of

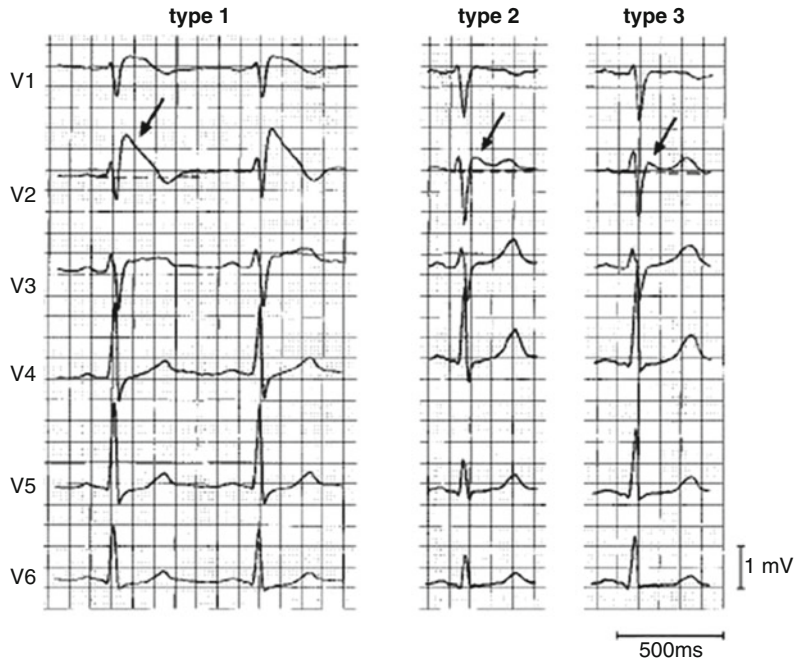


Fig. 19.6 Three types of QRS morphology in the Brugada syndrome (Reprinted with permission from Wilde AA, et.al. Proposed diagnostic criteria for the Brugada syndrome: consensus report. Circulation 2002;106(19): 2514–9. With permission from Wolters Kluwer Health)

the provocative testing has not been established and, in a patient that does have BS, may precipitate significant ventricular arrhythmias including ventricular fibrillation. Furthermore, there is some evidence to suggest that asymptomatic patients, who only demonstrate ECG changes with provocative testing, may have a benign course [18].

Genetic testing will have an increasingly important role in helping to understand the clinical spectrum of BS. Current genetic testing formats may only detect a putative mutation in approximately 20–30 % of the BS cases but exome-wide sequencing, which is being increasingly utilized in the clinical setting, may reveal additional cases of the rare genetic causes and identify novel genes, especially when performed in families with more than one affected individual. In the future, as more BS genes are identified and their manifestations more uniquely characterized, genetic testing may help make the diagnosis and guide the course of therapy.

Management

Treatment is required for all symptomatic BS patients. Unfortunately, pharmacotherapy has not proven to be beneficial. There is some theoretical argument for the use of quinidine to treat this disorder since quinidine, at low doses, is a potent inhibitor of the Ito potassium current. However, quinidine has not been prospectively studied in BS patients. Interestingly, there is also data to suggest that mexiletine, a sodium channel blocker, may improve trafficking of the mutant protein, allowing it to be transported correctly to the cell membrane where its function can help improve sodium conductance into the myocyte. However, the only treatment currently demonstrated to be effective in reducing mortality in BS patients is placement of an ICD. While ICD placement is clearly indicated in all BS patients with symptoms of syncope, there is controversy concerning their use in asymptomatic BS patients, particularly children and young adults. When an individual is identified during the screening of a family with symptomatic Brugada syndrome, it could be

argued that ICD placement should be considered. Approximately 30 % of asymptomatic individuals will have a ventricular arrhythmia within 3 years of evaluation, the same as the percentage of symptomatic individuals that will experience a recurrent ventricular arrhythmia within 3 years. The only major risk factor identified in asymptomatic patients is a spontaneous type I ECG pattern, which confers an intermediate risk of ventricular arrhythmias. A 24-h Holter monitor may be useful in determining whether a spontaneous type I pattern emerges at times of higher vagal tone in these patients, such as after a large meal or during the night. While provocative drug challenge is useful diagnostically, it does not identify a higher risk group with Brugada syndrome. Electrophysiologic testing was initially shown to identify patients with inducible ventricular fibrillation who appeared to have a higher risk of clinical events. However, subsequent studies have questioned whether inducible VF is a reliable marker of events in Brugada syndrome.

Short QT Syndrome

While the dangers of prolongation of the QT interval have been recognized since the LQTS was first described in the late 1950s and early 1960s, only recently has it been discovered that a very short QT interval may also predispose to life-threatening arrhythmias and sudden death [19]. The short QT syndrome is very rare in comparison to LQTS and is characterized by a QTc (Bazett's formula) less than 320 ms (Fig. 19.7). It is frequently associated with atrial fibrillation to the extent that the diagnosis should be strongly considered in young patients with isolated atrial fibrillation [20]. Establishing the diagnosis is vital since patients with the disorder have a high incidence of syncope and sudden death due to ventricular tachyarrhythmias. As with the LQTS, the short QT syndrome is a heterogeneous disorder with mutations in at least three different genes capable of causing the clinical manifestations. The mutations described to date are all

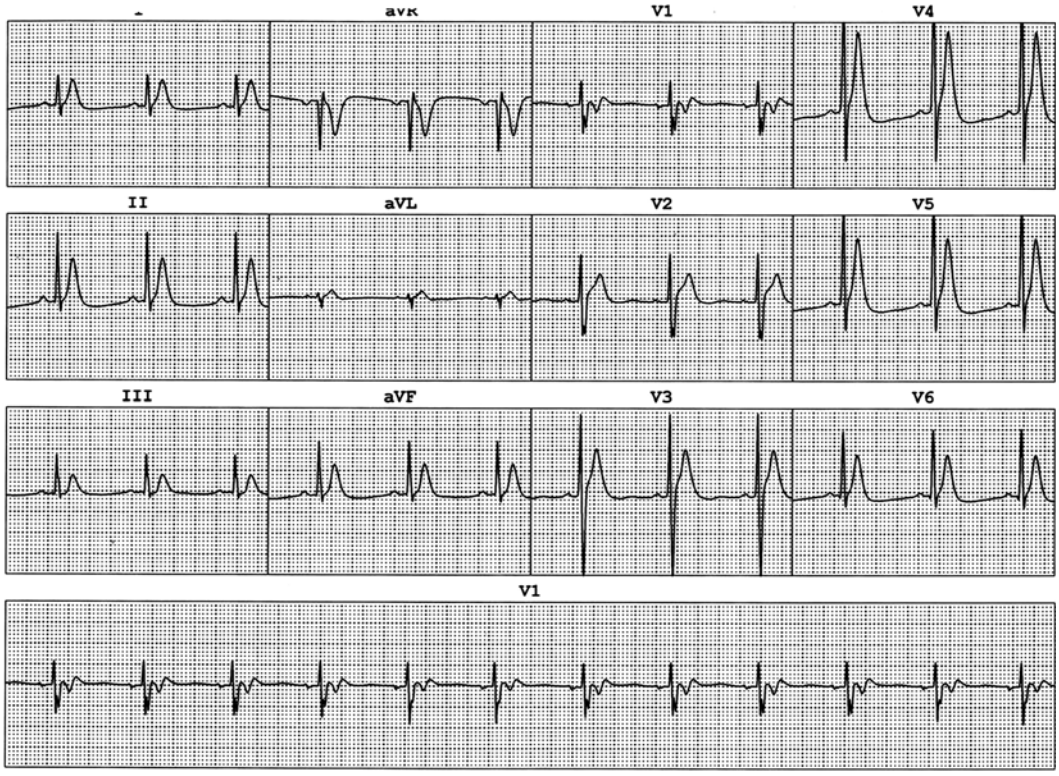


Fig. 19.7 ECG from 14-year-old boy with aborted ventricular fibrillation. Note the QT 0.28 s

gain-of-function mutations in genes in which loss of function can lead to the long QT or Anderson syndromes: *KCNH2* (I_{Kr}), *KCNQ1* (I_{Ks}), and *KCNJ2* (I_{Kt}). Treatment guidelines are still being established but case reports have recommended the use of ICD devices. Furthermore, quinidine may be of benefit, as adjunctive therapy in those patients with an ICD or primary therapy in those without, at least in patients with short QT syndrome due to mutations in the KCNH2 (HERG) channel.

Early Repolarization-Associated Ventricular Arrhythmias

Early repolarization was long known as a benign clinical entity until the last decade. Several isolated reports, followed by population studies and case series have now suggested an increased risk of ventricular arrhythmias related to early repolarization, though this risk appears to be very modest on a population level. In the largest case series of patients with sudden cardiac arrest of unknown cause ($n=206$), early repolarization, defined as a J point elevation regardless of ST elevation, was much more common than in controls (31 % vs. 5 %, $p<0.001$) [21]. Subsequent to this report, there has been an argument that the key ECG feature potentially associated with ventricular arrhythmias is the J point elevation with a subsequent horizontal ST segment, as opposed to the ascending ST elevation frequently seen in the young, especially in male athletes, which is likely benign [22]. Other population studies have countered these findings, with no evidence of an increased risk of sudden death, regardless of the type of J point or ST segment elevation [23]. While the genetic underpinnings of early repolarization are not yet understood, Gourraud et al. published a series of 22 sudden deaths among 4 families associated with early repolarization. They did extensive screening and evaluation of these families (171 screened relatives), and their findings suggest that early repolarization in these families is inherited as an autosomal dominant trait with an increased risk of sudden death [24]. Therefore, while the vast majority of individuals with an early repolarization pattern on ECG, regardless of the morphology of the pattern, will not suffer from life-threatening arrhythmias, there may be selected individuals and families that require closer monitoring. A family history of early sudden cardiac death and syncope suspicious for arrhythmia may warrant closer scrutiny for the possibility of familial early repolarization patterns. More precise characterization of the clinical features that could distinguish those at risk from the large number of individuals with the common, apparently benign, variant of early repolarization will be a major challenge.

Familial Ventricular Fibrillation

Several families have been described with familial ventricular fibrillation (FVF). In one instance, the disorder was attributed to a mutation of the *SCN5A* gene but the patients did not demonstrate the electrocardiographic findings of Brugada syndrome. Additional FVF genes likely remain to be identified since not all patients with the disorder have been demonstrated to have *SCN5A* defects. A second locus was definitively linked to chromosome 7q36.2 in a Dutch cohort. A noncoding mutation was noted in the promoter region for the *DPP6* gene which encodes for a component of the transient outward current in cardiac myocytes.

Catecholaminergic Polymorphic Ventricular Tachycardia

Catecholaminergic polymorphic ventricular tachycardia has been demonstrated to be due to abnormal calcium release from the sarcoplasmic reticulum. It is a relatively rare heritable disorder that is characterized by adrenergic-induced ventricular tachyarrhythmia and sudden death (see Fig. 19.8). CVPT has been determined to result most commonly from an autosomal dominant mutation in the cardiac ryanodine receptor type 2 (*RYR2*), the channel that releases calcium from sarcoplasmic reticulum (SR) stores, or an autosomal recessive mutation (or compound heterozygous

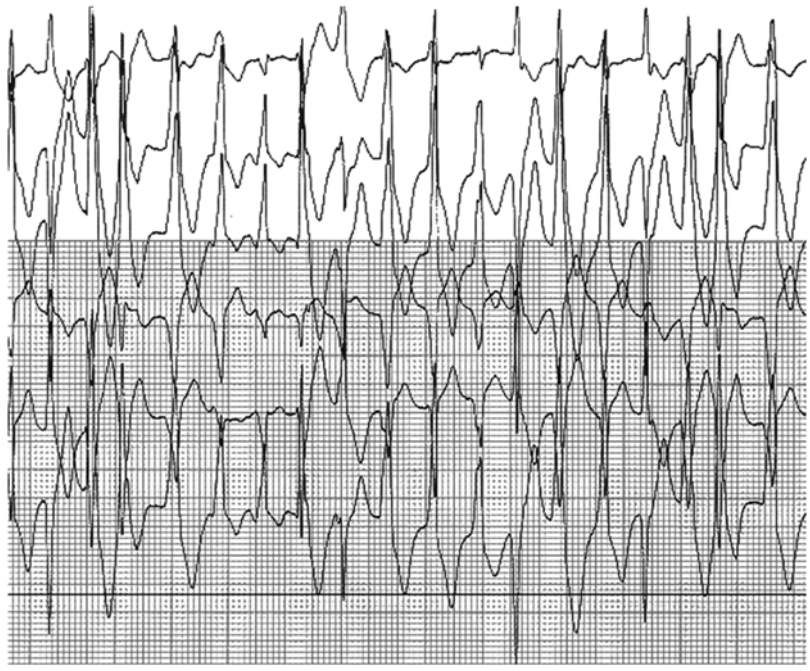


Fig. 19.8 ECG tracing in a 9-year-old girl with a normal QTc and recurrent seizure-like episodes due to polymorphic VT or torsade des pointes. She was genotype positive for RyR2 mutation; both parents were negative for the mutation

mutations) in calsequestrin, a molecule that helps to sequester calcium in the SR and interacts with ryanodine. More recently, CPVT-causing mutations have also been identified in *CALM1* (which encodes for calmodulin, a key calcium-binding protein involved in intracellular calcium regulation), and *TRDN* (which encodes for triadin, a regulator of calcium release that links calsequestrin to the ryanodine receptor). Therefore, CPVT is primarily attributable to disordered calcium regulation.

Clinical Features

Patients with CPVT often develop symptoms of syncope and sudden death early in childhood, usually around the age of 8, with more severely affected individuals demonstrating an earlier onset of symptoms [25]. However, a great degree of variability is seen even among members of the same family who carry the same mutation. Some individuals may be silent carriers of these mutations only to have the condition diagnosed through screening exercise ECGs or through genetic testing. Symptoms almost exclusively occur with stress or exercise, and there is a 30–50 % incidence of sudden death by 20–30 years of age in symptomatic patients if the condition is left untreated. In patients with CPVT, isolated premature ventricular contractions and atrial arrhythmias occur early after the onset of exercise. After continued exercise, runs of monomorphic or bidirectional ventricular tachycardia can degenerate into polymorphic ventricular tachycardia and, ultimately, ventricular fibrillation. The other consistent clinical feature is resting bradycardia.

Diagnosis

The diagnosis of CPVT depends on the demonstration of ventricular tachyarrhythmias that are elicited or exacerbated by exercise testing in a patient without either structural heart disease or the LQTS. Exercise testing clearly should be performed in any individual with a history of exercise-induced syncope and normal electrocardiographic and echocardiographic studies to evaluate for the possibility of CPVT. Screening exercise testing is critical in family members, regardless of the

presence of symptoms, whenever a diagnosis of CPVT is made or when there is a family history of sudden death of unknown etiology at a young age (i.e., <35 years). Genetic testing can be very helpful in establishing the diagnosis and tracking it through families to identify asymptomatic individuals who may be at risk for sudden death. Establishing the diagnosis prior to the onset of symptoms in these families is a major advance since the first manifestation of the disease may be sudden death in an otherwise healthy child.

Management

Treatment with beta-blockade has been highly effective in reducing morbidity and mortality [25]. Verapamil has shown some benefit as an adjunctive treatment when beta blockade is not completely effective, though it has not been extensively studied. In addition, small case series have suggested benefit of flecainide, due to its modulation of the ryanodine channel (an activity only seen with flecainide as compared to other class IC antiarrhythmic agents). A randomized clinical trial is currently underway to determine the efficacy of flecainide in CPVT. Some patients with persistent stress-induced arrhythmias despite beta blockade may require ICD placement, though this decision should not be made lightly, as some patients with CPVT may experience frequent ICD shocks due to extensive ventricular ectopy that may trigger ICD storm. Left cardiac sympathetic denervation has been advocated by some centers.

Andersen Syndrome

Andersen syndrome is characterized by potassium-sensitive periodic paralysis, ventricular ectopy, and dysmorphic features. The phenotype can be highly variable but may include short stature, mandibular hypoplasia, low-set ears, and clinodactyly. The paralysis may occur at low, normal, or high serum potassium and is usually responsive to potassium treatment. There can be prolongation of the QT interval, but that is a minor criterion for the diagnosis and the arrhythmias are usually catecholamine induced, making the syndrome functionally similar to CPVT. The ventricular arrhythmias, characteristically bidirectional ventricular tachycardia (Fig. 19.9), may lead to syncope and sudden death. In at least some cases, the syndrome is due to a mutation of the gene encoding for the *KCNJ2* potassium channel. Disease-causing *KCNJ2* mutations are thought to decrease the strength of the channel interactions with phosphatidylinositol 4,5-bisphosphate. With treatment, long-term outcomes have been very good [26].

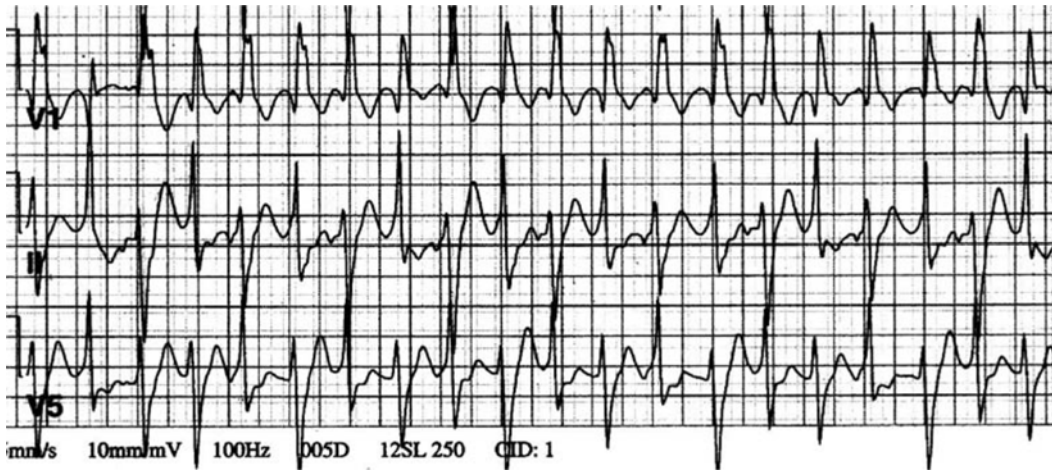


Fig. 19.9 Rhythm strip (V_1, II, V_5) in a 16-year-old girl with clinodactyly, short stature, small mandible, and a mutation in the KCNJ2 gene. Note the bidirectional pattern (alternating axes) of the ventricular arrhythmia. She received an ICD but has had no discharges over 10 years

Familial Atrial Fibrillation

Atrial fibrillation, the most common sustained cardiac-rhythm disturbance in adults, is very rare in children (see Chap. 9). It becomes increasingly prevalent with advancing age and is a common antecedent for stroke in patients over 65. The rare incidences of familial AF have led to the identification of 14 different genetic loci that are responsible for the disorder in at least one family. For 4 loci, the genetic defect responsible for causing the atrial fibrillation has not yet been determined. Of the ten that have been identified, several of the genes have also been determined to be responsible for other types of cardiac dysrhythmias, including *KCNQ1* (LQTS; Short QT), *KCNJ2* (LQTS/Andersen Syndrome; Short QT), *KCNE2* (LQTS), *SCN5A* (LQTS; BS; Heart Block; Ventricular Fibrillation; Sick Sinus Syndrome; DCM), and *SCN1B* (BS). The remaining FAF-causing mutations have been identified in *KCNA5* (which encodes for a delayed rectifier potassium channel), *SCN2B* (a beta subunit of sodium channels), *GJA5* (encodes for the gap junction protein, connexin40), *NPPA* (atrial natriuretic peptide precursor), and *ABCC9* [ATP-binding cassette protein, part of the K(ATP) channel]. The diversity of genetic etiologies suggests that there may not be a common pathogenic process. Ultimately, therapy may require targeted approaches depending on the predisposing genetic defect.

Cardiomyopathies

Abnormalities of components of the sarcomere and of the cytoskeletal array of the myocytes can cause cardiomyopathy and a predisposition to cardiac arrhythmias. The cardiomyopathies can be divided into hypertrophic, dilated, and dysplastic subtypes.

Hypertrophic Cardiomyopathy

The hypertrophic cardiomyopathies (HCMs) are a heterogeneous group of disorders characterized by cardiac hypertrophy not attributable to either hypertension or structural defect. It is the most common heritable cardiovascular disorder with an estimated incidence of 0.2 %. In HCM, the abnormal hypertrophic growth results in enlarged and disordered myocytes that displace adjacent myocytes, causing the characteristic microscopic pathologic appearance of myocyte disarray. Despite the marked pathologic abnormalities, ventricular systolic function is usually normal or even super-normal. Due to the thickened stiff ventricular walls, diastolic function is often impaired, causing dyspnea on exertion, orthopnea, and angina. There is a variably increased risk of atrial and ventricular arrhythmias and sudden death that does not always correlate with the degree of ventricular hypertrophy.

Based on genetic studies, HCM has been referred to as a disease of the sarcomere [27]. To date, at least 20 different genes have been determined to be responsible for causing familial HCM. Many of the known genes (Table 19.3) encode for a component of the sarcomere, the highly ordered contractile unit of striated muscle. The sarcomere can be divided into the thin filament (cardiac actin, the troponins, and α-tropomyosin), the thick filament (myosin heavy chain, the myosin light chains, and myosin-binding protein C), and the structural elements (titin and muscle LIM protein). Usually, HCM occurs as an isolated finding, but it can be associated with a skeletal myopathy in patients with mutations of the essential or regulatory myosin light chains, or can be part of a syndrome such as the Noonan or Leopard syndrome.

Mutations in genes encode for β-myosin heavy chain, cardiac troponin T, and myosin-binding protein C account for greater than 90 % of genetically defined cases. The other genes, cardiac troponin I, regulatory and essential myosin light chains, titin, α-tropomyosin, α-actin, and α-myosin heavy chain, each account for a minority of HCM cases. Since a significant number of patients with HCM (approximately 30 %) do not have a mutation of one of the previously identified genes, additional HCM-causing genes remain to be identified.

The clinical manifestations of HCM vary widely, even between patients that have identical mutations of the same gene. A variety of modulating factors such as systemic blood pressure,

Table 19.3 Genes in which mutation result in Hypertrophic Cardiomyopathy

HCM category	Gene	Associated features
Sarcomeric HCM	MYBPC3 (cardiac myosin-binding protein C)	
	MYH7 (beta myosin heavy chain)	
	MYL2 (ventricular myosin regulatory light chain)	
	MYL3 (ventricular myosin alkali light chain)	
	TNNC1 (cardiac troponin C)	
	TNNI3 (cardiac troponin I)	
	TNNT2 (cardiac troponin T)	
	ACTC1 (cardiac alpha actin)	
	TPM1 (cardiac tropomyosin)	
Other HCM	CAV3 (calveolin)	Mutations can also cause DCM, LQTS, and rippling muscle disease
	MTTG (mitochondrial transfer RNA glycine)	
	MTTI (mitochondrial transfer RNA isoleucine)	Sensorineural hearing loss
	MTTK (mitochondrial transfer RNA lysine)	Sensorineural deafness; cognitive decline
	MTTQ (mitochondrial transfer RNA glutamine)	
Noonan syndrome HCM	RAF1 (c-raf)	Noonan syndrome; Leopard syndrome
	PTPN11 (protein-tyrosine phosphatase 1D)	Noonan syndrome; Leopard syndrome
Friedreich's ataxia HCM	FXN (Frataxin)	Progressive ataxia; neurodegenerative disorder
Storage/infiltrative disorders, pseudo-HCM	PRKAG2 (AMP-activated protein kinase, gamma subunit)	Assoc. with WPW syndrome
	GLA (alpha-galactosidase A)	Andersen-Fabry disease; renal insufficiency
	LAMP2 (lysosome-associated membrane protein 2)	Danon disease; variable skeletal muscle and neurologic involvement
	TTR (transthyretin)	Amyloidosis

autonomic tone and genetic variation, including in some cases, a mutation in the same or second gene associated with HCM, can affect the degree of hypertrophy. Each of the genes responsible for causing HCM presents a slightly different disease spectrum. Myosin-binding protein C mutations, in general, cause cardiac hypertrophy later in life while troponin T mutations may be associated with a higher incidence of sudden death despite even with only mild hypertrophy. However, a great degree of variability exists across families even with identical mutations in these genes, posing a significant challenge to genotype–phenotype prediction. Clearly, other genetic loci, as well as environmental factors, play a substantial role in determining the disease severity in a particular individual.

Diagnosis

The diagnosis of HCM depends on the echocardiographic finding of significant (>95th percentile for age) cardiac hypertrophy in the absence of other causes of hypertrophy such as hypertension or structural heart disease. The exact morphology

of the hypertrophy may vary widely between patients but is often asymmetric with hypertrophy of the septum being much more prominent than that of the posterior free wall. This asymmetric septal hypertrophy can lead to subaortic narrowing and systolic anterior motion (SAM) of the mitral valve. This process can result in significant left ventricular outflow tract obstruction (LVOTO), increased left ventricular systolic pressures and further acceleration of the hypertrophic process. Although the observation of LVOTO, termed hypertrophic obstructive cardiomyopathy (HOCM) or idiopathic hypertrophic subaortic stenosis (IHSS), accounted for the original detection of HCM, it is now evident that many, if not most, HCM patients do not demonstrate significant LVOTO. The ECG pattern is abnormal in approximately 70–90 % of the patients with clinical HCM and differs widely depending on the nature of the hypertrophy. Left atrial enlargement may be the first electrocardiographic sign of the diastolic dysfunction that accompanies HCM even before there is a significant increase in left ventricular forces consistent with left ventricular hypertrophy. Other electrocardiographic abnormalities that may be present include deep QS patterns in V_1–V_3, partial or complete bundle branch block, ST segment elevation/depression, or an abnormal T wave axis or morphology.

If the hypertrophy is symmetric and the ECG is normal, the diagnosis of HCM can be very difficult to make, especially in the absence of a suggestive family history or positive genetic test result. Trained athletes are known to have mild to moderate increases in their measured left ventricular wall thickness making the differentiation between "athlete's heart" and mild HCM complex yet critical. The type of athletic activity is important in this distinction, since endurance athletics (e.g., long distance running, rowing) will cause mostly ventricular chamber dilation, while high-intensity burst athletics (e.g., football) will cause prominent left ventricular hypertrophy (Table 19.4 from suggested reading [28]).

Furthermore, while the degree of cardiac hypertrophy does correlate with the risk of sudden death, even patients with mild hypertrophy can have serious ventricular arrhythmias and sudden death and may need to be restricted from competitive sports. Family history may be helpful in that some families appear to have very high incidence of sudden death while in other families the affected individuals appear to have a normal life span. Genetic testing has become an important adjunct to clinical testing in establishing the diagnosis of HCM. While a negative test cannot exclude the diagnosis, a positive test can help support the diagnosis, especially in patients where there is a clinical suspicion. Currently, genetic testing may be most helpful in the assessment of other family members of a patient in whom a genetic defect has been identified. Those family members that do not inherit the mutation may not need to be followed with serial echocardiograms and those individuals that did inherit the mutation may be followed more closely.

Table 19.4 Differentiation between HCM and an athlete's heart

HCM		Athlete's heart
Yes	Unusual pattern LVH (ECHO)	No
Yes	LV cavity size <45 mm (ECHO)	No
No	LV cavity size >55 mm (ECHO)	Yes
Yes	LA enlargement (ECHO)	No
Yes	Strange ECG pattern	No
Yes	Abnormal LV filling (ECHO)	No
Yes	Female gender	No
No	Decreased LV thickening with deconditioning	Yes
Yes	Family history HCM	No

Adapted from Maron BJ, et.al The heart of a trained athletes: cardiac remodeling and the risks of sports, including sudden death. Circulation 2006; 114:1633–1644. With permission from Wolter Kluwers Health

Management

Current management of the patient with HCM is dependent upon the patient's symptoms, cardiac evaluation and family history. A cardiac evaluation in all patients with HCM should include an echocardiogram, an exercise test, a 24 h Holter ECG recording and an extended family medical history. A cardiac MRI may be helpful for precise measurement and quantification of cardiac hypertrophy, especially for hypertrophy localized to

the anterior wall, which may not be readily visualized on echocardiogram, and for detection of myocardial fibrosis.

Beta blockade or treatment with calcium channel blockers may slow the progression of the cardiac hypertrophy through modification of the hyper-contractile state characteristic of the condition. While there are no strong data to support any effect on disease progression or symptoms, these agents may be beneficial in improving symptoms in some patients. Treatment with antiarrhythmic agents has not proved to have a significant effect on the natural history of the disease and patients with symptomatic ventricular arrhythmias appear to be best treated with placement of an ICD. Considerations for placement of an ICD include the following: aborted sudden death, unexplained syncope (particularly in childhood), family history of sudden death due to HCM (particularly in first-degree family members), ventricular tachycardia during Holter monitoring or exercise test, and severe septal thickening (>30 mm). A blunted blood pressure response with exercise (lack of rise in systolic pressure >20 mmHg) in individuals younger than 40 years old is also considered a risk factor, though with less strength of evidence. Left atrial enlargement and the presence of delayed gadolinium enhancement on MRI (indicative of myocardial scar) are emerging risk factors for disease progression and sudden death in HCM, but the optimal cut-offs for risk stratification have yet to be precisely determined. A composite risk score calculation has recently been proposed for adult patients with HCM [29]. A similar scoring system has not been validated for pediatric patients with HCM. It is anticipated that the risk factors are similar but may need to be weighted differently and may require adjustments of the threshold values (for instance, in pediatric patients a maximal wall thickness of >25 mm may be associated with sufficient risk to consider ICD placement depending on other factors).

Left ventricular outflow tract obstruction occurs in approximately 30 % of patients and can lead to myocardial ischemia, syncope, exercise intolerance and, presumably, acceleration of the hypertrophic process. LVOTO may be a weak predictor of sudden death in HCM, though this has not been consistently demonstrated in studies. Medical treatment for LVOTO with a beta blocker and/or calcium channel blocker is the first-line treatment and often results in substantial improvement in symptoms. Disopyramide, a sodium channel blocker that decreases cardiac contractility, can diminish LVOTO without causing a significant decrease in blood pressure, and can be used as an adjunctive agent to a beta blocker or calcium channel blocker. An ECG at baseline and at intervals during initiation of therapy is important since disopyramide can lengthen the QT interval; a QTc interval longer than 450 ms would mandate cessation of the medication.

Since invasive treatment for LVOTO has not been proven to improve survival in HCM, it is largely reserved for patients with refractory symptoms despite medical therapy. In these patients, invasive therapy, either with surgical septal myectomy or intracoronary ethanol septal ablation, can result in a marked improvement of symptoms. Surgical septal myectomy is generally preferred, particularly for patients who do not have a high operative risk (especially in young patients) since the rate of complete heart block requiring permanent pacemaker implantation is much lower, the efficacy is higher, and the long-term risk of scar formation (and ventricular arrhythmia) after ethanol ablation may be significant. Referral to a high volume center for surgical myectomy is of critical importance for both safety and efficacy. Ethanol septal ablation has not been used in the pediatric population due to relatively high complication rates which can include coronary dissection and early and late ventricular arrhythmias due to ischemia and infarction of the affected region.

Cardiac "Hypertrophy" with Wolff–Parkinson–White Syndrome

In the age of molecular diagnosis, an important distinction is now able to be drawn between the more common sarcomere-mutation HCM and phenocopies of HCM that present as ventricular

wall thickening (pseudo-hypertrophy). In these disorders, the myocytes are enlarged not by an increase in contractile elements (true hypertrophy) but by cytoplasmic glycogen inclusions (pseudo-hypertrophy). The most common of these disorders are (a) Fabry disease (X-linked alpha-galactosidase deficiency), (b) *PRKAG2* glycogen storage disease (mutated regulatory subunit of cAMP-activated protein kinase results in glycogen build up), and (c) Danon disease (X-linked lysosomal storage disease due to mutations in the *LAMP2* gene). The latter two diseases (*PRKAG2* glycogen storage cardiomyopathy and Danon disease) are often associated with abnormal atrioventricular connections resulting in Wolff–Parkinson–White syndrome. Atrial fibrillation also commonly develops in these conditions, with a heightened risk of sudden death due to rapid conduction across the accessory pathways. These diseases all more commonly present with concentric left ventricular hypertrophy and often at young age with a more rapid disease progression (except for females in the X-linked Fabry or Danon diseases). Cases with asymmetric hypertrophy and even LV outflow tract obstruction occur, highlighting the potential benefit of genetic testing in these cases. The typical risk stratification schemes for sarcomere-mutation HCM likely do not apply to these conditions.

Dilated Cardiomyopathy

Dilated cardiomyopathy is a common disorder that is characterized by enlargement and decreased function of the left ventricle. It is the most frequent reason for heart failure and cardiac transplantation and places patients at high risk for both atrial and ventricular tachyarrhythmias. The causes of DCM include myocarditis, ischemia/infarction, metabolic disorder, drug induced (e.g., Adriamycin), and genetic mutation. A genetic cause is identified in approximately 40 % of cases with autosomal dominant transmission being the most common mode of inheritance. X-linked, autosomal recessive, and mitochondrial inheritance have also been reported, though less frequently. The search to identify the genes responsible for causing DCM has led to an increase in the understanding of the sarcomere structure–function relationship. To date, approximately 50 DCM-causing genes have been identified [30, 31] (Table 19.5). Each of the genes responsible for DCM can cause significantly different manifestations of the disease.

Isolated DCM

Nine of the genes responsible for DCM, including *Titin*, *TNNT2*, *ACTC*, *MYH7*, *TPM1*, *TNNC1*, *MYH6*, *TNNI3*, and *MYBPC3*, encode sarcomeric proteins some of which have also been noted to be altered in some patients with HCM. Therefore, different mutations of the same gene can lead to hypertrophy or dilatation, depending on how the mutation affects the physiologic properties of the sarcomere. However, DCM-causing alterations of one of these sarcomeric proteins usually result in isolated DCM without evidence of other abnormalities.

DCM/Skeletal Myopathy

Other mutations resulting in DCM have been identified in the structural proteins that anchor the sarcomere to the cell membrane and the extracellular matrix such as dystrophin, δ-sarcoglycan, and desmin. These proteins stabilize the sarcomere and assist the transduction of force. Mutations in one of these genes often results in a skeletal myopathy in conjunction with a DCM. Whether the skeletal muscle or cardiac pathology predominates can depend on where within the gene the mutation occurs.

DCM/Conduction System Disease

Emery–Dreifuss muscular dystrophy (EDMD) is characterized by early contractures of elbows and Achilles tendons, slowly progressive muscle wasting, and a cardiomyopathy with conduction block. The disorder can be inherited in an autosomal dominant, autosomal recessive, or X-linked pattern. At least some of the autosomal dominant and autosomal recessive cases have been determined to be due to mutations in the lamin A/C gene, a gene that encodes for two proteins of the nuclear lamina, lamin A and lamin C. The

Table 19.5 Genes in which mutations result in dilated cardiomyopathy

DCM category	Gene
Sarcomeric	MYBPC3 (cardiac myosin-binding protein C)
	MYH7 (beta myosin heavy chain)
	MYH6 (alpha myosin heavy chain)
	TNNC1 (cardiac troponin C)
	TNNI3 (cardiac troponin I)
	TNNT2 (cardiac troponin T)
	ACTC1 (cardiac alpha actin)
	TCAP (telethonin)
	ACTN2 (alpha actinin-2)
	TTN (titin)
	MYPN (myopalladin)
	TPM1 (cardiac tropomyosin)
Calcium signaling	PLN (phospholamban)
Cytoskeleton/ extracellular matrix	LAMA4 (alpha4-Laminin)
	CSRP3 (cysteine- and glycine-rich protein 3)
	VCL (vinculin)
	DMD (dystrophin)
	FKTN (fukutin)
	DES (desmin)
	DSP (desmoplakin)
	DSG2 (desmoglein)
	SCN5A (cardiac sodium channel, alpha subunit)
	SGCD (sarcoglycan, delta)
	NEXN (nexin)
Nuclear envelope	LMNA (lamin A/C)
	SYNE1 (spectrin repeat containing, nuclear envelope 1)
	SYNE2 (spectrin repeat containing, nuclear envelope 2)
	PSEN1 (presenilin 1)
	PSEN2 (presenilin 2)
	TMPO (thymopoietin)
	EMD (emerin)
Transcriptional control	FOXD4 (forkhead box D4)
	EYA4 (homolog of eyes absent-4)
	GATAD1 (GATA zinc finger domain-containing protein-1)
	ANKRD1 (ankyrin repeat domain 1, cardiac)
Mitochondrial	DNAJC19 (DNAJ/HSP40 homolog, subfamily C, member 19)
	SDHA (succinate dehydrogenase complex, subunit A)
	TAZ (tafazzin)
	BAG3 (BCL2-associated athanogene 3)
Other	ABCC9 (ATP-binding cassette, subfamily C, member 9)
	PRDM16 (PR domain-containing protein-16)
	CYRAB (crystallin, alpha-B)
	RBM20 (RNA-binding motif protein-20)

X-linked cases have been determined to be due to mutations in emerin, another nuclear lamina-associated protein. In contrast to some of the other causes of DCM, patients with EDMD are at risk for ventricular arrhythmias and sudden death even with relatively mild levels of ventricular dysfunction. Risk factors for serious ventricular arrhythmias include (a) documented nonsustained ventricular tachycardia, (b) left ventricular ejection fraction <45 % at the time of presentation, (c) male sex, and (d) non-missense mutations (truncating or splicing mutations). Patients with two or more risk factors are at risk for serious ventricular arrhythmias and should be considered for ICD placement.

Diagnosis/Management

Affected individuals are defined as those that have a left ventricular ejection fraction of <50 % on echocardiography, a regional fractional shortening of <27 % on M-mode analysis or both in the presence of a left ventricular internal diastolic dimension of >2.7 cm/m^2 of body surface area in the absence of other common causes of DCM (coronary artery disease, myocarditis, and hypertension). Genetic testing is being increasingly used in the clinics for DCM, since the yield of testing has increased to >40 %. Genetic testing should be focused primarily on those with positive family histories for DCM. Screening of family members for genetic mutations causative of DCM allows an opportunity for closer and more frequent scrutiny for left ventricular dilation with potentially more prompt initiation of ACE inhibition and beta blockade. Treatment of preclinical DCM (mutation positive with normal LV size and function) with these medications has not yet been studied. Genetic testing may be most useful when there are signs of a recognizable condition such as EDMD, other associated skeletal myopathy, or conduction system disease. In general, risk stratification for ventricular arrhythmias is the same regardless of genetic basis of the DCM (i.e., ICD most strongly considered when LV EF <35 % or history of ventricular arrhythmias). An exception is EDMD, when an ICD might be considered with only mild LV systolic dysfunction.

Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy

ARVC, characterized by fatty infiltration and fibrosis of the right ventricle, is the most common cause of sudden cardiac death in Italy, accounting for 17 % of the cases, and an increasingly recognized cause in many other countries. It is primarily transmitted as an autosomal dominant disorder and molecular genetic studies on ARVC families have determined that at least 12 genes may lead to ARVC. ARVC has been characterized as a "disease of the desmosome" as at least 5 of the genes (desmocolin, desmoglein, desmoplakin, plakophilin, and plakoglobin) encode for components of the desmosome, a specific cell–cell adhesion complex that is abundant in the heart and the skin. Genetic testing in patients and families will identify a suspected causative mutation in approximately 50 %, nearly all of which occur in one of the desmosomal genes.

Mutations in *TMEM43* and *RYR2* are uncommon causes of ARVC. *RYR2* mutations more commonly lead to CPVT, which, like ARVC, is associated with exercise-induced ventricular arrhythmias but lacks the right ventricular structural and functional changes that characterize ARVC. Several other chromosomal loci have been identified genetic mapping but the responsible genes have not yet been identified. The number of genes potentially responsible makes ARVC a very heterogeneous disorder, making diagnosis and disease characterization difficult [32].

Diagnosis

ARVC can be extremely difficult to diagnose clinically, even in families where there is a definite family history of the disorder. Unfortunately, the first symptom is often sudden cardiac death. Surface ECG abnormalities suggestive of the disorder include inverted T waves in the right precordial leads and right ventricular arrhythmias (PVCs or ventricular tachycardia with an LBBB configuration). The arrhythmias may be exacerbated by adrenergic stimulation or exercise and may be induced by electrophysiologic stimulation. Biopsy evidence of right ventricular fatty infiltration and fibrosis can establish the diagnosis.

However, since the fibrosis usually begins in the RV free wall and then spreads to the interventricular septum where a biopsy would be performed, there are many "false negative" biopsies in patients with ARVC. The European Society of Cardiology and International Society and Federation of Cardiology established diagnostic criteria for ARVC that relies on structural and functional features of the right ventricle (based on MRI and echocardiographic assessment), fibrofatty infiltration of the right ventricle (based on biopsy), electrocardiographic evidence of depolarization and/or repolarization abnormalities, demonstration of ventricular arrhythmias of right ventricular origin, family history of confirmed ARVC, and genetic testing [33]. Major and minor criteria were established, the combination of which is used to categorize patients as having definite ARVC, borderline ARVC, or possible ARVC (Table 19.6). As with the other conditions covered in this chapter, genetic testing is becoming an increasingly important both for family screening and diagnosis. The presence of a clearly pathogenic gene mutation is included as a major criterion in the revised Task Force Criteria.

Table 19.6 Arrhythmogenic right ventricular cardiomyopathy (ARVC) diagnostic criteria (from [33])

Global or regional RV dysfunction and structural alterations
Major criteria
Regional RV akinesia, dyskinesia, or aneurysm (ECHO, MRI, or RV angiography)
And one of the following (measured at end-diastole)
– PLAX RVOT ≥32 mm (corrected for BSA ≥19 mm/m^2) (ECHO)
– PSAX RVOT ≥36 mm (corrected for BSA ≥21 mm/m^2) (ECHO)
– Fractional area change ≤33 % (ECHO)
– Ratio of RV end diastolic volume to BSA ≥110 mL/m^2 (male) or ≥100 mL/m^2 (female) (MRI)
– RV ejection fraction ≤40 % (MRI)
Minor criteria
Regional RV akinesia, dyskinesia, or aneurysm (ECHO, MRI, or RV angiography)
And one of the following (measured at end-diastole)
– PLAX RVOT 29–32 mm (corrected for BSA of 16–19 mm/m^2) (ECHO)
– PSAX RVOT 32–36 mm (corrected for BSA of 18–21 mm/m^2) (ECHO)
– Fractional area change of 33–40 % (ECHO)
– Ratio of RV end diastolic volume to BSA of 100–110 mL/m^2 (male) or 90–100 mL/m^2 (female) (MRI)
– RV ejection fraction of 40–45 % (MRI)
Tissue characterization of RV wall
Major criteria
Residual myocytes <60 % by morphometric analysis (or <50 % if estimated), with fibrous replacement of the RV
Free wall myocardium in ≥1 sample, with or without fatty replacement of tissue (endomyocardial biopsy)
Minor criteria
Residual myocytes 60–75 % by morphometric analysis (50–65 % if estimated), with fibrous replacement of the RV
Free wall myocardium in ≥1 sample, with or without fatty replacement of tissue (endomyocardial biopsy)
Repolarization abnormalities
Major criteria
Inverted T waves in right precordial leads (V_1, V_2, and V_3) or beyond in individuals >14 years of age (in the absence of complete right bundle-branch block QRS ≥120 ms) (ECG)
Minor criteria
Inverted T waves in right precordial leads (V_1 and V_2) in individuals >14 years of age (in the absence of complete right bundle-branch block QRS ≥120 ms) or in leads V_4, V_5, and V_6 (ECG)
Inverted T waves in leads V_1, V_2, V_3, and V_4 in individuals >14 years of age in the presence of complete right bundle-branch block (ECG)

(continued)

Table 19.6 (continued)

Depolarization/conduction abnormalities
Major criteria
Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V_1–V_3) (ECG)
Minor criteria
Late potentials by SAECG in ≥1 of 3 parameters (in the absence of a QRS duration of ≥110 ms on ECG)
Filtered QRS duration (fQRS) ≥114 ms (SAECG)
Duration of terminal QRS <40 μV (low-amplitude signal duration) ≥38 ms (SAECG)
Root-mean-square voltage of terminal 40 ms ≤20 μV (SAECG)
Terminal activation duration of QRS ≥55 ms measured from the nadir of the S wave to the end of the QRS, including R′, in V_1, V_2, or V_3, (in the absence of complete right bundle-branch block) (SAECG)
Arrhythmias
Major criteria
Nonsustained or sustained ventricular tachycardia of left bundle-branch morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)
Minor criteria
Nonsustained or sustained ventricular tachycardia of RV outflow configuration, left bundle-branch block morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis >500 ventricular extrasystoles per 24 h (Holter)
Family history
Major criteria
ARVC confirmed in a first-degree relative who meets current criteria
ARVC confirmed pathologically at autopsy or surgery in a first-degree relative
Identification of a pathogenic mutation categorized as associated or probably associated with ARVC in the patient under evaluation
Minor criteria
History of ARVC in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current criteria
Premature sudden death (<35 years of age) due to suspected ARVC in a first-degree relative
ARVC confirmed pathologically or by current criteria in second-degree relative
Diagnosis
Definite: 2 major or 1 major and 2 minor criteria or 4 minor from different categories
Borderline: 1 major and 1 minor or 3 minor criteria from different categories
Possible: 1 major or 2 minor criteria from different categories

PLAX parasternal long-axis view, *RVOT* RV outflow tract, *BSA* body surface area, *PSAX* parasternal short-axis view
Reprinted from Ackerman MJ, Priori SG, Willems S, Berul C, et.al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Heart Rhythm. 2011;8:1308–1339. With permission from Elsevier

Management

Potential therapeutic options for patients with symptomatic ARVC include pharmacologic suppression of the ventricular arrhythmias and electrophysiologic radiofrequency ablation of the arrhythmogenic focus. However, since these therapies are often not completely effective, an ICD should be strongly considered in those at significant risk. Prior cardiac arrest, ventricular fibrillation, and sustained VT are the strongest risk factors for sudden death. Syncope is also a very strong risk factor for sudden death, while family

history of sudden death due to ARVC is a weak risk factor [34]. Asymptomatic patients may not warrant an ICD, though the detection of nonsustained VT by Holter monitor identifies an intermediate risk group. Induction of VF by programmed ventricular stimulation has been reported to discriminate a high risk group, but had overall low predictive accuracy in the largest cohort published to date [34].

As with other autosomal dominant disorders, there is a 50 % chance of passing the disorder to each offspring, so all first-degree family members (offspring, siblings, and parents) of every ARVC patient should be screened and followed for the disorder (or its potential emergence).

Conduction System Abnormalities

Complete Heart Block

The cardiac homeobox gene *Nkx2.5* is a transcription factor involved in the development of many different cardiac myocyte lineages. It is not surprising therefore that mutations of *Nkx2.5* have been associated with a range of cardiovascular defects that include atrial septal defects, tetralogy of Fallot and other conotruncal defects, Ebstein's anomaly, and anomalous pulmonary venous return. Not infrequently, mutations of *Nkx2.5* will lead not only to structural cardiac abnormalities but also to progressive atrioventricular block [35]. Several families with structural heart disease, most commonly atrial septal defects and cardiac conduction abnormalities have been shown to have mutations of *Nkx2.5*. Mutations of *Nkx2.5* have also been noted in patients with isolated heart block and no structural heart defects. The exact cause of the conduction abnormality due to *Nkx2.5* mutation is not known, but it has been proposed to be due to abnormalities of connexin expression. Connexin 40 and 43, two cardiac gap junction proteins responsible for establishing the electrochemical link between myocytes, are markedly downregulated in mice that lack or have mutant *Nkx2.5* genes [36].

Kearns–Sayre Syndrome

Kearns–Sayre syndrome is a multisystem disorder characterized by external opthalmoplegia, pigmentary degeneration of the retina, and a DCM, often with progressive conduction defect. The syndrome was first recognized by Kearns in 1965 and involves deletions of mitochondrial DNA [37]. Most cases represent new deletions, but there are reports of familial transmission of the disorder. Depending on the exact size and location of the mitochondrial DNA deletion, patients may also exhibit weakness of facial, pharyngeal, trunk and extremity muscles, deafness, short stature, and markedly increased cerebrospinal fluid protein.

Progressive Cardiac Conduction Defect

Progressive cardiac conduction defect (PCCD), also called Lenegre or Lev disease, is one of the most common cardiac conduction disturbances in adults. It is characterized by progressive slowing of conduction through the His-Purkinje system leading to right or left bundle branch block and, ultimately, to complete atrioventricular block, syncope, and sudden death. The cardiac sodium channel (*SCN5A*) was demonstrated to be mutated in two families with PCCD. Those families did not demonstrate features of either LQTS or Brugada Syndrome, again demonstrating that different mutations of the same gene can cause very different clinical manifestations. Mutations of the *TRPM4* gene (a calcium-permeable cation channel strongly expressed in the atrium and His-Purkinje system) have also been noted in families and isolated patients with cardiac conduction defects [38].

Myotonic Dystrophy

Myotonic dystrophy is an autosomal dominant disorder which is due to nucleotide repeat expansions in one of two genes, *DMPK* and *ZNF9*. The disease manifestations correlate with the length

of the repeat expansion which tends to increase from one generation to the next (a process called anticipation). Mutations in either gene cause a very similar clinical presentation characterized by myotonia, muscular dystrophy, hypogonadism, frontal balding, and arrhythmias. The cardiac manifestations include progressive conduction block which may require pacemaker placement. ECG findings may include marked PR prolongation, QRS prolongation (including RBBB or bifascicular block), and complete heart block. In addition, affected patients can have atrial and ventricular arrhythmias, including atrial flutter, atrial fibrillation, and ventricular tachycardia. Sudden death can be an important complication of the condition and was determined to be the most common cause of death in a large cohort of patients with *DMPK*-type (DM1) myotonic dystrophy.

Screening of Families with a Heritable Disorder of the Cardiac Impulse

All first-degree relatives of any patient with a heritable disorder of the cardiac impulse should be examined, including, in some cases, provocative testing. While those family members that demonstrate the disorder only during provocative testing may not need treatment, depending on the nature of the disorder, they are important to identify because they will help indicate which other family members will require testing. When an affected relative is identified, then the first-degree relatives of that individual (parents and siblings) should be examined. This manner of cascade screening within the family should continue antegrade and retrograde through the family pedigree until all potentially affected individuals are identified. Guidance for screening of family members in cases of heritable disorders of the cardiac impulse is provided in several professional consensus statements (e.g., HFSA 2009 [39], 2011 ACCF/AHA Guideline for HCM [29], HRS/EHRA/APHRS 2013 Consensus for Inherited Arrhythmias [40]).

Current and Potential Uses of Genetic Testing

Genetic testing is being increasingly performed on patients with known or suspected LQTS, HCM, Brugada Syndrome, ARVC, and others to confirm the diagnosis, to track the condition through families, to characterize the range of genetic defects that can cause these clinical syndromes, and to help define their pathophysiology. In some cases, genetic information can help to guide treatment options. A role for genetic testing is recognized for patients with LQTS, in which responses to medical therapy differ by the type of LQTS. A table summarizing the role of genetic testing for these conditions [13] (can be found in the HRS/EHRA Expert Consensus Statement, Heart Rhythm, 2011). Importantly, genetic information is considered as a part of a comprehensive clinical evaluation and treatment decisions are not based on the result of a genetic test alone. In the future, genetic testing may be used to help guide gene-specific therapy in disorders with very similar clinical features but with different genetic defects that may lead to different clinical responses (such as LQTS type 3 which has a different risk profile and response to therapy).

Heritable disorders of the cardiac impulse have heterogeneous-genetic causes. Clinical genetic testing is available as multigame panels are structured according to a specific diagnosis. An accurate and specific clinical diagnosis can help direct testing to a specific gene or small set of genes. A more indefinite clinical diagnosis or a clinical diagnosis with a heterogeneous disease pathogenesis will require broader testing. Development of next-generation sequencing technology now allows for simultaneous testing of multiple genes at once. In fact, in cases where the clinical presentation is particularly unusual and/or traditional genetic tests have not yielded an answer, sequencing of all genes simultaneously can be performed (called whole exome sequencing). In addition to testing for gene mutations, in some cases it is relevant to consider testing for copy number changes of a specific

gene caused by small chromosomal deletions or duplications. Standard sequencing methodology may not detect copy number variants so other testing methods may be used [e.g., multiplex ligation-dependent probe amplification (MLPA), chromosomal microarray, or next-generation sequencing methods].

As noted above, selection of a genetic test is based on the suspected clinical diagnosis. The sensitivity of testing varies depending on the specific diagnosis and level of clinical suspicion. Sensitivity ranges from around 30 % in cases of familial BS to around 80 % in familial LQTS. Individuals with a suspected inherited condition, but negative family history, have a lower diagnostic yield with genetic testing. Initial testing in a family should always begin in a person who is clearly affected to determine whether a familial mutation can be identified. If there are multiple affected family members, it is preferable to perform initial testing on the person with the youngest onset or more severe presentation since (a) there can sometimes be more than one causative mutation present in a family and the most severely affected individual is the one most likely to inherit the most severe mutation or multiple mutations, and (b) for some disorders there may be clinical overlap with normal individuals or with individuals whose arrhythmia or cardiomyopathy is not due to a heritable condition. Genetic testing may not identify a specific genetic cause in an affected person and it is important to remember that this would not rule out a specific clinical diagnosis or mean that family members may not be at risk.

The identification of gene variants with uncertain clinical significance limits the utilization of genetic information in many cases. Interpretation of genetic test results can be complicated by a lack of information about tolerated variation in specific genes, and a lack of segregation data (linkage analysis in a family pedigree) or functional data (testing the function of the mutation—such as a specific ion channel) about specific gene variants. Unless a high level of certainty can be established for a particular gene variant, testing for the variant in family members with no clinical evidence of disease is not recommended. Over time, increased knowledge about the genetics of these conditions should allow reclassification of many variants. Interpretation of genetic test results can be challenging and referral to centers with expertise in cardiovascular genetics is suggested in order to maximize the likelihood of obtaining a genetic test result that is useful for a patient and family and for support with evolving genetic knowledge.

Once a specific genetic defect responsible for a patient's condition is known, then a specific, accurate test is available to distinguish those relatives who carry the same genetic risk from those who do not. The process of genetic testing in a patient and their family should include genetic counseling about the implications of testing for each individual. Referral to or consultation with personnel with expertise in the disorder can aid the diagnosis and management of these conditions and can help direct the appropriate genetic testing and the interpretation/communication of the results.

One important effect of the increased utilization of genetic testing and tracking of these disorders through families is the identification of individuals who have a genetic predisposition to a cardiac disorder (based on the inheritance of disease-causing mutation identified in a symptomatic family member) but have no clinical manifestation of the condition. These individuals (called genotype positive/phenotype negative) can present important therapeutic questions especially for those conditions where the clinical diagnosis can be challenging. In most cases, these individuals are at low immediate risk of any severe disease-related complication; however, they require careful and life-long follow-up. Medical treatment and lifestyle changes may be considered in certain cases, depending on the patient's and family's viewpoints (e.g., beta blocker therapy in LQTS, ACE inhibitor therapy in DCM, sports avoidance in LQTS, CPVT, and ARVC). Documented patient and family understanding of the risk for each condi-

tion may allow a more liberal and mutually agreed upon (often with legal consultation) consideration for athletic (even some competitive) and recreational activities.

An emerging challenge of modern genetic testing is the spurious sequence variants found in individuals undergoing genome-wide (usually exome sequencing) for a non-cardiac reason (e.g., to help identify the cause of developmental delay or other undiagnosed medical condition). Whole exome sequencing (sequencing of the patient's gene-encoding DNA) is increasingly utilized to determine the genetic etiology of medical conditions without a known cause. The current recommendations are, regardless of the reason for performing the exome sequencing, if a significant mutation is identified in a gene known to be responsible for sudden cardiac death, the mutation should be reported to the referring physician and patient/family. In the absence of symptoms or a family history, it can be difficult to determine if a particular DNA variant is capable of causing disease, especially if it has never been previously observed in either individuals with a cardiac condition or in normal controls. Referral to or consultation with a specialist with expertise in the clinical and genetic spectrum of the suspected cardiovascular condition will help to guide further evaluation.

Summary

Advances in the genetic characterization of a broad range of cardiac rhythm disorders has advanced our understanding of disease pathogenesis and assisted in establishing diagnoses and tracking procedures through families to identify at-risk family members. The ability to identify individuals at risk for serious cardiac arrhythmias before they have events that result in sudden death holds great potential for substantially reducing the morbidity and mortality associated with these conditions. In the future, the identification of specific genetic defects may lead to novel and mutation-specific treatment.

References

1. Jervell A, Lange-Nielsen F. Congenital deaf-mutism, functional heart disease with prolongation of the Q-T interval and sudden death. Am Heart J. 1957;54:59–68.
2. Romano C, Gemme G. Pongiglione R [rare cardiac arrythmias of the pediatric age. Ii. Syncopal attacks due to paroxysmal ventricular fibrillation. (Presentation of 1st case in Italian pediatric literature)]. Clin Pediatr (Bologna). 1963;45:656–83.
3. Ward OC. A new familial cardiac syndrome in children. J Ir Med Assoc. 1964;54:103–6.
4. Tester DJ, Will ML, Haglund CM, Ackerman MJ. Compendium of cardiac channel mutations in 541 consecutive unrelated patients referred for long QT syndrome genetic testing. Heart Rhythm. 2005;2:507–17.
5. Zareba W, Moss AJ, Sheu G, Kaufman ES, et al. Location of mutation in the KCNQ1 and phenotypic presentation of long QT syndrome. J Cardiovasc Electrophysiol. 2003;14:1149–53.
6. Barsheshet A, Goldenberg I, O-Uchi J, Moss AJ, et al. Mutations in cytoplasmic loops of the KCNQ1 channel and the risk of life-threatening events: implications for mutation-specific response to beta-blocker therapy in type 1 long-QT syndrome. Circulation. 2012;125:1988–96.
7. Sanguinetti MC, Jiang C, Curran ME, Keating MT. A mechanistic link between an inherited and an acquired cardiac arrhythmia: Herg encodes the IKr potassium channel. Cell. 1995;81:299–307.
8. Yang Y, Liang B, Liu J, Li J, Grunnet M, et al. Identification of a Kir3.4 mutation in congenital long QT syndrome. Am J Hum Genet. 2010;86:872–80.
9. Remme CA. Cardiac sodium channelopathy associated with SCN5a mutations: electrophysiological, molecular and genetic aspects. J Physiol. 2013;591(Pt 17):4099–116.
10. Splawski I, Timothy KW, Decher N, Kumar P. Severe arrhythmia disorder caused by cardiac L-type calcium channel mutations. Proc Natl Acad Sci U S A. 2005;102:8089–96, discussion 8086–8.
11. Schwartz PJ, Moss AJ, Vincent GM, Crampton RS. Diagnostic criteria for the long QT syndrome. An update. Circulation. 1993;88:782–4.
12. Schwartz PJ, Crotti L. QTc behavior during exercise and genetic testing for the long-QT syndrome. Circulation. 2011;124:2181–4.
13. Ackerman MJ, Priori SG, Willems S, Berul C, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Heart Rhythm. 2011;8:1308–39.
14. Chockalingam P, Crotti L, Girardengo G, Johnson JN, et al. Not all beta-blockers are equal in the management of long QT syndrome types 1 and 2: higher recurrence of events under metoprolol. J Am Coll Cardiol. 2012;60:2092–9.

15. Calvillo L, Spazzolini C, Vullo E, Insolia R, et al. Propranolol prevents life-threatening arrhythmias in LQT3 transgenic mice: implications for the clinical management of LQT3 patients. Heart Rhythm. 2014;11:126–32.
16. Schwartz PJ, Priori SG, Locati EH, Napolitano C, et al. Long QT syndrome patients with mutations of the SCN5a and HERG genes have differential responses to Na+ channel blockade and to increases in heart rate. Implications for gene-specific therapy. Circulation. 1995;92:3381–6.
17. Brugada J, Brugada R, Brugada P. Right bundle-branch block and ST-segment elevation in leads V1 through V3: a marker for sudden death in patients without demonstrable structural heart disease. Circulation. 1998;97:457–60.
18. Wilde AA, Antzelevitch C, Borggrefe M, Brugada J, et al. Proposed diagnostic criteria for the Brugada syndrome: consensus report. Circulation. 2002;106:2514–9.
19. Gussak I, Antzelevitch C. Early repolarization syndrome: clinical characteristics and possible cellular and ionic mechanisms. J Electrocardiol. 2000;33:299–309.
20. Schimpf R, Wolpert C, Gaita F, Giustetto C, Borggrefe M. Short QT syndrome. Cardiovasc Res. 2005;67:357–66.
21. Haissaguerre M, Derval N, Sacher F, Jesel L, et al. Sudden cardiac arrest associated with early repolarization. N Engl J Med. 2008;358:2016–23.
22. Adler A, Rosso R, Viskin D, Halkin A, et al. What do we know about the "malignant form" of early repolarization? J Am Coll Cardiol. 2013;62:863–8.
23. Uberoi A, Jain NA, Perez M, Weinkopff A, et al. Early repolarization in an ambulatory clinical population. Circulation. 2011;124:2208–14.
24. Gourraud JB, Le Scouarnec S, Sacher F, Chatel S, et al. Identification of large families in early repolarization syndrome. J Am Coll Cardiol. 2013;61:164–72.
25. Priori SG, Napolitano C, Tiso N, Memmi M, et al. Mutations in the cardiac ryanodine receptor gene (hRyR2) underlie catecholaminergic polymorphic ventricular tachycardia. Circulation. 2001;103:196–200.
26. Delannoy E, Sacher F, Maury P, Mabo P, et al. Cardiac characteristics and long-term outcome in Andersen-Tawil syndrome patients related to KCNJ2 mutation. Europace. 2013;15:1805–11.
27. Maron BJ, Maron MS, Semsarian C. Genetics of hypertrophic cardiomyopathy after 20 years: clinical perspectives. J Am Coll Cardiol. 2012;60:705–15.
28. Maron BJ, Pelliccia A, Spirito P. Cardiac disease in young trained athletes. Insights into methods for distinguishing athlete's heart from structural heart disease, with particular emphasis on hypertrophic cardiomyopathy. Circulation. 1995;91:1596–601.
29. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2011;124:2761–96.
30. Towbin JA, Bowles NE. Molecular genetics of left ventricular dysfunction. Curr Mol Med. 2001;1:81–90.
31. McNally EM, Golbus JR, Puckelwartz MJ. Genetic mutations and mechanisms in dilated cardiomyopathy. J Clin Invest. 2013;123:19–26.
32. Fontaine G, Fontaliran F, Hebert JL, Chemla D, et al. Arrhythmogenic right ventricular dysplasia. Annu Rev Med. 1999;50:17–35.
33. Marcus FI, McKenna WJ, Sherrill D, Basso C, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. Circulation. 2010;121:1533–41.
34. Corrado D, Calkins H, Link MS, Leoni L, et al. Prophylactic implantable defibrillator in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia and no prior ventricular fibrillation or sustained ventricular tachycardia. Circulation. 2010;122:1144–52.
35. Schott JJ, Benson DW, Basson CT, Pease W, et al. Congenital heart disease caused by mutations in the transcription factor nkx2-5. Science. 1998;281:108–11.
36. Kasahara H, Wakimoto H, Liu M, Maguire CT, et al. Progressive atrioventricular conduction defects and heart failure in mice expressing a mutant Csx/Nkx2.5 homeoprotein. J Clin Invest. 2001;108:189–201.
37. Kearns TP. External ophthalmoplegia, pigmentary degeneration of the retina, and cardiomyopathy: a newly recognized syndrome. Trans Am Ophthalmol Soc. 1965;63:559–625.
38. Kruse M, Schulze-Bahr E, Corfield V, Beckmann A, et al. Impaired endocytosis of the ion channel TRPM4 is associated with human progressive familial heart block type I. J Clin Invest. 2009;119:2737–44.
39. Hershberger RE, Lindenfeld J, Mestroni L, Seidman CE, et al. Genetic evaluation of cardiomyopathy—a Heart Failure Society of America practice guideline. J Card Fail. 2009;15:83–97.
40. Priori SG, Wilde AA, Horie M, Cho Y, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: 2013. Heart Rhythm. 2013;10:1932–63.

Fetal Arrhythmias

20

Elizabeth Vickers Saarel and Carlen G. Fifer

Fetal Electrophysiology

Fetal Heart Rate: Normal Sinus

The sinus node (SN), formed by the 7th week of gestation, generates the normal fetal rhythm. Important normal characteristics of fetal heart rate (FHR) include baseline rate, beat-to-beat variability, and periodic changes (transient decelerations or accelerations). Baseline rate is significantly higher early in gestation than at term. At a normal gestation of 20 weeks, the FHR is close to 160 bpm; by the mid-second trimester, baseline FHR ranges from 110 to 160 bpm; and at normal term, it is near 120 bpm. Although during gestation the autonomic sympathetic input has the predominant role on the fetal SN and heart rate, there is a gradual decline in baseline FHR modulated by a progressive parasympathetic (vagal) influence. If atropine is administered (to the mother), FHR reverts to the higher baseline of 160 bpm.

Beat-to-beat or short-term variability refers to changes in FHR (cycle length) between successive cardiac impulses. Periodic changes in FHR or long-term variability refer to changes in FHR between successive time intervals (seconds to minutes). A decrease in heart rate variability may herald fetal distress. Short- and long-term heart rate variability tends to be reduced or exaggerated in a parallel fashion, and there is no clear evidence that distinguishing between the two entities is clinically helpful.

A baseline FHR less than 110 bpm arising from the SN with normal conduction has been defined as sinus bradycardia. A baseline FHR greater than 160 bpm generated and propagated in a normal manner has been defined as sinus tachycardia. As in infants and children, sinus arrhythmia, evidenced by heart rate variability, is normal in the fetus.

Overview: Fetal Arrhythmia

Consideration of fetal arrhythmia is usually triggered by auscultation of a fetal irregular heart rate, bradycardia, or tachycardia during a prenatal visit. Abnormal FHR occurs in 0.2–2 % of pregnancies, with 10 % of these having significant arrhythmia. If the arrhythmia is sustained at a markedly fast or slow rate, or if associated with

E.V. Saarel, M.D. (✉)
Department of Pediatrics, University of Utah, Primary Children's Hospital, 100 N. Mario Capecchi Dr., Ste 1500, Salt Lake City, UT 84113, USA
e-mail: tess.saarel@utah.edu

C.G. Fifer, M.D.
Pediatric Cardiology, The University of Michigan Congenital Heart Center, Department of Pediatrics and Communicable Diseases, University of Michigan, Ann Arbor, MI, USA
e-mail: cago@med.umich.edu

M. Dick, II (ed.), *Clinical Cardiac Electrophysiology in the Young*,
DOI 10.1007/978-1-4939-2739-5_20

structural congenital heart disease, fetal well-being may be compromised. A less common presentation of fetal arrhythmia is hydrops fetalis—generalized edema that represents an end-stage fetal response to significant stress and signifies end-stage fetal heart failure. Moreover, several maternal conditions are associated with fetal arrhythmia, making maternal assessment essential in all cases of abnormal FHR.

The suspicion of a fetal arrhythmia calls for a prompt detailed fetal echocardiogram by an experienced pediatric cardiology prenatal echocardiographic team. Although referral patterns vary by institution, abnormal FHR prompts roughly 25 % of prenatal cardiology referrals. In addition to the fetal echocardiographic evaluation of the fetal heart rhythm, cardiac anatomy, and function during these visits, it is important to obtain a thorough maternal and family history. Up to 50 % of fetuses with arrhythmia (particularly those with heart block) have associated structural cardiac malformations.

Optimal patient evaluation and treatment requires a medical team approach, consisting of obstetricians, maternal–fetal medicine specialists, and pediatric cardiologists with fetal echocardiographic expertise, social workers, and nurses that work closely with pediatric electrophysiologists to care for affected fetuses. Other relevant ad hoc members may include neonatologists, anesthesiologists, geneticists, and endocrinologists. If significant structural heart disease is identified, pediatric cardiothoracic surgeons should be alerted before delivery and can assist with consultation. A team approach streamlines patient care, allows more accurate prognosis, enhances communication between family and the healthcare team, and improves medical outcomes.

Techniques for Diagnosis of Fetal Arrhythmia

Electrocardiography

Several noninvasive techniques are available for fetal arrhythmia analysis. In contrast to postnatal evaluation, electrocardiography is not practicable for diagnosis. Although fetal electrocardiograms can be recorded from electrodes placed on the maternal abdomen, signal detection is not reliable due to a low signal-to-noise ratio. Fetal cardiac electrical activity is low in amplitude, on the order of about 10 μV, 1/10th the amplitude of maternal cardiac electrical activity. In addition, maternal abdominal wall musculature adds low amplitude noise to the electrocardiogram, obscuring fetal myocardial electrical activity.

Magnetocardiography

A magnetocardiogram records the magnetic field generated by cardiac electrical activity. This technique has been applied to the fetus for a number of years. There have been multiple reports from several institutions describing magnetocardiograms that detail fetal cardiac electrical activity, including P-wave and QRS inscription, similar to a postnatal body surface electrocardiogram. Magnetocardiographic equipment is complex and large, requires lead shielding and dedicated space, is very expensive (>1 M dollars), and is not yet commercially available; therefore widespread use is not available. Fetal magnetocardiography would undoubtedly become more widespread if technical refinements decreased cost and increased accessibility.

Echocardiography

Currently echocardiography is the only widely available and technically practical method for the diagnosis of fetal arrhythmias. Evaluation for an arrhythmia begins by examining the timing of and relationship between the fetal atrial and ventricular contractions, best accomplished through M-mode and Doppler echocardiography.

M-mode echocardiography displays motion of the cardiac tissue with respect to time. An M-mode tracing of the fetal heart chambers is obtained by placing the cursor line across both the atrial and ventricular walls simultaneously (Fig. 20.1). The display shows movement of both chamber walls with time, reflecting atrial and ventricular systole.

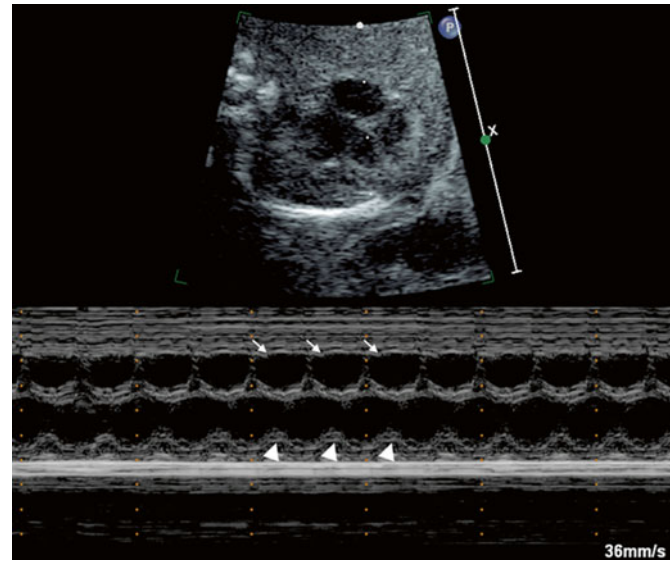


Fig. 20.1 M-mode echocardiogram from fetus in sinus rhythm. *Upper image* demonstrates beam position through the atrium and ventricle. *Small arrows* mark atrial contractions, and *arrowheads* mark ventricular contraction. Note 1:1 ratio of atrial to ventricular contractions

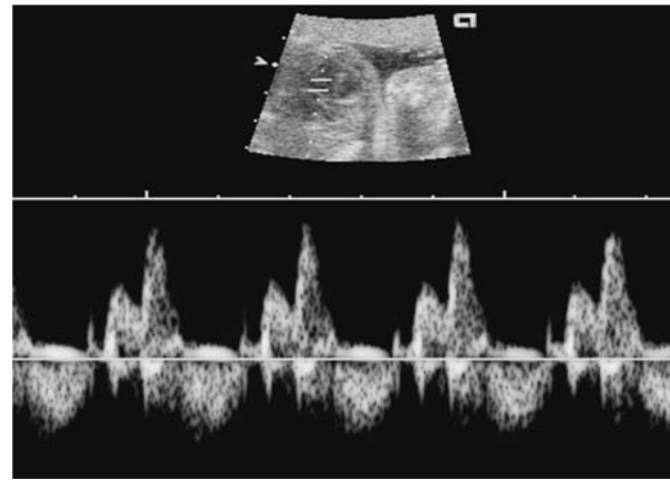


Fig. 20.2 Doppler echocardiogram from fetus in sinus rhythm. *Upper image* demonstrates beam position in the ventricle. Note 1:1 relationship of normal mitral inflow (E- and A-waves above baseline) and normal aortic outflow (below baseline)

Many factors influence the quality of the M-mode tracing. First, alignment with both fetal heart chambers can be challenging, and several different probe positions and angles should be attempted to optimize the tracing. Second, a clearer tracing will be obtained where chamber walls have the greatest excursion with contraction, such as the atrial appendage, or lateral ventricular wall.

Doppler echocardiography utilizes spectral blood flow patterns during systole and diastole as representation of atrial and ventricular contraction. The standard method is to obtain an apical four-chamber image of the fetal heart, with the pulsed Doppler cursor positioned with the gate spanning the mitral inflow as well as the aortic outflow (Fig. 20.2). The mitral "A" wave represents atrial contraction, and the systolic aortic wave represents ventricular contraction. An alternate spectral Doppler approach is to position the pulsed Doppler cursor across the SVC and ascending aorta simultaneously (Fig. 20.4a). Brief reversal of flow in the SVC during atrial systole denotes atrial contraction, with the forward systolic flow

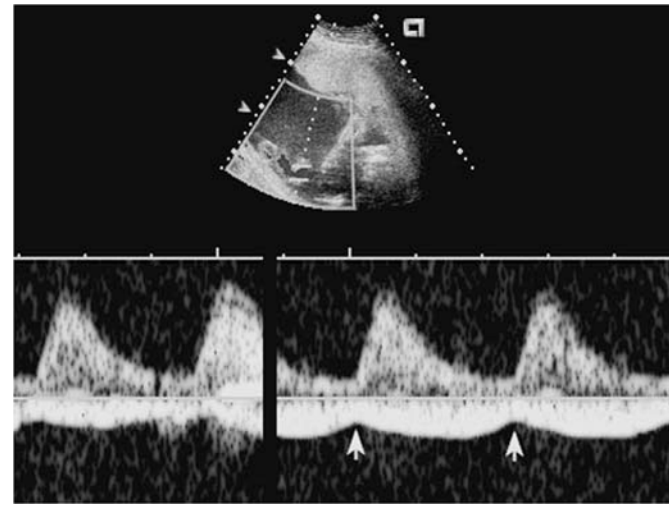


Fig. 20.3 Pulsed spectral Doppler tracing from the umbilical vein in a fetus with hydrops fetalis. *Upper panel* demonstrates gate position in the umbilical vein. *Arrows* indicate pulsations with atrial systole, consistent with high atrial pressure

wave in the aorta showing ventricular systole. From any of these methods, the mechanical PR interval can be measured from the onset of the atrial contraction to the onset of ventricular contraction, however depicted.

New techniques including tissue velocity imaging, with creation of a "fetal kinetocardiogram," as well as strain rate imaging have recently been described. Tissue velocity and strain rate imaging may significantly enhance current fetal echocardiographic diagnostic capabilities.

In addition to determination of the arrhythmia mechanism, echocardiographic evaluation of the fetus should incorporate assessment for any hemodynamic and anatomic abnormality. Both tachyarrhythmias and bradyarrhythmias can cause fetal heart failure, and ultimately hydrops fetalis. Complete evaluation for fetal heart failure includes assessment of heart size, ventricular systolic function, atrioventricular valve incompetence, venous Doppler patterns (increased reversal with atrial contraction) including hepatic vein, ductus venosus and umbilical venous Doppler (Fig. 20.3), and documentation of presence and size of pleural, pericardial, and abdominal effusions. All of these indices require ongoing assessment for progression by serial echocardiographic studies as well as obstetrical evaluation of fetal well-being during the mother's pregnancy.

Specific Fetal Arrhythmias

Extrasystoles

Extrasystoles account for 60–90 % of fetal arrhythmia. Ectopic beats may arise in the atria, junctional tissue, or ventricle. Supraventricular ectopy (SVE) is most common. Ventricular ectopy (VE) comprises fewer than 10 % of fetal extrasystole. Frequency of ectopic beats in the normal fetus has not been well established; however, the rate of extrasystoles in healthy premature infants is 20–30 %, with a slightly lower frequency in term infants.

Ectopic beats present as an irregular FHR. As in older patients, very early occurring SVE results in blocked atrioventricular conduction, either complete or partial (in the form of bundle branch block with aberrant depolarization). Hence, SVE can present as bradycardia. The majority of fetuses with premature beats are healthy, and the ectopy resolves over time.

Although the vast majority of fetuses with extrasystoles have a structurally normal heart, SVE and VE can be associated with anatomic congenital heart disease, cardiac tumors, and fetal genetic abnormalities such as Trisomy 18. In addition, SVE precedes supraventricular tachycardia (SVT) in a number of cases. Thus, all

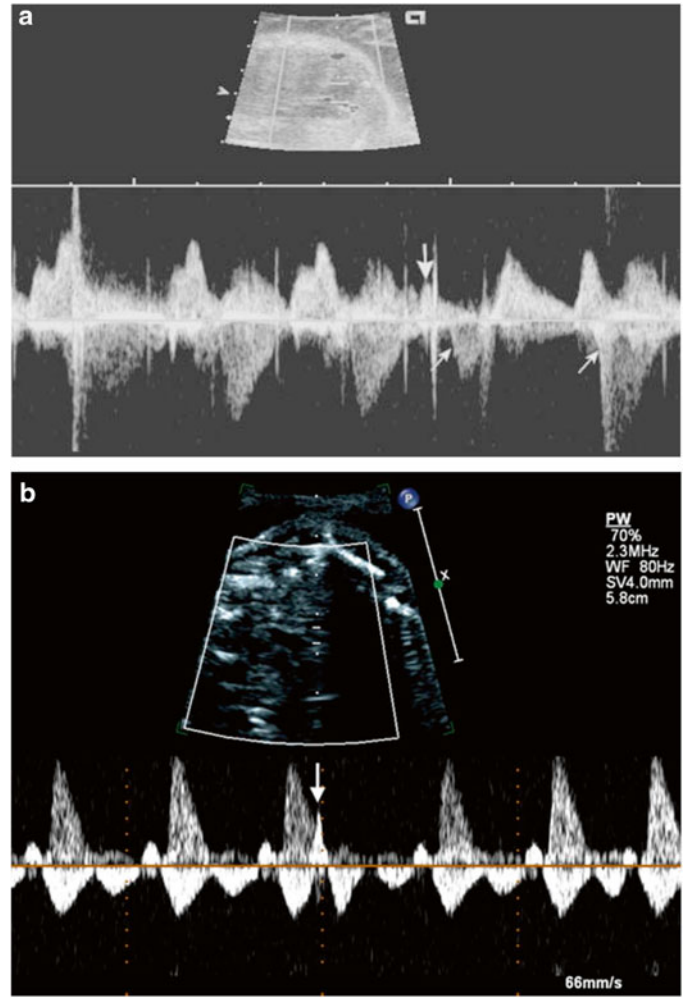


Fig. 20.4 Doppler echocardiogram from fetuses with SVE. (**a**) Doppler cursor through mitral inflow and aortic outflow. The *large arrow* marks the premature atrial contraction. The *first small arrow* marks the diminished aortic outflow volume with the SVE, and the *second small arrow* shows the increased aortic outflow volume during the post-extrasystolic contraction. Note the prolonged diastolic time interval following the SVE. (**b**) Doppler cursor through SVC and ascending aorta with blocked SVE. Note the atrial contractions represented by reversal in SVC above the baseline. The *large arrow* marks the premature atrial contraction, with no aortic outflow following the blocked SVE

fetuses with frequent premature beats should have more frequent FHR monitoring until delivery, or until resolution of the ectopy has been sustained.

Supraventricular Ectopy

Premature atrial and junctional depolarizations occur most often as single beats. Diagnosis is made with a combination of Doppler and M-mode echocardiography. With M-mode, simultaneous atrial and ventricular recording is performed, demonstrating a normal sequence of A–V contractions and an early atrial contraction wave. The atrial beat after the premature contraction demonstrates an incomplete compensatory pause.

Doppler sampling during normal rhythm displays at the junction of the mitral inflow and left ventricular outflow tract an E-wave (early, rapid ventricular filling) followed by an A-wave (atrial contraction with active ventricular filling) and ventricular systole (with semilunar valve outflow). SVE will cause early active ventricular filling (A-wave), obscuring part of the early ventricular filling (E-wave) tracing with subsequent early ventricular systole (Fig. 20.4a). In cases of fully blocked SVE, no ventricular systole will follow the premature atrial contraction. The post-extrasystolic contraction will demonstrate a prolonged filling (diastolic) time interval. Doppler sampling of the SVC/ascending aorta will demonstrate an early flow reversal wave in

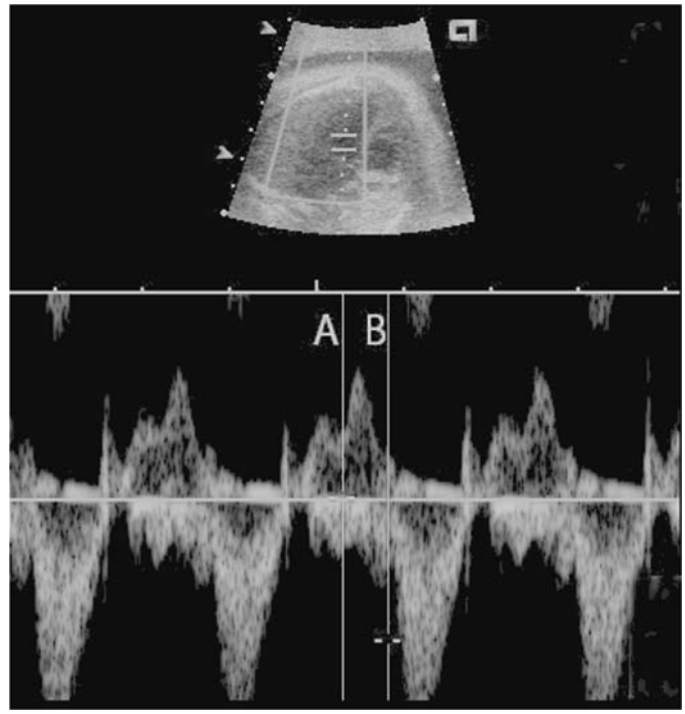


Fig. 20.5 Pulsed spectral Doppler through the mitral inflow and aortic outflow in a normal fetus, demonstrating mechanical PR interval measurement. E- and A-wave components of mitral inflow are above the baseline, whereas the aortic outflow signal is below the baseline. Calipers measure from the beginning of the A-wave (*line A*) to the beginning of the aortic outflow signal (*line B*)

the IVC during early atrial contraction, and lack of systolic wave in the aorta with a blocked SVE (Fig. 20.4b).

The fetal PR interval can be measured using a gated pulsed Doppler technique. Premature atrial contractions should demonstrate a normal or prolonged PR interval (if slow conduction occurs, Fig. 20.5).

The prognosis is favorable for the majority of fetuses with SVE. In addition to the conditions mentioned earlier, fetal SVE can be associated with maternal drug use or hyperthyroidism. For patients with associated maternal disease, structural congenital heart disease, tumors, or sustained tachyarrhythmias, the prognosis correlates with the associated condition. No treatment is indicated for isolated fetal SVE.

Ventricular Ectopy

M-mode echocardiography may demonstrate subtle distortion of normal ventricular contraction due to aberrant muscle conduction (Fig. 20.6). Also, a complete atrial compensatory pause is seen after most premature ventricular depolarizations. Doppler ultrasound demonstrates a characteristic AV valve inflow pattern with decreased diastolic antegrade flow. Marked retrograde flow in the IVC is seen during atrial contraction.

In addition to conditions mentioned previously, VE has been associated with fetal myocarditis, cardiomyopathy, long QT syndrome, and complete AV block with a slow escape rate. Premature ventricular contractions also occur in healthy fetuses as well as those with structural or functional abnormalities. Prognosis is dependent on the associated abnormality if present. No treatment of isolated premature ventricular contractions is indicated.

Tachyarrhythmias

Most cases of elevated FHR are due to sinus tachycardia. SVT and atrial flutter are less common and atrial fibrillation and ventricular tachycardia (VT) are rare. In one large single-center retrospective

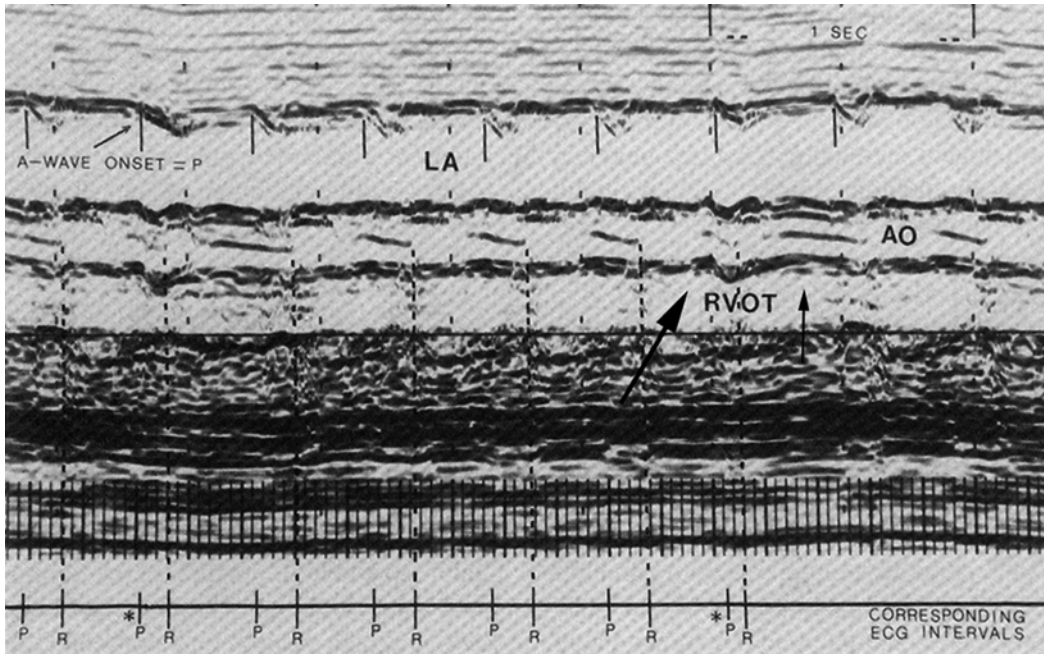


Fig. 20.6 M-mode recording from a 36-week fetus with its back toward the transducer presenting an inverted view of the heart. Premature aortic valve opening (*large arrow*) can be clearly seen to be followed by atrial wall contraction but with no variation in P–P interval (A-wave interval), giving a compensatory pause (*small arrow*, allowing diagnosis of ventricular premature beat). *LA* left atrium, *AO* aorta, *RVOT* right ventricular outflow tract (5 MHz transducer) [Reprinted from Crowley DC, Dick M, Rosenthal A, et al. Two-dimensional and M-mode echocardiographic evaluation of fetal arrhythmia. Clinical Cardiology 1985;8:1–10. With permission from John Wiley & Sons]

report, SVT and atrial flutter together accounted for 12 % of fetal arrhythmia diagnoses.

Sinus Tachycardia

Fetal sinus rates rarely exceed 210 bpm, whereas fetal SVT rarely falls below 200 bpm. In sinus tachycardia, fetal M-mode echocardiography shows synchronous atrioventricular contractions. Sinus arrhythmia with varying cycle lengths may be present. Certain tachyarrhythmias that tend toward longer and more variable cycle lengths, such as persistent junctional reciprocating tachycardia and ectopic atrial tachycardia, are difficult to differentiate from sinus tachycardia using current ultrasound techniques.

In sinus tachycardia, Doppler tracing of atrioventricular valve inflow often demonstrates amalgamation of the E- and A-waves. The mechanical PR interval, as measured by gated Doppler ultrasound, should be constant and of normal duration.

Fetal sinus tachycardia is most often due to an underlying fetal or maternal stress such as drug exposure, hyperthyroidism, myocarditis, infection, hypoxia, or other causes of fetal distress. Treatment is directed at the primary cause of sinus tachycardia.

Supraventricular Tachycardia

Fetal SVT can be sustained or intermittent. Typical rates are 240–250 bpm, with a range from 200 to 320 bpm. Detection is most common after 15 weeks gestation, although earlier presentation has been reported. Fetal tolerance of SVT depends on the duration and rate of arrhythmia; intermittent and slower (≤260 bpm) rhythms are

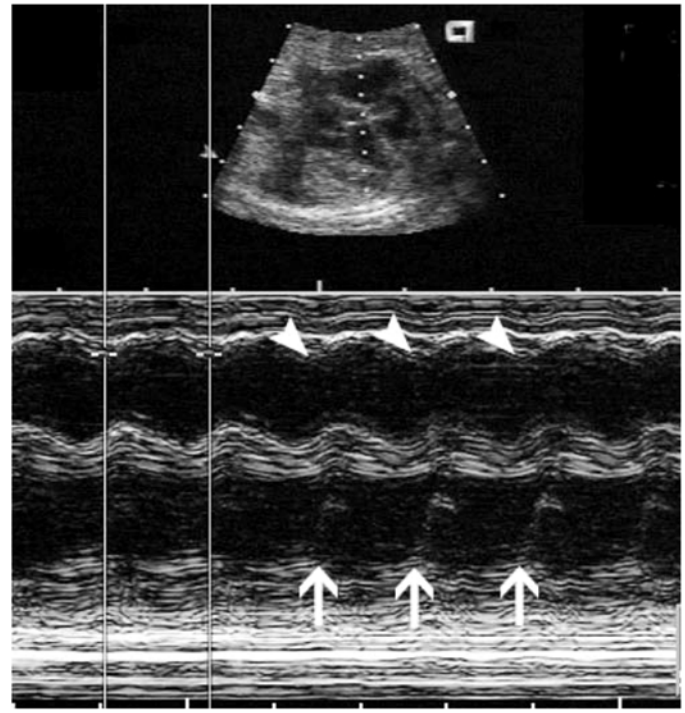


Fig. 20.7 M-mode echocardiogram from a fetus with supraventricular tachycardia. *Arrowheads* indicate atrial contractions, and *large arrows* indicate ventricular contractions. Note the 1:1 relationship of atrial and ventricular contractions. The calipers measure 243 ms between successive ventricular contractions, indicating a heart rate of approximately 250 bpm

less malignant. Mechanisms of SVT in the fetus are similar to those in neonates.

Atrioventricular reentry tachycardia, utilizing an accessory connection between the atria and ventricles, is most common when patients are examined postpartum. AV node reentry tachycardia, ectopic atrial foci, persistent junctional reciprocating tachycardias, and junctional tachycardias are less common. Although an abrupt onset and termination of the tachycardia, if observed during the fetal echocardiogram, would support the diagnosis of a reentry tachycardia, it is not possible to distinguish with certainty between these entities using current ultrasound techniques.

Diagnosis of SVT is consistent with an M-mode tracing through the atria and ventricle showing sequential 1:1 contractions at retrograde time intervals of 80–120 ms (Fig. 20.7). Similarly, Doppler ultrasound of ventricular inflow and outflow demonstrates sequential atrial and ventricular contractions. If measurable by gated Doppler, the PR interval will be constant in reentry tachyarrhythmias.

Treatment is predicated on the effect of the tachyarrhythmia on fetal well-being. If SVT is intermittent and late in pregnancy, fetal health is usually not jeopardized. In such patients, prognosis is generally excellent, and no treatment is indicated. If tachycardia is sustained at fast rates (>260 bpm), prenatal morbidity and even demise may be as high as 25 %. It is therefore important to frequently (every 3–5 days) assess all fetal patients who remain in SVT. Both obstetricians and cardiologists should be involved in the care of patients. Of note, patients with structural congenital heart disease are at greater risk for tachycardia-associated complications. One of the earliest signs of fetal compromise is an exaggerated systemic venous (inferior vena cava or hepatic) flow reversal (greater than 30 %) on the venous Doppler. This may progress to reversal in the ductus venosus, and eventual notching in the umbilical venous tracing in more advanced fetal heart failure. Other signs of fetal distress include cardiomegaly, decreased ventricular systolic function, atrioventricular valve regurgitation, and hydrops

fetalis (pericardial effusion, pleural effusion, ascites, and/or skin edema).

Fetal treatment options include early delivery, transplacental (maternal) pharmacotherapy, or direct fetal pharmacotherapy. In addition, there is one report of fetal SVT conversion using transabdominal umbilical cord compression. Although not described in humans, there has been a single report of fetal SVT conversion using fetal transesophageal pacing in fetal sheep. Labor induction with delivery is the treatment of choice for term and near-term pregnancies with sustained fetal tachycardia or evidence of fetal compromise.

Although controversy exists, it is generally agreed upon that transplacental digoxin should be the first-line treatment of choice in pre-term pregnancies with sustained tachycardia without fetal compromise (Table 20.1). Digoxin treatment is safe and often effective. The drug can be administered to the mother in oral or IV form at relatively high maternal doses (up to 1 mg q day orally) in order to achieve an adequate level in the fetus. SVT cessation is achieved in approximately three-quarters of cases with maternal oral therapy. If conversion has not been achieved after 2 weeks of therapy with adequate maternal digoxin levels (1–2 ng/mL), a second antiarrhythmic agent may be added. Flecainide, along with other drug choices are reasonable (Table 20.1). When there are signs of fetal compromise, it is reasonable to begin dual therapy immediately (digoxin along with a second-line agent such as flecainide). Several studies in the literature as well as clinical experience have suggested that transplacental transfer of digoxin is limited in the hydropic fetus, whereas placental transfer of flecainide and sotalol are not as affected. Cardioversion with flecainide is generally achieved within 3–4 days. Other medications with reported efficacy include procainamide, verapamil, quinidine, amiodarone, or sotalol. There have been no definitive large, randomized published studies comparing fetal antiarrhythmic agents. Success with sotalol or the combination of digoxin with amiodarone has been described.

In case of significant fetal distress or rapid, sustained SVT where prompt treatment is essential, antiarrhythmic agents can be given directly to the fetus through umbilical vein, intramuscular, or intra-peritoneal administration; however, the latter two routes are unreliable due to unpredictable drug absorption. Umbilical cordocentesis carries a significant risk in the compromised fetus, and therefore the risk/benefit ratio must be carefully weighed and discussed with the maternal–fetal medicine specialists performing the procedure.

Atrial Flutter

Atrial flutter accounts for approximately one-third of non-sinus fetal tachyarrhythmias. Atrial rates vary from 400 to 550 bpm. As in postnatal patients, ventricular response is variable, but ventricular rates are greater than 200 bpm in a majority of untreated fetuses. Variations in atrioventricular conduction frequently lead to an irregular FHR. When conduction is consistent, there is greater elevation of the FHR and 2:1 atrioventricular block is most common. Although atrial flutter is usually sustained, intermittent flutter does occur.

The diagnosis of prenatal atrial flutter is confirmed by characteristic echocardiographic findings. M-mode tracings through the atria and ventricle demonstrate regular, fast atrial contractions with variable atrioventricular block, and thus less frequent ventricular depolarizations (Fig. 20.8). Atrial rate is calculated with measurement of the time interval between successive atrial contractions (the mechanical P–P interval), and ventricular rate is calculated with measurement of the time interval between successive ventricular contractions (the mechanical R–R interval). Using this information, the degree of atrioventricular block can be determined. Doppler echocardiography of ventricular inflow or outflow can also be used to calculate the ventricular response rate.

Cardiac lesions reported in association with fetal atrial flutter include atrial septal defect, Ebstein's malformation of the tricuspid valve, atrioventricular septal defect with atrioventricular valve regurgitation, right ventricular outflow

Table 20.1 Pharmacotherapy for treatment of fetal tachyarrhythmia

Drug	Route of administration	Starting dosage	Maximum dosage	SVT	AFL	VT	Maternal/fetal adverse effects
Adenosine	Fetal IV	0.1 mg/kg	0.2 mg/kg	Yes	No	No	Tachycardia commonly recurs requiring additional agent
Amiodarone	Maternal PO (fetal IV; fetal IM; fetal IP)	800–1,200 mg QD X 2–7 days load; then 200–800 mg QD maint.	800 mg QD maint.	Yes	No	Yes	Maternal or fetal hypothyroidism (common); bradycardia (common); IUGR; premature delivery; hepatotoxicity; monitor maternal QTc
Digoxin	Maternal PO; maternal IV (fetal IV; fetal IM; fetal IP)	PO: 0.25–1.5 mg load, then 0.125–0.25 mg PO BID-TID maint. IV: 1–2 mg load (may repeat), then 0.5 mg QD maint.	PO: 0.25 mg BID-TID maint. IV: 1.0 mg QD maint. Goal level 1.0–2.0 ng/mL	Yes[a]	Yes[a]	No	Maternal overdose; heart block; arrhythmia induction
Flecainide	Maternal PO	Start at 100 mg BID, advance to 200 mg BID-TID	Total daily dose not to exceed 600 mg; maternal blood level not to exceed 1,000 ng/mL, goal 200–1,000 ng/mL	Yes[b]	Yes	Yes	Dizziness; headache; paraesthesias; tremors; visual disturbances; nausea; vomiting; flushing; possible neonatal conjugated hyperbilirubinemia or neonatal prolonged QT; monitor maternal QRS duration
Lidocaine	Maternal IV	1 mg/kg load over 2 min, mayw repeat in 10–15 min × 2 (alternate 20–50 mg/kg/min)	3–5 mg/kg within first hour	No	No	Yes	Hypotension: asystole; seizures; respiratory arrest
Mexiletine	Maternal PO	200 mg PO q8 h; therapeutic level 0.5–2 mg/L	Max 100–200 mg/day; maternal blood level not to exceed 2 mg/L	No	No	Yes	Atrial and ventricular arrhythmias; bradycardia; hypotension; confusion; dizziness; nervousness; tremor; ataxia; numbness of fingers or toes; weakness; blurred vision; tinnitus; nausea; hepatotoxicity; monitor maternal QTc

Procainamide	Maternal IV; maternal PO	IV: 100 mg load over 2 min., then 1–6 mg/min PO: 1 g load then 200–500 mg q3–6 h	IV: 6 mg/min PO: 500 mg q3 h; plasma levels 4–10 mg/L	Yes	Yes	Yes	Hypotension; nausea; vomiting; blood dyscrasias; lupus-like syndrome; rash; confusion; prolonged QT; monitor maternal QRS duration and QTc
Quinidine	Maternal PO (sulfate form); maternal IV (gluconate form)	PO: test dose 200 mg; 800–1,000 mg load, then 200 mg q4–6 h maint. IV: 0.3 mg/kg/min (infuse <10 mg/min)	PO: 600 mg q4–6 h IV: 0.5 mg/kg/min (infuse < 10 mg/min)	Yes	No	Yes	Idiosyncratic reaction (prolonged QRS > 0.02 s); prolonged QT; torsades de pointes; nausea; vomiting; diarrhea; hypotension; tinnitus' confusion; blood dyscrasias; rash; heart block; monitor maternal QRS duration and QTc
Sotalol[c]	Maternal PO	80 mg BID	320 mg BID	Yes	Yes[b]	Yes[a]	Myocardial depression; arrhythmia induction; torsades de pointes; monitor maternal QTc
Verapamil	Maternal IV	5–10 mg over 3–5 min (alternate 0.005 mg/kg/min)	May give second 10 mg dose after 30 min	Yes	Yes	Yes	Myocardial depression; bradycardia; heart block; hepatotoxicity

[a]Recommended first-line agent
[b]Recommended second-line agent
[c]Use with extreme caution if hydrops fetalis is present

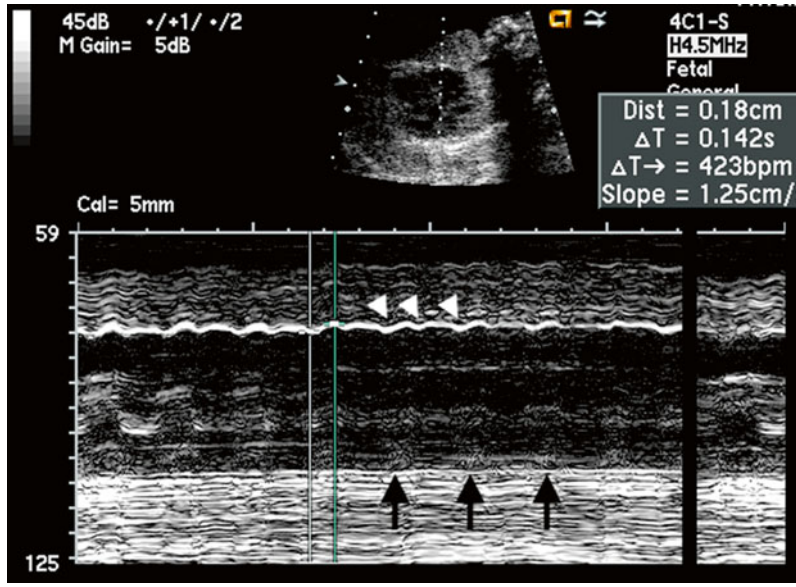


Fig. 20.8 M-mode echocardiogram from fetus with atrial flutter. *White arrowheads* mark atrial flutter waves (423 bpm), and *large dark arrows* mark less frequent ventricular contractions (~210 bpm), demonstrating 2:1 conduction

tract obstruction with tricuspid regurgitation, hypoplastic left heart syndrome, cardiomyopathy, and endocardial fibroelastosis. As in older patients, it is likely that atrial dilatation due to a variety of causes will predispose to atrial flutter.

Treatment of fetal atrial flutter is similar to that of SVT (Table 20.1). Unfortunately, atrial flutter tends to be less responsive to drug therapy in terms of cardioversion rates, as compared to other forms of reentry-mediated SVT in the fetus. Therefore, it is reasonable to advance to a second-line agent earlier in the treatment course, either as single agent therapy or in addition to digoxin. In atrial flutter, sotalol appears to have a slightly higher conversion rate as a second-line antiarrhythmic agent, in contrast to flecainide in SVT, though both have been reported to be effective. Fortunately, postnatal treatment of atrial flutter, via transesophageal overdrive pacing or DC cardioversion, is highly successful and postnatal recurrence is exceedingly rare.

Figure 20.9 outlines one step by step approach to the treatment of supraventricular tachyarrhythmias in the fetus, and highlights the slight differences in treatment of reentrant SVT and atrial flutter.

Other Forms of Supraventricular Tachyarrhythmias

Other reported forms of fetal SVT include atrial fibrillation, junctional ectopic tachycardia, persistent junctional tachycardia, and chaotic atrial tachycardia. Prenatal definitive diagnosis of these arrhythmias is not possible using current echocardiographic techniques. All published reports of these unusual fetal arrhythmias rely on postnatal confirmation with an inferred mechanism of the prenatal arrhythmia. Currently, patients thought to have these fetal tachyarrhythmias are evaluated and treated in the same manner as fetuses with other forms of SVT.

Ventricular Tachyarrhythmias

Ventricular tachyarrhythmias (VT) occur in fetal patients, but as in infants and children are quite rare (Fig. 20.10). In many reports, observed VT rates are slow, raising the possibility of an accelerated ventricular rhythm. Slow VT is usually well tolerated, and the prognosis for this group of patients is generally good. In contrast, fast

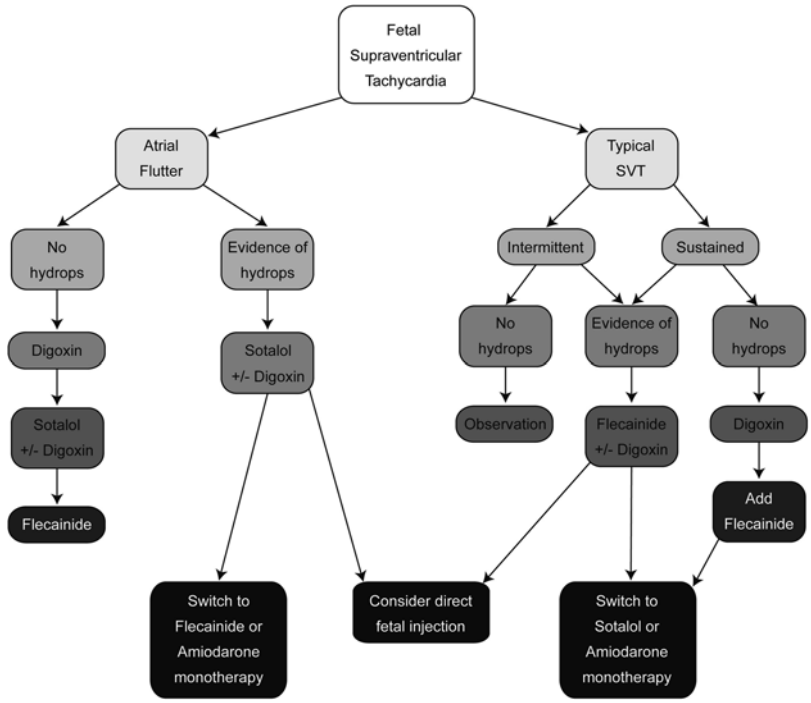


Fig. 20.9 Fetal supraventricular tachycardia treatment strategy flow chart

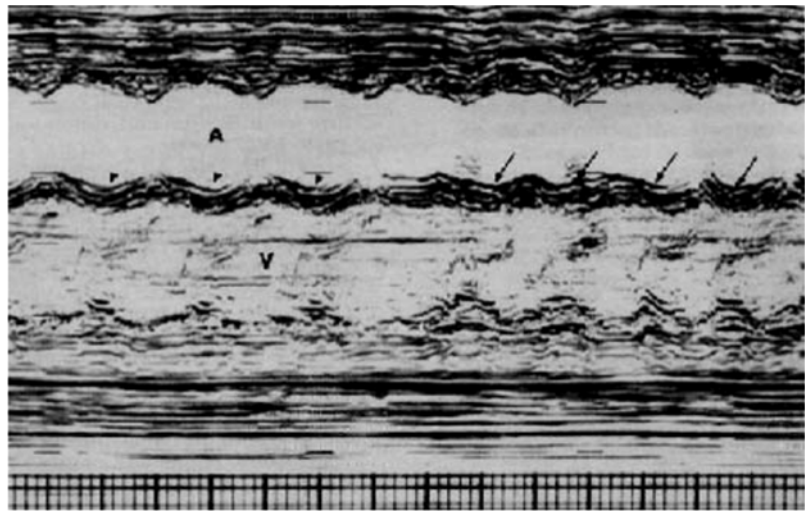


Fig. 20.10 M-mode echocardiogram from fetus with intermittent ventricular tachycardia. When the fetus is in ventricular tachycardia (*large arrows*), the ventricular (V) rate exceeds the atrial (A) rate. When the fetus is in sinus rhythm (*small arrows*), the rates of the ventricular and atrial contractions are the same

ventricular tachycardia is poorly tolerated in the fetus, and the prognosis is extremely poor.

M-mode and Doppler echocardiography show atrioventricular dissociation with a competing atrial sinus rhythm in all types of ventricular arrhythmia. Recently, Doppler tissue imaging has been reported useful for detection of atrioventricular dissociation. In addition, atrioventricular block has been reported in conjunction with VT.

When treatment of a ventricular arrhythmia is indicated due to fetal compromise or persistence of a fast ventricular rate, the choice of pharmacologic agent is based on postnatal infant data. Multiple fetal VT case reports have been published, using an assortment of antiarrhythmic agents (all of which have been previously mentioned for treatment of SVT and are listed in Table 20.1). Given the known prenatal and postnatal treatment options, sotalol is reasonable for first-line treatment for prenatal VT. In addition, the use of transplacental and trans-cordal lidocaine has been suggested for refractory cases.

Bradyarrhythmias

Sinus bradycardia (<120 bpm) is the most common cause of slow FHR. Other sources of fetal bradycardia include blocked premature atrial contractions (previously discussed) and atrioventricular block (AV block). The incidence of congenital complete heart block is approximately 1:20,000 live newborns. Fetal incidence of complete heart block is likely higher, given that some cases may result in fetal demise. AV block comprises about 5 % of fetal arrhythmias.

Sinus Bradycardia

Transient fetal sinus bradycardia is very common, and is likely related to episodic parasympathetic stimulation. Sinus pauses have been documented in the healthy fetus, and prenatal sinus arrhythmia is common. Sequential atrioventricular 1:1 conduction can be observed with M-mode ultrasound through both the atria and ventricles when the fetus is in sinus rhythm (Fig. 20.1). Doppler tracing of atrioventricular valve inflow shows normal E- and A-wave configuration and size, and Doppler of ventricular outflow will be of normal velocity in patients with normal cardiovascular anatomy (Fig. 20.2). The mechanical PR interval, measured with gated Doppler ultrasound, will be of normal duration and constant length from beat to beat (Fig. 20.5).

As with sinus tachycardia, sustained sinus bradycardia is most often a reaction to noxious extracardiac fetal stimuli with no underlying primary cardiac etiology. In addition, maternal medications, such as beta-blockers, may cross the placenta and decrease the FHR. In cases of severe hydrops fetalis, sinus bradycardia is a terminal rhythm.

Rarely, fetal sinus bradycardia can be a manifestation of prenatal long QT syndrome. The diagnosis of long QT syndrome cannot be proven definitively with ultrasound. Definitive diagnosis requires documentation of cardiac electrical activity with techniques such as magnetocardiography, or perhaps in the future with a trans-abdominal or fetal transesophageal ECG recording. A presumptive diagnosis can be made in cases of fetal bradycardia with a strong family history of long QT syndrome.

Treatment of sinus bradycardia is directed at correction of the underlying cause of fetal distress. If thorough investigation shows that the fetus is healthy and careful family history is negative, sinus bradycardia is most probably a normal variant and no treatment is indicated.

Atrioventricular Conduction Block

First-Degree Atrioventricular Block

First-degree AV block may or may not be associated with bradycardia. Diagnosis of first-degree AV block requires measurement of the fetal PR interval (Fig. 20.5). M-mode and Doppler studies will show 1:1 atrioventricular conduction and normal Doppler tracings. The mechanical PR interval will be prolonged, and can be estimated using gated Doppler ultrasound. The upper limit of normal for the fetal mechanical PR interval has been reported to be 130 ± 20 ms. Measurement

of the true electrical PR interval requires magnetocardiography or another method of fetal ECG recording.

Second- and Third-Degree Atrioventricular Block

Second- and third-degree AV block are the most common sustained fetal bradyarrhythmias. In half of cases, the fetus has associated structural congenital heart disease, most commonly atrioventricular discordance or endocardial cushion defects (especially in conjunction with heterotaxy syndromes). In the majority of patients, a normal atrial rate is present. Ventricular rate may range from low normal to marked bradycardia (45–70 bpm).

In the majority of cases of fetal AV block and normal cardiac anatomy, maternal autoimmune disease is present. Systemic lupus erythematous (SLE) is the most commonly identified maternal condition, but other comorbid maternal disorders, such as Sjögren's syndrome, rheumatoid arthritis, Raynaud's syndrome, and mixed connective tissue disease, have been reported. Often the fetal conduction disturbance is the first presentation of maternal disease. Nearly all cases occur in the presence of circulating maternal Ro (Sjögren's syndrome A/SSA), and La (Sjögren's syndrome B/SSB) autoantibodies. Of note, not all fetuses exposed to anti-Ro/SSA and anti-La/SSB antibodies will develop heart block.

In cases of anti-Ro/SSA and anti-La/SSB associated fetal conduction disorders, antibodies are directed against cellular ribonucleoproteins and are deposited in the fetal cardiac tissue, instigating an inflammatory response. Inflammation leads to eventual fibrosis, calcification, and disruption of the normal cardiac conduction tissue (see Chap. 15). Severely affected fetuses will develop signs of generalized myocardial dysfunction and hydrops fetalis. In some severe cases, cardiac muscle and other fetal tissues are directly affected by local antibody deposition.

Second- and third-degree AV block typically present with fetal bradycardia in the second or third trimester. Although the overall rate of fetal demise is approximately 50 % with complete AV block, most fetuses with normal cardiac anatomy do well. The presence of structural congenital heart disease, sinus bradycardia (atrial rate less than 120 bpm), or extreme bradycardia (ventricular rate less than 55 bpm), are indicators of poor prognosis. In addition, evidence of hydrops fetalis, including pericardial effusion and progressive slowing of the atrial rate, indicate impending fetal demise.

Progression from second- to third-degree AV block in the fetus has been documented. Moreover, return of sinus rhythm following second-degree AV block has been documented in a few case reports in fetuses exposed to maternal autoantibodies, after treatment with transplacental corticosteroids. There has been no published report of resolution of persistent fetal third-degree AV block with or without treatment.

Diagnosis of second-degree AV block can be made using M-mode through the atria and ventricles. This technique demonstrates normally timed atrial contractions with intermittent AV block and missing ventricular contractions (Fig. 20.11a). If fetal mechanical PR intervals are measured using gated Doppler, they show progressive lengthening in Mobitz type I second-degree AV block. Constant PR intervals with intermittent loss of AV conduction will be seen in Mobitz type II AV block. Doppler of ventricular inflow will show abnormal E- and A-wave morphology during AV block.

The fetal echocardiographic diagnosis of third-degree (complete) AV block can be made with M-mode or Doppler techniques showing complete atrioventricular discordance (Fig. 20.11b). Atrial rate is calculated after measurement of the time interval between successive atrial contractions (the mechanical P–P interval). Similarly, ventricular rate is calculated after measurement of the time interval between successive ventricular contractions (the mechanical R–R interval). All affected fetuses show some degree of ventricular dilatation.

Treatment goals for prenatal second- and third-degree AV block are focused on enhanced patient survival and continuance of pregnancy until near term. To date, ongoing prospective randomized trials with traditional anti-inflammatory medications, including IVIG and corticosteroids

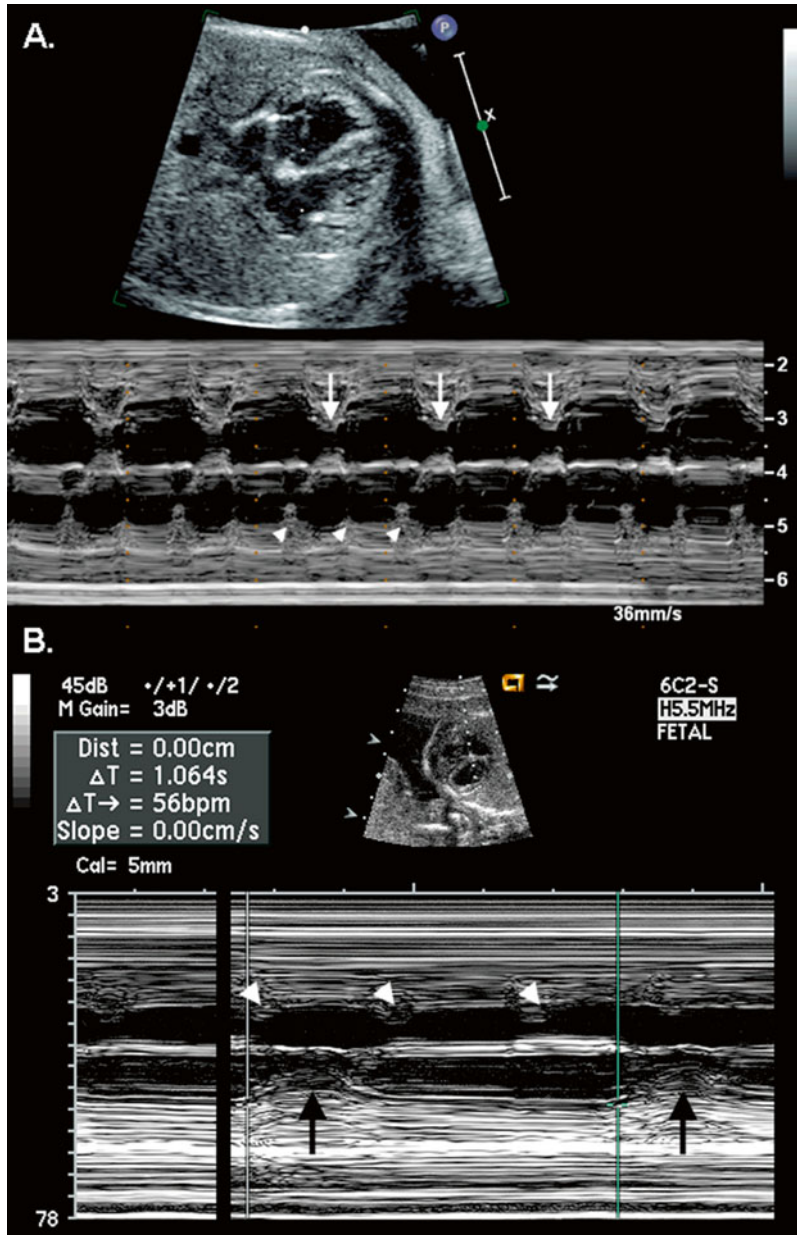


Fig. 20.11 M-mode echocardiogram from fetus with second-degree Mobitz type II (**a**) and third-degree (**b**) heart block. (**a**) *White arrowheads* mark atrial contractions and *large arrows* mark ventricular contractions. Note 2:1 relationship in (**a**) and complete A–V dissociation in (**b**)

have not convincingly prevented progression to complete AV block in the fetus exposed to maternal anti-Ro/SSA and anti-La/SSB antibodies. Further trials of newer medications, such as hydroxychloroquine, are ongoing and may prove more efficacious for prevention or improvement in progression to complete heart block and congestive heart failure.

As with other fetal arrhythmias, current treatment is determined by the effect of bradycardia on fetal well-being. If the fetus is otherwise healthy, showing no signs of distress, no

treatment is indicated. Delivery of fetuses with heart block should be performed at a facility capable of emergency postpartum pacing, even if the fetus appears to be healthy prior to birth. Maternal prenatal empiric treatment with corticosteroids can be considered if there is evidence of recent prolongation of AV conduction or progression to AV block, though no clear data documenting benefit exists.

Other attempted treatment for fetal heart block and heart failure has included transplacental pharmacotherapy with digoxin, furosemide, and beta-receptor agonists. All of these drugs are of limited efficacy, and all have potential side effects. If the fetal ventricular rate is below 55 bpm, atrial rate is decreasing or below 120 bpm, or if signs of hydrops fetalis are present, early delivery is indicated in anticipation of postpartum pacing. Postnatal initial pacing is best accomplished through temporary transvenous or epicardial leads. External pacing, if used at all, should be transient given the frequency of severe burns in neonates. Aggressive treatment of postpartum pericardial, pleural, and ascitic effusions should be performed. Standard methods of intensive systemic support, including mechanical ventilation, inotropic therapy, and correction of acidosis, should be utilized, as for any neonate with cardiac failure. Experimental in utero pacing has been described, but to date there has been no published report of an infant survivor.

Future Directions

Current understanding of the fetal conduction system development and function is limited, but recently published molecular genetic studies have considerably advanced our knowledge. Molecular cardiology will eventually deliver a large impact on fetal diagnosis and therapeutics. Tissue velocity imaging, strain rate imaging, magnetocardiography, and fetal transesophageal electrocardiography are emerging techniques for improving fetal arrhythmia diagnosis.

Finally, present treatment of fetal arrhythmias is imperfect. There is no consensus regarding fetal antiarrhythmic pharmacotherapy, largely due to the orphan status of the disease, and consequently, insufficient data. Moreover, all antiarrhythmic agents currently available have significant side effects for the fetus or mother. Multicenter trials addressing treatment of fetal arrhythmias are essential for refining and improving the management of these challenging patients.

Suggested Reading

Anderson RH, Becker AE, Wenink AC, Janse MJ. The development of the cardiac specialized tissue. In: Wellens HJJ, Lie KI, Janse MJ, editors. The conduction system of the heart. Philadelphia: Lea and Febiger; 1976. p. 3–28.

Buyon JP, Waltuck J, Kleinman C, Copel J. In utero identification and therapy of congenital heart block. Lupus. 1995;4(2):116–21.

Cotton JL. Identification of fetal atrial flutter by Doppler tissue imaging. Circulation. 2001;104(10):1206–7.

Crowley DC, Dick M, Rayburn WF, Rosenthal A. Two-dimensional and M-mode echocardiographic evaluation of fetal arrhythmia. Clin Cardiol. 1985; 8(1):1–10.

Ferrer PL. Fetal arrhythmias. In: Deal BJ, Wolff GS, Gelband H, editors. Current concepts in diagnosis and management of arrhythmias in infants and children. Armonk: Futura; 1998. p. 17–63.

Friedman AH, Copel JA, Kleinman CS. Fetal echocardiography and fetal cardiology: indications, diagnosis and management. Semin Perinatol. 1993;17(2):76–88.

Friedman DM, Kim MY, Copel JA, et al. Prospective evaluation of fetuses with autoimmune-associated congenital heart block followed in the PR Interval and Dexamethasone Evaluation (PRIDE) Study. Am J Cardiol. 2009;103(8):1102.

Glickstein JS, Buyon J, Friedman D. Pulsed Doppler echocardiographic assessment of the fetal PR interval. Am J Cardiol. 2000;86(2):236–9.

Hosono T, Kawamata K, Chiba Y, et al. Prenatal diagnosis of long QT syndrome using magnetocardiography: a case report and review of the literature. Prenat Diagn. 2002;22(3):198–200.

Jaeggi ET, Carvalho JS, De Groot E, et al. Comparison of transplacental treatment of fetal supraventricular tachyarrhythmias with digoxin, flecainide, and sotalol: results of a nonrandomized multicenter study. Circulation. 2011;124(16):1747–54.

Kohl T, Kirchoff PF, Gogarten W, et al. Fetoscopic transesophageal electrocardiography and stimulation in fetal sheep: a minimally invasive approach aimed at diagnosis and termination of therapy-refractory supraventricular tachycardias in human fetuses. Circulation. 1999;100(7):772–6.

Machado MV, Tynan MJ, Curry PV, Allan LD. Fetal complete heart block. Br Heart J. 1988;60(6):512–5.

Macones GA, Hankins GD, Spong CY, et al. The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring: update on definitions, interpretation, and research guidelines. Obstet Gynecol. 2008;112(3): 661–6.

Martin Jr CB, Nijhuis JG, Weijer AA. Correction of fetal supraventricular tachycardia by compression of the umbilical cord: report of a case. Am J Obstet Gynecol. 1984;150(3):324–6.

Michaelsson M, Engle MA. Congenital complete heart block: an international study of the natural history. Cardiovasc Clin. 1972;4(3):85–101.

Mitchell JL, Cuneo BF, Etheridge SP, et al. Fetal heart rate predictors of long QT syndrome. Circulation. 2012;126(23):2688.

Oudijjk MA, Michon MM, Kleinman CS, et al. Sotalol in the treatment of fetal dysrhythmias. Circulation. 2000;101(23):2371.

Oudijk MA, Ruskamp JM, Ververs FF, et al. Treatment of fetal tachycardia with sotalol: transplacental pharmacokinetics and pharmacodynamics. J Am Coll Cardiol. 2003;42(4):765.

Peters M, Crowe J, Piéri JF, et al. Monitoring the fetal heart non-invasively: a review of methods. J Perinat Med. 2001;29(5):408–16.

Pisoni CN, Brucato A, Ruffatti A, et al. Failure of intravenous immunoglobulin to prevent congenital heart block: findings of a multicenter, prospective, observational study. Arthritis Rheum. 2010;62(4):1147.

Quartero HW, Stinstra JG, Goldbach EG, et al. Clinical implications of fetal magnetocardiography. Ultrasound Obstet Gynecol. 2002;20(2):142–53.

Rein AJ, Levine JC, Nir A. Use of high-frame rate imaging and Doppler tissue echocardiography in the diagnosis of fetal ventricular tachycardia. J Am Soc Echocardiogr. 2001;14(2):149–51.

Rein AJJT, O'Donnell C, Geva T, et al. Use of tissue velocity imaging in the diagnosis of fetal cardiac arrhythmias. Circulation. 2002;106(14):1827–33.

Rein AJJT, Perles Z, Nir A, et al. Strain rate imaging is superior to tissue velocity imaging for measuring atrioventricular time interval in the fetus. J Am Coll Cardiol. 2003;41(6 Suppl A):494A.

Rentschler S, Zander J, Meyers K, et al. Neuroregulin-1 promotes formation of the murine cardiac conduction system. Proc Natl Acad Sci U S A. 2002;99(16):10464–9.

Schmidt KG, Ulmer HE, Silverman NH, et al. Perinatal outcome of fetal complete atrioventricular block: a multicenter experience. J Am Coll Cardiol. 1991;17(6): 1360–6.

Serwer GA, Vermilion RP, Snider AR, et al. Prognostic indicators for fetuses with in utero diagnosed complete heart block. Circulation. 1988;78(Suppl II):396.

Shenker L. Fetal cardiac arrhythmias. Obstet Gynecol Surv. 1979;34(8):561–72.

Strasburger JF. Fetal arrhythmias. Prog Pediatr Cardiol. 2000;11(1):1–17.

Strasburger JF, Cuneo BF, Michon MM, et al. Amiodarone therapy for drug-refractory fetal tachycardia. Circulation. 2004;109(3):375.

Van Engelen AD, Weijtens O, Brenner JI, et al. Management outcome and follow-up of fetal tachycardia. J Am Coll Cardiol. 1994;24:1371–5.

Veille JC, Covtiz W. Fetal cardiovascular hemodynamics in the presence of complete atrioventricular block. Am J Obstet Gynecol. 1994;170(5 Pt 1):1258–62.

Wong SF, Chau KT, Ho LC. Fetal bradycardia in the first trimester: an unusual presentation of atrial extrasystoles. Prenat Diagn. 2002;22(11):976–8.

Sudden Cardiac Death in the Young

21

Christopher B. Stefanelli, Aarti Dalal, and Robert Campbell

Sudden cardiac death (SCD) can be defined as biologic death resulting from abrupt, unexpected cardiovascular collapse from which an individual does not recover or regain consciousness. Sudden arbitrarily implies an interval of less than 1 h from the onset of symptoms to the time of death. Sudden cardiac arrest (SCA) can be defined as abrupt cardiovascular collapse requiring resuscitation and connotes a high recurrence risk in the majority of cases. These definitions are imperfect and under most circumstances SCA and SCD imply confirmed or presumed ventricular fibrillation. Sudden arrhythmic and non-arrhythmic cardiac death in infants, children, and adolescents can occur in the absence or presence of known heart disease or other underlying medical condition, but the former is much more common. Patients with repaired congenital heart disease are at greater risk for SCD than healthy individuals and require continued surveillance as they advance in age, particularly beyond the second and third decade of life. Table 21.1 links symptoms to the major potential cardiac causes of SCD.

The incidence of SCD in young persons is unknown and difficult to accurately estimate because of its rarity, marked differences among different age groups, and inconsistent reporting methods. Published retrospective and prospective studies estimate annual incidence rates of SCD in children and adolescents ranging from 0.8 to 6.2 per 100,000 patient-years. The risk is many times higher under 1 year of age. An estimated 4,000–8,000 children (≤18 years) in the USA die from SCD annually, primarily victims of sudden infant death syndrome (SIDS). SCD in young athletes is rare. Reported incidence rates in the USA range from 1 to 10 per 100,000 patient-years. The risk in male athletes is two- to fivefold higher than females. There also appears to be a higher incidence in African-American athletes in comparison to white athletes.

In most cases of SCD in children and young competitive athletes, a specific, often congenital associated underlying cardiovascular abnormality, cardiovascular can be determined (Tables 21.2 and 21.3). The causes vary with age. In older children and young athletes in the USA, hypertrophic cardiomyopathy (HCM) is the most frequent cause. In infants, coronary

C.B. Stefanelli, M.D.
Department of Pediatric Cardiology, Hawaii Permanente Medical Group, Honolulu, HI, USA

A. Dalal, D.O. (✉) • R. Campbell, M.D.
Sibley Heart Center, Children's Healthcare of Atlanta, Department of Pediatrics, Emory University School of Medicine, Atlanta, GA, USA
e-mail: dalala@kidsheart.com; campbellr@kidsheart.com

M. Dick, II (ed.), *Clinical Cardiac Electrophysiology in the Young*,
DOI 10.1007/978-1-4939-2739-5_21

Table 21.1 Signs and symptoms that may suggest cardiac and non-cardiac disorders

Sign/symptom	Differential diagnosis for SCA
Respiratory symptoms	Hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy, left ventricular outflow tract obstruction (LVOTO), restrictive or LV noncompaction cardiomyopathy
Chest pain	HCM, coronary anomalies, LVOTO, aortic rupture/Marfan, mitral valve prolapse (MVP), postoperative congenital heart disease
Seizures, syncope	Long QT syndrome, WPW, Brugada syndrome, CPVT, short QT syndrome, complete heart block
Palpitations	HCM, DCM, myocarditis, MVP, arrhythmogenic right ventricular cardiomyopathy, LQTS, WPW, Brugada syndrome
Drowning/near drowning	LQTS, CPVT
SIDS	LQTS, Brugada syndrome, CPVT, SQTS
Febrile seizures	Brugada syndrome
Congenital deafness	LQTS

Table 21.2 Causes of SCD in the young

Condition	Types
Myocardial abnormalities	Myocarditis
Primary electrical disorders	Primary ventricular tachycardia/fibrillation
	Complete heart block, congenital and surgical
	Commotio cordis
Coronary abnormalities	Anomalous origins from the aorta
	Anomalous origins from the pulmonary artery
	Ostial abnormality
	Myocardial bridge (tunneled)
	Kawasaki disease
	Transplant vasculopathy
	Cocaine vasospasm
	Coronary atherosclerosis
Congenital heart disease	Aortic stenosis
	Coarctation of the aorta
	Tetralogy of Fallot (including variants)
	Transposition of the great arteries
	Atrioventricular discordance
	Hypoplastic left heart syndrome
	Single ventricle/Fontan
	Ebstein's anomaly
	Truncus arteriosus
Miscellaneous	Primary pulmonary hypertension
	Marfan's syndrome
	Eisenmenger syndrome
	Mitral valve prolapse

Table 21.3 Genetic causes of sudden cardiac death

Hypertrophic cardiomyopathy
Arrhythmogenic right ventricular cardiomyopathy
Marfan syndrome (aortic rupture)
Dilated cardiomyopathy/restrictive cardiomyopathy
Long QT syndrome
Brugada syndrome
Catecholamingergic polymorphic ventricular tachycardia
Short QT syndrome
Primary pulmonary hypertension

artery anomalies are the most common. In many infants, no structural cause can be identified, even after a thorough review of the history and death scene and a complete autopsy. This later group, by definition, is sudden infant death syndrome (SIDS). In patients less than 21 years of age, the most frequent causes are HCM, channelopathies, particularly the long QT syndromes (LQTSs), coronary artery abnormalities, and known, preexisting, structural congenital heart disease.

Sudden Infant Death Syndrome

SIDS is a diagnosis of exclusion, loosely defined as unexpected death under a year of age that occurs during sleep and remains unexplained after thorough clinical history and postmortem examination (standard autopsy). The incidence is relatively high but has decreased to less than 1/1,000, at least in part related to well-publicized supine (on the infant's back) sleeping recommendations. SIDS remains a leading cause of infant death in developed countries. It is generally accepted that SIDS deaths occur as a result of a variety of causes, including metabolic, environmental, and immunologic.

A number of genetically mediated arrhythmias have been postulated as a probable cause of SIDS. To date, mutations in 16 cardiac ion channel genes have been identified in victims of SIDS, most of them known to be functionally significant or disease causing. The spectrum of channelopathy genes represented in SIDS cases includes those associated with many forms of the LQTS, the Brugada syndrome, the short QT syndrome, and catecholaminergic polymorphic ventricular tachycardia (CPVT). A minority of the cardiac ion channel gene defects associated with SIDS have not been established to be functionally significant or malignant. On the other hand, there is evidence that some isoforms, as a result of alternative splicing of affected may behave more malignantly in fetuses and young infants. To what extent LQTS contributes to SCD is unclear. Early series implicated LQTS as a cause of SCD in a relatively low percentage, but SCD in the young is often unexplained after a standard autopsy. With postmortem genetic testing (molecular autopsy) becoming more commonplace, it appears that LQTS is the cause of SCD in the young in 10–20 %, potentially more in younger patients (see Chap. 19).

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM; see Chap. 19) is a diverse disease in its genetic, biochemical, cellular, phenotypic, and clinical features. In infants and children, HCM phenotype can be caused by inborn errors of metabolism, neuromuscular disorders, and malformation syndromes, but in the majority of cases it is a result of a mutation in 1 of at least 20 genes that encode protein elements of the cardiac sarcomere. These mutations are inherited, as autosomal dominant with variable penetrance, similar to most defects in structural proteins. With an estimated prevalence of 1 in 500, it is the most common inherited cardiovascular disease. Despite early observations suggesting a high risk in all patients with HCM, it does not uniformly herald an unfavorable prognosis; overall, the annual mortality is about 1 %, with a near normal life expectancy and little morbidity in most patients. There exists, however, a subset of patients, 10–20 % of those with HCM, in which the annual mortality from SCD exceeds 5 %.

A sudden arrhythmia is the most frequent means of sudden death, often as the first clinical manifestation of the disease, and typically in association with exertion. It occurs most commonly in young adults, adolescents, and children, a population with an estimated annual SCD of 2–5 %. Primary ventricular tachycardia and its degeneration to ventricular fibrillation is the predominant mechanism. Patchy and confluent myocardial scars, as a result of abnormal coronary architecture, diminished coronary flow reserve, coronary-myocardial mismatch and consequent myocardial ischemia, in addition to collagen infiltration, cellular disarray, dispersion of impulse conduction and refractory periods, and abnormal calcium handling serve as electrophysiologic substrates for the ventricular arrhythmias. Acute ischemia and vascular instability with hypotension are proposed triggers.

Major risk factors for SCD in adults with HCM are listed in Table 19.5. Most patients are free of risk factors and SCD in such patients is uncommon, although this has not been established in young patients. It is clear that adults with two or more major risk factors are at a substantially increased risk. Patients with no risk factors have been shown to have a 6-year SCD-free survival rate of 95 %, while the corresponding rate for those with two or more risk factors was 72 %.

Implantable cardioverter-defibrillator therapy is recommended for secondary prevention following events of resuscitated SCD and should be considered for primary prevention in those with at least one major risk factor. Patients and families should be well informed because ICD complication rates, including a high number of inappropriate shocks, are common in this population. There is consensus that individuals with HCM should be excluded from most competitive sports, with exception of those designated low static, low dynamic. Recommendations for genotype-positive–phenotype-negative individuals identified by cascade genetic screening are less clear. Studies are underway to help define the risk of exercise in this genotype-positive group but without ventricular hypertrophy on the echocardiogram.

Arrhythmogenic Right Ventricular Cardiomyopathy (See Chap. 19)

Arrhythmogenic right ventricular cardiomyopathy (ARVC), formerly arrhythmogenic right ventricular dysplasia, is characterized by fibro-fatty replacement of the right ventricular myocardium with progressive right ventricular dilation and dysfunction and less evident involvement of the left ventricular myocardium. The prevalence is estimated to be 1/2,000 to 1/5,000, but an associated genetic abnormality may be as prevalent as 1/200. It appears that at least 50 % have genetic abnormalities of desmosome proteins. Intense endurance sports may lead to a similar phenotype or, more likely, vigorous exercise may increase penetrance and risk of arrhythmia. ARVC may result from an inflammatory or remodeling process adversely modulated by genetic alterations in desmosome proteins.

ARVC most often presents with SCA in adolescents and young adults and is more common in males. Inheritance is autosomal dominant with variable penetrance and about 30 % have a positive family history. In Italian series of SCD, roughly ¼ have ARVC. This is in contrast to less than 2 % in series from the USA. The diagnosis can be challenging to make and standard echocardiography is not sensitive in the absence of a high index of suspicion. Cardiac magnetic resonance and electro-anatomic and voltage mapping have been shown to be more sensitive. ECGs are abnormal in about 80 %, characterized by T wave inversion and epsilon waves and/or delayed S upstroke in $V_1 - V_3/V_4$, and low voltages in limb leads. Age-related changes in the T wave polarity in the right precordial leads (so-called *juvenile T waves*) can confound the diagnosis; the usual negative T waves seen in preadolescence revert to a positive direction at ages 12–18 years (Fig. 21.1). Italian series have reported success in reducing the number of SCD in young athletes using screening programs, largely attributed to identification and subsequent strict activity limitation of individuals with ARVC.

Myocarditis

Myocarditis is an inflammatory process of the myocardium. There are a multitude of etiologies, including drugs, toxins, autoimmune diseases, Kawasaki disease, rheumatic fever, and a wide variety of infectious pathogens. The majority of cases are caused by viral infections, most commonly Coxsackie group B enteroviruses, adenoviruses, human herpesvirus 6, and parvovirus B19. Viral cytopathic injury followed by immune-mediated myocardial damage results in myocyte necrosis and diffuse inflammatory infiltrates. This and subsequent patchy fibrosis and persistence of a low-grade inflammatory state

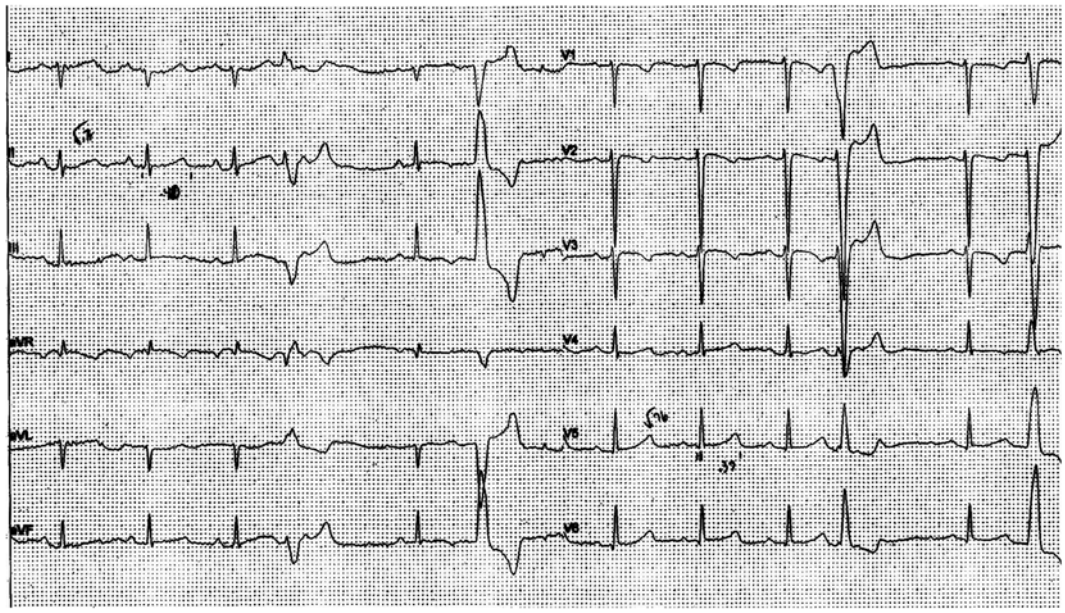


Fig. 21.1 Premature ventricular beats (multiform) and negative T waves in V2–V3 in an asymptomatic 17-year-old girl suggesting ARVC. She was genotype positive for a plakophilin mutation

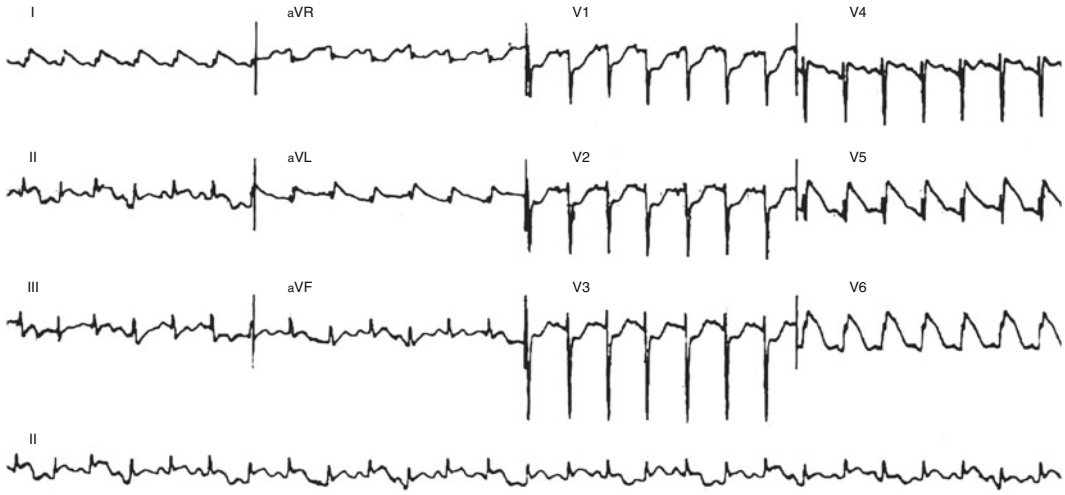


Fig. 21.2 Sinus tachycardia with ST elevation in a 10-month-old with myocarditis (autopsy proven)

can serve as arrhythmogenic substrates for ventricular tachycardia (Fig. 21.2). Myocarditis can be subclinical and is a well-recognized cause of acute heart failure and subsequent dilated cardiomyopathy, but it is probably under-appreciated as a cause of SCD. A recent study of all autopsy referrals to a single center in the UK showed 5 % of all pediatric deaths over age 5 were secondary to myocarditis and more than half of those were sudden. Ventricular ectopy or SCD may be the initial clinical manifestation of acute myocarditis and can occur in the presence of preserved ventricular function, in some cases confounding the diagnosis. Treatment is largely

supportive. Recovery is complete in most, but a minority may experience SCD, develop chronic dilated cardiomyopathy or are lost due to fulminant heart failure.

Congenital LQTS (See Chap. 19)

Congenital long QT syndrome (LQTS) (Chap. 19, Figs. 19.1–19.4) represents a spectrum of channelopathies that share in common the prolongation of ventricular repolarization and clinical manifestations of syncope and SCA, often associated with physical exertion or high adrenergic states. The estimated prevalence is 1:2,000–2,500. Inheritance is autosomal dominant in the majority of cases (Romano–Ward syndrome). The more severe Jervell and Lange-Nielsen syndrome is associated with congenital deafness.

The prolongation of repolarization can lead to delayed after-depolarization-mediated polymorphic ventricular tachycardia, torsades de pointes (TdP). TdP (Fig. 21.3), translated as twisting of points, is a distinctive, uncommon form of rapid VT characterized by a variable QRS amplitude and axis that appear to twist around a baseline. TdP is often self-limiting producing syncope, seizures, dizziness, or fleeting palpitations; but it can degenerate into ventricular fibrillation and result in SCA or SCD.

Arrhythmia triggers, to an extent, have been shown to be gene specific. Individuals with LQT1 are at risk during exercise or emotional stress. Swimming-related events in particular have been closely linked to LQT1. Events triggered by sudden or loud noises have been linked to LQT2. Individuals with LQT3 are at higher risk while asleep or at rest. Risk stratification is challenging largely because of the significant degree of inter-gene and intra-gene variability, in addition to incomplete penetrance and variable expressivity. Risk is clearly and most reproducibly increased in the presence of very long corrected QT intervals, irrespective of gene defect. A QTc of ≥500 ms is an indicator of high risk. The risk is higher in children, infants, and fetuses. The risk appears to be higher in female patients with LQT2 and slowly but significantly increases with age while decreasing in males. Male patients with LQT3 are at higher risk. The risk may be lower in individuals with LQT1, possibly because a larger percentage of KCNQ1 genotype-positive individuals have normal QT intervals (incomplete penetrance).

The genetic and phenotypic heterogeneity contributes to challenges in diagnosing and managing patients with LQTS. Importantly, it makes

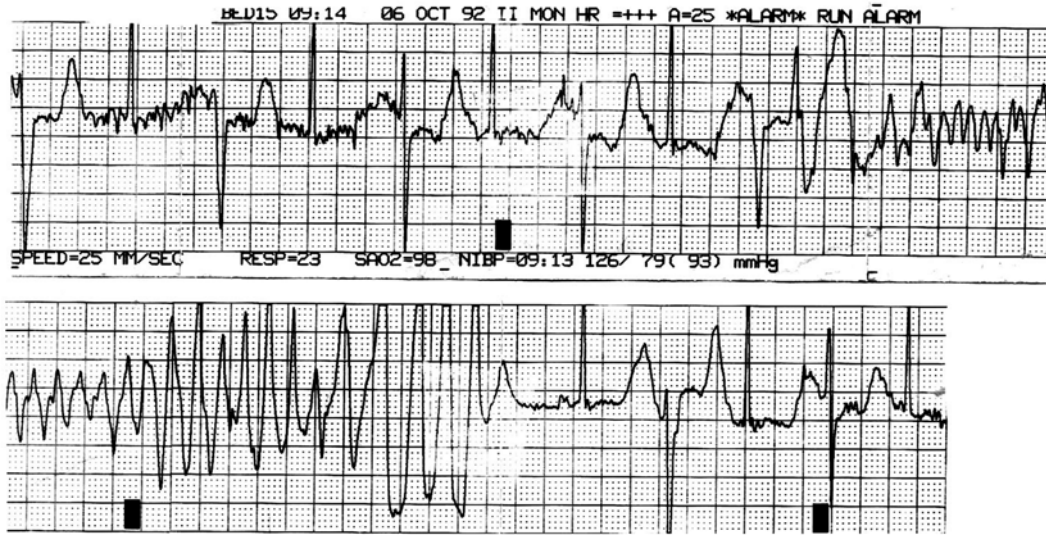


Fig. 21.3 ECG strip forma 16-year-old girl with TdP. She had a long QT on her resting ECG. Genetic testing was not available

excluding the diagnosis challenging as well. There are wide ranges of corrected QT interval values in unaffected and affected individuals, even among individuals with the same gene defect. Age-related variations in conduction system properties, heart rates, and sinus arrhythmia also confound the diagnosis, particularly in the absence of symptoms or family history. Interpreting QT intervals should be done in context. A QTc of 450 ms in an individual with a genetically confirmed first-degree relative or recurrent exertional syncope has a higher predictive value than a QTc of 475 ms in an asymptomatic individual with no family history. In the absence of concerning symptoms or family history, QTc intervals of greater than 460–470 ms for males and 470–480 ms for females are reasonable thresholds to seriously consider the diagnosis. T-wave morphology can be helpful. Notched, biphasic, and very late peaking T-waves are suggestive; T-wave alternans is highly suggestive. Using the LQTS Clinical Probability Score (Chap. 19, Table 19.2) is helpful. Exercise stress testing, Holter monitoring, and pharmacologic challenge can be useful. Commercially available genetic testing can confirm the genetic diagnosis, screen family members, and to help guide clinical management (see Chap. 19).

Therapy includes a beta-blocker in almost all patients. Propranolol and nadolol have been shown to be more effective than metoprolol. Sodium channel blockers, such as mexiletine, are a useful adjunct in some patients with LQT3, but it is recommended that the QT shortening effect be tested because the response appears to be mutation dependent. Left cardiac sympathetic denervation has been shown to be effective in some cases, including those with breakthrough symptoms, those with very long QTc intervals, and those with Jervell and Lange-Nielsen syndrome or homozygous or compound heterozygous mutations. ICD implantation may be indicated for secondary prevention and other high risk situations. It is important that patients and families are counseled about avoidance of medications that cause QT interval prolongation and avoidance of potentially dangerous situations, such as unobserved swimming in those with LQT1 and alarms and startling noises in those with LQT2.

The 36th Bethesda Conference Guidelines (2005) and the European Society of Cardiology (2006) recommend against involvement in nearly all athletics for individuals with symptomatic or genetically confirmed LQTS in the presence of significant QTc prolongation. In asymptomatic individuals with borderline QTc prolongation and in genotype-positive–phenotype-negative individuals, appropriate guidance is not clear. As described, risk stratification is, at best, challenging and there is some evidence of very low rates of events in treated patients who choose to participate in athletics. There is also evidence that arrhythmias are less common in individuals with QTc intervals less than 500 ms. It is very likely that recommendations will continue to evolve.

Brugada Syndrome (See Chap. 19)

Brugada syndrome is characterized by SCD and the ECG findings of coved-type ST elevation in the right precordial leads and right bundle branch block (Chap. 19, Figs. 19.5 and 19.6). This type I Brugada ECG pattern is intermittent and may be unmasked by pharmacologic challenge with sodium channel blockers such as procainamide, ajmaline, or flecainide (the latter two are not available as IV preparations in the USA). This pattern is not specific and can be seen with electrolyte abnormalities or myocardial infarction. The diagnosis of Brugada syndrome requires, in addition to the Brugada ECG pattern, documented VT/VF, a history of agonal nocturnal breathing or unusual syncope, suggestive family history of SCD, or Brugada syndrome (or Brugada ECG pattern) in family members. The prevalence is unknown and estimates vary widely from 1/1,000 to 1/100,000; the diagnosis is often made based on ECG pattern only. There is a higher prevalence in certain populations or areas, notably in Southeast Asia.

Brugada syndrome is genetically heterogeneous and complex. Approximately 75 % of those phenotypically affected are male with manifestations typically occurring in the third, fourth, and fifth decade. Most arrhythmias occur at rest, but fever and consumption of large meals are established triggers.

Early reports suggested that Brugada syndrome was highly malignant, but more recent studies have concluded that the yearly incidence of arrhythmic events is between 0.4 and 4 %. Risk factors include persistent type I Brugada ECG pattern in the absence of provocation and history of syncope or SCA. There is debate as to the utility of invasive electrophysiology study to risk stratify asymptomatic patients. Implantable cardioverter-defibrillators are indicated for symptomatic patients or for secondary prevention. Quinidine has been shown to be effective in preventing arrhythmia recurrences and is being studied in asymptomatic individuals with Brugada. Interestingly, patients with Brugada syndrome with ICDs have a high rate of inappropriate shocks related to a high incidence of supraventricular tachyarrhythmias, most commonly atrial fibrillation. Given the relatively low rate of arrhythmic events and the high rate of inappropriate shocks, ICDs are no longer routinely recommended for primary prevention in individuals with Brugada syndrome.

Catecholaminergic Polymorphic Ventricular Tachycardia (Chap. 19)

Catecholaminergic polymorphic ventricular tachycardia is a rare heritable arrhythmia that is characterized by adrenergic-induced ventricular tachyarrhythmia and sudden death (see Chap. 19, Fig. 19.8). Patients with CPVT often develop symptoms of syncope and sudden death early in childhood. A great degree of variability is seen even among members of the same family who carry the same mutation. Symptoms usually occur with stress or exercise. Sudden death in early adulthood in symptomatic patients is a risk if the condition is left untreated.

Other Repolarization Abnormalities

Other repolarization abnormalities have been reported: the short QT syndrome (Chap. 19) comprises QTc < 320 ms, very tall T waves, and SCD. Management usually requires an ICD. Finally the emergence of other repolarization syndromes is less well defined but likely contributes to SCD in the young (Chap. 19).

Wolff–Parkinson–White Syndrome (See Chap. 4)

The prevalence of ventricular preexcitation or Wolff–Parkinson–White (WPW) ECG pattern is estimated to be 1–3/1,000. The risk of SCD in those with WPW is very low. Symptomatic patients have an estimated risk of approximately 0.25 % per year or 3–4 % over a lifetime. The risk in asymptomatic patients is lower, approximately 1 per 1,000 patient-years. The mechanism of SCD is rapid anterograde conduction across a fast-conducting accessory pathway(s) with short anterograde effective refractory period (ERP) during atrial fibrillation (Fig. 21.4).

Risk factors for SCD include a short preexcited RR interval during atrial fibrillation or rapid atrial pacing (Fig. 21.4), a short anterograde ERP (<220–250 ms) of the accessory pathway, multiple pathways, inducible AVRT or history of AVRT, male gender, and history of syncope. Arrhythmia inducibility and young age are associated with a significantly increased risk of arrhythmic events, including SCD, in previously asymptomatic patients. However, because of a small atrial mass, atrial fibrillation is very uncommon in infants and young children.

The major limitation of accurate risk stratification is the very low SCA/SCD event rate. Holter monitoring or exercise stress testing can be helpful in assessing risk. Abrupt and persistent delta wave disappearance at physiologic heart rates is indicative of very low risk (Chap. 4, Fig. 4.9). When this cannot be established, more invasive testing should be considered. Some advocate trans-esophageal pacing in pediatric patients to establish ERP. In terms of invasive SCD risk stratification, it is well established that the negative predictive value of a shortest RR interval (or antegrade ERP) >250 ms approaches 100 %. The sensitivity, however, is very low with a positive predictive value in the range of 10–20 %.

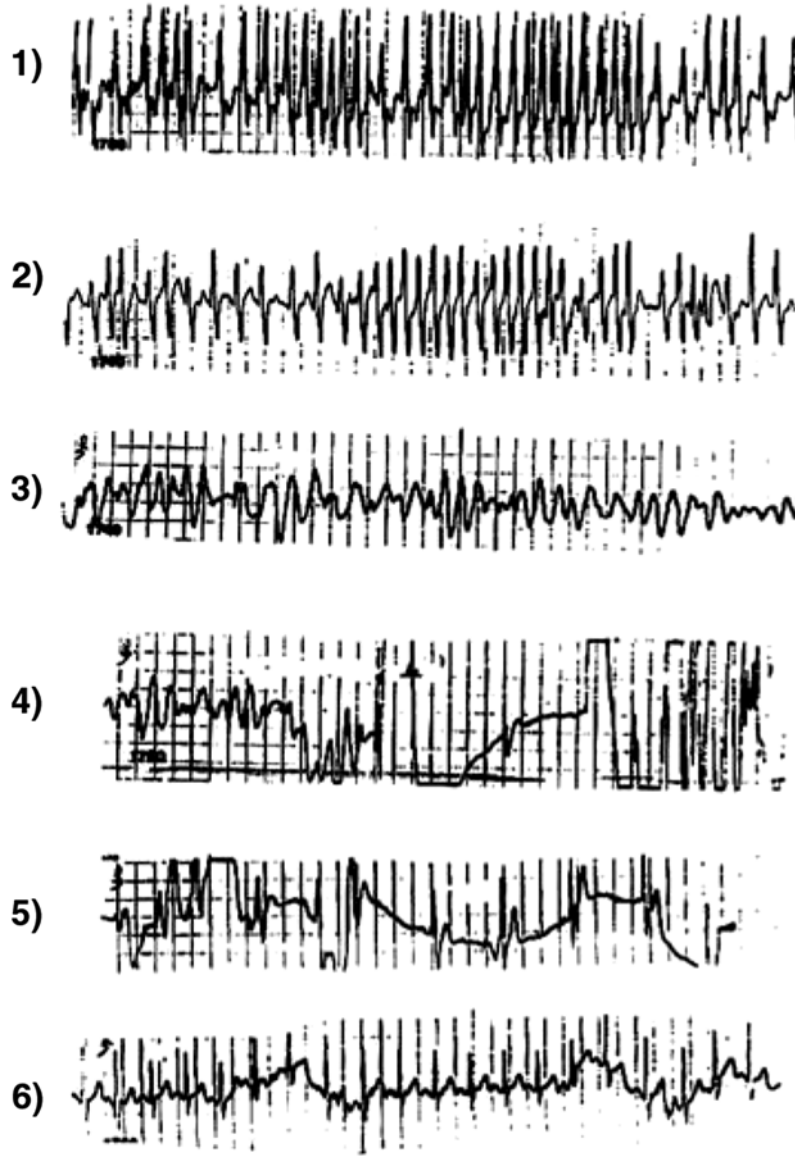


Fig. 21.4 Panels 1 and 2: Atrial fibrillation in a 9-year-old boy with a very rapid ventricular response deteriorating into ventricular fibrillation (Panels 3 and 4) and cardiac arrest. He was successfully defibrillated (Panels 4 and 5) into sinus tachycardia with no preexcitation (Panel 6). At electrophysiologic study had an intermittent anterograde left lateral accessory pathway with an effective refractory period of 190 ms. It was successfully interrupted by radiofrequency ablation

The indications for radiofrequency ablation in patients with WPW and SVT are individualized, depending upon the frequency, duration, and associated symptoms of arrhythmias, involvement in athletics, patient and family preference, and presence or absence of congenital heart disease. Management of the asymptomatic WPW patient should also be individualized and should be based on decisions made by well-informed patients and families in consideration of involvement in athletics, the very low risk of SCD, and the very low risk associated with invasive electrophysiology study and ablation. A consensus statement on the management of asymptomatic young

patients with ventricular preexcitation has recently been published by the Pediatric and Congenital Electrophysiology Society and the Heart Rhythm Society.

Congenital Coronary Artery Anomalies

Congenital coronary artery anomalies (Fig. 21.5) are common with incidence estimates ranging from 1 to 6 %. They are also very diverse and many are benign. Anomalous coronary origin from the wrong or opposite coronary sinus is the subgroup of coronary anomalies clearly associated with a significant risk of SCD (Fig. 21.2). The incidence of this subgroup has been reported to be between 0.17 (by echocardiography) and 1.07 % (by angiography). Anomalous right coronary artery from the left sinus is at least five times more common than anomalous left coronary from the right sinus. It is clear that the latter is much higher risk for SCD. Despite the much lower incidence, the literature suggests that approximately 90 % of SCD attributed to anomalous coronary sinus origins are due to the left coronary artery arising from the right sinus.

When right or left coronary arteries arise from the opposite sinus, the proximal course of the vessel is most commonly inter-arterial, between the aorta and pulmonary artery. Less common variations, including retro-aortic, anterior to the pulmonary trunk, and intra-ventricular septal courses, do not appear to be associated with a significant risk of SCD. When the course of the anomalous vessel is within the wall of the aorta (intramural), there tends to be an acute angle at its mouth. Using intravascular ultrasound imaging, such intramural coronary segments have been shown to be hypoplastic or stenotic relative to the distal vessel, in addition to being laterally compressed and non-circumferential. Anomalous left coronary origin from the right sinus is the second or third most common cause of SCD in the young in the USA. SCD occurs during or immediately after intense physical exertion, most likely as a result of relative ischemia in the presence of high demand, when the flow through the stenotic or hypoplastic segment becomes further compromised by aortic distension. The significantly increased risk associated with the left from the right is most likely, at least in part, related to the amount of and degree to which the myocardium is compromised.

Other congenital coronary anomalies implicated in SCD include acute angle of origin, ostial stenosis or atresia, and muscular bridge. These subtle abnormalities can be more challenging to diagnose and have been implicated in a number of infantile cases of SCD. When abnormalities are discovered either fortuitously or following resuscitated SCD, revascularization can be curative. Unfortunately, SCD is often the initial manifestation, particularly in adolescents and infants. Surgical correction is generally recommended for anomalous left coronary origin from the right sinus. There is debate regarding primary prevention for anomalous right coronary origin from the left sinus. Approaches include unroofing, reimplantation, osteoplasty of the anomalous artery and creating a new ostium at the distal end of an intramural vessel within the appropriate sinus.

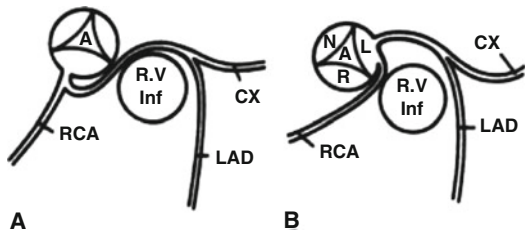


Fig. 21.5 Panel (**a**): Left coronary artery arising from the right coronary artery and coursing between the aorta and right ventricular outflow tract. Panel (**b**): The right artery arises from the left coronary cusp and courses between the aorta and right ventricular outflow tract

Structural Congenital Heart Disease

Tetralogy of Fallot

Tetralogy of Fallot has long been associated with ventricular arrhythmias and SCD. The risk of SCD is small, however, estimated to be 1–2 per 1,000 patient-years. Risk factors include older

age, older age at repair, multiple surgeries, significant pulmonary or conduit insufficiency or stenosis, severe right ventricular dilation, significant left ventricular systolic or diastolic dysfunction, prolonged QRS duration (>180 ms), recurrent syncope, and documented high grade ventricular ectopy. The risk of SCD among patients more recently repaired appears to be substantially less, as there have been trends toward earlier repair, trans-atrial approach to the ventricular septal defect, avoidance of ventriculotomy, and greater efforts to preserve right ventricular outflow valve competence. Catheter ablation for monomorphic ventricular tachycardia may be effective, but there is a high recurrence rate. For patients at high risk, pharmacologic therapy alone is not recommended and ICD placement is generally warranted.

Transposition of the Great Arteries

Late postoperative arrhythmias, most commonly intra-atrial reentrant tachycardia (IART, Chap. 8) and sick sinus syndrome (SSS, Chap. 13), are common following atrial switch (Mustard or Senning) procedures, as is systemic right ventricular dysfunction; both are risk factors for SCD, which occurs as often as 5–10 per 1,000 patient-years. Mechanisms include IART with rapid atrioventricular conduction and subsequent hemodynamic and metabolic instability, and pause-dependent dispersion of ventricular refractoriness associated with SSS. The risk of SCD associated with the arterial switch operation appears to be considerably less due to fewer atrial incisions and suture lines and a normal left ventricle (rather than the right) functioning as the systemic pump. Some risk exists in the presence of compromised coronary flow following suboptimal coronary transfer or with some coronary anatomic variants. The risk of SCD with L-TGA (ventricular inversion, atrioventricular discordance) is variable and dependent on the anatomy, surgical repair(s), and conduction system disease (late complete heart block), but it is neither well established nor negligible.

Fontan Operation

Single ventricle palliation with variations of the Fontan operation (cavopulmonary or atriopulmonary anastomosis) is associated with a high incidence of IART (Chap. 8), sinus node dysfunction, and ventricular dysfunction. Patients appear to be at risk for SCD secondary to mechanisms similar to those following atrial switch procedures; however the risk level is highest in following the first 2 stages (Norwood and Bidirectional Glenn procedures) of the repair sequence. Lateral tunnel and external cardiac conduit Fontan connections, as well as strategically placed surgical incisions or cryo-ablation lesions have been reported to address the atrial arrhythmias and, possibly, SCD.

Left Heart Obstructive Lesions

SCD occurs in association with unrepaired aortic stenosis, almost exclusively with moderately severe or severe left ventricular outflow obstruction. Resultant left ventricular hypertrophy results in acute and chronic subendocardial ischemia, a substrate for ventricular arrhythmias. Embolism in association with endocarditis is a known cause of SCD with aortic stenosis. Symptoms, including chest pain, presyncope, syncope, and palpitations, should not be taken lightly. Associated coronary artery abnormalities, most commonly ostial stenosis, contribute to risk. Surgical relief of the obstruction alleviates, but does not nullify the risk of SCD, particularly among those with aortic regurgitation, residual left ventricular dysfunction, or a mechanical aortic valve.

SCD occurs very infrequently following repair for coarctation of the aorta. Mechanisms include aneurysm rupture associated with aortoplasty and progressive left ventricular hypertrophy, despite relief of repair.

Hypoplastic left heart syndrome in the newborn left untreated is uniformly fatal in several days to weeks. SCD can occur following the three stages of repair. It occurs most often following the Norwood procedure, when coronary

perfusion is tenuous and reliant on balance between the pulmonary and systemic vascular resistances. Diastolic "runoff" to the low-resistance pulmonary bed compromises coronary (particularly subendocardial) perfusion. The Sano operation (right ventricular to pulmonary artery conduit, i.e., "shunt") is designed and advanced, in part, as an antidote to the diastolic "runoff."

Truncus arteriosus also is subject to the mechanism of diastolic "runoff." It can lead to congestive heart failure, ventricular arrhythmias, and SCD in patients with unrepaired in the first several weeks of life as pulmonary vascular resistance decreases, only to later increase as pulmonary vascular disease develops, i.e., Eisenmenger disease.

Commotio Cordis

A blunt, non-penetrating chest wall blow to an otherwise normal child or adolescent that results in SCD, commotio cordis, is a rare and unfortunate event. The mechanism involves a precisely timed and precisely located precordial impact, typically of a low-energy, relatively low-velocity, and solid core projectile object. The impact must occur during a very narrow window of ventricular repolarization, just prior to the T-wave peak. It appears that the rapid rise in left ventricular pressure results in nonuniform activation of ion channels via mechanic–electrical coupling. Ventricular tachycardia and fibrillation, unusually recalcitrant to resuscitative efforts, follows. Prompt defibrillation is the major survival determinant.

Commotio cordis occurs most often in school age, adolescent, and young adult males participating in competitive athletics, particularly baseball, and less often ice hockey and lacrosse (presumably because of fewer participants). Several cases have occurred under unusual circumstances that were not regarded as threatening, such as a snowball or the head of a pet dog impacting the chest of a small child. Prevention is challenging. Reduced injury factor (RIF, soft) baseballs reduce inducible commotio cordis is swine models, but commercially available chest protectors have been shown to be largely ineffective.

Pulmonary Hypertension

The risk of SCD is significant among patients with pulmonary arterial hypertension (PAH), both primary and associated with congenital heart disease (Eisenmenger disease). The mechanism involves an acute imbalance in systemic and pulmonary vascular resistances, resulting in diminished cardiac output or increased right to left shunt. Resultant hypoxia and acidosis in myocardium already suffering from perfusion abnormalities provides a substrate for lethal arrhythmias. Risk factors include severely elevated pulmonary vascular resistance, PAH recalcitrant to therapy, and previous symptoms such as recurrent syncope. Pregnancy, labor and the postnatal period, surgical procedures, and strenuous activity are particularly hazardous in at-risk patients.

Some patients are responsive to calcium channel blockers, which is a good prognostic indicator. Phospodiesterase 5 inhibitors, endothelin receptor antagonists, and prostacyclin and prostacyclin analogs are other therapeutic options and have slightly but significantly improved the patients' outcomes. Combination therapy and lung transplant are options for those with an inadequate clinical response.

Prevention of SCD in the Young

Despite the several recognized causes of pediatric SCD, detection and prevention are confounded by the rarity of SCD, the cost of preventive measures and the complexity and expense of intervention and management (e.g., ICDs). Nonetheless, efforts of primary and secondary prevention are underway to identify children at risk and prevent SCD. Clinicians must become aware of this small but critical at-risk population in order to offer the appropriate guidance and testing. Increased public and medical education and awareness could lead to detection of some at-risk individuals as well as enhanced first responder intervention to address these frightening, if uncommon, tragedies.

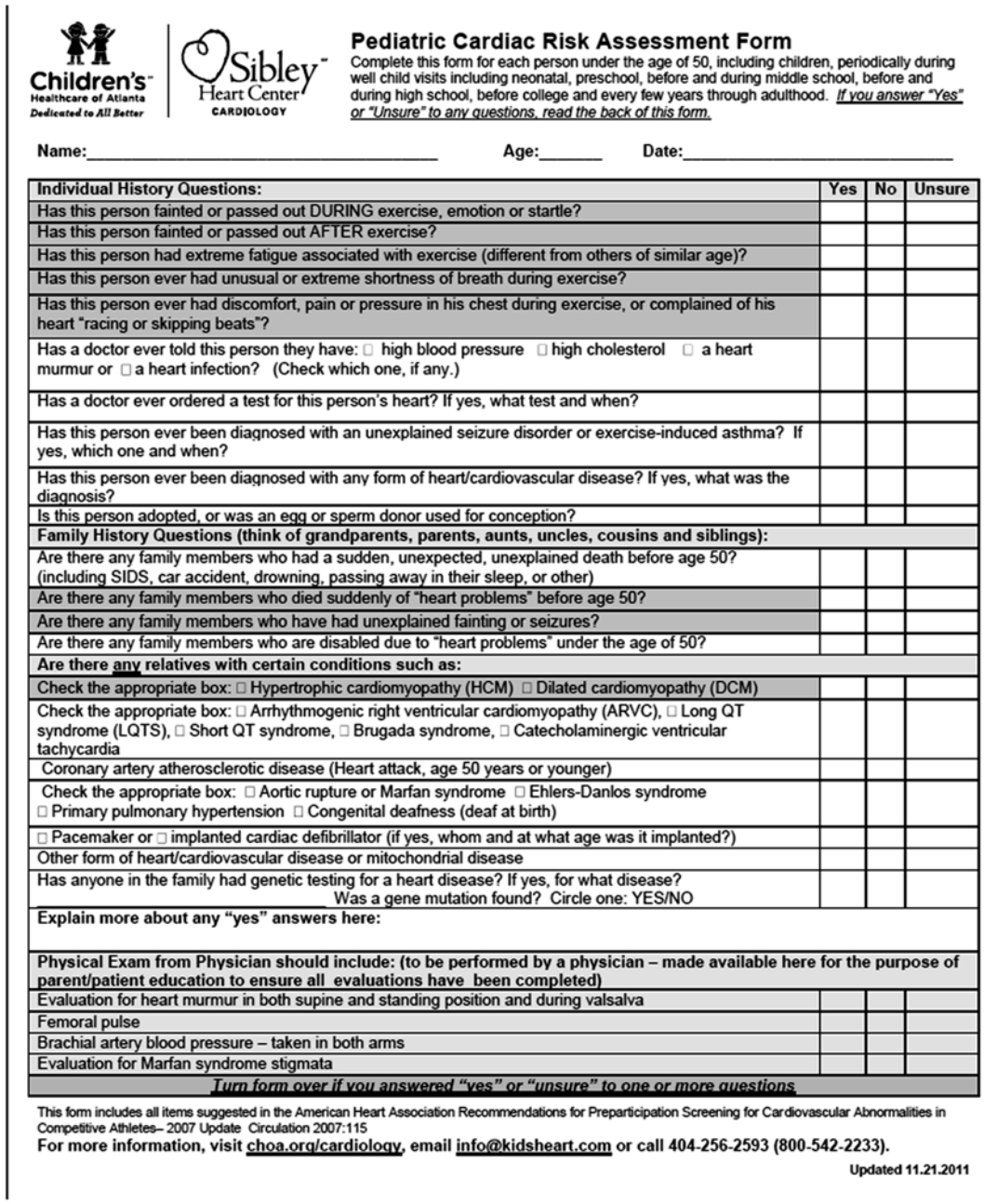
Primary Prevention

Primary prevention of SCA depends on identifying patients and families affected by the rare cardiac disorders that predispose to SCA and implementing avoidance strategies (exercise restrictions or certain medications) and/or medical management (medications, ICDs, AED readiness) to prevent SCD. Screening is the first step to identifying patients affected by these anatomic, structural, or primary electrical cardiac disorders. In the past the existing history and exam questionnaires alone were inadequate to identify patients at risk for SCD. Newer experience suggests that many patients and families can be identified through the use of a detailed, comprehensive, and accurate patient and family history process. A 1996 article, summarizing the results from nine previous publications, reported that preceding symptoms of dizziness, chest pain, syncope, palpitations, or dyspnea and a family history of premature, unexpected sudden death were noted in 25–61 % of the study population. Exertion-related death was reported in 8–33 % of the cases. A 2012 study described a retrospective report from families who had experienced SCD in a child or young adult family member. 72 % of victims were identified as having greater than one cardiovascular sign or symptom prior to their death, with fatigue (44 %) and near syncope (30 %) the most common finding. Approximately ¼ of the victims had a history of prior syncope or seizure, incompletely defined. Cardiovascular signs and symptoms first appeared on average 30 months prior to SCD. 26 % of families reported a history of unexplained SCA in a family member ≤50 years of age.

Key warning signs and symptoms of disorders predisposing to pediatric and young adult SCA include (1) exercise, emotion, and/or startle-induced syncope or seizure; (2) unexplained or atypical and persistent exercise chest pain or shortness of breath; (3) family history of sudden unexpected and unexplained death before age 50 years; and (4) a known family history of a genetic cardiomyopathy, channelopathy, or aortopathy. Patients and families can present with signs and symptoms suggestive of non-cardiac disorders; these can be thought of as "misdirects" (Table 21.1). These include, but are not limited to, respiratory symptoms, most commonly considered to be due to exercise-induced bronchospasm, but may alternatively be the first manifestation of underlying cardiomyopathy or left ventricular outflow tract obstruction. Seizures and syncope may be the initial manifestation of channelopathies including LQTS and CPVT; in this case seizures do not represent a primary neurologic event but rather the result of hypoxia and cerebral ischemia. Some cases of drowning/near drowning and SIDS have now been associated with the channelopathies. Congenital deafness, often evaluated by ENT specialists, audiologists, and/or neonatologists, may be a presenting sign of LQTS. Healthcare providers need to know the list of misdirects and remember that these may be the first and only presenting signs of an underlying cardiac disorder.

Using standardized forms like the American Academy of Pediatrics' fourth edition Preparticipation Physical Evaluation (PPE) template, or a specific cardiovascular specific risk assessment form (Fig. 21.6), may also be used to alert practitioners to high risk patients. PPEs are typically first used for clearance of high school athletes; a cardiovascular risk assessment form can be used for a child of any age, at any time, by any practitioner, and may unmask warning signs or symptoms in a family. An unusual or alarming family history can identify the first family member (proband) affected by a heritable disorder, initiating complete clinical and/or genetic cascade screening of other potentially affected relatives.

Given the known genetic nature of many of the cardiomyopathies, channelopathies, and aortopathies, the importance of family history cannot be understated (Table 21.3, Fig. 21.6). A three-generation family history pedigree is a highly effective tool during clinical evaluation. A multidisciplinary approach to evaluation of patients and families can often be aided with the expertise of a genetic counselor. These specialists can create multigenerational pedigrees and organize genetic testing, ensuring up to date testing and educating families regarding the risks, benefits, and limitations of genetic assessment. In a 2005 publication it was reported that genetic



Children's Healthcare of Atlanta — Dedicated to All Better

Sibley Heart Center CARDIOLOGY

Pediatric Cardiac Risk Assessment Form

Complete this form for each person under the age of 50, including children, periodically during well child visits including neonatal, preschool, before and during middle school, before and during high school, before college and every few years through adulthood. *If you answer "Yes" or "Unsure" to any questions, read the back of this form.*

Name:_____ Age:_____ Date:_____

Individual History Questions:	Yes	No	Unsure
Has this person fainted or passed out DURING exercise, emotion or startle?			
Has this person fainted or passed out AFTER exercise?			
Has this person had extreme fatigue associated with exercise (different from others of similar age)?			
Has this person ever had unusual or extreme shortness of breath during exercise?			
Has this person ever had discomfort, pain or pressure in his chest during exercise, or complained of his heart "racing or skipping beats"?			
Has a doctor ever told this person they have: ☐ high blood pressure ☐ high cholesterol ☐ a heart murmur or ☐ a heart infection? (Check which one, if any.)			
Has a doctor ever ordered a test for this person's heart? If yes, what test and when?			
Has this person ever been diagnosed with an unexplained seizure disorder or exercise-induced asthma? If yes, which one and when?			
Has this person ever been diagnosed with any form of heart/cardiovascular disease? If yes, what was the diagnosis?			
Is this person adopted, or was an egg or sperm donor used for conception?			
Family History Questions (think of grandparents, parents, aunts, uncles, cousins and siblings):			
Are there any family members who had a sudden, unexpected, unexplained death before age 50? (including SIDS, car accident, drowning, passing away in their sleep, or other)			
Are there any family members who died suddenly of "heart problems" before age 50?			
Are there any family members who have had unexplained fainting or seizures?			
Are there any family members who are disabled due to "heart problems" under the age of 50?			
Are there any relatives with certain conditions such as:			
Check the appropriate box: ☐ Hypertrophic cardiomyopathy (HCM) ☐ Dilated cardiomyopathy (DCM)			
Check the appropriate box: ☐ Arrhythmogenic right ventricular cardiomyopathy (ARVC), ☐ Long QT syndrome (LQTS), ☐ Short QT syndrome, ☐ Brugada syndrome, ☐ Catecholaminergic ventricular tachycardia			
Coronary artery atherosclerotic disease (Heart attack, age 50 years or younger)			
Check the appropriate box: ☐ Aortic rupture or Marfan syndrome ☐ Ehlers-Danlos syndrome ☐ Primary pulmonary hypertension ☐ Congenital deafness (deaf at birth)			
☐ Pacemaker or ☐ implanted cardiac defibrillator (if yes, whom and at what age was it implanted?)			
Other form of heart/cardiovascular disease or mitochondrial disease			
Has anyone in the family had genetic testing for a heart disease? If yes, for what disease? _____ Was a gene mutation found? Circle one: YES/NO			
Explain more about any "yes" answers here:			
Physical Exam from Physician should include: (to be performed by a physician – made available here for the purpose of parent/patient education to ensure all evaluations have been completed)			
Evaluation for heart murmur in both supine and standing position and during valsalva			
Femoral pulse			
Brachial artery blood pressure – taken in both arms			
Evaluation for Marfan syndrome stigmata			

Turn form over if you answered "yes" or "unsure" to one or more questions

This form includes all items suggested in the American Heart Association Recommendations for Preparticipation Screening for Cardiovascular Abnormalities in Competitive Athletes– 2007 Update Circulation 2007:115

For more information, visit choa.org/cardiology, email info@kidsheart.com or call 404-256-2593 (800-542-2233).

Updated 11.21.2011

Fig. 21.6 Cardiovascular risk assessment form

testing established a likely cause of death in 17/43 autopsy-negative victims (40 %); cascade genetic testing of family members revealed an additional 151 presymptomatic and undiagnosed disease carriers (average 8.9 per family). Even though genetic testing has become widely available, helping to identify specific gene mutations for LQTS, HCM, and CPVT, it is important to realize that no currently available clinical genetic testing is 100 % sensitive, and therefore negative genetic test does not exclude the disorder under evaluation.

The utility of ECG screening as a tool for large populations of asymptomatic patients has been, and continues to be, debated amongst experts in the USA and internationally. The European Society of Cardiology recommends pre-participation ECG screening for young competitive athletes in addition to review of family and personal history and physical exam. Italy and Israel have mandated pre-participation ECG for all athletes. However, in the USA, the American Heart Association has endorsed a targeted 12-point history and physical exam for the screening of high school and collegiate athletes. This AHA statement has not endorsed standardized ECG screening due to lack of definitive data demonstrating added benefit but also because of logistical, financial, and infrastructure challenges. It should be noted that professional sports organizations like the National Basketball Association and the National Football League perform mandatory participant ECGs. Many universities are following suit on their own, and recommending such screenings for their competitive athletes. This debate over mass ECG screening remains unresolved in the USA at this time.

Secondary Prevention

When primary prevention strategies fail, SCA may still occur; secondary prevention (resuscitative) efforts are then required. The concept of secondary prevention is well formulated through the "Chain of Survival" defined by the American Heart Association. This five step process begins with early recognition of cardiac arrest and the need to immediately activate the 911 EMS response systems. Step 2 is early effective bystander cardiopulmonary resuscitation. For witnessed adult cardiac arrest, new guidelines call for "compression only" CPR, which may be more effective than standard CPR with ventilation. Compressions only are most appropriate for witnessed arrest, when it can be determined that the patient is unlikely to have suffered cardiac arrest due to respiratory insufficiency. To date there are no pediatric studies with respect to compression only CPR. Step 3 is early defibrillation; public access defibrillation uses automatic external defibrillators (AEDs), now much more widely distributed and available. Witnessed ventricular fibrillation arrest in adults may be successfully resuscitated with the appropriate use of AEDs and lead to long-term survival rates greater than 70 % in some reports. Even with this knowledge, only approximately 30 % of children receive effective bystander CPR. It is known that effective bystander CPR more than doubles patient survival rates. Steps 4 and 5 of the Chain of Survival involve effective advanced care at a hospital system and finally coordination of care during hospitalization and post-discharge.

A 2007 American Academy of Pediatrics policy statement addressed the current pathophysiology of ventricular fibrillation and the recommendations for AED use in children. The 36th Bethesda Guidelines echo the AHA guidelines and recommend that AEDs should be available at educational facilities that have competitive athletic programs, especially when students with known cardiac disorders predisposing to SCA attend the school and anticipated EMS response time to the school would be $\geq$5 min.

The success of a school-based AED programs like Project ADAM (Automatic Defibrillator in Adam's Memory) in Wisconsin and Project SAVE (Sudden Cardiac Arrest, Awareness, Vision, and Education) in Georgia have been reported. A recent prospective study shows that >85 % of athletes who suffer SCA can survive if a school-based emergency action plan was previously established and early effective CPR and defibrillation is initiated.

Conclusion

Anxiety surrounding SCD in young adults has motivated communities to become proactive in an effort to prevent future life threatening events in this population. School personnel look to clinicians to help guide them when preparing for and reacting to these catastrophic events. Increasing professional and public awareness of the common causes of SCD will help to identify individuals and family members at risk

and direct them to the current guidelines for follow up. When a cardiac arrest does occur, ready access to AEDs and initiation of an emergency action plan can prevent death. Supporting community CPR education and school-based AED programs will help to increase bystander involvement and help prevent another cardiac death.

Suggested Reading

2011 The Joint Commission: sudden cardiac arrest: meeting the challenge.

36th Bethesda conference: eligibility recommendations for competitive athletes with cardiovascular abnormalities. 2005.

Ackerman MJ, Tester DJ, Driscoll DJ. Molecular autopsy of sudden unexplained death in the young. Am J Forensic Med Pathol. 2001;22(2):105–11.

Angelini P, Velasco JA, Ott D, Khoshnevis GR. Anomalous coronary artery arising from the opposite sinus: descriptive features and pathophysiologic mechanisms, as documented by intravascular ultrasonography. J Invasive Cardiol. 2003;15(9):507–14.

Angelini P, Vidovich MI, Lawless CE, Elayda MA, et al. Preventing sudden cardiac death in athletes: in search of evidence-based, cost effective screening. Tex Heart Inst J. 2013;40(2):148–55.

Barsheshet A, Peterson DR, Moss AJ, Schwartz PJ, et al. Genotype-specific QT correction for heart rate and the risk of life-threatening cardiac events in adolescents with congenital long-QT syndrome. Heart Rhythm. 2011;8(8):1207–13.

Barsheshet A, Dotsenko O, Goldenberg I. Genotype-specific risk stratification and management of patients with long QT syndrome. Ann Noninvasive Electrocardiol. 2013;18(6):499–509.

Berg M. Part 13: pediatric basic life support: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2010;122 Suppl 3:S862–75.

Campbell R. Preventing pediatric sudden cardiac death: where do we start; 2006. Pediatrics. 2006;118(2): 802–4.

Campbell R, Berger S, et al. Sudden cardiac arrest in children and young athletes: the important of a detailed personal and family history in the pre-participation evaluation. Br J Sports Med. 2009;43:336–41.

Chaitman B, Myerberg R. Should an electrogram be included in routine preparticipation screening of young athletes? Circulation. 2007;116:2610–26.

Chandra N, Bastiaenen R, Papadakis M, Sharma S. Sudden cardiac death in young athletes: practical challenges and diagnostic dilemmas. J Am Coll Cardiol. 2013;61(10):1027–40.

Cohen MI, Triedman JK, Cannon BC, Davis AM, et al. PACES/HRS expert consensus statement on the management of the asymptomatic young patient with a Wolff-Parkinson-White (WPW, ventricular preexcitation) electrocardiographic pattern: developed in partnership between the Pediatric and Congenital Electrophysiology Society (PACES) and the Heart Rhythm Society (HRS). Endorsed by the governing bodies of PACES, HRS, the American College of Cardiology Foundation (ACCF), the American Heart Association (AHA), the American Academy of Pediatrics (AAP), and the Canadian Heart Rhythm Society (CHRS). Heart Rhythm. 2012;9(6):1006–24.

Corrado D, et al. Cardiovascular pre-participation screening of young competitive athletes for prevention of sudden death: proposal for a common European protocol. Eur Heart J. 2005;26:516–24.

ECG Guidelines. Part 4: the automated external defibrillator: key link the chain of survival. Circulation. 2000;102:I-60–76.

Eggebrecht H, Mohlenkamp S. Images in clinical medicine. Myocardial bridging. N Engl J Med. 2003; 349(11):1047.

Epstein AE, Dimarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: executive summary. Heart Rhythm. 2008;5(6):934–55.

Frommelt PC, Frommelt MA, Tweddell JS, Jaquiss RD. Prospective echocardiographic diagnosis and surgical repair of anomalous origin of a coronary artery from the opposite sinus with an interarterial course. J Am Coll Cardiol. 2003;42(1):148–54.

Gatzoulis MA, Balaji S, Webber SA, Siu SC, et al. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicenter study. Lancet. 2000;356:975–81.

Goldenberg I, Thottathil P, Lopes CM, Moss AJ, et al. Trigger-specific ion-channel mechanisms, risk factors, and response to therapy in type 1 long QT syndrome. J Am Coll Cardiol. 2011;57(8):941–50.

Harmon KG, Asif IM, Klossner D, Drezner JA. Incidence of sudden cardiac death in National Collegiate Athletic Association athletes. Circulation. 2011;123:1594–600.

Humbert M, Sitbon O, Simonneau G. Treatment of pulmonary arterial hypertension. N Engl J Med. 2004;351(14):1425–36.

Kaltman JR, Thompson PD, Lantos J, Berul CI, et al. Screening for sudden cardiac death in the young: report from a National Heart, Lung, and Blood Institute Working Group. Circulation. 2011;123:1911–8.

Klaver EC, Versluijs GM, Wilders R. Cardiac ion channel mutations in the sudden infant death syndrome. Int J Cardiol. 2011;152(2):162–70.

Kong MH, Fonarow GC, Peterson ED, Curtis AB, et al. Systematic review of the incidence of sudden cardiac death in the United States. J Am Coll Cardiol. 2011;57:794–801.

Liberthson RR. Sudden death from cardiac causes in children and young adults. N Engl J Med. 1996;334(16): 1039–44.

Liu JF, Jons C, Moss AJ, McNitt S, et al. International long QT syndrome registry. Risk factors for recurrent syncope and subsequent fatal or near-fatal events in

children and adolescents with long QT syndrome. Heart Rhythm. 2012;9(1):49–56.

Longmuir PE, Brothers JA, de Ferranti SD, Hayman LL, et al.; American Heart Association Atherosclerosis, Hypertension and Obesity in Youth Committee of the Council on Cardiovascular Disease in the Young. Promotion of physical activity for children and adults with congenital heart disease: a scientific statement from the American Heart Association. Circulation. 2013;127(21):2147–59.

Mahle WT, Sable CA, Matherne PG, Gaynor JW, et al. Key concepts in the evaluation of screening approaches for heart disease in children and adolescents: a Science Advisory from the American Heart Association. Circulation. 2012;125:2796–801.

Maron BJ. Sudden death in young athletes. N Engl J Med. 2003;349(11):1064–75.

Maron BJ. Counterpoint: mandatory ECG screening of young competitive athletes. Heart Rhythm. 2012; 9(10):1646–9.

Maron B, Pelliccia A, Spirito P. Cardiac disease in young trained athletes. Insights into the methods for distinguishing athlete's heart from structural heart disease, with particular emphasis on hypertrophic cardiomyopathy. Circulation. 1995a;91:1596–601.

Maron B, Poliac LC, Kaplan JA, Mueller FO. Blunt impact to the chest leading to sudden death from cardiac arrest during sports activity. N Engl J Med. 1995b;333:337–42.

Maron BJ, et al. Cardiovascular preparticipation screening of competitive athletes: a statement for health professionals from the Sudden Death Committee and Congenital Cardiac Defects Committee, American Heart Association. Circulation. 1996;94:850–6.

Maron B, Friedman R, et al. Assessment of 12 lead electrocardiogram as a screening test for a detection of cardiovascular disease in general healthy populations of young people (12–22 years of age). Circulation. 2001;103:327–34.

Maron B, et al. Recommendations for physical activity and recreational sports participation for young patients with genetic diseases. Circulation. 2004;109:2807–16.

Maron BJ, et al. Recommendations and considerations related to preparticipation screening for cardiovascular abnormalities in competitive athletes: 2007 update: a scientific statement from the American Heart Association Council on nutrition, physical activity, and metabolism: endorsed by the American College of Cardiology Foundation. Circulation. 2007;115:1643–55.

Maron BJ, Haas TS, Doerer JJ, Thompson PD, et al. Comparison of U.S. and Italian experiences with sudden cardiac deaths in young competitive athletes and implications for preparticipation screening strategies. Am J Cardiol. 2009;104:276–80.

Maron BJ, Spirito P, Ackerman MJ, Casey SA, et al. Prevention of sudden cardiac death with implantable cardioverter-defibrillators in children and adolescents with hypertrophic cardiomyopathy. J Am Coll Cardiol. 2013;61(14):1527–35.

Maron BJ, Friedman RA, Kligfield P, et al.; American Heart Association Council on Clinical Cardiology; Advocacy Coordinating Committee; Council on Cardiovascular Disease in the Young; Council on Cardiovascular Surgery and Anesthesia; Council on Epidemiology and Prevention; Council on Functional Genomics and Translational Biology; Council on Quality of Care and Outcomes Research, and American College of Cardiology. Assessment of the 12-lead electrocardiogram as a screening test for detection of cardiovascular disease in healthy general populations of young people (12–25 years of age): a scientific statement from the American Heart Association and the American College of Cardiology. J Am Coll Cardiol. 2014;64(14):1479–514.

Meaney P, Bobrow BJ, Mancini ME, Christenson J, et al. Cardiopulmonary resuscitation quality: improving cardiac resuscitation outcomes both inside and outside the hospital: a consensus statement from the American Heart Association. Circulation. 2013;128:417–35.

Mogayzel C, et al. Out-of-hospital ventricular fibrillation in children and adolescents: cause and outcomes. Ann Emerg Med. 1995;25:484–91.

Munger TM, Packer DL, Hammill SC, et al. A population study of the natural history of Wolff-Parkinson-White syndrome in Olmsted County, Minnesota, 1953–1989. Circulation. 1993;87(3):866–73.

Neary MT, Breckenridge RA. Hypoxia at the heart of sudden infant death syndrome? Pediatr Res. 2013a;74(4):375–9.

Neary MT, Breckenridge RA. Hypoxia at the heart of the sudden death syndrome? Peadiatr Res. 2013b;74(4): 375–83.

Pappone C, Santinelli V, Manguso F, et al. A randomized study of prophylactic catheter ablation in asymptomatic patients with the Wolff-Parkinson-White syndrome. N Engl J Med. 2003;349(19):1803–11.

Pappone C, Manguso F, Santinelli R, et al. Radiofrequency ablation in children with asymptomatic Wolff-Parkinson-White syndrome. N Engl J Med. 2004; 351(12):1197–205.

Potter RN, Pearse LA, Virmani R. Sudden death in young adults: a 25-year review of autopsies in military recruits. Ann Intern Med. 2004;141:829–34.

Proceedings of the 5th world symposium on pulmonary hypertension. J Am Coll Cardiol. 2013;62(25 Suppl D).

Schwartz PJ, Ackerman MJ, George Jr AL, Wilde AA. Impact of genetics on the clinical management of channelopathies. J Am Coll Cardiol. 2013;62(3):169–80.

Sen-Chowdhry S, McKenna WJ. Sudden death from genetic and acquired cardiomyopathies. Circulation. 2012;125:1563–76.

Sharma S. Point/mandatory ECG screening of young competitive athletes. Heart Rhythm. 2012;9(10): 1642–5.

Silka MJ, Kron J, Walanc KCG, et al. Assessment and follow-up of pediatric survivors of sudden cardiac death. Circulation. 1990;82(2):341–9.

Silka MJ, Hardy BG, Menashe VD, Morris CD. A population-based prospective evaluation of risk of sudden cardiac death after operation for common congenital heart defects. J Am Coll Cardiol. 1998;32(1):245–51.

Steinberger J, Lucas RV, Edwards JE, Titus JL. Causes of sudden unexpected cardiac death in the first 2 decades of life. Am J Cardiol. 1996;77:992–5.

Stojanovska J, Garg A, Patel S, Melville DM, et al. Congenital and hereditary causes of sudden cardiac death in young adults: diagnosis, differential diagnosis, and risk stratification. Radiographics. 2013;33(7): 1977–2001.

Tan H, Hofman N, et al. Sudden unexplained death: heritability and diagnostic yield of cardiological and genetic examination in surviving relatives. Circulation. 2005;112(2):207–13. Epub 2005 Jul 5.

Tester DJ, Spoon DB, Valdivia HH, et al. Targeted mutational analysis of the RyR2-encoded cardiac ryanodine receptor in sudden unexplained death: a molecular autopsy of 49 medical examiner/coroner's cases. Mayo Clin Proc. 2004;79(11):1380–4.

Van Norstrand DW, Ackerman MJ. Sudden infant death syndrome: do ion channels play a role? Heart Rhythm. 2009;6:272–8.

Villafañe J, Feinstein JA, Jenkins KJ, Vincent RN, et al.; Adult Congenital and Pediatric Cardiology Section, American College of Cardiology. Hot topics in tetralogy of Fallot. J Am Coll Cardiol 2013;62(23): 2155–66.

Weber MA, Ashworth MT, Risdon RA, et al. Clinicopathological features of paediatric deaths due to myocarditis: an autopsy series. Arch Dis Child. 2008;93:594–8.

Wellens HJ. Catheter ablation for cardiac arrhythmias. N Engl J Med. 2004;351(12):1172–4.

Wilson MG, et al. Efficacy of personal symptom and family history questionnaires when screening for inherited cardiac pathologies: the role of electrocardiography. Br J Sports Med. 2008;42(3):207–11.

Young KD, Gausche-Hill M, McClung CD, Lewis RJ. A prospective, population-based study of the epidemiology and outcome of out-of-hospital pediatric cardiopulmonary arrest. Pediatrics. 2004;114(1): 157–64.

Pharmacology of Anti-arrhythmic Agents

22

Peter S. Fischbach and Srikant Das

Anti-arrhythmic drugs, like many drugs currently used in pediatric medicine, rely on data from adult studies for dosing and efficacy. There are relatively limited data concerning anti-arrhythmic drug use in children. Nearly all of the studies addressing the clinical efficacy of anti-arrhythmic medications in children are retrospective. Large controlled studies comparing different drugs and dosing schedules are lacking.

This chapter discusses anti-arrhythmic medications according to the Vaughan Williams scheme, which remains the most widely used in clinical practice. The Vaughan Williams system divides anti-arrhythmic drugs into four classes based on their predominant mechanism of action. The classification system is, however, an oversimplification and does not address several drugs whose actions cross over multiple groups. Thus, although the grouping of anti-arrhythmic agents into four classes is convenient, it should be understood that such a classification falls short of explaining the underlying mechanisms by which many drugs ultimately exert their therapeutic anti-arrhythmic effect.

P.S. Fischbach, M.D., M.S. (✉)
Sibley Heart Center, Children's Healthcare of Atlanta, Department of Pediatrics, Emory University School of Medicine, Atlanta, GA, USA
e-mail: fischbachp@kidsheart.com

S. Das, M.D.
Department of Pediatric Cardiology, Arkansas Children's Hospital, University of Arkansas for Medical Sciences, One Children's Way, Slot 512-3, Little Rock, AR 72223, USA
e-mail: sdas@uams.edu

Class I

Class I anti-arrhythmic drugs block the voltage-gated sodium channel delaying the rapid upstroke of the action potential (phase 0, Fig. 22.1), indicating transmembrane depolarization, and thereby slowing the cell-to-cell conduction velocity in the tissue. These drugs act when the channel is either in the open or inactivated state rather than in the resting state. Sodium channel inhibition also prolongs the effective refractory period of fast-response fibers by necessitating a more hyperpolarized membrane potential (more negative) be achieved prior to a return of excitability. Although many Class I anti-arrhythmic drugs possess local anesthetic actions and can depress myocardial contractile force, these effects are usually observed only at higher plasma concentrations. In addition to the effects on conduction velocity, Class I drugs also suppress both normal Purkinje fiber and His bundle automaticity in addition to abnormal automaticity resulting from myocardial damage. Suppression of abnormal automaticity permits the sinoatrial (SA) node to resume the role of the dominant pacemaker.

M. Dick, II (ed.), *Clinical Cardiac Electrophysiology in the Young*,
DOI 10.1007/978-1-4939-2739-5_22

Fig. 22.1 Ia lengthens the action potential (right shift); Ic does not significantly affect the action potential (no; Ib shortens the action potential (left shift) shift)

Class I anti-arrhythmic agents are subdivided into three groups: (1) Class IA drugs slow the rate of rise of phase 0 (V_{max}) of the action potential and prolong the refractory period; (2) Class IB drugs have a minimal effect on V_{max} and the refractory period of healthy myocardium while causing conduction block in diseased myocardium; and (3) Class IC drugs cause a marked depression in the conduction velocity with minimal effects on refractoriness in all cardiac tissue. Many Class I anti-arrhythmic drugs have effects on other ion channels and membrane receptors (Table 22.1).

Class IA

Quinidine

Quinidine (*Quinidex*) is the dextro-isomer of quinine and was one of the first clinically used anti-arrhythmic agents (Tables 22.1 and 22.2). Due to the high incidence of ventricular pro-arrhythmia (Table 22.3) and numerous equally efficacious agents, quinidine is now used sparingly. Quinidine shares all of the pharmacological properties of quinine, including anti-malarial, antipyretic, oxytocic, and skeletal muscle relaxant actions.

Electrophysiological actions. Quinidine's effect depends on the parasympathetic tone and the dose. The anticholinergic actions of quinidine predominate at lower plasma concentrations and direct electrophysiological actions predominate at higher serum levels.

SA node and atrial tissue: At low concentrations a slight increase in heart rate results from the anticholinergic effects while at higher concentrations spontaneous diastolic depolarization is slowed. Quinidine slows the V_{max} of phase 0 slowing conduction through all tissues. Quinidine also has "local anesthetic" properties.

AV node: The anticholinergic effect of quinidine enhances conduction through the AV node. Quinidine's direct electrophysiological actions on the AV node decreases conduction velocity and increases the ERP.

His–Purkinje system and ventricular muscle: Quinidine decreases the slope of phase 4 depolarization, inhibiting automaticity. Depression of automaticity in the His–Purkinje system is more pronounced than depression of SA node pacemaker cells. Quinidine also prolongs repolarization in ventricular muscle resulting in an increase in the duration of the action potential and QT interval on ECG a result of blocking the delayed rectifier potassium channel (I_{Kr}).

Electrocardiographic changes. Quinidine prolongs the PR, QRS, and QT intervals. QRS and QT prolongation is more pronounced than with other anti-arrhythmic agents. The magnitude of prolongation is directly related to the plasma concentration.

Hemodynamic effects. Myocardial depression is not a problem in patients with normal cardiac function while patients with compromised myocardial function may experience a decrease in cardiac function. Quinidine relaxes vascular smooth muscle directly as well as indirectly by inhibition of alpha-1-adrenoceptors.

Pharmacokinetics. Quinidine has nearly complete oral bioavailability with an onset of action within 1–3 h, and peak effect within 1–2 h. The plasma half-life is 6 h with primarily hepatic metabolism. Therapeutic serum concentrations are 2–4 μg/mL.

Clinical uses. The use of quinidine is limited by the poor side effect profile and the availability of equally or more efficacious agents. Quinidine

Table 22.1 Properties of Class I anti-arrhythmic drugs

Drug	Recovery from Na channel block	K^+ channels	Other receptor effects	ECG changes	Elimination	Bio-availability (%)	Time to peak concentration after oral dose (h)	Elimination half life (h)	Dose modification
Class IA									
Procainamide	Intermediate	$\downarrow I_{Kr}$	Inhibits β-adrenergic and muscarinic receptors	↑QT	Hepatic (40–70 %), renal (30–60 %)	100	1	2–4	↓RD
Quinidine	Intermediate	$\downarrow I_{TO}$, $\downarrow I_{Kr,}$ $\downarrow I_{Ks}$		↑QT	Hepatic (50–90 %), renal (10–30 %)	70	1.5–3	3–19	↓HD
Disopyramide	Intermediate	$\downarrow I_{TO}$, $\downarrow I_{Kr}$, $\downarrow I_{KAch}$	Inhibits muscarinic receptors	↑QT	Hepatic (20–30 %), renal (40–50 %)	80–90	1–2	6–8	↓RD, ↓HD
Class IB									
Lidocaine	Rapid				Hepatic			1.5–4	↓HD, ↓CHF
Mexiletine	Rapid				Hepatic	90	2–4	8–20	↓HD, ↓CHF
Class IC									
Propafenone	Slow	$\downarrow I_{Kr}$, $\downarrow I_{Kur}$	Inhibits β-adrenergic receptors	↑PR, ↑QRS	Hepatic	10–50	2–3	2–24	
Flecainide	Slow	$\downarrow I_{Kr}$, $\downarrow I_{Kur}$	Inhibits β-adrenergic receptors	↑PR, ↑QRS, slight ↑QT	Hepatic (70 %), renal (30 %)	90–95	2	14–20	↓RD, ↓HD

↓ = Reduce or block, *HD* heart disease, *CHF* congestive heart failure, *RD* renal disease

Table 22.2 Class I drugs

Drug	Class	Dose	$T_{1/2}$	Route of elimination	Therapeutic serum levels	ECG changes		
						PR	QRS	QTc
Quinidine gluconate	Ia	PO: 10–30 mg/kg/d ÷ bid–tid	6 h	H	26 mg/mL	±	↑↑	↑↑↑
Procainamide	Ia	PO: 15–50 mg/kg/d ÷ tid–qid IV: load: 7–15 mg/kg over 1 h Infusion: 20–100 μg/kg/min	2.5–4.5 h (68 h for SR)	HR	48 μg/ml NAPA: 48 μg/mL	±	↑	↑↑
Lidocaine	Ib	IV: load = 1 mg/kg (may repeat × 3), infusion = 20–50 μg/kg/min	12 h	H	1.5–6.0 μg/mL	±	±	±
Mexiletine	Ib	PO: 6–15 mg/kg/d ÷ tid	10–12 h	HB	0.5–2.0 μg/mL	±	±	±
Flecainide	Ic	PO: 4–6 mg/kg/d ÷ bid–tid or 50–200 mg/m^2 ÷ bid–tid	12–30 h	HR	0.2–1.0 μg/mL	↑↑	↑↑	↑
Propafenone	Ic	PO: 8–10 mg/kg/d ÷ tid, may increase dose slowly to 20 mg/kg/d with careful monitoring	2–10 h	HR, 1/3 unchanged in urine	0.06–0.1 μg/mL	↑↑	↑↑	±

H Hepatic metabolism, *HR* hepatic metabolism with renal excretion, *HB* hepatic metabolism with biliary excretion, ↑ = increase, ± = no significant change

The antiarrhythmic doses discussed are for children. It is always important to check adult doses for adolescents and large children to avoid over dosage

may be used in combination with other agents such as mexiletine for the control of ventricular arrhythmias. Since the CAST study, the use of quinidine has declined. Currently, the inclusion of quinidine should be limited to patients with ICDs due to the significant risk of pro-arrhythmia. More recently, it may be useful in patients with short QT syndrome (Chap. 19).

Adverse effects. The most common adverse effects are diarrhea, upper gastrointestinal distress, and light-headedness. Other relatively common adverse effects include fatigue, palpitations, headache, angina-like pain, and rash. These adverse effects are dose related and reversible with cessation of therapy. Thrombocytopenia may also occur.

The cardiac toxicity of quinidine includes AV and intraventricular block, ventricular tachyarrhythmias, and depression of myocardial contractility. Ventricular pro-arrhythmia with loss of consciousness, referred to as "quinidine syncope," is more common in women and may occur at therapeutic or subtherapeutic plasma concentrations.

Large doses of quinidine can produce a syndrome known as cinchonism, which is characterized by ringing in the ears, headache, nausea, visual disturbances or blurred vision, disturbed auditory acuity, and vertigo. Larger doses can produce confusion, delirium, hallucinations, or psychoses. Quinidine can also cause hypoglycemia.

Contraindications. One absolute contraindication is complete AV block with a junctional or idioventricular escape rhythm that may be suppressed leading to cardiac arrest. Persons with congenital QT prolongation may develop torsades de pointes and should not be exposed to quinidine. Owing to the negative inotropic action of quinidine, the drug is contraindicated in congestive heart failure and hypotension. Digitalis intoxication and hyperkalemia accen-

Table 22.3 Pro-arrhythmia syndromes and their management

Syndrome	Mechanism	Clinical presentations	Therapy*
Digitalis intoxication	Na^+-K^+ATPase inhibition → intracellular calcium overload	Ectopic activity, with suppressed sinus and AV nodal function	Mild: observe; possible temporary pacing
		Atrial or junctional tachycardia	Serious: anti-digoxin antibody
		Bidirectional VT	
Torsades de pointes	I_{Kr} block	Pause-dependent polymorphic VT, with QT prolongation and deformity	Mild: magnesium
			Serious: pacing, isoproterenol
Sodium channel blocker toxicity	Block of cardiac sodium channels, often exacerbated by underlying tachycardia or ischemia	Atrial flutter slowing with 1:1 AV conduction	Mild: no therapy or heart rate slowing (β-blocker)
		Frequent or difficult to cardiovert monomorphic or polymorphic VT	
		Incessant SVT	Serious: intravenous sodium bicarbonate
		Increase death rate during long-term therapy after myocardial infarction	
β-Blocker withdrawal	Up regulation of receptor number with chronic therapy; withdrawal → more receptors available for agonist	Sinus tachycardia, other sympathetically mediated arrhythmia, hypertension	β-Blocker
Ventricular fibrillation	Three drug-related mechanisms:	VF	No specific therapy beyond drug withdrawal and resuscitation
	Digitalis in manifest preexcitation with atrial fibrillation		
	Coronary vasoconstriction (many drugs: cocaine, ergot)		
	Inappropriate use of verapamil for sustained VT		
Calcium channel blocker toxicity	Calcium channel blocker excess, often in overdose	Hypotension, bradycardia, AV block	Temporary pacing, IV calcium

tuate the effect of quinidine on conduction velocity. The use of quinidine and quinine should be avoided in patients who have previously shown evidence of quinidine-induced thrombocytopenia.

Drug interactions. Quinidine increases the plasma concentrations of digoxin, requiring a downward adjustment in the digoxin dose. Drugs that inhibit the hepatic metabolism of quinidine and increase the serum concentration include acetazolamide, certain antacids (magnesium hydroxide and calcium carbonate), and cimetidine. Phenytoin, rifampin, and barbiturates increase the hepatic metabolism of quinidine and reduce its plasma concentrations.

Procainamide

Procainamide (*Pronestyl*, *Procan SR*) is a derivative of the local anesthetic agent procaine (Tables 22.1 and 22.2). Procainamide compared with procaine has a longer half-life, does not cause CNS toxicity at therapeutic plasma concentrations, and is effective orally. Procainamide is effective in the treatment of supraventricular, ventricular, and digitalis-induced arrhythmias. Its use is limited by its short serum half-life and frequent side effects when used chronically.

Electrophysiological actions. Procainamide's direct electrophysiological effects are nearly identical to quinidine's, although it has a significantly weaker anticholinergic effect. The ECG changes are similar to quinidine.

Hemodynamic effects. Hemodynamic compromise is less profound than with quinidine and seldom occurs after oral administration.

Pharmacokinetics. Procainamide is highly bioavailable (75–95 %) with an onset of action of 5–10 min. The peak response following an oral dose is 60–90 min with a plasma half-life of 2.5–4.5 h (6–8 h for the sustained release preparation). The drug is metabolized hepatically and 50–60 % is excreted unchanged in the urine. The primary metabolite *N*-acetylprocainamide (NAPA) is cardioactive with Class III properties and is eliminated unchanged in the urine. In patients who are rapid acetylators or have renal dysfunction, NAPA may accumulate more rapidly than procainamide. Therapeutic levels range from 4 to 8 μg/mL and may need to be slightly higher in neonates. NAPA levels should be considered separately from procainamide levels rather than combined and are also in the range of 4–8 μg/mL.

Clinical uses. Procainamide is useful in the treatment of accessory pathway-mediated tachycardia, atrial fibrillation of recent onset, all types of ventricular dysrhythmias, and combined with patient cooling for the treatment of postoperative junctional ectopic tachycardia.

Care should be used when initiating therapy in patients with atrial flutter or IART as procainamide may slow conduction in the flutter circuit allowing for 1:1 AV conduction and an increase in the ventricular rate. Additionally, procainamide may slow conduction velocity in other macroreentrant circuits (such as AVRT) and convert self-limited tachycardia into slower incessant tachycardia.

Intravenous administration for Brugada syndrome has emerged as a possible diagnostic test.

Adverse effects. Acute cardiovascular reactions to procainamide administration include hypotension, AV block, intraventricular block, ventricular tachyarrhythmias, and complete heart block. The drug dosage must be reduced, or even stopped, if severe depression of conduction (severe prolongation of the QRS interval) or repolarization (severe prolongation of the QT interval) occurs. Long-term drug use may result in a clinical lupus-like syndrome. The symptoms disappear within a few days of cessation of therapy.

Procainamide, unlike procaine, has little potential to produce CNS toxicity. Rarely, patients may experience mental confusion or hallucinations. Procainamide, along with other class 1 drugs may produce lupus erythematosus-like picture; it resolves after withdrawal of the drug.

Contraindications. Contraindications are similar to those for quinidine. Procainamide should be administered with caution to patients with second-degree AV block and bundle branch block. The drug should not be administered to patients who have shown previous procaine or procainamide hypersensitivity. Prolonged administration should be accompanied by hematologic studies, since agranulocytosis may occur. Because of a potential hypotensive effect, intravenous administration should be titrated carefully monitoring blood pressure at no faster rate than 10–15 mg/kg/over 5–10 min. Procainamide currently is difficult to obtain in the United States.

Drug interactions. Cimetidine inhibits the metabolism of procainamide. Simultaneous use of alcohol will increase the hepatic clearance of procainamide. The simultaneous administration of quinidine or amiodarone may increase the plasma concentration of procainamide.

Class IB

Lidocaine

Lidocaine (*Xylocaine*) is a local anesthetic that blocks sodium channels, binding to channels in both the open and inactivated state. Lidocaine, like other Class IB agents acts preferentially in diseased tissue causing conduction block and interrupting reentrant tachycardias (Tables 22.1 and 22.2).

Electrophysiological Actions

SA node and atrium: At therapeutic doses (1–5 mg/kg), lidocaine has no effect on the sinus rate and weak effects on atrial tissue.

AV node: Lidocaine has minimal effects on the conduction velocity and ERP of the AV node.

His–Purkinje system and ventricular muscle: Lidocaine reduces membrane responsiveness and decreases automaticity. Lidocaine in very low concentrations slows phase 4 depolarization in Purkinje fibers. In higher concentrations, automaticity may be suppressed, and phase 4 depolarization eliminated.

Electrocardiographic changes. The PR, QRS, and QT intervals are usually unchanged, although the QT interval may be shortened in some patients. The paucity of electrocardiographic changes reflects lidocaine's lack of effect on healthy myocardium and conducting tissue.

Hemodynamic effects. At usual doses, lidocaine does not depress myocardial function, even in the patient with heart failure.

Pharmacokinetics. Due to extensive first pass metabolism, lidocaine is not used orally. The onset of action is immediate when given intravenously with a plasma half-life of 1–2 h. Elimination is primarily via the liver (90 %) with the rest unchanged in the urine. Therapeutic serum levels range from 1.5 to 6.0 μg/mL. Lidocaine clearance is reduced by CHF, hepatic dysfunction, and concomitant treatment with cimetidine or beta-blockers.

Clinical uses. Lidocaine is useful in the control of ventricular arrhythmias. It is not useful for the treatment of supraventricular arrhythmias. Lidocaine's use has decreased as amiodarone is frequently being used primarily for postoperative ventricular ectopy.

Adverse effects. CNS toxicity is the most frequent adverse effect. Paresthesias, disorientation, and muscle twitching may forewarn of more serious deleterious effects, including psychosis, respiratory depression, and seizures. Myocardial depression may occur at very high doses.

Contraindications. Contraindications include hypersensitivity to local anesthetics of the amide type (a very rare occurrence), severe hepatic dysfunction, or a previous history of grand mal seizures due to lidocaine. Care must be used in the presence of second- or third-degree heart block as it may increase the degree of block and abolish all idioventricular pacemakers.

Drug interactions. The concurrent administration of lidocaine with cimetidine, but not ranitidine, may cause an increase in the plasma concentration of lidocaine. The myocardial depressant effect of lidocaine is enhanced by phenytoin administration.

Mexiletine

Mexiletine (*Mexitil*) is a structural analog of lidocaine altered to prevent first pass metabolism. Mexiletine has properties similar to lidocaine and is frequently combined with quinidine to increase efficacy while decreasing the risk of proarrhythmia (Tables 22.1 and 22.2).

Electrophysiological actions. Mexiletine slows conduction velocity with a negligible effect on repolarization. Mexiletine demonstrates a rate-dependent blocking action on the sodium channel with rapid onset and recovery kinetics.

Hemodynamic effects. Although its cardiovascular toxicity is minimal, the drug should be used with caution in patients who are hypotensive or who exhibit severe left ventricular dysfunction.

Pharmacokinetics. Mexiletine has an oral bioavailability of 90 %. Its onset of action is 0.5–2.0 h with a plasma half-life of 10–12 h. Mexiletine is metabolized in the liver and excreted in the bile with 10 % renal excretion. Therapeutic serum concentrations range from 0.5 to 2.0 μg/mL.

Clinical uses. Mexiletine is useful in the management of both acute and chronic ventricular arrhythmias. While not currently an indication for use, there is interest in using mexiletine to treat the congenital long QT syndrome caused by a mutation in the SCN5A gene (*LQTS 3*).

Adverse effects. A very narrow therapeutic window limits mexiletine use. The first signs of toxicity are a fine tremor of the hands, followed by dizziness and blurred vision. Side effects include upper gastrointestinal distress, tremor, light-head-

edness, and coordination difficulties. These effects generally are not serious and can be reduced by downward dose adjustment or administering the drug with meals. Cardiovascular-related adverse effects are less common and include palpitations, chest pain, and angina or angina-like pain.

Contraindications. Mexiletine is contraindicated in the presence of cardiogenic shock or preexisting second- or third-degree heart block in the absence of a cardiac pacemaker. Caution must be exercised in administration of the drug to patients with sinus node dysfunction or disturbances of intraventricular conduction.

Drug interactions. An upward adjustment in dose may be required when mexiletine is administered with phenytoin or rifampin, due to increased hepatic metabolism of mexiletine.

In the search for new anti-arrhythmic drugs, single enantiomers of existing drugs that are racemic mixtures are being developed. One such drug is Mexiletine-m-Hydroxymexiletine (MHM), a minor metabolite of the Class IB anti-arrhythmic drug mexiletine. It is approximately twofold more potent than the parent compound on human cardiac voltage-gated sodium channels (hNav1.5), and equipotent to mexiletine on human skeletal muscle voltage-gated sodium channels (hNav1.4). An alternative and simplified synthesis of this promising compound has been accomplished avoiding the use of oxidizing agents, such as the meta-chloroperoxybenzoic acid. At the time of publication, this medication has not been put into clinical trials.

Class IC

Flecainide

Flecainide (*Tambocor*) slows conduction throughout the heart, most notable in the His–Purkinje system and ventricular myocardium. Flecainide also weakly inhibits the delayed rectifier potassium channel (slightly prolonging repolarization) and inhibits abnormal automaticity (Tables 22.1 and 22.2).

Electrophysiological Actions

SA node and atrium: Flecainide causes a clinically insignificant decrease in heart rate. In the atrium, flecainide decreases the conduction velocity, shifts the membrane responsiveness curve to the right, and prolongs the action potential in a use-dependent fashion.

AV node: Atrioventricular conduction is prolonged.

His–Purkinje system and ventricular muscle: Flecainide slows conduction in the His–Purkinje system and ventricular muscle to a greater degree than in the atrium. Flecainide may also cause block in accessory AV connections, which is the principal mechanism for its effectiveness in treating atrioventricular reentrant tachycardia.

Electrocardiographic changes. Flecainide increases the PR, QRS, and to a lesser extent, the QTc intervals. The rate of ventricular repolarization is not affected and the QT interval prolongation is caused by the increase in the QRS duration.

Hemodynamic effects. Flecainide produces modest negative inotropic effects that may become significant in the subset of patients with compromised left ventricular function.

Pharmacokinetics. Flecainide is well absorbed with a bioavailability of 90–95 %. Oral absorption may be inhibited by milk and milk-based formulas. The onset of action is 1–2 h with a serum half-life of 12–30 h. The drug is primarily metabolized in the liver and excreted in the urine. Therapeutic serum concentrations are 0.2–1.0 μg/mL. The dose should be halved in patients with severe renal impairment.

Clinical uses. Flecainide is effective in treating atrial arrhythmias, particularly those supported by reentrant mechanisms, and is also used for life-threatening ventricular arrhythmias. Based on the results of the CAST study in adults with ischemic heart disease, and several reports of pro-arrhythmia in patients with repaired congenital

heart disease, flecainide should be used with caution in patients with acquired or congenital structural heart disease. Flecainide crosses the placenta with fetal levels approximately 70 % of maternal levels and in many centers is the second-line drug after digoxin for therapy of fetal arrhythmias. Flecainide is also the second-line drug for SVT in children who are not well controlled on beta-blockers in many centers. Due to the possibility of pro-arrhythmia (Table 22.3), initiation of therapy or significant increases in dosing may be performed as an inpatient. Based on murine studies and a retrospective clinical report, flecainide may have selective properties for the management of catecholaminergic polymorphic ventricular tachycardia; a randomized trial is underway.

Adverse effects. Most adverse effects are observed within a few days of initial drug administration and include dizziness, visual disturbances, nausea, headache, and dyspnea. Worsening of heart failure and prolongation of the PR and QRS intervals may occur. The risk of pro-arrhythmia appears to be less than that observed in the adult population. The most frequent pro-arrhythmic effect is the occurrence of slow incessant SVT. Ventricular arrhythmias have been observed in patients following repair of congenital heart disease.

Contraindications. Flecainide is contraindicated in patients with preexisting second- or third-degree heart block unless a pacemaker is present to maintain ventricular rhythm. The drug should not be used in patients with cardiogenic shock.

Drug interactions. Cimetidine may reduce the rate of flecainide's hepatic metabolism, thereby increasing the potential for toxicity. Flecainide may increase digoxin concentrations.

Propafenone

Propafenone (*Rythmol*) blocks the sodium channel, and like flecainide, propafenone weakly blocks potassium channels. Additionally propafenone is a weak β-receptor antagonist and L-type calcium channel blocker (Tables 22.1 and 22.2).

Electrophysiological Actions

SA node: Propafenone causes sinus node slowing.

Atrium: The action potential duration and effective refractory period are prolonged while the conduction velocity is decreased. Similar to other Class I drugs, these effects may slow atrial flutter to a rate that allows for more rapid conduction into the ventricle.

AV node: Intravenous administration slows conduction through the AV node.

His–Purkinje system and ventricular muscle: Propafenone slows conduction and inhibits automatic foci.

Electrocardiographic changes. Propafenone causes dose-dependent increases in the PR and QRS intervals.

Hemodynamic effects. In the absence of cardiac abnormalities, propafenone has no significant effects on cardiac function. Intravenous administration may result in a decrement in decreased myocardial performance in patients with ventricular dysfunction.

Pharmacokinetics. Propafenone is nearly 10 to 50 % absorbed following an oral dose. It has a serum half-life of 2–10 h. It is metabolized in the liver with nearly one-third of the drug excreted unchanged in the urine. Therapeutic serum concentrations are 0.06–0.10 μg/mL.

Clinical uses. Propafenone is useful for the treatment of supraventricular arrhythmias and life-threatening ventricular arrhythmias in the absence of structural heart disease. Propafenone should be used with caution in patients with congenital heart disease (especially in the absence of an implanted pacemaker) due to the increased risk of ventricular pro-arrhythmia. Like flecainide, some clinicians initiate therapy as an inpatient.

Adverse effects and drug interactions. Concurrent administration of propafenone with digoxin, warfarin, propranolol, or metoprolol increases the serum concentrations of the latter four drugs. Cimetidine slightly increases the propafenone

serum concentrations. Additive pharmacological effects can occur when lidocaine, procainamide, and quinidine are combined with propafenone. As with other members of Class IC, propafenone may interact in an unfavorable way with other agents that depress AV nodal function, intraventricular conduction, or myocardial contractility. The most common adverse effects are dizziness, light-headedness, a metallic taste, nausea, and vomiting.

Contraindications. Propafenone is contraindicated in the presence of severe congestive heart failure, cardiogenic shock, atrio-ventricular and intraventricular conduction disorders, and sick sinus syndrome. Other contraindications include severe bradycardia, hypotension, obstructive pulmonary disease, and hepatic and renal failure. Because of its weak β-blocking action, propafenone may cause dose-related bronchospasm.

Class II

Class II anti-arrhythmic drugs competitively inhibit β-adrenoceptors. In addition, some members of the group (e.g., propranolol and acebutolol) cause electrophysiological alterations in Purkinje fibers that resemble those produced by Class I anti-arrhythmic drugs. The latter actions have been referred to as "membrane-stabilizing" effects.

Class II: β-Blockers

Propranolol

Propranolol (*Inderal*, *Inderal LA*) is the prototype β-blocker. It decreases the effects of sympathetic stimulation by competitively binding to β-adrenergic receptors (Table 22.4).

Electrophysiological actions. Propranolol has two separate and distinct effects. The first is a consequence of the drug's β-adrenergic receptor blocking properties and the subsequent removal of adrenergic influences on the heart. The second is associated with the direct myocardial effects (membrane stabilization) of propranolol. The latter action, especially at the higher clinically employed doses, may account for its effectiveness against arrhythmias in which enhanced β-receptor stimulation does not play a significant role in the genesis of the rhythm disturbance.

SA node: Propranolol slows the spontaneous firing rate of nodal cells by decreasing the slope of phase 4 depolarization.

Atrium: Propranolol possesses local anesthetic properties and decreases action potential amplitude and excitability. The serum concentrations at which the membrane stabilizing effects are evident are similar to those that produce β-blockade; hence, it is impossible to determine whether the drug acts by specific receptor blockade or via a "membrane-stabilizing" effect.

AV node: Propranolol administration results in a decrease in AV conduction velocity and an increase in the AV nodal refractory period.

His–Purkinje system and ventricular muscle: Propranolol at usual therapeutic concentrations produces a depression of catecholamine-stimulated automaticity. At supra-normal concentrations, propranolol decreases Purkinje fiber membrane responsiveness and reduces action potential amplitude.

Electrocardiographic changes. The PR interval is prolonged with no change in the QRS interval. The QT interval may be shortened by propranolol administration.

Table 22.4 Class II drugs

Drug	Receptor	$T_{1/2}$	Metabolized	Excreted	Dose
Propranolol	$\beta_1 + \beta_2$	3–5 h	Hepatic	Renal	1–4 mg/kg/d ÷ qid
Atenolol	β_1	9–10 h	Minimal	Renal	1–2 mg/kg/d ÷ bid
Nadolol	$\beta_1 + \beta_2$	20–24 h	Minimal	Renal	1 mg/kg/d ÷ qd–bid
Esmolol	β_1	7–10 min	Esterases in erythrocytes		Load: 500 μg/kg over 1 min, maintenance 200–800 μg/kg

Hemodynamic effects. β-Adrenoceptor blockade leads to a decrease in the positive inotropic and chronotropic effects of catecholamines. Clinically, the heart rate and blood pressure falls and the myocardial oxygen consumption is decreased.

Pharmacokinetics. See Table 22.4.

Clinical uses. Propranolol is useful for a wide spectrum of arrhythmias. Propranolol, atenolol, or nadolol (see below) is usually the initial therapy for SVT in all age groups. It is also effective in several forms of ventricular ectopy/tachycardia including the suppression of symptomatic PVCs and catecholamine-dependent idiopathic VT. Propranolol is the drug of choice for treating patients with the congenital long QT syndrome, especially in infants as a propranolol solution is available.

Adverse effects. Cardiac adverse effects include bradycardia and hypotension. Propranolol may result in bronchospasm in patients with asthma, which may be life threatening. Propranolol crosses the blood–brain barrier and is associated with mood changes and depression. School difficulties may be seen in children. Propranolol may also cause hypoglycemia in infants. Since propranolol crosses the placenta and enters the fetal circulation, fetal cardiac responses to the stresses of labor and delivery are blunted.

Contraindications. Propranolol should be used with caution in patients with depressed myocardial function. It may be contraindicated in the presence of digitalis toxicity because of the possibility of producing complete AV block and ventricular asystole. It should be used with caution in patients with asthma. An up-regulation of β-receptors follows long-term therapy making a tapered withdrawal of β-blockers advisable.

Atenolol

Atenolol (*Tenormin*) is selective for the β_1-receptor. Atenolol's advantages relative to propranolol are its longer serum half-life and limited diffusion across the blood–brain barrier leading to a marked reduction in CNS effects (Table 22.4).

Electrophysiological actions and electrocardiographic changes. Identical to propranolol.

Pharmacokinetics. See Table 22.4.

Clinical uses. Atenolol has been used for all supraventricular tachycardias and for control of ventricular ectopy. In many centers it is the drug of choice for the initial therapy of SVT.

Adverse effects. The side effect profile is favorable compared with propranolol due to the lack of penetration across the blood–brain barrier. Despite its relative selectivity for the β_1-receptor, a worsening of bronchospasm may result and therefore it should be used with caution in patients with a history of reactive airway disease.

Contraindications. Relatively contraindicated in patients with reactive airway disease.

Nadolol

Nadolol (*Corgard*) is a long-acting nonselective β-adrenergic antagonist without membrane-stabilizing or intrinsic sympathomimetic activity (Table 22.4).

Electrophysiological actions and hemodynamic effects. Similar to propranolol.

Pharmacokinetics. See Table 22.4.

Clinical uses. Nadolol has been used for the treatment of various forms of supraventricular tachycardia and for patients with the long QT syndrome. Like atenolol, its long serum half-life and reduced CNS effects make nadolol an attractive alternative to propranolol.

Adverse effects and contraindications. Similar to propranolol.

Esmolol

Esmolol (*Brevibloc*) is a short-acting, intravenously administered β_1-selective adrenoceptor blocking agent. It does not possess membrane-stabilizing activity or sympathomimetic activity (Table 22.4).

Electrophysiological actions and hemodynamic effects. Similar to propranolol.

Pharmacokinetics. See Table 22.4.

Clinical uses. Esmolol is useful for the acute treatment of supraventricular and ventricular tachyarrhythmias, as well as for acutely lowering blood pressure. Discontinuation of administration is followed by a rapid reversal of its pharmacological effects because of its rapid hydrolysis by plasma esterases.

Adverse effects and contraindications. The most frequently reported adverse effects are hypotension, nausea, dizziness, headache, and dyspnea. As with many β-blocking drugs, esmolol is contraindicated in patients with overt heart failure or for those in cardiogenic shock.

Class III

Class III anti-arrhythmic drugs prolong the duration of the membrane action potential by delaying repolarization without altering depolarization or the resting membrane potential. Class III drugs have a significant risk of pro-arrhythmia due to action potential duration prolongation and the induction of torsades de pointes.

Amiodarone

Amiodarone (*Cordarone*, *Pacerone*) is an iodine-containing benzofuran derivative identified as a Class III agent due to its predominant action potential-prolonging effects. Amiodarone also blocks sodium and calcium channels, as well as being a non-competitive β-receptor blocker (Class I, II, and IV actions). Amiodarone is an effective agent for the treatment of most arrhythmias. Toxicity associated with amiodarone has led the FDA to recommend that the drug be reserved for use in patients with life-threatening arrhythmias (Tables 22.5 and 22.6).

Electrophysiological actions. The electrophysiological effects of amiodarone are complex and still not completely understood. Notably, the acute effects differ significantly from the chronic effects (Table 22.4). The most prominent electrophysiological effect of amiodarone after long-term administration is a prolongation of repolarization and refractoriness in all cardiac tissues, an action that is characteristic of Class III anti-arrhythmic agents.

Table 22.5 Amiodarone—pharmacological therapy

	Acute therapy	Chronic therapy
Heart rate	±	↓↓↓
QTc	±	↑↑↑
AV node conduction	± to ↓	↓↓
Accessory pathway ERP	↑	↑↑↑
β-Blockade	++	+++
Negative inotropic effect	+	±

SA node: Amiodarone and its metabolite desethylamiodarone inhibit nodal function. It may profoundly inhibit SA nodal activity in patients with underlying sick sinus syndrome and require permanent pacing due to hemodynamically significant bradycardia. This is a common problem in patients following the Fontan and atrial switch operations.

His–Purkinje system and ventricular muscle: Amiodarone and desethylamiodarone increase AV nodal conduction time and refractory period. The dominant effect on ventricular myocardium with chronic treatment is a prolongation in the action potential duration and increase in the refractory period with a modest decrease in conduction velocity.

Electrocardiographic changes. The predominant electrocardiographic changes include a prolongation of the PR and QTc intervals, the development of U-waves, and changes in T-wave contour.

Hemodynamic effects. Amiodarone relaxes vascular smooth muscle and improves regional myocardial blood flow. In addition, its effects on the peripheral vascular bed lead to a decrease in left ventricular stroke work and myocardial oxygen consumption. Intravenous administration may be associated with hypotension requiring volume expansion.

Pharmacokinetics. The pharmacokinetic characteristics of amiodarone are extremely complex. Absorption is slow and the oral bioavailability is

Table 22.6 Class III drugs

Drug	Dose	$T_{1/2}$	Therapeutic serum levels	Route of elimination	ECG changes		
					PR	QRS	QTc
Amiodarone	Loading: PO: 10–20 mg/kg/d bid × 5–10 days; IV: 5 mg/kg over 1/2 h (may repeat × 1)	26–107 days	0.5–2.5 μg/mL	B	Acute: ±	±	±
	Maintenance: PO: 5 mg/kg qd; IV: 10–15 mg/kg/d				Chronic: ↑	↑	↑↑↑
Sotalol	PO: starting dose = 2 mg/kg/d bid, may increase slowly to 8 mg/kg/d	9.5 h in children	None established	HR	↑	±	↑↑↑
Dofetilide	No pediatric dosing. For creatinine clearance >60 mL/min = 500 μg bid, for creatinine clearance 40–60 mL/min = 250 μg bid	7–10 h	None established	R	±	±	↑↑↑
Ibutilide	>60 kg = 1 mg IV over 10 min, repeat × 1 if necessary 10 min after completion. <60 kg = 10 μg/kg IV over 10, repeat × 1 if necessary 10 min after completion	6 h	Serum levels not related to clinical efficacy	HR	±	±	↑↑↑
Vernakalant	Potassium channel blocker similar to Class II. Not used for arrhythmias						
Ranolazine	Potassium channel blocker similar to Class II not used for arrhythmias						

B Biliary, *HR* hepatic metabolism, renal excretion; *R* renal, ± = no significant change, ↑ = increase

low (35–65 %). The drug is almost completely protein bound and is concentrated in the myocardium (10–50× serum concentration), as well as in adipose tissue, the liver, and lungs (100–1,000× serum concentration). The serum half-life ranges from 26 to 107 days with chronic administration. The primary route of metabolism is hepatic with excretion via the biliary tract. Therapeutic serum concentrations are 0.5–2.5 μg/mL.

Clinical uses. Amiodarone is effective in a wide variety of cardiac rhythm disorders with minimal tendency for induction of torsades de pointes. The incidence of ventricular pro-arrhythmia is significantly less than other Class III agents. Its use, however, is limited by the multiple and severe non-cardiac side effects.

Intravenous amiodarone has been used to treat a wide range of arrhythmias, particularly in the postoperative period including supraventricular tachycardia, atrial flutter, atrial fibrillation, intra-atrial reentrant tachycardia, junctional ectopic tachycardia, and ventricular tachycardia. Chronic oral amiodarone administration is more efficacious than intravenous use. Oral amiodarone is effective in most forms of supraventricular and ventricular tachycardia with its use limited by the frequency and severity of its adverse effects. Because of its unknown effect on thyroid

function and growth, use of amiodarone for treating SVT is reserved for patients who have failed several other medications and is time limited.

Adverse effects. The most significant adverse effects include chemical hepatitis, worsening sinus node dysfunction, thyroid dysfunction (hypo or hyper), and pulmonary fibrosis (Table 22.7). Pulmonary fibrosis is frequently fatal and may not be reversed with discontinuation of therapy. Despite significant prolongation of the QT interval, the risk of torsades de pointes is relatively low.

Patients with underlying sinus node dysfunction tend to have significant worsening of nodal function, frequently requiring pacemaker implantation. Corneal microdeposits are common although complaints of halos or blurred vision are rare. The corneal microdeposits are reversible upon stopping the drug. Dermatological complaints are frequent including photosensitization and blue-gray discoloration. The risk is increased in patients of fair complexion. The discoloration of the skin regresses slowly, if at all, after discontinuation of amiodarone.

Amiodarone inhibits the peripheral and intrapituitary conversion of thyroxine (T_4) to triiodothyronine (T_3) by inhibiting 5′-deiodination. The serum concentration of T_4 is increased by a decrease in its clearance, and increased synthesis due to a reduced suppression of the pituitary thyrotropin. The concentration of T_3 in the serum decreases and reverse T_3 appears in increased amounts. Despite these changes, the majority of

Table 22.7 Adverse reactions to amiodarone

Adverse reaction	Diagnosis	Incidence (%)	Screening	Management
Pulmonary	Cough, especially with local or diffuse infiltrates on CXR, suggesting interstitial pneumonitis; and decrease in DLCO from baseline	1–20	Pulmonary function tests: baseline and for any unexplained dyspnea, especially in patients with underlying lung disease; and if there are suggestive CXR abnormalities. CXR: Baseline and then yearly	Discontinue amiodarone. Consider corticosteroids
GI	Nausea, anorexia, and constipation		History, physical exam	Symptoms may decrease with decreased dose
	AST or ALT elevations >2 times normal	15–50	Liver function tests at baseline and every 6 months	Exclude other causes of hepatitis
	Hepatitis and cirrhosis	<3	Liver function tests at baseline and every 6 months	Discontinue amiodarone, consider liver biopsy to evaluate for cirrhosis
Thyroid	Hypothyroidism	1–22	Thyroid function tests (T4 and TSH) at baseline and every 6 months	Thyroxin
	Hyperthyroidism	<3	Thyroid function tests (T4 and TSH) at baseline and every 6 months	Corticosteroids, propylthiouracil or methimazole, may need thyroidectomy if cannot discontinue amiodarone
Skin	Blue discoloration	<10	Physical exam	Reassurance and sunblock
	Photosensitivity	25–75	Physical exam	Sunblock

(continued)

Table 22.7 (continued)

Adverse reaction	Diagnosis	Incidence (%)	Screening	Management
CNS	Ataxia, paraesthesias, peripheral polyneuropathy, sleep disturbances, impaired memory and tremor	3–30	Physical exam, history	Often dose dependent and improves or resolves with dose adjustment
Ocular	Halo vision, especially at night	<5	History, ophthalmologic exam at baseline if visual impairment is present or for symptoms	Corneal deposits are the norm; if optic neuritis occurs, discontinue amiodarone
	Optic neuritis	1	History, ophthalmologic exam at baseline if visual impairment is present or for symptoms	Discontinue amiodarone
Heart	Bradycardia and AV block (exaggerated effect in the face of existing sick sinus syndrome)	5	History, ECG (every 6 months), Holter for symptoms	May require permanent pacing
	Pro-arrhythmia (much less common than other Class III agents)	<1	History, ECG (every 6 months), Holter for symptoms	Discontinue amiodarone
GU	Epididymitis and erectile dysfunction	<1	History and physical exam	Pain may resolve spontaneously

patients appear to be maintained in a euthyroid state. Manifestations of both hypo- and hyperthyroidism have been reported.

Tremors of the hands and sleep disturbances in the form of vivid dreams, nightmares, and insomnia have been reported in association with the use of amiodarone. Ataxia, staggering, and impaired ambulation have also been noted. Peripheral sensory and motor neuropathy or severe proximal muscle weakness develops infrequently. Both neuropathic and myopathic changes are observed on biopsy. Neurological symptoms resolve or improve within several weeks of dosage reduction (Table 22.7).

Contraindications. Amiodarone is contraindicated in patients with sick sinus syndrome and may cause severe bradycardia and second- and third-degree AV block. Amiodarone crosses the placenta causing fetal bradycardia and thyroid abnormalities. The drug is secreted in breast milk.

Drug interactions. Amiodarone interferes with the metabolism of many drugs, most notably warfarin and digoxin. Patients receiving digoxin should have their dose decreased by 50 %. Amiodarone also interferes with the metabolism and elimination of flecainide, propafenone, procainamide, phenytoin, and quinidine.

Dronedarone

Dronedarone is a non-iodinated benzofuran derivative that was approved in 2009 by the US FDA and by the European Medicines Agency for the treatment of patients with atrial fibrillation. Dronedarone is a modified amiodarone molecule without the iodine, which is considered the main cause of the thyroid side effect and pulmonary toxicity of amiodarone, but with the addition of a methane-sulfonyl group.

Electrophysiologic effects. Dronedarone has electrophysiologic effects similar to those of amiodarone, except for a shorter half life of 1–2 days. Similar to amiodarone, dronedarone blocks multiple ion channels including both the rapidly activating and the slowly activating delayed rectifier potassium currents, the inward rectifier potassium current, the acetylcholine-

activated potassium current, the sodium current, and the L-type calcium current, and has an anti-adrenergic effect.

Pharmacokinetics and pharmacodynamics. Dronedarone should be given with meals as absorption increases two- to threefold when it is taken with food. It undergoes first-pass metabolism that reduces its bioavailability to 15 %. Because it is less lipophilic than amiodarone, it does not require loading doses and has a shorter half-life of approximately 24 h. Elimination is mostly non-renal. Dronedarone partially inhibits the tubular transportation of creatinine; hence it can increase the serum creatinine level by 10–20 %, but does not reduce glomerular filtration.

Drug interactions. It should not be administered with potent CYP3A4 inhibitors such as macrolide antibiotics, ketoconazole, and other antifungals. Lower doses of dronedarone should be used in combination with verapamil or diltiazem. It can also increase the risk of statin-induced myopathy. Dronedarone also increases digoxin level by 1.7- to 2.5-fold.

Adverse effects. The biggest concern from adult trials with Dronedarone is its potential risk in patients with severe and/or acute heart failure. It did not exhibit pulmonary or thyroid toxicity. Side effects include bradycardia, QT prolongation, diarrhea, nausea, and rash.

Sotalol

Sotalol (*Betapace*) possesses nonselective β-adrenoceptor blocking properties in addition to Class III actions via potassium channel blockade. The β-blocking effects are most evident at lower doses, with action potential-prolonging effects predominating at higher doses.

Electrophysiological Actions

SA node and atrium: Pacemaker activity in the SA node is decreased and sotalol increases the refractory period of atrial muscle.

AV node: Sotalol decreases conduction velocity and prolongs the effective refractory period in the AV node.

His–Purkinje system and ventricular muscle: Sotalol's inhibition of the delayed rectifier potassium channel results in a prolongation of the effective refractory period in His–Purkinje tissue. Like other Class III drugs, sotalol prolongs repolarization and increases the ERP of ventricular muscle.

Electrocardiographic changes. Sotalol is associated with a dose and concentration-dependent decrease in heart rate and a prolongation of the PR and QTc intervals. The QRS duration is not affected with plasma concentrations within the therapeutic range.

Hemodynamic effects. A modest reduction in systolic pressure and cardiac output may occur due to sotalol's β-adrenoceptor antagonist activity. Ventricular stroke volume is unaffected and the reduction in cardiac output is a consequence of the lowering of heart rate. In patients with normal ventricular function, cardiac output is maintained despite the decrease in heart rate due to a simultaneous increase in the stroke volume.

Pharmacokinetics. Sotalol has an oral bioavailability of 50 % with an onset of action of 0.5 h and a plasma half-life of 4 h. The primary route of metabolism is hepatic with excretion primarily in the urine (20 % unchanged and 40 % as metabolite).

Clinical uses. Sotalol possesses a broad spectrum of anti-arrhythmic effects in ventricular and supraventricular arrhythmias. Use is limited by concerns for ventricular pro-arrhythmia. Sotalol is also used in many centers as second-line medication for fetal arrhythmias (see Chap. 19).

Adverse effects. Side effects include those attributed to both β-adrenoceptor blockade and pro-arrhythmia. Other adverse effects of sotalol include, in decreasing order of frequency, fatigue, dyspnea, chest pain, headache, nausea, and vomiting.

Contraindications. Contraindications include severe heart failure or poor ventricular function. Use in patients with hypokalemia or prolonged

QT intervals may be contraindicated, as they enhance the possibility of pro-arrhythmic events.

Drug interactions. Drugs with inherent QT interval-prolonging activity (i.e., thiazide diuretics and terfenadine) may enhance the Class III effects of sotalol.

Dofetilide

Dofetilide (*Tikosyn*) is a "pure" Class III drug. It prolongs the cardiac action potential and the refractory period by selectively inhibiting the rapid component of the delayed rectifier potassium current (I_{Kr}).

Electrophysiological actions. Dofetilide blocks the cardiac ion channel carrying the rapid component of the delayed rectifier potassium current, I_{Kr}, over a wide range of concentrations with no significant effects on other repolarizing potassium currents.

The effects of dofetilide are exaggerated with hypokalemia and reduced with hyperkalemia. Dofetilide demonstrates reverse use dependence (i.e., less influence on the action potential at faster heart rates).

SA node and atrium: Dofetilide induces a minor slowing of the spontaneous discharge rate of the SA node via a reduction in the slope of the pacemaker potential and a hyperpolarization of the maximum diastolic potential. Dofetilide prolongs the plateau phase of the action potential thereby lengthening the refractory period of the myocardium. The effects on atrial tissue appear to be more profound than those observed in the ventricle. The reason for this is unclear.

AV node: There is no effect on the conduction through the AV node.

His–Purkinje system and ventricular muscle: Dofetilide increases the ERP of ventricular myocytes and Purkinje fibers. The ERP-prolonging effects on the ventricular tissue are somewhat less than that in atrial tissue.

Electrocardiographic changes. There are no changes in the PR or QRS intervals while the QT interval is prolonged. The increase in the QT interval is directly related to the dofetilide dose and plasma concentration.

Hemodynamic effects. Dofetilide does not significantly alter the mean arterial blood pressure, cardiac output, cardiac index, stroke volume index, or systemic vascular resistance. There is a slight increase in the dP/dt in the ventricles.

Pharmacokinetics. The absorption of dofetilide is delayed by ingestion of food; however, the total bioavailability is not affected and is greater than 90 %. The onset of action is a half hour with a plasma half-life of 7–10 h. More than 60 % of the drug is excreted unchanged in the urine with the remainder metabolized in the liver.

Clinical uses. Dofetilide is approved for the treatment of atrial fibrillation and atrial flutter in adults. Due to the lack of significant hemodynamic effects, it may be useful in patients with CHF who are in need of therapy for supraventricular tachyarrhythmias. Dofetilide has been used in a few patients following Fontan operation with refractory IART with favorable results.

Adverse effects. The incidence of non-cardiac adverse events is not different from that of placebo in controlled clinical trials. The principal cardiac adverse effect is the risk of torsades de pointes due to QT prolongation, which is approximately 3 % in adult trials. Most pro-arrhythmic events are observed in the first 3 days. As such, initiation of therapy should be performed as an inpatient.

Contraindications. Contraindications include baseline prolongation of the QT interval or use of other QT-prolonging drugs, history of torsades de pointes, creatinine clearance <20 mL/min, simultaneous use of verapamil, cimetidine, or ketoconazole, uncorrected hypokalemia (<4.0 mEq/100 mL), or hypomagnesemia and pregnancy or breast-feeding.

Drug interactions. Verapamil increases serum dofetilide levels. Additionally, drugs that inhibit cationic renal secretion such as ketoconazole and cimetidine raise serum levels.

Ibutilide

Ibutilide (*Corvert*) is a structural analog of sotalol and produces cardiac electrophysiological effects similar to Class III agents. Due to its significant first pass metabolism, ibutilide is only available as an intravenous preparation.

Electrophysiological actions. Ibutilide prolongs action potential duration in isolated adult cardiac myocytes and increases both atrial and ventricular refractoriness in vivo. Ibutilide administration leads to activation of a slow, inward current (predominantly sodium) in addition to blocking the delayed rectifier potassium current. By prolonging the duration of sodium channel conductance during depolarization and by inhibiting outward potassium currents, the net effect is one of increasing the duration of atrial and ventricular action potentials and refractoriness.

SA node and atrium: There is no significant change in heart rate in healthy adult volunteers. Ibutilide causes an increase in the atrial effective refractory period with little if any reverse use dependence, which is different than most Class III agents.

AV node: Experimental evidence suggests that ibutilide slows conduction through the AV node; however, there is no change in the PR interval on ECG.

His–Purkinje system and ventricular muscle: Ibutilide increases the ERP of ventricular myocytes and Purkinje fibers.

Electrocardiographic changes. There are no changes in the PR or QRS intervals reflecting a lack of effect on the conduction velocity. Although there is no relationship between the plasma concentration of ibutilide and the anti-arrhythmic effect, there is a dose-related prolongation of the QT interval. The maximum effect on the QT interval is a function of both the dose of ibutilide and the rate of infusion.

Hemodynamic effects. Ibutilide has no significant effects on cardiac output, mean pulmonary arterial pressure, or pulmonary capillary wedge pressure in patients with and without compromised ventricular function.

Pharmacokinetics. The pharmacokinetics are highly variable between patients and due to extensive first pass metabolism, ibutilide is not suitable for oral administration. The drug is extensively metabolized by the liver and is excreted in the urine. It is 40 % protein bound and has an elimination half-life of 6 h (range: 2–12 h).

Clinical uses. Ibutilide is approved for the intravenous chemical cardioversion of recent onset atrial fibrillation and atrial flutter in adults. It appears to be more effective in terminating atrial fibrillation than atrial flutter. Ibutilide has also been demonstrated to lower the defibrillation threshold (DFT) for atrial fibrillation resistant to chemical cardioversion. It has been used successfully in a limited number of pediatric patients both with and without congenital heart disease for the conversion of IART.

Adverse effects. The major adverse effect associated with the use of ibutilide is the risk of torsades de pointes due to QT prolongation occurring in approximately 4 % of adult patients usually within 40 min of initiating the infusion. Continuous ECG monitoring with the availability of equipment for urgent DC cardioversion is a necessity for up to 4–6 h after administration. Other reported adverse cardiovascular events (all <2 %) include hypo- and hypertension, brady- and tachycardia, and varying degrees of AV block. The incidence of non-cardiac adverse events with the exception of nausea did not differ from that of placebo in controlled clinical trials.

Contraindications. Contraindications include baseline prolongation of the QTc interval, use of other QT-prolonging drugs, history of torsades de pointes, or hypersensitivity to ibutilide, uncorrected hypokalemia (<4.0 mEq/100 mL) or hypomagnesemia, pregnancy or breast-feeding.

Drug interactions. No significant drug interactions.

Vernakalant

Vernakalant is a relatively atrial-selective anti-arrhythmic agent. It mainly blocks the ultra-rapid potassium channel but also blocks other ion currents such as the transient outward current and the inward sodium current. Vernakalant is currently only available in the IV formulation.

Electrophysiologic effects. Vernakalant prolongs atrial effective refractory period without significantly prolonging the ventricular effective refractory period. AV node refractoriness and the sinus node recovery time are also increased.

Clinical use. Trials have been done mainly in the acute conversion of atrial fibrillation and atrial flutter in adults. Most common side effects are dysgeusia (alteration in taste) and nausea.

Ranolazine

Ranolazine, like amiodarone, was developed as an anti-anginal agent, but later it was found to have blocking effects on multiple ion channels including the late sodium current, both the rapidly activating and the slowly activating delayed rectifier potassium currents, and the L-type calcium current. In adult trials it has showed a significant decrease in the incidence of new-onset atrial fibrillation, supraventricular tachycardia, and ventricular tachycardia. Interestingly, Ranolazine, a blocker of the late inward sodium current approved for treatment of angina, might induce atrial post-repolarization refractoriness and reduce intracellular sodium levels by inhibiting the late sodium current. This can prevent torsades de pointes, at least in models of the long QT syndrome. Pediatric dosing is not available at this time.

Class IV

Class IV drugs block the slow inward Ca^{2+} current (L-type calcium channel). The most pronounced electrophysiological effects are exerted on cardiac cells dependent on the Ca^{2+} channel for initiating the action potential, such as those found in the SA and AV nodes. The administration of Class IV drugs slows conduction velocity and increases refractoriness in the AV node, thereby reducing the ability of the AV node to conduct rapid impulses to the ventricle. This action may terminate supraventricular tachycardias and can slow conduction during atrial flutter or fibrillation.

Table 22.8 Class IV drugs

Drug	Dose	$T_{1/2}$ (h)	Metabolized
Verapamil	5–15 mg/kg ÷ tid–qid IV dose 0.1–0.2 mg/kg (equal to or less than 12 months); 0.1–0.3 mg/kg (age 1 to 15 years). May repeat twice in 10 to 30 min	37	Hepatic
Diltiazem	IV: bolus: 0.25 mg/kg over 5 min	4	Hepatic
	Infusion: 0.05–0.15 mg/kg/h		
	P.O.: 1.5–2.0 mg/kg/d ÷ tid		

Class IV Calcium Channel Blockers

Verapamil

Verapamil (*Isoptin*, *Covera*) selectively inhibits the voltage-gated calcium channel, vital for action potential genesis in slow response myocytes such as those found in the SA and AV nodes (Table 22.8).

Electrophysiological Actions

SA node and atrium: Verapamil decreases the rate of SA nodal cells firing. Verapamil does not exert any significant electrophysiological effects on atrial muscle.

AV node: Verapamil slows conduction through the AV node and prolongs the AV nodal refractory period.

His–Purkinje system and ventricular muscle: Verapamil has no effect on intraatrial and intraventricular conduction. The predominant electrophysiological effect is on AV conduction proximal to the His bundle.

Hemodynamic effects. Usual intravenous doses of verapamil are not associated with marked alterations in arterial blood pressure, peripheral vascular resistance, heart rate, left ventricular end-diastolic pressure, or contractility in adults and older children.

Pharmacokinetics. Verapamil is nearly completely absorbed but undergoes extensive first pass metabolism with only 10–20 % of an oral dose reaching the systemic circulation. The bioavailability is dramatically increased in patients with hepatic dysfunction and/or decreased hepatic blood flow. It is metabolized by the p450 system with the majority eliminated in the urine. The serum half-life during chronic oral therapy is 3–7 h. Therapeutic serum levels range between 0.12 and 50.4 μg/mL

Clinical uses. Verapamil is useful for slowing the ventricular response to atrial tachyarrhythmias such as atrial flutter and fibrillation. Verapamil is also effective in arrhythmias supported by enhanced automaticity such as ectopic atrial tachycardia and idiopathic LV-tachycardia. Verapamil is effective for the acute termination of supraventricular tachycardia that uses the AV node as a critical component such as AVNRT and accessory pathway-mediated tachycardia.

Adverse effects. Orally administered verapamil is well tolerated by the majority of patients. Most complaints are with respect to gastrointestinal side effects of constipation and gastric discomfort. Other complaints include vertigo, headache, nervousness, and pruritus.

Contraindications. Verapamil must be used with extreme caution or not at all in patients who are receiving β-adrenoceptor blocking agents due to exaggerating the depressant effects on heart rate, AV node conduction, and myocardial contractility. The use of verapamil in children less than 1 year of age, especially if in heart failure, is contraindicated due to the risks of cardiovascular collapse. Verapamil should be used with extreme caution in patients with ventricular dysfunction.

Diltiazem

The anti-arrhythmic actions, electrophysiological effect, and clinical uses of diltiazem (*Cardizem*) are similar to those of verapamil (Table 22.8)

Electrophysiological actions. Similar to verapamil.

Hemodynamic effects. Similar to verapamil.

Pharmacokinetics. Similar to verapamil, diltiazem is nearly completely absorbed but undergoes extensive first pass metabolism with only 45 % of an oral dose reaching the systemic circulation. The serum half-life is 4–7 h. Diltiazem is metabolized in the liver, but unlike verapamil, the majority is excreted via the GI tract (65 %). Therapeutic serum levels range between 0.50 and 300 ng/mL.

Clinical uses. Similar to verapamil. Experience in pediatrics is limited.

Adverse effects. Similar to verapamil with perhaps less ventricular depression.

Contraindications. Same as verapamil.

Miscellaneous Anti-arrhythmic Agents

Digitalis Glycosides

Digitalis glycosides, especially digoxin (*Lanoxin*), due to their positive inotropic effects are widely used for treating patients with congestive heart failure. Additionally they continue to be used for the management of patients with supraventricular arrhythmias. Digoxin slows conduction through the AV node making it useful for use in reentrant arrhythmias that utilize the AV node as one limb of the circuit. It has fallen

out of favor for limiting AV conduction during rapid atrial arrhythmias such as atrial fibrillation. Digitalis glycosides have theoretic advantages when compared with other medications that limit conduction through the AV node such as β-blockers and Ca^{2+} channel blockers by providing a positive rather than negative inotropic effect on the ventricles. The effects on the AV node are limited however in states of heightened sympathetic tone such as during advanced heart failure. Due to a potentially shortening effect on the effective refractory period of manifest accessory pathways (appears to be very low incidence), digitalis should be avoided in older patients with Wolff–Parkinson–White syndrome.

Adenosine

Adenosine (*Adenocard*) is an endogenously occurring nucleoside that is an end product of the metabolism of adenosine triphosphate. It is used for the rapid termination of supraventricular arrhythmias following rapid bolus dosing.

Electrophysiological actions. Adenosine receptors located on atrial myocytes and myocytes located in the SA and AV nodes act via a G-protein signaling cascade to open the same outward potassium current activated by acetylcholine. Adenosine stimulation leads to a hyperpolarization of the resting membrane potential, decrease in the slope of phase 4 depolarization and shortening of the action potential duration. The effects on the AV node may result in complete conduction block with termination of tachycardias utilizing the AV node as a limb of a reentrant circuit. Adenosine does not affect the action potential of ventricular myocytes because the adenosine-stimulated potassium channel is absent in ventricular myocardium.

Electrocardiographic changes. The most profound effect of adenosine is the induction of AV block (both antegrade and retrograde) within 10–20 s of administration. Mild sinus slowing may initially be observed followed by sinus tachycardia resulting from mild vasodilation and hypotension. There is no effect on the QRS duration or QT interval.

Hemodynamic effects. The administration of a bolus dose of adenosine is associated with a biphasic pressor response. There is an initial brief increase in blood pressure followed by vasodilatation and a secondary tachycardia.

Pharmacokinetics. Adenosine has a nearly instantaneous onset of action and is rapidly metabolized by red blood cells with a plasma half-life of less than 10 s. Due to its rapid metabolism, there is no orally available form.

Clinical uses. Adenosine is useful for the acute termination of supraventricular tachycardia that utilizes the AV node. Adenosine is also helpful for the diagnosis of narrow complex tachycardias by unmasking such as atrial flutter and ectopic atrial tachycardia (Fig. 22.2).

Adverse effects. Adverse reactions to the administration of adenosine are not uncommon; however, the short half-life of the drug limits the duration of such events. The most common adverse effects are flushing, chest pain, and dyspnea. Adenosine may induce profound bronchospasm in patients with known reactive airway disease. The mechanism for bronchospasm is unclear and the effect may last for up to 30 min despite the short half-life of the drug. Rarely, adenosine may induce atrial fibrillation (Fig. 22.2) due to shortening of the atrial refractory period. This is potentially dangerous in the face of an accessory pathway that could rapidly conduct the atrial signal to the ventricles leading to ventricular arrhythmias.

Contraindications. As indicated previously, the use of adenosine in asthmatic patients may exacerbate the asthmatic symptoms. Known hypersensitivity to adenosine precludes its use.

Drug interactions. Methylxanthines (such as theophylline) antagonize the effects of adenosine via blockade of the adenosine receptors and necessitate increased doses.

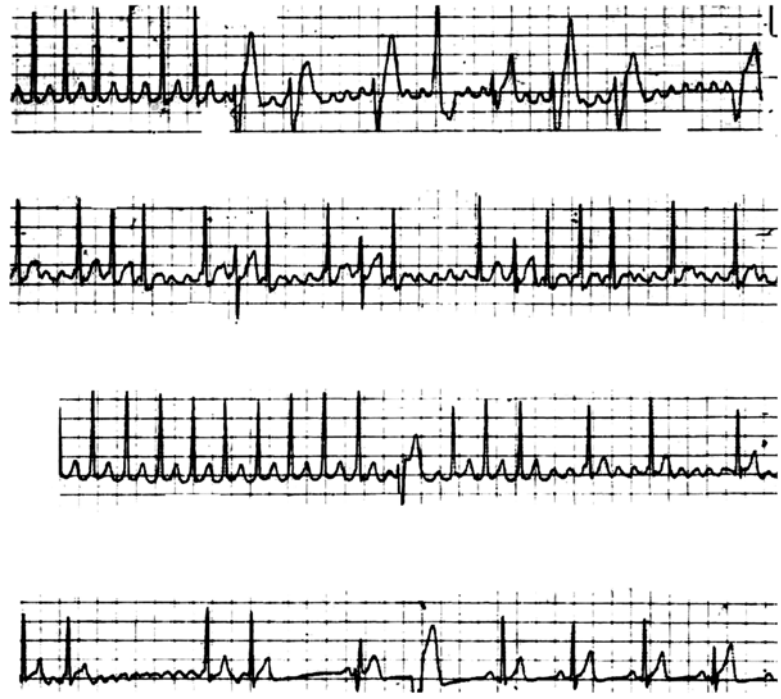


Fig. 22.2 Continuous monitor electrocardiogram lead in 15-year-old boy. Adenosine unmasked atrial flutter (*top tracing*) by inducing AV block and underlying atrial flutter. Conduction was then variable. The flutter converted to atrial fibrillation (*bottom tracing*) which then spontaneously terminated and sinus rhythm returned

Magnesium Sulfate

Magnesium sulfate may be effective in terminating refractory ventricular tachyarrhythmias, particularly polymorphic ventricular tachycardia. Digitalis-induced arrhythmias are more likely in the presence of magnesium deficiency. There has also been a suggestion that hypomagnesemia increases the likelihood of postoperative junctional ectopic tachycardia. Magnesium sulfate can be administered orally, intramuscularly, or, preferably, intravenously, when a rapid response is intended. The loss of deep tendon reflexes is a sign of overdose.

Ivabradine

Ivabradine acts on the I_f (funny) ion current, which is highly expressed in the sinoatrial node. I_f is a mixed Na+–K+ inward current activated by hyperpolarization and modulated by the autonomic nervous system. It is one of the most important ionic currents for regulating pacemaker activity in the sinoatrial (SA) node. Ivabradine selectively inhibits the pacemaker I_f current in a dose-dependent manner. This current, most likely generated by ion flow through proteins coded by the HCN gene family, is an attractive drug target because the target protein isoform is predominantly expressed only in the sinus node and in the retina. Hence, side effects are rare and are mainly limited to intermittent flash-like visual sensations secondary to interactions of the drug with retinal channels. These rarely limit therapy in adult patients. Ivabradine has been approved for the treatment of patients with angina pectoris who have contraindications to β-adrenoreceptor blockade and its use as an anti-arrhythmic drug is off-label at present for patients with inappropriate sinus tachycardia.

Table 22.9 Effects of anti-arrhythmic drugs on defibrillation thresholds

No change	Increase	Decrease
Quinidine	Amiodarone	Sotalol
Procainamide	Flecainide	Dofetilide
Disopyramide	Lidocaine	
Digitalis	Propafenone	
β-Blockers	Mexiletine	

Drug–Device Interactions

The use of ICDs in the pediatric population is expanding. Several large adult clinical trials performed in the 1990s demonstrated the superiority of ICDs compared with pharmacological therapy for secondary prevention of arrhythmic death (AVID, CASH, CIDS). Improvements in diagnostic techniques and slow improvement in risk stratification have increased the use of ICDs for primary prevention of sudden arrhythmic death in pediatrics. Combination therapy employing both anti-arrhythmic drugs and ICDs is becoming more common. Anti-arrhythmic drugs continue to be an important component of therapy following device implantation to suppress both ventricular and supraventricular arrhythmias. While the anti-arrhythmic drugs have multiple positive effects on the overall therapy, there are several possible deleterious effects. The principle adverse effects include an increase in the frequency of ICD discharges due to drug-induced pro-arrhythmia (Table 22.3), a slowing of the VT rate to below the detection rate despite being hemodynamically unstable, and changing the electrogram morphology, which may affect the ability of the device to detect VT. An additional concern is the potential for a drug to increase the DFT thereby rendering the device ineffective.

The DFT is a statistical prediction of the amount of energy that is required to defibrillate the heart. The effects that anti-arrhythmic drugs have on DFTs are somewhat inconsistent (Table 22.9). In general, drugs that block the sodium channel and shorten the action potential tend to increase the DFT. Drugs that prolong repolarization tend to decrease the DFT with the notable exception of amiodarone. Amiodarone appears to decrease the DFT acutely after intravenous administration; however, long-term therapy is associated with a significant increase in DFT energy requirements. These changes have obvious important ramifications for patients with ICDs.

Summary

Clinicians have a number of therapeutic options from which to choose in an effort to suppress or eliminate the sources or structures that support the arrhythmias, as well as to convert the heart to normal rhythm if other therapies fail. While recent technological advances have led to an increase in the use of non-pharmacological strategies including transcatheter radiofrequency or cryothermal ablation, intraoperative cryoablation as well as implantable pacemakers and defibrillators, pharmacological therapy remains a valuable tool for monotherapy or as adjunctive therapy in combination with device therapy.

Suggested Reading

Anonymous. The Sicilian gambit. A new approach to the classification of antiarrhythmic drugs based on their actions on arrhythmogenic mechanisms. Task Force of the Working Group on Arrhythmias of the European Society of Cardiology. Circulation. 1991;84(4):1831–51.

Brugada J, Blom N, Sarquella-Brugada G, Blomstrom-Lundqvist C, et al. Pharmacological and non-pharmacological therapy for arrhythmias in the pediatric population: EHRA and AEPC-Arrhythmia Working Group joint consensus statement. Europace. 2013;15(9):1337–82.

Carmeliet E, Mubagwa K. Antiarrhythmic drugs and cardiac ion channels: mechanisms of action. Prog Biophys Mol Biol. 1998;70:1–72.

Cavero I, Mestre M, Guillon JM, Crumb W. Drugs that prolong QT interval as an unwanted effect: assessing their likelihood of inducing hazardous cardiac dysrhythmias. Expert Opin Pharmacother. 2000;1:947–73.

Gillis AM. Effects of antiarrhythmic drugs on QT interval dispersion—relationship to antiarrhythmic action and proarrhythmia. Prog Cardiovasc Dis. 2000;42:385–96.

Glassman AH, Bigger Jr JT. Antipsychotic drugs: prolonged QTc interval, torsades de pointes, and sudden death. Am J Psychol. 2001;158:1774–82.

Hohnloser SH. Proarrhythmia with class III antiarrhythmic drugs: types, risks, and management. Am J Cardiol. 1997;80(8A):82G–9.

Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. N Engl J Med. 2001;345: 1473–82.

Link MS, Homound M, Foote CB, et al. Antiarrhythmic drug therapy for ventricular arrhythmias: current perspectives. J Cardiovasc Electrophysiol. 1996;7(7):653–70.

Nattel S, Singh BN. Evolution, mechanisms, and classification of antiarrhythmic drugs: focus on class III actions. Am J Cardiol. 1999;84(9A):11R–9.

Patel C, Yan GX, Kowey PR. Dronedarone. Circulation. 2009;120:636–44.

Roden DM, George Jr AL. The cardiac ion channels: relevance to management of arrhythmias. Annu Rev Med. 1996;47:135–48.

Schwartz PJ. Clinical applicability of molecular biology: the case of the long QT syndrome. Curr Control Trials Cardiovasc Med. 2000;1:88–91.

The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. N Engl J Med. 1989;321:406.

van der Werf C, Kannankeril PJ, Sacher F, et al. Flecainide therapy reduces exercise-induced ventricular arrhythmias in patients with catecholaminergic polymorphic ventricular tachycardia. J Am Coll Cardiol. 2011;57:2244–54.

Vaughan Williams EM. Significance of classifying antiarrhythmic actions since the cardiac arrhythmia suppression trial. J Clin Pharmacol. 1991;31:123.

Watanabe H, Chopra N, Laver D, et al. Flecainide prevents catecholaminergic polymorphic ventricular tachycardia in mice and humans. Nat Med. 2009; 15:380.

Transcatheter Ablation of Cardiac Arrhythmias in the Young

23

Martin J. LaPage, Ian H. Law,
and Macdonald Dick II

Transcatheter ablation of cardiac arrhythmias emerged in the early 1990s as definitive treatment for many forms of tachyarrhythmias in adults; the technique was rapidly adapted for treatment of arrhythmias in children. It is now the primary treatment for most tachyarrhythmias in both pediatric and adult patients. In 2002, the North American Society for Pacing and Electrophysiology (NASPE), now the Heart Rhythm Society (HRS), published an expert consensus statement on the indications for and performance of radiofrequency catheter ablation (RFCA) in children. New guidelines are under review and will be published in 2016 by the Heart Rhythm Society. While the development of new technologies, including cryoablation and computerized electroanatomic mapping, has been extensive since this consensus was developed, the basic tenets of the consensus remain applicable.

M.J. LaPage, M.D., M.S. • M. Dick, II , M.D. (✉)
Pediatric Cardiology, The University of Michigan Congenital Heart Center, Department of Pediatrics and Communicable Diseases, University of Michigan, Ann Arbor, MI, USA
e-mail: mlapage@med.umich.edu; mdick@med.umich.edu

I.H. Law, B.S.E., M.D.
Division of Cardiology, Department of Pediatrics, University of Iowa Children's Hospital, University of Iowa Carver College of Medicine, Iowa City, Iowa City, IA, USA
e-mail: ian-law@uiowa.edu

Indications for RFCA Procedures in Pediatrics (2002)

Class I (RFCA Is Recommended: Expert Broad Agreement, Supportive Data, Likely Beneficial)

- Wolff–Parkinson–White (WPW) syndrome following aborted sudden cardiac death
- WPW with syncope AND shortest preexcited RR or accessory pathway effective refractory period (APERP) < 250 ms at electrophysiology study (EPS)
- Chronic or recurrent supraventricular tachycardia (SVT) w/ventricular dysfunction
- Recurrent ventricular tachycardia (VT) with hemodynamic compromise that is amenable to RFCA

Class IIA (RFCA May Be Useful: Evidence/Opinion Divergent, Evidence/Opinion Favor Benefit)

- Planned cardiac operation which may restrict chamber access
- Chronic (6–12 months) or incessant SVT w/normal ventricular function
- Recurrent, chronic intra-atrial reentry tachycardia (IART)
- Palpitations with inducible SVT at EPS
- Recurrent/symptomatic SVT refractory to medical management and age > 4 years age

M. Dick, II (ed.), *Clinical Cardiac Electrophysiology in the Young*,
DOI 10.1007/978-1-4939-2739-5_23

Class IIB (RFCA May Be Considered: Evidence/Opinion Divergent; Benefit Not Well Established)

- Asymptomatic ventricular preexcitation, age > 5 years; risks/benefits of arrhythmia and ablation explained
- SVT, age > 5 years; alternative to effective anti-arrhythmic drugs
- SVT, age < 5 years; ineffective anti-arrhythmic drugs, including sotalol and amiodarone or intolerable side effects.
- IART, 1–3 episodes/year
- Atrioventricular (AV) node ablation for recurrent or intractable IART
- Single episode VT associated with hemodynamic compromise and amenable to RFCA

Class III (RFCA Is Not Indicated: Evidence and/or Agreement That Procedure Is Not Useful and May Be Harmful)

- Asymptomatic ventricular preexcitation, <5 years
- SVT, age < 5 years; effective AAD
- NS-VT (not incessant—hours) no hemodynamic compromise
- NS-SVT no Rx required, minimally symptomatic

Since this consensus was formulated the pediatric catheter ablation has grown immensely and the adaption of cryoablation as an alternative to RFCA has led to more liberal use. Many pediatric electrophysiologists would advocate for attempting ablation in some patients with SVT younger than 5 years old as an alternative to chronic anti-arrhythmic therapy, especially amiodarone. Although the 2002 guidelines base the dichotomy of recommendations for children largely on patient age, patient weight less than 15 kg was also identified as an independent risk factor for complications and provides a more rational basis, than an arbitrary chronological age. Cryoablation has been shown to be a safe modality for ablation in patients <5 years old and <15 kg though efficacy was not as high as in older children, likely due to difficulty in manipulating the relatively bulky cryocatheter in a small heart.

As with all consensus statements, these serve as guidelines to patient management and the individual characteristics of the patient and managing electrophysiologists will determine if and when catheter ablation is indicated as appropriate treatment. Because medical management with anti-arrhythmic agents carries its own risks and side effects, families may elect a treatment that has been shown to be safe and which can be expected to be successful. Finally, after frank discussion regarding the potential risks and the expected benefits of all possible management strategies are outlined in detail with full understanding by the patient (if competent) and parents (legal guardian), the decision to manage the arrhythmias with ablation techniques outside the specific guidelines may be a reasonable course.

Currently, the decision to use radiofrequency (RF) or cryoablation in the child depends on several factors including substrate, substrate location, and patient size. Equally important is operator preference and experience. Cryoablation is commonly used for AV nodal reentry tachycardia (AVNRT) due to its proven safety when used near the AV node. However, an unpublished 2012 survey of 100 pediatric electrophysiologists showed that only about 44 % used cryo as the primary modality for AVNRT and 16 % had switched back to the primary use of RF after using cryoablation for AVNRT. The hesitation in fully adapting cryoablation stems from the perceived lower efficacy and higher recurrence rates in existing studies—all performed when the technique and application of cryoablation was still evolving. For substrates away from the AV node, RF remains the preferred energy source for ablation, demonstrating both high efficacy and safety. Nonetheless, both RF and cryo have functional and physiologic advantages which direct their use. While this chapter primarily describes the use of RF ablation for treatment of accessory pathways and focal tachycardias, cryoablation is often an interchangeable technique for elimination of these substrates.

Radiofrequency Ablation

RF ablation catheters deliver alternating current between the catheter tip electrode and a large electrode patch placed on the patient's skin. The current delivered from the catheter tip produces resistive heating at the catheter–tissue interface which results in selective destruction of the arrhythmia substrate. Pathologically, desiccation and coagulation necrosis occur at the target site; the lesion heals to form a dense small scar.

Tissue temperatures must reach at least 50 °C to achieve irreversible tissue damage. High temperature (≥75–80 °C) may result in blood coagulation and clot formation, indicated by a rise in the impedance and requiring cleaning of the catheter tip electrode. Temperatures of 100 °C boil the liquid contents of the myocytes and may produce an audible "pop" resulting in larger areas of necrosis and possible unintended collateral damage to adjacent structures. RF generators provide continuous graphic displays of impedance, watts (power), and, most importantly, temperature at the catheter tip—the chief indicator of tissue "burn" provided there is adequate catheter–tissue contact. Lesion size is directly proportional to the physician adjustable factors of tissue temperature, power delivered (Watts), electrode tip size (4, 5, 8, or 10 mm), and contact pressure. Temperature is regulated by the RF generator and directly related to the delivered power. Both the delivered power and or the regulated temperature may be adjustable through the generator to achieve temperatures between 50 and 80 °C at the electrode–tissue interface. The operator can often improve contact between catheter tip and tissue by careful monitoring for low impedance, indicating sufficient current flow and satisfactory temperature rise, and by sensing tension along the catheter shaft as the tip rests firmly against the target site. The half-time of lesion formation is 5–10 s, indicating 30–50 s (5 half times) is adequate for full lesion formation. A typical 4 mm tip RF ablation catheter operating to achieve a tissue temperature of 60° in experimental animal models will produce a lesion 5–6 mm in diameter and 2–3 mm deep.

Often atrial flutter and IART ablation may benefit from a different size or configured electrode tip and greater power delivery due to extensive scarring and fibrotic atrial walls due to prior operations (Mustard, Senning, Fontan). Increased lesion depth can be achieved with a cooled catheter due to the ability to deliver greater energy to the tissue. Because of the temperature-dependent risks of coagulum formation and steam "pops," the catheter tip temperature is controlled and in turn regulates the power output. Cooling the catheter tip with saline irrigation allows the tip to remain cool and therefore greater power can be delivered without reaching the "critical" tip temperature. Higher power produces a deeper lesion. However, this benefit also comes with the inability to regulate tip temperature and tissue temperature as a result. Steam "pops" is still possible as the deeper tissue heats. Typically, sufficient power output is in the range of 25–35 W. Non-irrigated catheters are cooled passively by blood flow. Therefore, irrigated RF catheters are especially useful in areas where blood flow is low—such as trabeculated tissue or the Fontan circuit.

Cryoablation

Cryothermal catheter ablation, cryoablation, is an alternative means to ablate arrhythmia substrates by freezing the tissue. Cryoablation catheters use a refrigerant fluid (NO_2) delivered through a catheter-housed closed capillary circuit to the catheter electrode tip. As the liquid-to-gas phase of the cryogenic fluid passes into the tip that is in good contact with the myocardial tissue, the tip and tissue temperature drop to a preset level. The gas is conducted away through a vacuum return tube. An iceball forms on the catheter tip at approximately −20 °C, resulting in adherence to the myocardium. In the early years of cryoablation catheter use, a 4 mm tip catheter was used and the system allowed for a "cryo-mapping" mode during which tip temperatures could be limited to −30 °C. Currently 6 and 8 mm tip catheters are used primarily and a "cryo-mapping" function is not available. The catheter tip achieves a goal temperature of −70 to −80 °C.

Tissue damage with cryoablation is the result of cell freezing which leads to intracellular ice formation and cell rupture. Both freezing and thawing of the tissue contributes to cell death. Time exposure to the ice formation also affects lethality full lesion size and is typically achieved by 4 min. The resultant cryogenic lesion is homogenous, acellular, and well demarcated, with no endocardial disruption and full of collagen fibers—fibrous stroma.

Cryoablation provides some significant safety and functional advantages compared to RF ablation. RF energy delivered to the triangle of Koch near the AV conduction tissue may pose a direct risk to the AV node, His bundle, or AV nodal artery by virtue of their proximity, placing the patient at risk for complete heart block. With cryoablation, the electrophysiologic function of the tissue is affected before complete freezing and cell death occurs. Therefore the electrical effect of the ablation (substrate termination or inadvertent collateral damage such as AV node block) will be noted when the cryo effect is still reversible. Terminating cryoapplication at this point allows for tissue thawing and functional recovery. This feature allows for ablations to be performed very near the normal conduction system safely. Permanent damage to the conduction system is still possible with cryoablation, but avoidable with vigilant attention to AV nodal function. At this time, there have been no published reports of cryoablation causing inadvertent AV block. The cryocatheter also adheres to the tissue allowing for complete catheter stability during pacing maneuvers or abrupt changes in heart rate, such that ablation can be performed in tachycardia without concern for catheter movement upon termination. Finally, cryo-lesions do not disrupt the endothelial layer of the endocardium and therefore has a much lower risk of thrombus formation compared to RF lesions.

A typical technique for applying cryoablation is to target the substrate with the catheter tip and initiate the freeze. Catheter adherence usually occurs at 10–15 s and initial effects on the substrate should be expected by 30 s. If there is no effect by 30 s, the application is terminated and additional mapping performed.

Techniques of Mapping and Ablation in Children

Catheter ablation in children requires a number of modifications and considerations, especially in those less than 25 kg. A number of anatomic and physiologic factors influence the approach and technique of the EPS and ablation in children. Many of these issues are addressed in Chap. 3.

Transseptal Access

When RF ablation was first introduced, access to accessory pathways or ventricular ectopic foci located in the left side of the heart was achieved by retrograde passage of the catheter from the femoral artery around the aortic arch into the ascending aorta and left ventricle (LV). Although this route provided access for simultaneous arterial monitoring (albeit attenuated with a catheter in it), it clearly was not applicable to small children (≤30 kg). Transseptal entry into the left atrium (LA) is now the more common approach to target tachycardia substrates on the left side of the heart in children.

Fluoroscopy is the primary imaging technique guiding transseptal entry into the LA (Fig. 23.1a–c). Although many authorities mandate biplane fluoroscopy for transseptal entry into the LA, in our experience single plane fluoroscopy in the left anterior oblique (LAO) view with diagnostic catheters in place is safe and effective (Fig. 23.1a–c). Additional imaging methods, such as transesophageal or intracardiac echo are in some use, but usually as adjuncts to fluoroscopy imaging. The transseptal apparatus, consisting of a transseptal needle (Cook Medical, Bloomington, IN, USA; St. Jude Medical, St. Paul, MN, USA; Bard Medical, Covington, GA, USA; Medtronic, Minneapolis, MN, USA) within a long dilator and sheath designed for ablation catheter positioning on the mitral valve annulus (most commonly Daig SL-1, St. Jude Inc., Minnetonka, MN) are inserted via the right femoral vein. The tip of the transseptal apparatus (with the long Brockenbrough needle tip located

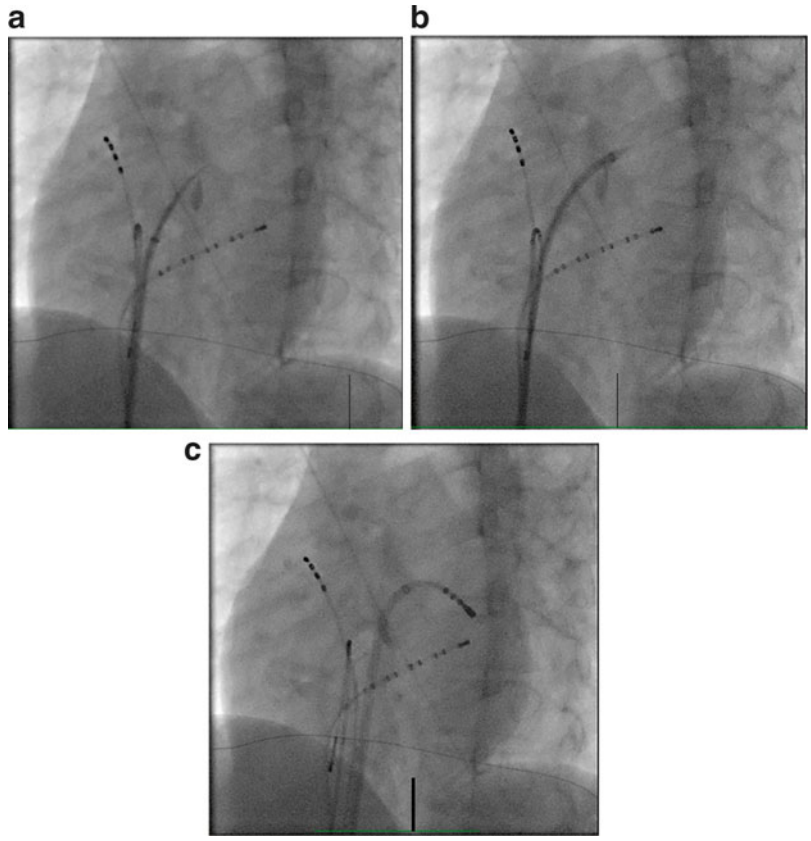


Fig. 23.1 Transseptal puncture access to left atrium: LAO fluoroscopy view during process of transseptal puncture. Decapolar catheter in coronary sinus. Quadripolar catheter in high right atrium. His/RV combo catheter obscured in a perpendicular to the image position. Panel (**a**) shows the transseptal apparatus positioned on the septum. Contrast has been injected into the septum creating a stain. The transseptal needle is protruding through the septum into the left atrium and the dilator is tenting the septum. In panel (**b**) the dilator has been advanced over the needle into the left atrium. The sheath is being advanced over the dilator and is crossing the septum marked by the stain. In panel (**c**) the sheath has been positioned across the septum and a radiofrequency ablation catheter is advanced through it to the lateral mitral valve annulus

proximal to the dilator tip by 0.5–1 cm) is positioned in the superior vena cava; the needle curve is oriented leftward and 30–50° posterior. Under continuous fluoroscopy visualization the transseptal apparatus is withdrawn while observing the tip pass into the right atrium (RA), across the torus aorticus and then "falls" into the fossa ovalis. The needle is then advanced to puncture the fossa with LA access confirmed by contrast injection into the LA. With the long needle held in place, the dilator is then advanced over the stable needle into the LA; once the dilator is in the LA, the needle is retracted back into the dilator and the sheath advanced into the LA, being careful not to puncture the left atrial free wall. An O_2 saturation is obtained but a LA pressure measurement is unnecessary. Anticoagulation with heparin is used to prevent thrombus formation in the left heart.

In small children, the anterior–posterior dimension of the LA is particularly shallow, so avoidance of entering the posterior pericardial space is critical. Procedural modifications for failure of "first pass" transseptal puncture include removal of the needle and rewiring the sheath/dilator in the SVC to begin the procedure again, manual formation of

modified curvature on the needle, or changing to a sharper needle type. Procedural modifications for patients with congenital heart disease include different needle orientation to adjust for variations in postoperative intracardiac anatomy. For lateral tunnel or extra-cardiac Fontan anatomy, the needle orientation remains leftward but slightly more anterior (2 o'clock position). Patients with Mustard or Senning intra-atrial baffle, the needle is typically oriented rightward and anterior ("11 o'clock"). Pre-procedural imaging such as CT or MRI can be very useful in planning the approach for transseptal or trans-baffle access in congenital heart disease patients.

Because the sheath, catheter, and delivery of RF on the left side of the heart present a risk of thrombus formation, anticoagulation with heparin is delivered during the procedure once entry into the LA is achieved. Bolus and/or continuous heparin infusion is delivered to maintain an activated clotting time of at least 220 s. If RF is delivered to the left side of the heart, the patient is placed on 81 mg of aspirin a day for 6 weeks following the procedure.

Catheter Navigation and Mapping

In the past, fluoroscopy has been the primary method by which catheter position was determined. The development and adaption of computerized electroanatomic mapping has revolutionized catheter navigation in cardiac electrophysiology. Commonly used systems are Ensite (St. Jude Inc., St. Paul, MN) and CARTO (Biosense Webster, Diamond Bar, CA). Both systems allow for "virtual" visualization of the ablation catheters movement within the space of the heart. This allows for catheter manipulation without the use of fluoroscopy. The Ensite system uses a localization system based on the changes in electrical impedance across the chest and can "visualize" (display on a monitor screen) any electrophysiologic catheter within the heart. CARTO systems utilize changes in the magnetic fields across the chest to "visualize" the ablation catheter; the newer iteration allows for "visualization" of all diagnostic catheters as well.

Critical to the ablation procedure is mapping the arrhythmia substrate—focus or reentrant pathway—to identify the target for ablation. There are several methods by which to map and target the substrate depending on the arrhythmia diagnosis. Anatomic targeting is the primary method for the slow pathway in AVNRT. A component of anatomic mapping is also essential for accessory pathway ablation, as the catheter must target the annulus between the atrium and ventricle. Pace mapping is a technique used in mapping ventricular arrhythmia substrates. In this technique, the ablation catheter is used to pace the heart at various locations in order to create a paced QRS morphology which matches the arrhythmia QRS morphology—suggesting the site is the origin of the arrhythmia breakout. Entrainment mapping is the process of identifying the course of a macroreentry tachycardia circuit using entrainment techniques (Chap. 3). This method can be used for intra-atrial reentry and ventricular reentry circuits. Voltage mapping can identify areas of scar or low voltage "bridges" in the heart which may be the substrate leading to reentry circuits. By far, the method most used is activation mapping, by which the timing of the local electrical activation is utilized to identify the location of the substrate. This may be the earliest electrical activity at a specific focus or at the earliest atrial or ventricular activation at the site of an accessory pathway.

Computerized electroanatomic mapping systems are used primarily for activation mapping but are also used for voltage mapping. These systems create a visual representation of the endocardial chamber based on local data points generated as the mapping catheter is moved within the chamber of interest. Local activation time is measured at any point the catheter contacts and compared to a predetermined reference location. The system then color coordinates the activation times, such that the earlier activated areas are differentiated from subsequently activated areas. Focal arrhythmia substrates essentially show a "bull's-eye" pattern with a single site being the earliest (Fig. 23.2). Macroreentrant arrhythmias will display a circumferential pattern

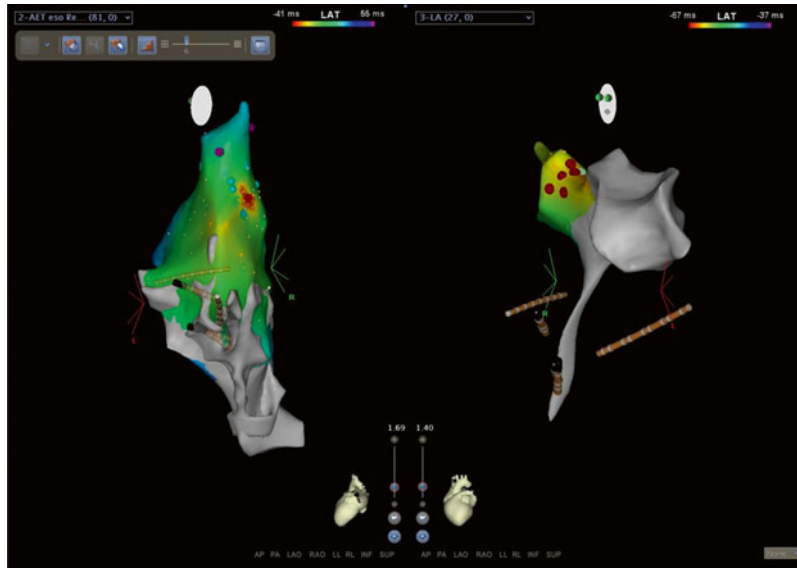


Fig. 23.2 CARTO3 screenshot of focal atrial tachycardia ablation. *Left panel* is a left lateral (slight posterior) view of the right atrium. Activation map of a focal atrial tachycardia is displayed. *Red* is the earliest sight with timing progressing through the spectrum to *blue*. This local area of activation was the target for ablation. RF here was not successful. This location in the RA was immediately anterior to the right upper pulmonary vein. The *right panel* is a left lateral view (slight anterior) of the left atrium (the "tail" inferiorly is the tract through the transseptal access point). The *red dots* on the map indicate the area targeted for ablation which coordinated with the point of interest on the RA map

with the latest activation sites continuous with the earliest activation sites (Fig. 23.3).

Both CARTO and Ensite use contact mapping, in which the catheter must be in contact with the endocardium to register a local electrogram. The Ensite system also allows for non-contact mapping—this currently requires a multi-electrode balloon catheter be placed in the chamber of interest; the electrogram timing is calculated from the far-field unipolar electrograms detected by the electrodes on the balloon surface. The benefit of non-contact mapping is that the entire arrhythmia circuit can be mapped in a single beat. The negative aspect of the non-contact mapping system is that the balloon catheter is rather large profile requiring a large sheath for placement and cannot readily be used in a smaller child.

Additional benefits to these mapping systems are the ability to incorporate additional images into the system. Previously obtained MRI or CT images of the cardiac anatomy can be uploaded into either Ensite or CARTO systems and used as the cardiac geometry for mapping the arrhythmia. CARTO also can incorporate intracardiac ultrasound imaging to create a detailed intracardiac anatomy.

Approach to Accessory Pathways

Basic terminology for describing accessory pathways is found in Table 23.1. The nomenclature for accessory pathway locations has been in a slowly evolving process over the past 2 decades. Initially the valve annuli have been described from the *en face* view of the valve from the RV apex and comprised anterior, posterior, septal, and lateral segments, with anterior being the portion near the aortic root and AV node and posterior being near the CS and CS os. The origin of this nomenclature is from early pathologic and surgical descriptions with the heart oriented in a non-anatomical position. In 1999, a NASPE (now

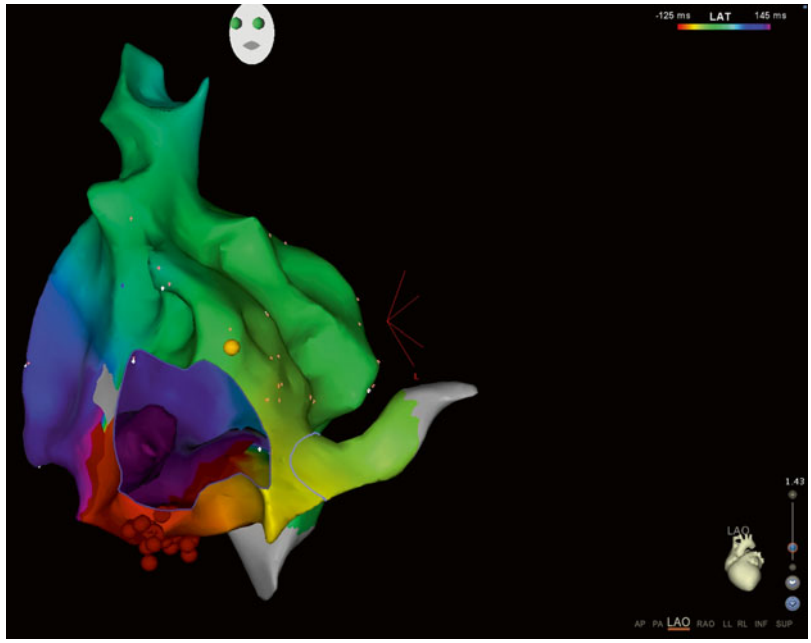


Fig. 23.3 CARTO3 map of macroreentry tachycardia: The view is LAO from the apex as demonstrated by the heart diagram in the right lower corner. The tricuspid valve annulus is shown as a "hole" in the map, giving the impression of looking "inside" beyond the valve ("M shaped shadow" in lower part of figure). The *yellow ball* in the right upper aspect of the tricuspid valve annulus is the location of the His. This is a map of CTI-dependent (typical counterclockwise) atrial flutter. The color pattern from red to green to blue reflects timing as the wave front moves counterclockwise around the tricuspid valve annulus. The late site meets the early site of activation at the red strip (purple meets red) indicating a continuous reentry circuit. The *red dots* at the inferior portion of the map are radiofrequency ablation lesions placed to terminate the tachycardia

Table 23.1 Terminology used in describing accessory pathways (APs)

Orthodromic	Describes AP mediated tachycardias in which there is normal conduction from the atria to the ventricle via the AV node-HPS
Antidromic	Describes AP mediated tachycardias which traverse the AP from atrium to ventricle and proceed backwards up the HPS
Antegrade	Conduction from atria to ventricle
Retrograde	Conduction from ventricle to atrium
Concealed	Pathway only conduct in the retrograde direction
Manifest	Pathways conduct in the antegrade direction with or without retrograde conduction

HRS) consensus statement was published to "correct" this terminology to superior (anterior), inferior (posterior), septal, posterior (mitral valve lateral), and anterior (tricuspid valve lateral). Adaption of this terminology has been slow, especially in the pediatric literature. The new terminology of superior and inferior is anatomically accurate and easy to interchange with the former anterior and posterior terminology, and has been widely adopted in many publications. There is obviously potential confusion with re-using the terms anterior and posterior to define the lateral annuli and this change has not been adopted. The descriptions of the annuli in this chapter will support the new terminology, using superior, inferior, and septal; but retain the use of left lateral and right lateral to describe the annular free walls (Fig. 23.4).

For both left- and right-sided accessory pathways, the amplitude of the atrial or ventricular electrograms confirms optimal proximity to the AV ring. Due to the dominant ventricular mass

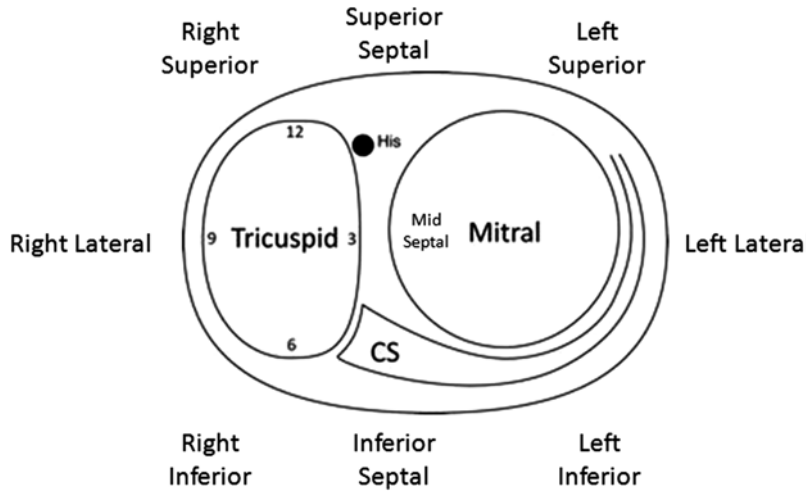


Fig. 23.4 Annular nomenclature for accessory pathway locations: cartoon of the annulus as viewed from the apex in the left anterior oblique view. The "new" annular anatomy is labeled. Correlated to traditional terminology: superior = anterior; inferior = posterior. *CS* coronary sinus

relative to the atrium, the ratio of the amplitude of the atrium to that of the ventricle should usually be less than 0.5. At the beginning of the ablation era, much of the inference that is contained in the amplitude of the electrograms and in the VA conduction times was dependent on operator integration of the anatomic and electrical data on the fly; more recently, computer-assisted mapping techniques produce an electro-anatomic map correlating in a three-dimensional image the activation sequence and the anatomic configuration.

Left-Sided Pathways

Approximately 60–65 % of accessory pathways are located on the left side. This left-sided dominance is higher in infants and small children. As the infant or child grows, functional or anatomic loss of the pathway may occur, perhaps due to molding of the AV groove or postnatal apoptosis of the cellular pathway substrate. Such a natural attrition would reduce the absolute incidence of left-sided pathways. In contrast, right-sided pathways may theoretically be somewhat protected from this "molding effect" by their closer proximity to the crux and by the fixation of the right side by the vena cavae compared to the relatively less tethered left lateral aspect of the heart.

Access to the left side is by way of the transseptal technique into the LA. Once in the LA, there should be free movement of the curve and catheter tip so that it can sweep in an arch from near the top of the LA down to the mitral inferior (posterior) rim for mapping and ablation. Left inferior (posterior) pathways require a slightly tighter curl to the catheter curve, achieved by gently decreasing the radius of the curve and moving the curved tip inferiorly by slightly withdrawing the catheter and sheath, and thus positioning the electrode–ablation tip slightly more medial on the inferior (posterior) mitral ring. Further tightening the curve and further withdrawing slightly the catheter and sheath will bring the catheter tip to the left inferior (posterior) septal region. The mapping and ablation apparatus (catheter and sheath) require continued clockwise torque on the catheter–sheath apparatus to ensure the catheter remains on the inferior (posterior) mitral ring. The superior septal region, the last site on the mitral ring, is a particularly difficult location to secure a stable position of the catheter tip, though this is adjacent to the aortomitral continuity and APs in this location are

extremely rare. Long sheaths specifically formed to position the catheter on the mitral annulus (and even steerable sheaths) are available and commonly used to position the catheter and provide for greater stability. Delivery of radiofrequency energy with the catheter tip at the mapped site of the accessory pathway often will ablate the pathway and terminate the tachycardia.

Left-sided accessory pathways are targeted by activation mapping. Several approaches may be used. The first is to map the site of earliest local preexcitation (Fig. 23.5) in patients with manifest pathways during sinus rhythm or an atrial pacing; local preexcitation at an optimal ablation site is usually ≥15 before the onset of the surface QRS. The second is to locate and the accessory pathway by mapping the retrograde activation sequence during ventricular pacing (Fig. 23.6) in patients with either manifest or concealed pathways. One must pace at a sufficiently fast rate (usually 150 bpm or greater) to ensure that retrograde conduction through the accessory pathway is not masked by robust retrograde AV nodal–His-Purkinje conduction often seen in young patients. Mapping may be performed during tachycardia; however, because abrupt termination can displace the catheter tip, ventricular pacing slightly faster than the tachycardia rate should be initiated prior to applying RF. Energy is then delivered during ventricular pacing which is continued for the duration of the lesion (Fig. 23.6). Cryoablation also provides secure catheter stability due to catheter adhesion. However cryoablation is not extensively used for this purpose due to a perceived higher recurrence risk.

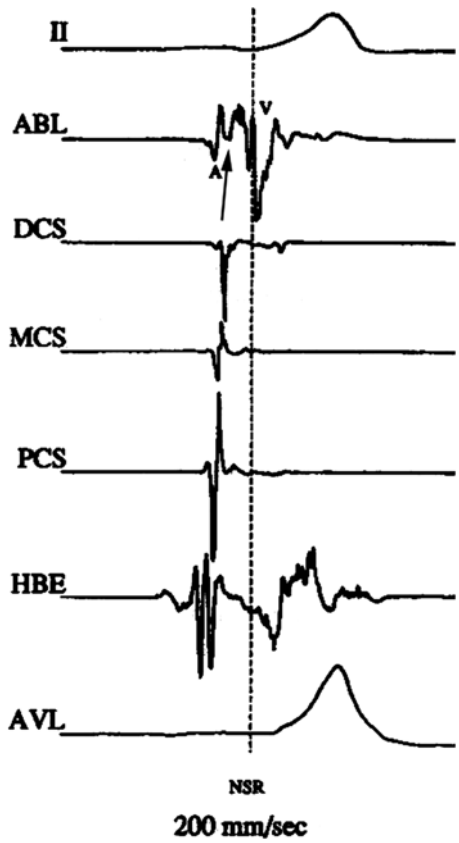


Fig. 23.5 Activation mapping of preexcitation: intracardiac electrograms displayed from *top* to *bottom*: surface lead II, ablation distal, distal CS, mid-CS, proximal CS, His bundle, surface lead aVL. Single beat with ventricular preexcitation. No His potential because it is buried in the ventricular electrogram. Note the local ventricular preexcitation in the ablation electrogram (*arrow*) precedes the global preexcitation expressed in the two surface leads. *A* atrial electrogram; *V* ventricular electrogram

Retrograde conduction through left-sided concealed pathways may be difficult to isolate if retrograde AV nodal conduction is vigorous. Two solutions are available. The first is the bolus administration of adenosine. This technique will usually block the AV node retrograde, but usually not the accessory pathway. However, its transient effect limits it usefulness. The second solution is to pace the ventricle from a site closer to the accessory pathway. This may usually be achieved with pacing from the septal base in the right ventricle. Occasionally, an LV pacing site is necessary and can be achieved by a second catheter places across the atrial septum, a retrograde catheter placed from the arterial side, or a CS catheter positioned down a lateral cardiac vein. This technique more selectively engages the left accessory pathway than does pacing from the RV apex, thus unmasking conduction in the left-sided pathway (Fig. 23.7).

Right-Sided Pathways

Access to right-sided structures is clearly less complicated than access to the left. On the other hand, catheter stability on the AV ring, especially

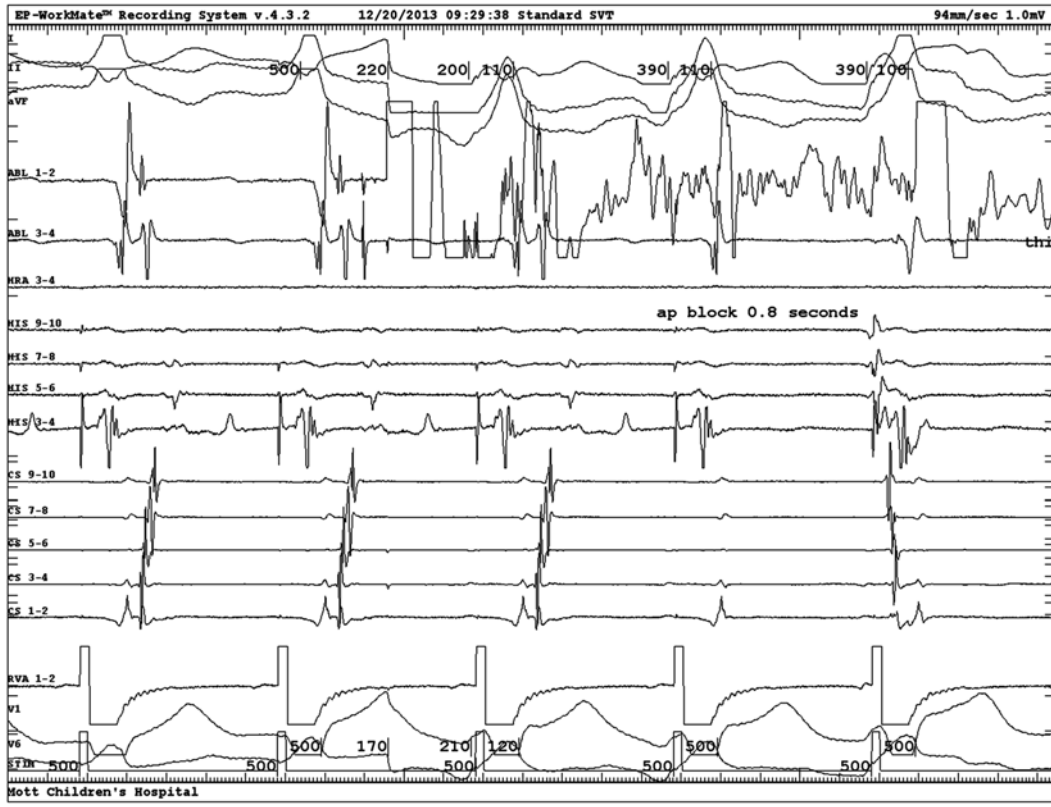


Fig. 23.6 Activation mapping and ablation of left lateral accessory pathway: intracardiac electrograms displayed from *top* to *bottom*: surface leads I, II, aVF, ablation distal to proximal, HRA, His proximal (9-10) to distal (3-4), CS proximal (9-10) to distal (1-2), RV apex, surface leads V1 and V6. Right ventricular pacing conducts to the atrium via a left lateral accessory pathway with CS activation proceeding from distal to proximal. The earliest activation is at the distal ablation electrogram. Application of radiofrequency energy causes artifact on the distal ablation electrogram and results in accessory pathway block at the fourth beat of the display. *HRA* high rate atrium, *CS* coronary sinus, *RV* right ventricle

along the right free wall and superior (anterior) areas, is less secure. In addition, delivery of radiofrequency energy to the tricuspid AV ring in the septal area places the AV node, His-Purkinje system, and AV nodal artery at greater risk.

Right-sided accessory pathways are targeted by activation mapping similar to left-sided accessory pathways. Earliest local preexcitation, usually ≥15 ms before the onset of the surface QRS, may be targeted during sinus rhythm if the pathway is manifest. Retrograde activation may also be targeted during ventricular pacing in patients with either manifest or concealed pathways. Isolation of right-sided APs during ventricular pacing is typically straightforward due to the RV catheter's proximity to the AP, though superior (anterior) and mid-septal APs may be very difficult to differentiate from AV nodal conduction. Mapping may be performed during tachycardia, however because abrupt termination can displace the catheter tip, ventricular pacing slightly faster than the tachycardia rate should be initiated prior to applying RF. Energy is then delivered during ventricular pacing which is continued for the duration of the lesion.

Right inferior (posterior) septal pathways are the most common and can be difficult to target because the inferior septum is essentially a dimensional triangle (pyramid) of space full of tissue. Successful ablation may occur from the

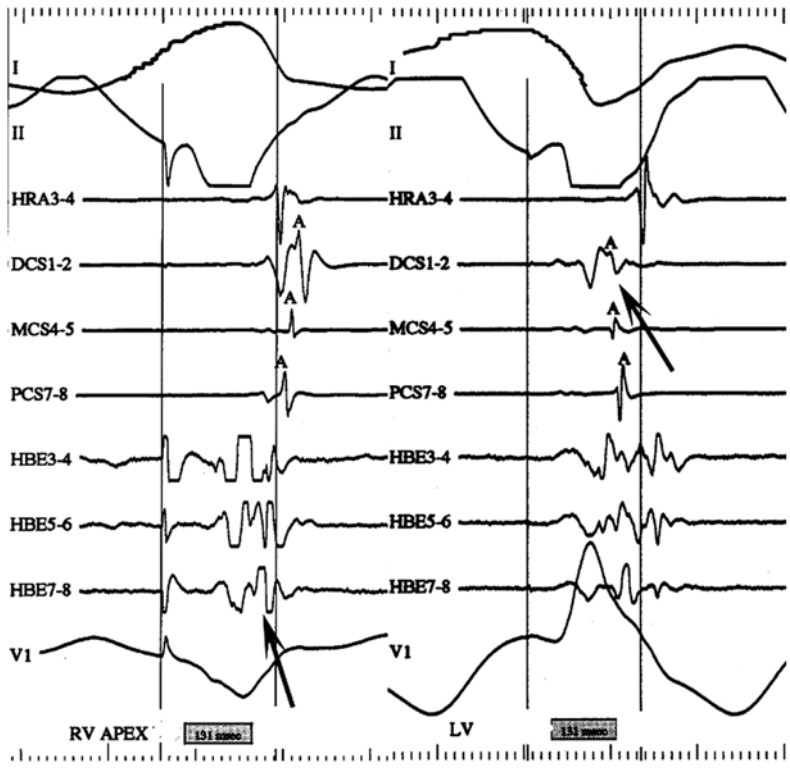


Fig. 23.7 LV pacing to isolate left lateral accessory pathway conduction: intracardiac electrograms displayed as surface lead I, II, HRA, distal CS (DCS), mid-CS (MCS), proximal CS (PCS), His bundle (HBE) distal to proximal, surface lead V1. *Left-hand panel*: pacing from the RV apex activates the atrium retrograde with earliest activation in at the His catheter. *Right-hand panel*: pacing from the LV posterior wall activates the atrium retrograde via a left lateral accessory pathway earliest at the distal CS. *HRA* high right atrium, *CS* coronary sinus, *RV* right ventricle (HRA), *MCS* mid-coronary sinus, *PCS* proximal coronary sinus

right inferior annulus, left inferior annulus, or inside the CS. Mapping of all three locations should be considered when local activation timing is not optimal. Occasionally, these pathways can be found slightly deeper into the middle cardiac vein. Caution should be used when applying RF energy in this area as the AV nodal artery traverses this region. Right coronary angiography can identify the exact location. If the artery is within 1–2 mm of the mapped site of the pathway, there is higher risk of complication. Cryoablation in this area has several distinct advantages: (1) injury to the coronary artery is not a known complication from clinical or pathologic studies and (2) the low blood flow state of the CS and middle cardiac vein does not affect cryoablation.

Ablation of right free wall pathways is confounded by the instability of the catheter tip at the target site on the AV groove. There are no intracardiac structures to stabilize the catheter tip. It is often necessary to utilize a long sheath with specially directed curves that orient the catheter tip toward the right AV groove. Positioning the curve of the catheter high in the right atrium with the tip approaching from above can also aid in catheter stability. Not infrequently, the atrial and ventricular electrograms, particularly after a few unsuccessful applications of the RF current, become attenuated and fragmented, falsely suggesting a poor site for the catheter tip for successful ablation. Since this observation may incorrectly imply that the catheter tip is not on the AV groove, the catheter position should be reviewed by

fluoroscopy in the right anterior oblique projection. The strongest indicators of correct location, which predicts successful ablation, are maximal local preexcitation if the pathway(s) is manifest, and the shortest ventriculo-atrial conduction time during either SVT or ventricular pacing if the pathway is concealed.

The right superior (anterior) septal and the right mid-septal sites are closest to the AV node and His bundle. Accordingly, application of RF ablation at these sites may jeopardize the normal conduction system. RF can be applied cautiously in this area provided there is not a His bundle potential on the distal ablation electrogram, though even then, collateral damage is still possible. Application during sinus rhythm with low power allows the operator to monitor closely the appearance of first-degree heart block or junctional acceleration or VA dissociation, which would allow for abrupt termination of current delivery. A stabilizing sheath of the appropriate size increases operator control of the catheter tip. Approaching the pathway from a right internal jugular vein access site may assist in catheter positioning and stability. This approach allows for the application of pressure to the catheter tip as the curve opens up to rest the distal (tip) electrode on the target site on the superior (anterior) AV groove and holds the tip more secure. Nonetheless, delivery of RF energy to the anterior and mid-septal pathways poses a direct risk to the AV node and His bundle. Cryoablation has largely replaced RF as the preferred favored energy source for ablation of accessory pathways in this region due to its safety when ablating near the AV node (Figs. 23.8 and 23.9). In addition, delivery of RF energy to the right inferior septal area may injure the AV node through damage to the AV artery. Cryotherapy is an alternative energy source in these situations.

Successful Ablation of an Accessory Pathway

Criteria for successful ablation of an accessory pathway are outlined in Table 23.2. The majority of accessory pathways, if one is at the optimal site, are interrupted in less than 5 s, the time it

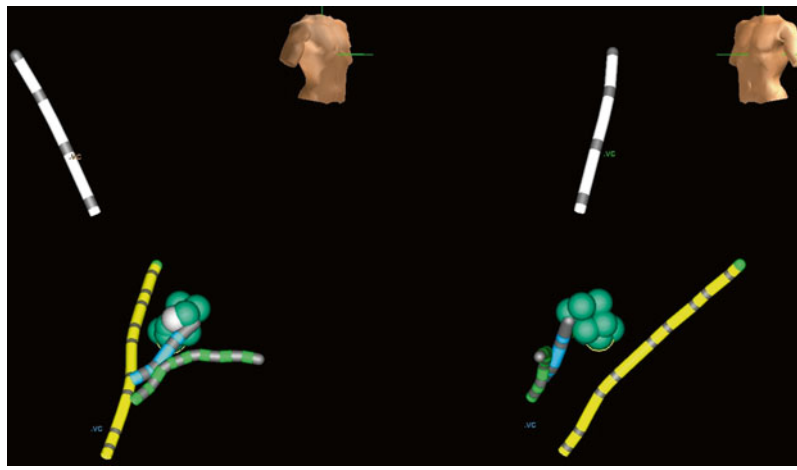


Fig. 23.8 Ensite velocity monitor image of superior septal accessory pathway ablation: the *left image* is a right anterior oblique view as indicated by the torso in the upper screen. The *right image* is a left anterior oblique view. The *white catheter* is a quadripolar in the high right atrium and superior vena cava. The *yellow catheter* is a decapolar in the coronary sinus. The *green catheter* is an octapolar His array from a His/RV combo catheter positioned on the mid-septum; it has been retracted slightly inferior from the true location of the His bundle. The *blue catheter* is a 6 mm tip Cryocath Freezer Extra positioned to ablate the superior septal accessory pathway shown in Fig. 23.9. *RV* right ventricle

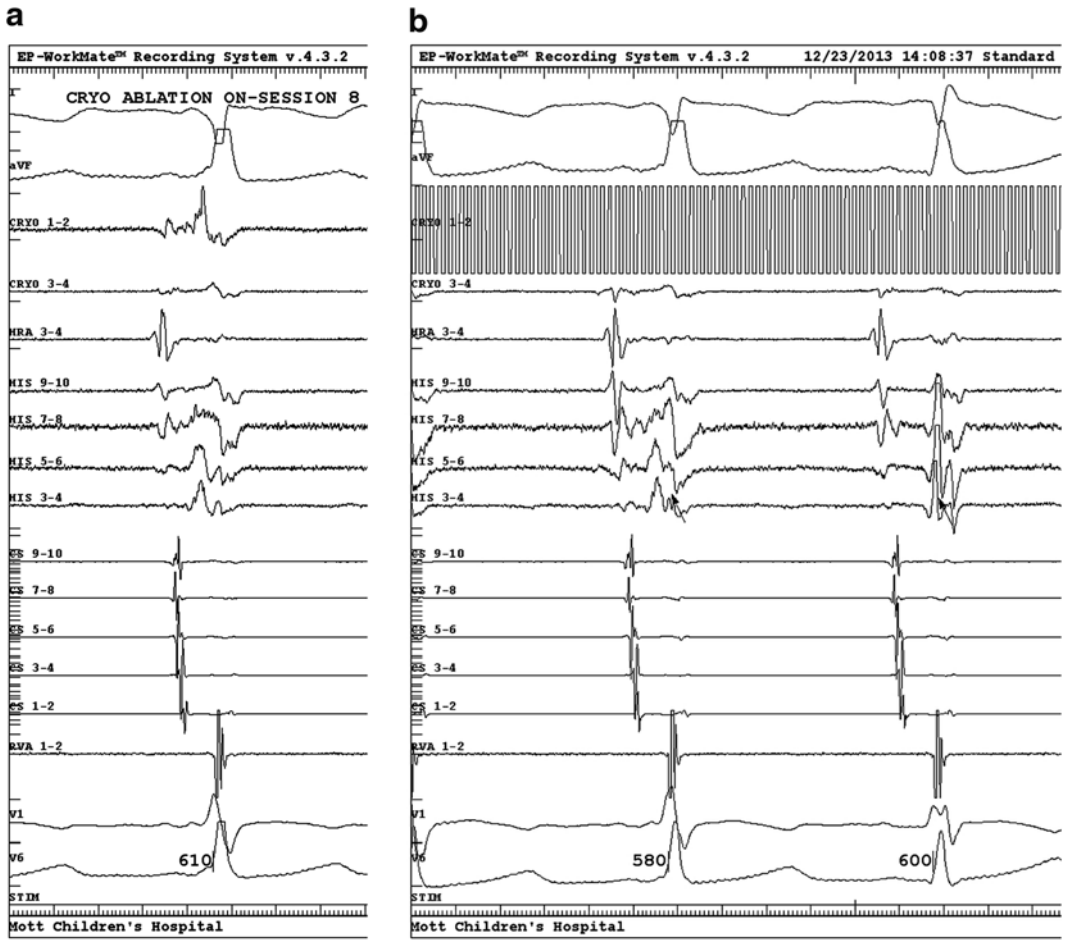


Fig. 23.9 Panels (**a**–**c**): cryoablation of superior septal accessory pathway. Intracardiac electrograms displayed from top to bottom as surface lead I (inverted), aVF, cryoablation distal and proximal (CRYO), high right atrium (HRA), His proximal (9-10) to distal (3-4), coronary sinus (CS) proximal (9-10) to distal (1-2), right ventricular apex (RVA), surface leads V1, and V6. Panel (**a**) shows a single beat of sinus rhythm with ventricular preexcitation and early ventricular activity at the His bundle catheter consistent with this patients diagnosis of superior septal manifest accessory pathway. The cryocatheter is positioned at an optimal location with continuous electrical activity and pre-delta wave local activation. Cryoablation is applied here. Panel (**b**) showed block in the accessory pathway at approximately 8 s after the freeze. The first beat shows early activation at the His catheter. On the second beat the accessory pathway has blocked and the local A–V interval is prolonged at the His catheter. This lesion was continued for 6 min and a second lesion placed for in a freeze–thaw–refreeze technique at the same location. Panel (**c**) shows the local electrogram at the distal cryocatheter between the cryo applications. There is a large His potential on the cryocatheter electrogram confirming the accessory pathway was paraHisian. This pathway was successfully ablated without adverse effect on normal AV conduction

takes to reach maximal power and the pre-set auto-regulated temperature of 50–65 °C. The routine procedure is to monitor for about 10 s and then terminate the energy delivery if the desired result is not achieved. If there is success, energy deliver is continued for 60 s.

Acute success for AP ablation is >99 %. The patient is routinely observed in the lab for 30 min after the successful application. Recurrence risk depends on both pathway location and difficulty of achieving the acute success. Left lateral APs have a 5 % risk of recurrence, right lateral

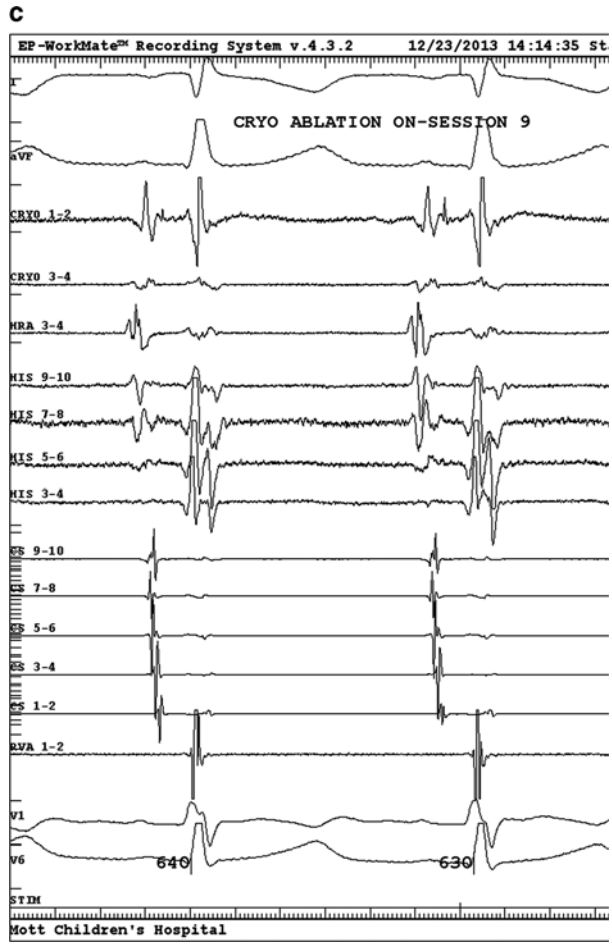


Fig. 23.9 (continued)

Table 23.2 Criteria for successful ablation of an accessory pathway

Criteria
Sustained, preferably rapid (≤4 s) loss of accessory pathway conduction during application of radiofrequency energy
Absence of preexcitation in sinus rhythm (if present prior to ablation) or with atrial pacing
Demonstration of AV and VA block with adenosine administration
No inducible tachycardia after ablation
VA block or concentric decremental VA conduction through the AV node after ablation

10–15 %, and septal pathways 15–20 % based on a large multicenter pediatric ablation study. These recurrences maybe safely treated by a second ablation attempt with similar success.

Approach to Focal Ectopic Atrial Tachycardias

LA foci are often near the orifices of the pulmonary veins. Their typical ECG pattern consists of a deformed (bimodal and long) P-wave that is purely negative in V1 and usually lead 1. RA foci vary in location, but the crista terminalis is a common site. Their P-wave axis varies depending on the origin high or low in the atrium. An ectopic focus in the orifice of the right atrial appendage near the sinus node exhibits a normal axis but is often markedly deformed (bimodal and long).

The approach to focal atrial tachycardias depends on their location. Left-sided foci require the transseptal approach whereas those on the

right side are immediately accessible. Special consideration for the form of analgesia and anesthesia are important as deep anesthesia may suppress the ectopic focus. Conscious sedation is often the best approach to preserve the atrial ectopic rhythm. Often the infusion of isoproterenol will bring out an otherwise suppressed rhythm. Endocardial mapping with an electrode catheter is directed toward identifying the earliest site of atrial activation prior to the onset on the P-wave.

Because of the heat generated during application of energy that excites the ectopic focus, the tachycardia rate usually transiently accelerates before extinguishing completely. Because the atrium is thin and thus requires less energy, it is wise to start at low power, monitoring the temperature rise until a temperature of 50–60 °C is reached; application should last 30–60 s. Termination of the tachycardia is the only confirming marker of success; therefore, delivery of RF energy during tachycardia is necessary. Dislodgement of the catheter tip from the target site is less frequent in this group. Computerized electroanatomic mapping can facilitate precise anatomic location (Fig. 23.2).

Pericardial Approach to Epicardial Sites

An epicardial approach is rarely necessary to successfully ablate the arrhythmia substrate. In such cases, the target—pathway or focus—may be located closer to or on the epicardial surface of the heart rather than on or near the endocardial surface. Percutaneous pericardial entry from a sub-xiphoid or sub-costal site permits access to the epicardial surface—particularly the AV groove for pathway-dependent and atrial tachycardias and the ventricular surface for VT. A critical part of this technique is to define by angiography the caliber and course of the right and left coronary arteries, both before and after energy delivery. This information, in conjunction with the recorded electrograms, serves as a roadmap to the appropriate ablation site. Furthermore, it assesses the effect of radiofrequency energy, if any, on the coronary circulation. The approach to epicardial ablation has been widely published in the adult EP literature, though not extensively in pediatrics. The potential for complications is highest during the access to the pericardial space which may result in liver injury, myocardial puncture, coronary artery damage, and hemopericardium. Epicardial mapping and ablation should be reserved for very specific cases, such as those with repeated failure with the standard endocardial approach and performed by someone experienced in the technique.

Approach to Atrioventricular Nodal Reentry Tachycardia

The substrate for ablation in AVNRT is the slow pathway of the AV node which is found in the inferior (posterior) aspect of the triangle of Koch—this anatomic region is bounded by the tendon of Todaro, the posterior leaflet of tricuspid valve, and the line drawn from the posterior margin of the tricuspid valve to the inferior rim of the coronary sinus (CS) os. The area of the triangle of Koch increases with growth in children. At less than 20 kg, the area is equal to or less than 50 mm^2. The slow pathway can most frequently be ablated from the area between the CS os and tricuspid valve annulus or just immediately superior to this region (Fig. 23.10). The ratio between the amplitude of the atrial and ventricular (A–V ratio) electrograms is optimally less than 1:2. The morphology of the atrial electrogram is helpful; an m-shaped (or w-shaped), fragmented atrial electrogram suggests an area of slow conduction and is a supporting marker of a successful site for interruption of the "slow" conducting pathway. Holding respiration (during general anesthesia) can help stabilize the catheter position. Either RF or cryo may be used to target the slow pathway and their use is center specific with about 50 % of pediatric electrophysiologists using RF primarily (as of 2013). Because of the risk of injury to the AV node artery and possibility of damage to the AV node in young persons, the University of Michigan Congenital Heart Center pediatric electrophysiologists use cryoablation almost exclusively for this substrate.

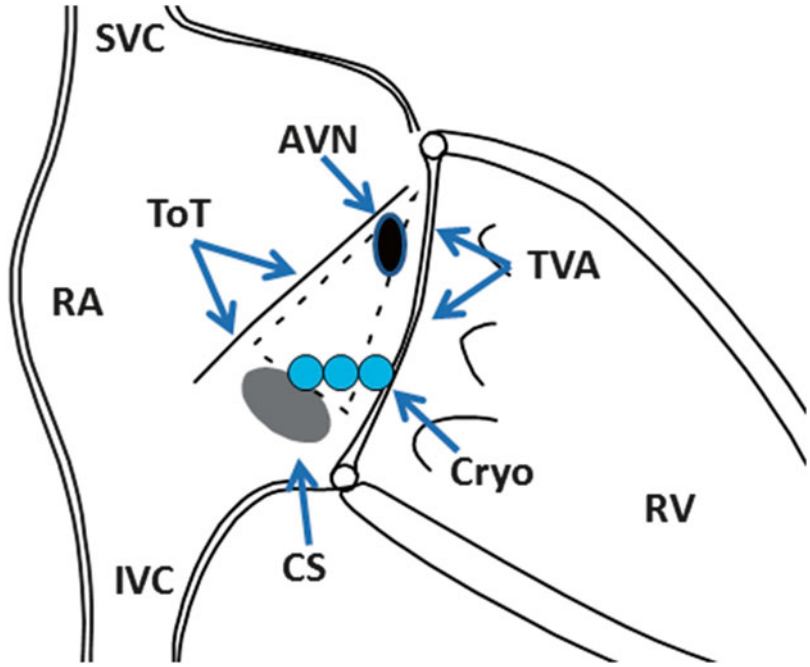


Fig. 23.10 RAO view cartoon of RA and RV with anatomy relevant to AVNRT ablation. Typical location for cryoablation of slow pathway for AVNRT shown by *blue dots* and marked with "cryo" label. *RA* right atrium, *SVC* superior vena cava, *IVC* inferior vena cava, *CS* coronary sinus, *ToT* tendon of Todaro, *AVN* atrioventricular node, *TVA* tricuspid valve annulus, *RV* right ventricle

RF Ablation of AVNRT

RF current is delivered during sinus rhythm for 60–120 s in the area of slow conduction within the triangle of Koch. During RF delivery careful attention is paid to an excessive acceleration of a junctional rhythm (appearance of a slow junctional rhythm due to the application of the RF heat [≤125 % of the baseline] is expected), continued atrial–junctional (ventricular) association (fixed constant simultaneous atrial and ventricular electrograms [or QRS complexes] during the junctional rhythm), as well as intact AV conduction (PR interval). Intermittent pacing during application may be helpful in monitoring antegrade conduction if junctional tachycardia appears. Indicators for successful ablation are the appearance of the slow junctional rhythm with constant intact junctional–atrial association during current delivery. An acceleration of the junctional rhythm beyond that level indicates excessive heat is being delivered to the AV node; current delivery should be immediately terminated. Repeat applications can be attempted at adjacent positions, if slow pathway conduction persists. Optimal temperature should not exceed 55 °C and often 47–48 °C is sufficient.

Cryoablation of AVNRT

The anatomical approach to the slow pathway is the same with cryo as with RF. Because of the benefit of cryocatheter adherence, AVNRT is usually ablated while the patient is in tachycardia. Once the ablation catheter tip electrode reaches freezing there is a large artifact masking the electrogram. Tachycardia termination will optimally occur shortly after this artifact is seen (Figs. 23.11 and 23.12). The application should continue for 20–30 s before abandoning it due to persisting SVT. Optimal application of cryoablation includes a continuous 4–6 min initial lesion at the site of success, a short thawing period (10–30 s), followed by a second immediate application for an additional 4 min. A third application after a second thawing period may also increase long-

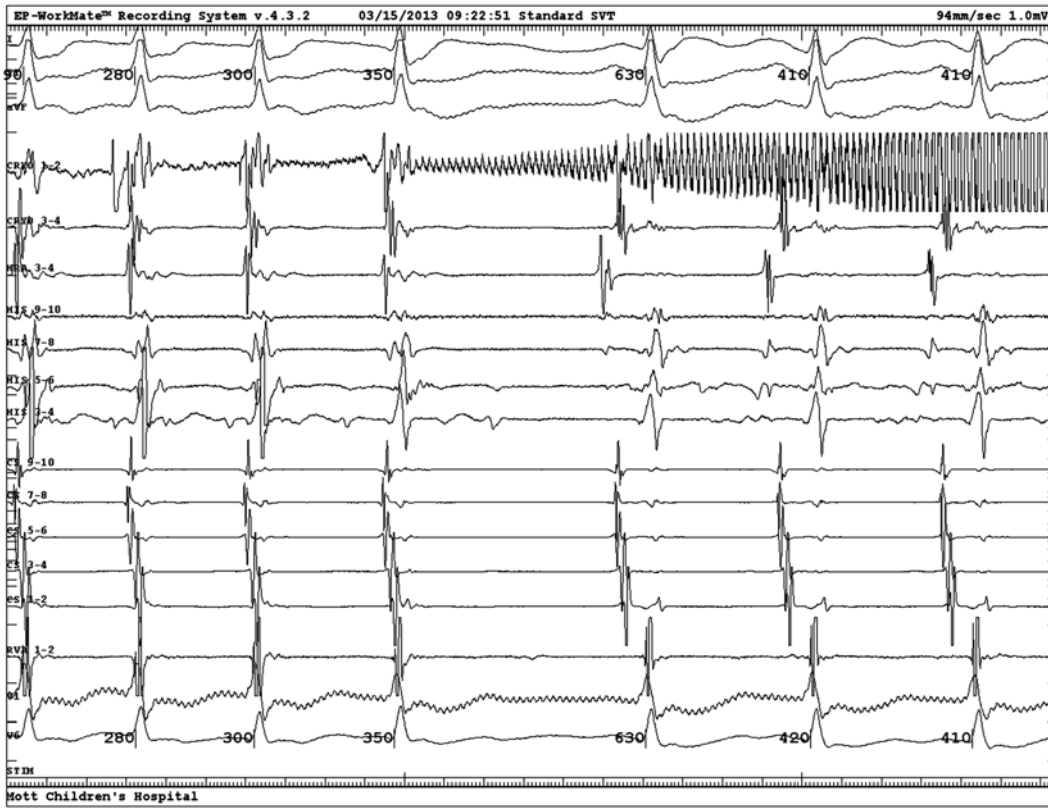


Fig. 23.11 Cryoablation of AVNRT: intracardiac electrograms displayed from top to bottom as surface lead I, aVF, cryoablation distal and proximal (CRYO), high right atrium (HRA), His proximal (9-10) to distal (3-4), coronary sinus (CS) proximal (9-10) to distal (1-2), right ventricular apex (RVA), surface leads V1, and V6. The rhythm is typical AVNRT. The artifact in the distal cryocatheter electrogram occurs during the onset of the cryoablation application and freeze. The arrhythmia slows and terminates with the freeze onset followed by sinus rhythm

term success. Further applications of cryo in a "bull's-eye" configuration around the original successful lesion or in a line from tricuspid valve annulus to CS os are often useful. Because of catheter adherence during the freeze, pacing maneuvers and attempts to re-induce tachycardia can be employed. The safety of the cryocatheter allows more superior positioning of the catheter (nearer the AV node) if more inferior ablation sites are unsuccessful.

Endpoint of AVNRT Ablation

The endpoint of AVNRT ablation is the topic of many studies. Inducibility of the tachycardia may be effected by general anesthesia and thereby result in assumed success when recurrence is imminent. Lack of tachycardia induction after acutely successful ablation is necessary but not sufficient to optimize the chance of long-term success. Post-ablation testing should also be performed during isoproterenol infusion. Induction should be attempted from at least two pacing sites including the proximal coronary sinus and include burst pacing and premature atrial extrastimuli. If the tachycardia is not induced during isoproterenol infusion, then elimination of residual dual AV node physiology or single echo beats is usually not necessary. Double echos or more should probably undergo more ablation applications.

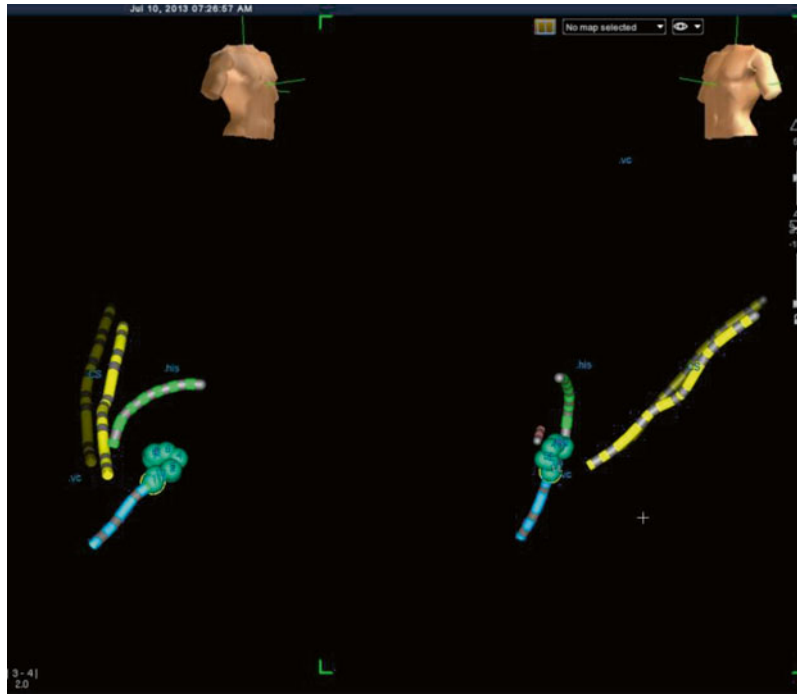


Fig. 23.12 Ensite velocity screen shot of AVNRT ablation. *Left panel* is a right anterior oblique view as shown by the torso in the upper screen. *Right panel* is a left anterior oblique view from the apex. The *green catheter* is the His array. The location of the His signal is marked in text. The *yellow catheter* is the coronary sinus catheter. The *blue catheter* is the cryocatheter. A group of lesions has been placed at the typical anatomic location of the slow pathway as displayed in Fig. 23.10

Interruption of the Atrioventricular Node by Radiofrequency Ablation

Although interruption of the AV node with RF ablation followed by pacemaker implant is an accepted optional treatment for symptomatic, drug-resistant chronic atrial fibrillation in adults, it is rarely necessary in children and young adults. When employed, it is usually for intractable atria arrhythmias in the setting of complex heart disease. Although the standard approach to the AV node is application of RF energy antegrade through the right atrium to the low septal area at the apex of the triangle of Koch (the home of the node), in patients with abnormal anatomy such as transposition of the aorta and AV septal, the only or best access to the conduction tissue may be retrograde through the aorta.

Ablation of Macroreentrant Atrial Tachycardias (See Chap. 8)

Atrial flutter is a macroreentrant atrial tachycardia occurring in anatomically normal hearts, typically at an atrial rate of 300 bpm. This arrhythmia most commonly circles around the tricuspid valve in a counterclockwise or clockwise direction. Less common variants may circle the SVC, IVC, or incorporate the CS os. IART is a macroreentrant atrial tachycardia occurring in hearts having undergone a congenital heart operation. These may traverse the typical atrial flutter circuits or circle around atrial scars imposed by the operation. Because of the multiple incision and suture lines and the resulting scar, conduction velocity through the circuit is slower and the P-wave amplitude smaller resulting in a slower atrial rate (<<300 bpm)

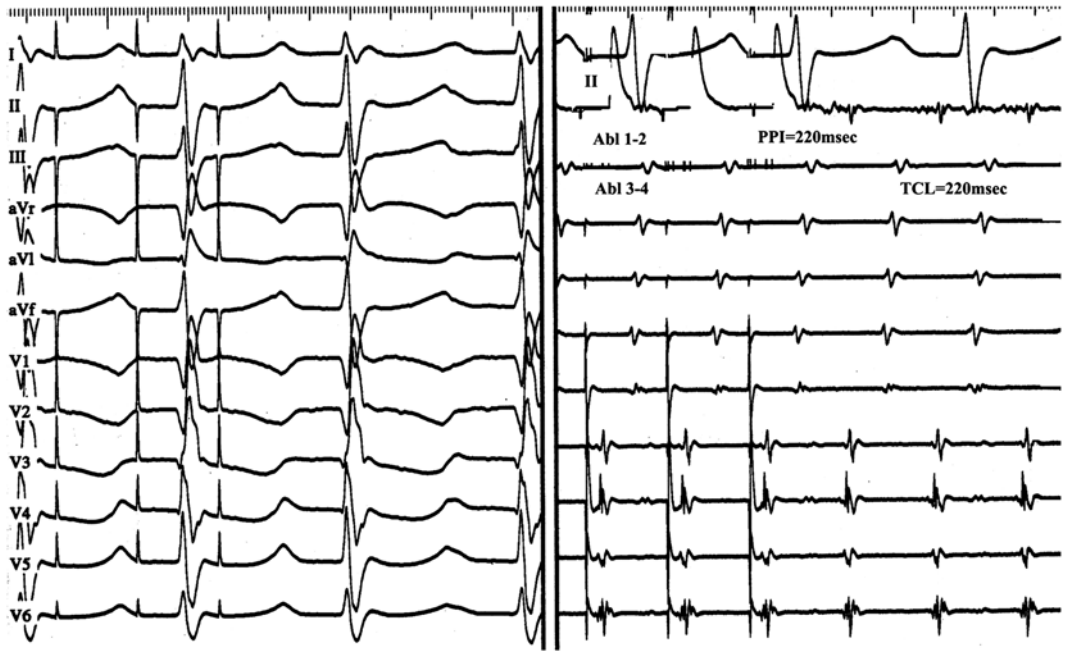


Fig. 23.13 Concealed entrainment in the systemic atrium in a 7-year-old boy with intra-atrial reentrant tachycardia 5 years after the Fontan operation (atrio-pulmonary connection). *Left-hand panel*: 12-Lead ECG at cessation of atrial pacing. Note the similarly shaped low amplitude (barely discernable—typical for flutter in a Fontan patient) P-waves during pacing and tachycardia, compatible with concealed entrainment. *Right-hand panel*: Lead II, ablation catheter (Abl 1-2, 3-4) and multiple intra-atrial electrograms (8 bottom tracings). Note the same atrial activation pattern within the 8 bottom tracings during both pacing and the tachycardia. Note also the match in ms between the post-pacing interval (PPI; interval from last pacing stimulus to first local electrogram at paced site) and the tachycardia cycle length (TCL). These findings indicate concealed entrainment and place the ablation catheter tip within the reentrant circuit

Atrial flutter around the tricuspid valve annulus—AKA cavo-tricuspid isthmus (CTI)-dependent flutter—can usually be ablated anatomically by creating an ablation line across the CTI between the inferior tricuspid valve annulus and the inferior vena cava orifice. Confirmation that the circuit is depended on the CTI can be confirmed by showing concealed entrainment (Chap. 3) when pacing from that location. Termination of tachycardia should be expected during the RF application. Demonstration of bidirectional electrical block across the CTI by pacing on both sides of the isthmus (i.e., the coronary sinus os on the left and the low RA wall on the right) is necessary to assure long-term success.

Non-CTI-dependent flutters and IART will require additional mapping to identify the circuit and optimal location for ablation. Entrainment mapping is still important to confirm the intended site of ablation is a dependent part of the circuit (Fig. 23.13). Computerized 3D electroanatomic mapping systems have become nearly essential for success of these macroreentrant arrhythmias. The tachycardia circuit can be fully mapped with these systems which also identify low voltage areas potentially indicating areas of scar. Computerized electroanatomic mapping is especially helpful in IART where patients may develop multiple arrhythmia circuits which all require treatment. The ablation target for IART is typically the area of slow conduction—a scarred region or anatomically isolated area such as the CTI. Alternatively, an ablation line can be drawn across the circuit between two electrically inactive areas thereby terminating the circuit. For most congenital heart disease patients with IART

the circuit involves the CTI as in atrial flutter. However in Fontan patients the circuit most commonly revolves around the atriotomy scar.

The achievable success rates for ablation in IART have improved considerably with electroanatomic mapping systems with some studies acute success of >90 %. Tachyarrhythmia recurrences are practically expected with complex congenital heart disease patients due to the natural history of their disease; frequently these turn out to be due to different circuits than the initial one.

Radiofrequency Ablation of Atrial Fibrillation

In contrast to the incidence of atrial fibrillation in adults, which has reached public health concern, atrial fibrillation in the young is exceedingly rare. Rarely, teenagers will experience paroxysmal ("lone," i.e., no associated heart disease) atrial fibrillation. Potentially underlining factors increasing the risk of atrial fibrillation such as hyperthyroidism and cardiomyopathy should be eliminated in this age group; however, ablation is not usually recommended. For the consideration of more definitive therapy for paroxysmal atrial fibrillation, referral to a medical electrophysiologist is appropriate.

Ablation of Non-ischemic Ventricular Tachycardia (See Chap. 12)

Idiopathic VT can arise from either the RV or LV. Because this tachycardia appears to be an ectopic mechanism, general anesthesia, which can suppress the tachyarrhythmia, is frequently avoided in favor of moderate-deep sedation. VTs can be targeted using activation mapping or less effectively, pace mapping. Electroanatomic mapping systems are highly useful though not essential for targeting these typically focal arrhythmia substrates.

Some tachycardias, which appear to arise from the RV outflow tract, may be within the right side of the conal septum or on the left side of the conal septum underneath the aortic valve. Ablation above the right coronary cusp, within the coronary cusp or within the ventricle beneath the right coronary cusp may localize these tachyarrhythmias and lead to successful ablation. RV tachycardia can occur from the muscular septum, as well as the inferior wall; these tachyarrhythmias are more difficult to ablate.

Left-sided structures giving rise to VT can be accessed either through the transseptal route with passage of the mapping/ablating catheter from the LA into the LV or by way of the retrograde route around the aortic arch, across the aortic valve into the left ventricle.

Unique from the more common focal outflow tract ventricular arrhythmias are the left fascicular tachycardias. Left posterior fascicular tachycardia (Belhassen's VT) demonstrates a rather narrow QRS with a RBBB pattern and superior axis. Left anterior fascicular VT has a RBBB pattern and inferior axis. Fascicular VTs can often be terminated and treated with calcium channel blocker. The arrhythmia arises from a small reentry circuit in the LV Purkinje system. The target of ablation is typically a sharp diastolic potential recorded from the slowly conducting portion of the circuit along the LV septum. The most distal (apical) site of the potential is targeted for ablation to avoid injury to more proximal His/Purkinje tissue in the LV.

Special Considerations for Ablation in Patients with Congenital Heart Disease

The most common arrhythmia in congenital heart disease patients is IART (Chap. 8). However, several cardiac malformations are associated with accessory pathways (Chap. 4). These are Ebstein's anomaly of the tricuspid valve, congenitally corrected transposition of the great arteries (L-TGA), some forms of hypertrophic cardiomyopathy, and some forms of single ventricle, including heterotaxy syndromes. When these defects are detected, the presence of a possible manifest or concealed pathway should be considered. Other congenital defects, such as

ventricular septal defects and atrial septal defects coarctation, may be complicated by accessory pathways, but do not have a sufficiently strong association that would warrant undertaking their investigation (in the absence of symptoms).

Ebstein's anomaly is frequently associated with right-sided accessory pathways. Because of the underdevelopment of the tricuspid valve and the often associated tricuspid regurgitation, placing the catheter on the AV groove is difficult, and can be facilitated by a long stabilizing sheath. Activation mapping may reveal a broad and diffuse area of favorable electrograms. Placement of the ablation catheter beyond the "true" AV groove deeper into the "atrialized" ventricle (Fig. 23.14) to locate a possibly constricted insertion end of the pathway may lead to a favorable ablation site.

If patients with congenitally corrected transposition have an accessory pathway, it is usually on the anatomic left side (relative to the thorax), but morphologic right (ventricular inversion) relative to the ventricles. The AV node in congenitally corrected transposition is displaced superiorly and slightly laterally around the superior mitral valve (right AV valve) annulus.

In patients with heterotaxy syndromes, two AV nodes have been described which may connect with one another comprising Monckeberg sling and providing the substrate for a macroreentrant circuit. The inferior "node" is the typical target for ablation, though functional testing of both nodes should be performed.

In the presence of an AV defect, the normal location and course of the AV node–His-Purkinje axis is displaced posteriorly. Ablation of an accessory pathway in the right posterior septal region may result in heart block. Close monitoring of the indicators of proximity to the AV node and attention to AV conduction during energy application is critical and cryoablation in this area may provide additional safety.

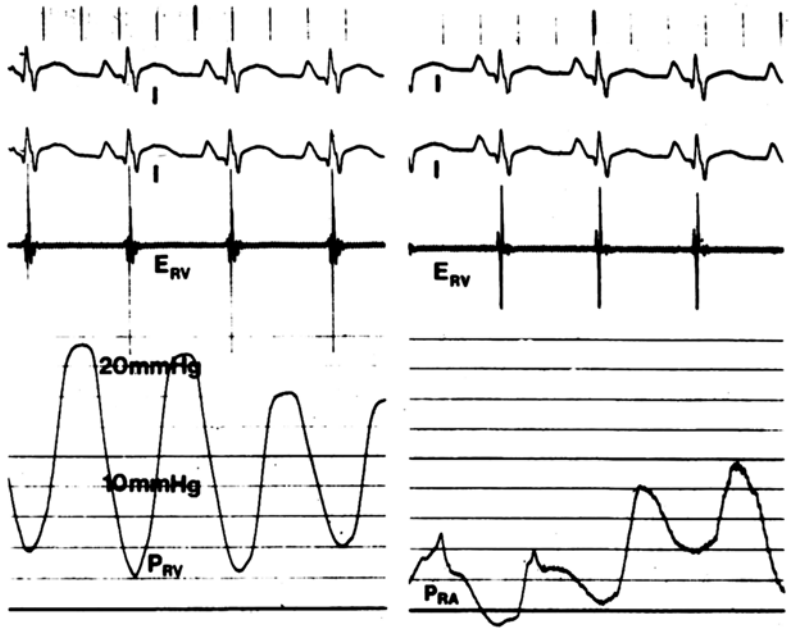


Fig. 23.14 Lead I (2). Intracardiac unipolar electrogram (E_{RV}) and intracardiac pressure tracing (P_{RV}) recorded through a single catheter with a lumen for pressure and a single electrode at the catheter tip in a patient with Ebstein's anomaly. *Left-hand panel*: Note simultaneous right ventricular pressure (20 mmHg) and ventricular electrogram. *Right-hand panel*: The catheter has been withdrawn slightly. Note that the pressure is now low at the atrial level while the electrogram is still ventricular in origin, indicating the "atrialized" portion of the right ventricle

Complications of Ablation

The complication rates are directly dependent on patient weight, patient age, and operator experience. For patients under 15 kg and <4 years of age, the reported incidence of complications by the Pediatric Radiofrequency Ablation Registry is higher than for older patients. Likewise, increased operator experience decreases the complication rate. Complications can be broken into two types: major (requiring intervention) and minor (resolve spontaneously with no consequence). In the Pediatric Radiofrequency Ablation Registry analysis, inadvertent ablation of the AV node with complete heart block, perforation, systemic thrombosis with central nervous system embolization, and death (1 in 3,187 patients without other heart disease) constitute the most significant complications. However, the occurrence of these adverse events has been significantly reduced since the early 1990s.

Aside from the perception of a higher risk of recurrence, there are fewer complications related to cryoablation compared to RF. Cryoablation is considerable safer to use around the AV node and inadvertent heart block has not been reported in the literature. Even direct intentional application of cryoablation for the purpose of AV node block is rarely successful. There is a lower risk of thrombus formation as endocardial disruption does not occur. Animal studies evaluating the effect of cryoablation on proximal coronary arteries have not shown any significant intimal damage.

Summary

Transcatheter ablation offers the possibility of complete, safe treatment of tachyarrhythmias in children. Although RF energy is the predominant form of energy delivery to ablate arrhythmia substrates in the human heart, cryoablation is widely used in children due to increased safety. During the past decade computerized electroanatomic mapping systems have revolutionized mapping and ablation and currently allow for very low fluoroscopy ablations to be performed, again increasing the safety of performing these procedures in children.

Suggested Reading

Andrade JG, Khairy P, Dubuc M. Catheter cryoablation: biology and clinical uses. Circ Arrhythm Electrophysiol. 2013;6:218–27.

Cosio FG, Anderson RH, Kuck KH, et al. Living anatomy of the atrioventricular junctions. A guide to electrophysiologic mapping. A consensus statement from the Cardiac Nomenclature Study Group, Working Group of Arrhythmias, European Society of Cardiology, and the Task Force on Cardiac Nomenclature from NASPE. Circulation. 1999;100:e31–7.

David H. Biophysics of ablation: application to technology. J Cardiovasc Electrophysiol. 2004;15:S2–11.

De Sisti A, Tonet J. Cryoablation of atrioventricular nodal reentrant tachycardia: a clinical review. Pacing Clin Electrophysiol. 2012;35:233–40.

Del Carpio MF, Buescher TL, Asirvatham SJ. Teaching points with 3-dimensional mapping of cardiac arrhythmia: what do the colors really mean? Circ Arrhythm Electrophysiol. 2010;3:e6–11.

Del Carpio MF, Buescher TL, Asirvatham SJ. Teaching points with 3-dimensional mapping of cardiac arrhythmia: how to overcome potential pitfalls during substrate mapping. Circ Arrhythm Electrophysiol. 2011a;4:e72–5.

Del Carpio MF, Buescher TL, Asirvatham SJ. Teaching points with 3-dimensional mapping of cardiac arrhythmia: mechanism of arrhythmia and accounting for the cycle length. Circ Arrhythm Electrophysiol. 2011b; 4:e1–3.

Del Carpio MF, Buescher TL, Asirvatham SJ. Teaching points with 3-dimensional mapping of cardiac arrhythmia: taking points: activation mapping. Circ Arrhythm Electrophysiol. 2011c;4:e22–5.

Friedman RA, Walsh EP, Silka MJ, et al. NASPE Expert Consensus Conference: radiofrequency catheter ablation in children with and without congenital heart disease. Report of the writing committee. North American Society of Pacing and Electrophysiology. Pacing Clin Electrophysiol. 2002;25(6):1000–17.

Huang SKS, Wood MA. Catheter ablation of cardiac arrhythmias. Philadelphia: Saunders; 2010.

Jackman WM, Wang XZ, Friday KJ, et al. Catheter ablation of accessory atrioventricular pathways (Wolff-Parkinson-White syndrome) by radiofrequency current. N Engl J Med. 1991;324:1605–11.

Jackman WM, Beckman KJ, McClelland JH, et al. Treatment of supraventricular tachycardia due to atrioventricular nodal reentry by radiofrequency catheter ablation of slow-pathway conduction. N Engl J Med. 1992;327:313–8.

Khairy P, Van Hare GF. Catheter ablation in transposition of the great arteries with Mustard or Senning baffles. Heart Rhythm. 2009;6:283–9.

Lustgarten DL, Spector PS. Ablation using irrigated radiofrequency: a hands-on guide. Heart Rhythm. 2008;5:899–902.

Miyake CY, Mah DY, Atallah J, et al. Nonfluoroscopic imaging systems reduce radiation exposure in children undergoing ablation of supraventricular tachycardia. Heart Rhythm. 2011;8:519–25.

Tai C-T, Chen S-A. Noncontact mapping of the heart: how and when to use. J Cardiovasc Electrophysiol. 2009;20:123–6.

Van Hare GF, Javitz H, Carmelli D, et al. Prospective assessment after pediatric cardiac ablation—demographics, medical profiles, and initial outcomes. J Cardiovasc Electrophysiol. 2004a;15:759–70.

Van Hare GF, Javitz H, Carmelli D, et al. Prospective assessment after pediatric cardiac ablation: recurrence at 1 year after initially successful ablation of supraventricular tachycardia. Heart Rhythm. 2004b;1:188–96.

Van Hare GF, Colan SD, Javitz H, et al.; Participating Members of the Pediatric Electrophysiology Society. Prospective assessment after pediatric cardiac ablation: fate of intracardiac structure and function, as assessed by serial echocardiography. Am Heart J. 2007;153:815–20.

Walsh EP. Interventional electrophysiology in patients with congenital heart disease. Circulation. 2007;115:3224–34.

Allied Professional Roles in the Management of Arrhythmias in the Young

24

Brynn E. Dechert and Sarah S. LeRoy

No man is more important than The Team. No coach is more important than The Team. The Team, The Team, The Team, and if we think that way, all of us, everything that you do, you take into consideration what effect does it have on [the] Team?

Glenn "Bo" Schembechler, University of Michigan Football Coach (1969–1989)

Effective teamwork in pediatric electrophysiology (EP) is imperative to providing high quality and patient-focused care. The care of children and adolescents with arrhythmias has significantly changed in response to major medical advances over the last few decades. These rapid technological advances along with the complexity of diagnosis and treatment of pediatric arrhythmias necessitates a multi-disciplinary approach and skilled, knowledgeable, EP personnel who function as a team. Allied professionals can play a vital role on the EP team. There are many different roles for allied professionals involved in the care of young patients with arrhythmias including EP technicians, nurses, advance practice nurses and others. Each member of the team plays a unique and collaborative role in the care of these patients.

Allied professionals adhere to the standards set by the Heart Rhythm Society (HRS). These standards describe necessary competencies for cardiac rhythm management, device implantation, and EP procedures. In addition to basic knowledge of cardiac electrophysiology, allied professionals must demonstrate technical knowledge, clinical skills, and adherence to safety standards as they care for young patients with arrhythmias. Allied professionals provide a wide variety of technical, clinical, and educational services for the EP team. In some centers, there can be one or two allied professionals who support EP but may not be dedicated to EP alone. In other centers, there can be many allied professionals with dedicated roles in EP. This chapter will describe the roles and activities of the different members on the pediatric EP team, emphasizing the necessary cross-training and overlap for centers with smaller clinical volume.

Electrophysiology Technicians

EP technicians work in a wide variety of roles in both the noninvasive and the invasive EP laboratories (lab). Noninvasive EP lab technicians must be proficient in the performance and basic interpretation of many tests such as ECGs, exercise tests, Holter, event monitoring, remote home monitoring of cardiac devices, and in-hospital

B.E. Dechert, M.S.N., C.P.N.P. (✉)
Pediatric Cardiology, The University of Michigan Congenital Heart Center, Department of Pediatrics and Communicable Diseases, DepUniversity of Michigan, Ann Arbor, MI, USA
e-mail: brynnd@umich.edu

S.S. LeRoy, R.N., M.S.N., D.N.P.
Department of Nursing, Wayne State University College of Nursing, Detroit, MI, USA

M. Dick, II (ed.), *Clinical Cardiac Electrophysiology in the Young*,
DOI 10.1007/978-1-4939-2739-5_24

telemetry. Physicians and patients rely on the technician's initial interpretation of the rhythm to identify problems that require more urgent attention. These team members provide patient and trainee education on many aspects of noninvasive EP testing. In addition, these technicians are often the "frontline of electrophysiology," often the first team member that patients meet. They provide a level of comfort and customer service to the young patients and families.

EP technicians also function in the invasive EP lab providing technical support during the procedures, utilizing their knowledge of cardiac and electrophysiology. The EP lab technical staff communicates with all members of the team performing the procedure including nurses, advanced practice nurses (APNs), anesthesia staff, trainees, and physicians. Their technical expertise enables them to trouble shoot equipment malfunction efficiently. The EP lab technicians prepare the patient for the procedure, placing the surface ECG leads and skin patches appropriately. In addition, they can manage the complex array of equipment connections and operate the computer-supported 3D electro-anatomic mapping systems. The EP lab technical staff monitor rhythm, perform laboratory tests and record results. They provide patient care during the procedure and immediate post-procedure. The EP lab technical staff educate and train tone another about the technical aspect of procedures. The EP team must stay current with education about changes in current and upcoming technology.

Especially important in the Pediatric EP Laboratory is attention to the physical and emotional welfare of the child or adolescent. Knowledge regarding fluid management and temperature regulation in the infant and toddler, sensitivity to the privacy of the older child and adolescent and special care in safe placement and positioning of patients of all sizes and needs on the procedure table is central to their role.

Nurses

EP nurses have many roles spanning the inpatient, outpatient, and procedural EP service. Nurses in the EP lab direct patient care as well as manage daily operation of the lab team. The role of the nurse in the EP lab begins before the procedure. They work with the anesthesia team to provide pre-procedure care to the patient and the family, specifically assuring that the developmental stage of the patient is considered when providing education and comfort. They may obtain vital signs, facilitate pre-procedural testing, obtain intravenous access, and provide appropriate pre-procedural monitoring. Nurses are in direct patient contact through the entire patient experience and are often the cornerstone of communication between the EP team members.

During the procedure, EP lab nurses may have many roles including assistance with catheter or device selection, venous access, operative assistance, and operation of EP recording and ablation equipment. They also focus on overall patient safety. They continually communicate with the anesthesia team to provide comfort to the patient. While the physician manipulates the catheters at the patient table, the highly trained EP lab nurse may often operate the recording system and stimulator supplying experienced eyes, quick interpretation, and control of the system. The EP lab nurses communicate with APNs, physicians, and recovery room nurses about the procedure discussing the plan for post-procedure care. EP lab nurses provide a smooth flow of information to fellows, residents, and other trainees throughout the procedure.

Postoperatively, EP patients continue to require specialized care. Recovery room nurses monitor vital signs, post-procedure telemetry, and the catheter puncture sites. Recovery room nurses assure that post-procedure testing is completed. They provide pain comfort management and assess for postoperative complications. They communicate with the anesthesia team, advance practice nurses, physicians, and families.

Advanced Practice Nurses

APNs function in a diverse role. APNs have an advanced degree in clinical nursing and health care; they serve children and families in a broad range of practice settings. APNs work collaboratively with physicians and other members of the

EP team. Beginning with outpatient care expanding to intra-procedural care and inpatient care, APNs provide continuity to the family and expertise in EP to patients.

APNs in Outpatient Care

Prior to an outpatient clinic, APNs determine and arrange any possible testing needed for patients during their visit. Throughout clinic, APNs assist in the management of children and adults with congenital heart disease and arrhythmias. They provide continued care in subsequent visits or via telephone. APNs provide test results and consultation to the patient and family regarding symptoms and concerns. If necessary, they recommend further testing and follow-up. In addition, APNs often function independently in a outpatient setting.

APNs in Pre-, Intra- and Post-procedural Care

There are a number of different procedures that may be indicated for the management of children with arrhythmias; they include noninvasive procedures such as tilt table testing to invasive procedures such as device implantation. Pre-procedure preparation, usually beginning with a phone call, is a critical role. Pre-procedure preparation decreases child and parent anxiety and increases patient and family satisfaction. APNs provide support to the family throughout the pre-procedure process. A phone call or outpatient visit prior to the procedure provides an excellent opportunity to establish rapport with the family, to initiate the assessment of child/family needs, and to provide anticipatory education and information about the proposed procedure (Tables 24.1, 24.2, and 24.3). This is especially important if the diagnosis is

Table 24.1 Pre-procedure screening phone call

Medical screening	Psychosocial screening	Anticipatory guidance
Update health history	Child/family response to planned procedure	Ask parent/guardian to identify concerns; address concerns
Identify co-morbidities	Assess family composition, support systems and coping methods	Describe procedure, post-procedure care, discharge plan, restrictions
Develop plan as needed		
Consult with specialist as needed		
Obtain brief family health history including anesthesia reaction, bleeding problems, allergies	Identify any current psychosocial problems needing plan or referral	Describe recovery period including return to physical activities
Identify and obtain missing medical information (documentation of arrhythmia, echocardiogram)	Identity social needs; financial, insurance, transportation, housing	Offer information to patient and child if needed
Determine other testing needed	Refer to social work as needed	Refer to child life as needed

Table 24.2 Preoperative education: device implantation

Operative detail	Device details	Restrictions
Length of procedure	ICD vs. pacemaker: purpose of device	No overhead reaching for 6 weeks for transvenous system
Incision type: axillary vs. subcutaneous	If ICD, discuss risk of inappropriate shocks	Avoid heavy lifting for 6 weeks
Length of hospital stay	Single vs. dual chamber	Return to school/work: 1 week
	Battery and lead longevity	
	Device features: anti-tachycardia pacing, MRI compatibility, etc.	
	Remote monitoring education	

new and the family and patient are unfamiliar with the institution. Collaborating with the social work team, the APN can highlight social concerns such as the need for assistance with lodging, transportation, and other concerns. The APN reviews patient diagnosis, anatomy, and history in preparation for delivering the pre-procedure instructions such as discontinuing medications, NPO instructions; he or she can arrange further testing if needed.

APNs provide detailed education to patients and families prior to EP procedures tailored to their individual needs. Anticipatory education, especially important for those undergoing device implantation, emphasizes the planned follow-up care and the importance of long-term device monitoring; it decreases anxiety for the patient and family (Table 24.2). Education regarding generator replacement is dependent on the type of device selected. For example, wound care for a device generator change is similar to that of an implantation of new devices, but overhead arm movement restrictions are usually not necessary.

On the day of the procedure, APNs work closely with the EP physician, nurses, and technical staff throughout the patient's experience. APNs perform preoperative history and physical that is reviewed by the anesthesia team and the EP physician. Throughout the procedure APNs provide continued support, education, and updates to the family. Following the procedure, APNs communicate with the recovery room nurses and physicians to ensure continuity and high quality care. APNs order and review post-procedure testing, provide pain/anti-nausea medication, and address other patient care needs.

At discharge APNs, in collaboration with attending physicians, ensure appropriately programmed pacemaker function and determine necessary clinic follow-up to monitor device safety and continued normal device function. APNs provide detailed information about the procedure outcome and follow up care to the family (Tables 24.4 and 24.5). APNs follow up with patient and families via telephone following the procedure to assess for concerns. APNs assess

Table 24.3 Preoperative education: day of ablation

Procedure details	Restrictions
Length of procedure	Return to school: 1–2 days
Description of catheter ablation	Return to sports: 3 days or when groin sites are well healed
Cryoablation vs. radiofrequency ablation	

Table 24.4 Discharge instructions for device implantation

Wound care	Activity instructions	Follow-up
When to remove initial dressing	If transvenous lead(s), avoid overhead reaching for 6 weeks	Discharge with Holter ×24 h
Cover with light dressing and protect from clothing and leave open to air as much as possible	Use sling as needed for comfort	Wound check in 1–2 weeks (via telemedicine or PCP)
Post-implant oral antibiotics often advised	With reaching restrictions, promote range of motion of that arm to prevent stiffness	In-office interrogation and appointment 2–6 weeks after implant
Avoid shower for 72 h; protect from water until that time	Return to school/work in a week	Remote monitoring education
Avoid complete submersion water (swimming/bath) until well-healed		Schedule routine remote monitoring schedule
		Encourage remote monitoring transmission with any concerning symptoms
Call immediately with signs of infection: fever, wound redness/drainage/tenderness/swelling	Return to sports/gym in 6 weeks	Discuss triage/access to medical system with concerns

Table 24.5 Discharge instructions for ablation

Wound care	Activity restrictions	Follow-up
Pressure dressing removed prior to discharge or upon arrival home	Avoid gym/ sports until groin sites are healed (usually 3–5 days)	Discharge medications: pre-procedure medications as needed, aspirin daily ×6 weeks with left sided ablation
Place small bandage over site for 2 days	Return to school/work within 1–2 days	Discharge Holter as needed ×24 h
May shower after 24 h after Holter removed		Call with symptoms of infection
Avoid submersion of puncture sites in water ×3 days		

for complications, recurrences and other concerns and can manage these issues if they occur. Lastly, for patients who underwent device implantation, telemedicine has become increasingly useful. Wounds can be accessed via digital photo and emailed to the APN through a smart phone, making follow-up extremely convenient for the patient, especially those who live far from the implanting center.

Because school reentry after diagnosis of arrhythmia, post-ablation and especially after device implantation is often a source of considerable concern for parents and school professionals, education of school personnel with parental permission is important. APNs can provide education about the child's arrhythmia, what symptoms to assess, and how the cardiac device works. Especially important is to discuss what to do if the ICD discharges (shock), medication side effects, and an emergency plan for school personnel if needed. During these discussions, APNs emphasize the protection afforded by cardiac devices and that the purpose of undergoing device implantation is to permit the child to live a normal life, as much as possible.

Device Support

Allied professional members of the EP team may be responsible for the processing and initial interpretation of remote home monitoring of cardiac devices and are often the first contact for the patient and family regarding the telemedicine reports. Remote monitoring can decrease cost and increase efficiency by monitoring for device concerns from home. Home monitoring can detect lead fracture arrhythmia or decrease in generator battery life. This essential service provides peace of mind to patients and families with cardiac devices and provides information to the EP team long after the family has been discharged from the hospital. In many instances, through this service, the allied professionals build long-term relationships and become advocates for these patients and their families. In addition, they communicate with other members of the health care team as issues arise.

Allied members of the EP team assist the physician or surgeon during device implantation by testing stimulation and sensing thresholds for new devices during implantation. They also are trained in device interrogation and often perform it in both the outpatient and inpatient settings. Under HRS guidelines, these team members can determine stimulation and sensing threshold of leads and assess intrinsic rhythms, pacemaker dependency programming changes, determine frequency of remote monitoring, and anticipate device or lead replacement. In addition, team members in collaboration with the EP physician determine if a device requires reprogramming prior to surgical or other invasive procedures. They assess for device malfunction by performing postoperative interrogation.

Psychological Support for Patients with Cardiac Devices

A major therapeutic goal for children with arrhythmias and implanted devices is to facilitate positive child and family adjustments so as to prevent avoidable negative psychosocial out-

comes. Important tasks for parents of children with arrhythmias or devices include participation in all aspects of the treatment, preservation of both their child's and their emotional well-being, and preparation for the uncertain future. Adaptive parental strategies include maintaining family integrity through cooperation and maintenance of an optimistic outlook, maintaining social support, self-esteem, and psychological stability, and understanding the medical situation through communication with other parents and healthcare providers. Allied professional team members provide this support to the family through both the clinic visits and telemedicine contact.

Support groups and specialty summer camps have shown to be helpful in promoting positive adjustments to chronic illness for children and young adults. Patients with ICDs often undergo significant adjustment after implantation. Professionals working with these young people report that many individuals do not participate in ongoing adult patient support groups because the groups do not address issues of young patients and their concerns such as work, intimate relations, childbirth, school, friends, and dating. Also, the relatively small numbers of young defibrillator patients in any one geographical area have limited the ability to initiate support groups specifically for this population. In an attempt to address these needs, allied professionals collaborate with other services such as social work, psychiatry, and other specialty services. In many centers, a yearly support group for patients with ICDs has been formed. "The Young ICD Connection" is a support conference that occurs once yearly sponsored by the Michigan Congenital Heart Center and the Medical Electrophysiology Service at the University of Michigan. It has been very successful and reproduced in a number of other institutions throughout the country. "The Young ICD Connection" provides educational workshops on topics of interest to young patients in addition to professionally facilitated support groups divided by patient, spouse, and parent. Most importantly, children, adults, and families have fun and are able to provide support to one another. Post-conference evaluations reveal that the children and adolescents who interact with one another during this support see firsthand that they are not alone and that a meaningful future is possible for them.

Cross-Training and Overlapping Roles

In all, cross-training is very useful if not essential. The roles of these team members overlap on many occasions. For example, the EP lab technician and nurse both have knowledge of catheter and device type. In some centers, fellows or other trainees may fill these roles as part of their educational experience. Although overlapping and cross-training is essential to the function of the team, it is important to support various team members as they develop their special interests and niches.

Research

Collaborative research may be performed by all allied professional team members. EP technicians typically examine and report on the technical aspects of the EP or ECG lab. APNs and nurses investigate outcomes of arrhythmias and device management. These efforts promote progress in the technique, therapy, diagnosis, and management of pediatric arrhythmia patients. Participating in research promotes the career and long-term goals of the allied professional. All team members can participate in quality assurance research.

Teaching and Collaboration

In many instances, allied professional members offer education to staff and medical trainees, encompassing informal sessions as during device interrogation or formal at didactic sessions. Venues include the local institution along with regional and national forums.

Allied professional members collaborate with other disciplines for clinical care as well as education, including other specialty cardiology

services such as adult congenital, adult cardiology, fetal cardiology, primary cardiology, and pediatric practices. This collaboration is essential in providing comprehensive patient care.

Professional Organizations and Specialty Training

EP allied professionals come from a wide variety of backgrounds and training experiences. EP technicians are typically credentialed as Registered Cardiac Electrophysiology Specialist (RCES). This process involves an education through an accredited medical technology program followed by a certification examination. Many EP technicians have bachelor's or associate's degree in various scientific fields. Registered nurses have completed either an associate's degree or bachelor's degree in nursing and have passed the licensing examination. In addition to their undergraduate degree, APNs have experience as nurses, have a graduate degree in nursing, and have passed their certification examination. Currently, there is no specific standardized education or curriculum for entry into EP practice for many allied professionals. There are specialty certifications for allied professionals in EP. The International Board of Heart Rhythm Examiners (IBHRE) has two examinations for associate professionals: Certification Examination for Competency in Cardiac Rhythm Device Therapy and Certification Examination for Competency in Cardiac Electrophysiology. These certification examinations provide formal recognition for those who are experts in their field and ensure competency for many allied professionals. In addition, specialty certification can enhance credibility and promote the allied professional role in pediatric EP.

The HRS and the Pediatric and Congenital Electrophysiology Society (PACES) serve as the two main professional organizations for pediatric cardiac electrophysiology. HRS is a broad source of education for both the patients and associate professional members. The HRS Scientific Sessions occur on a yearly basis and are the main educational meeting for clinical cardiac electrophysiology. Throughout HRS, there are specific pediatric EP sessions and allied professional sessions. Many of the pediatric sessions are supported by PACES. Frequently PACES provides pre-conference educational sessions for pediatric EP topics. The HRS website (www.hrsonline.org) offers published clinical guidelines developed by experts in their field. Many PACES members, including allied professionals, participate in the development and writing of these guidelines. Both PACES and HRS include allied professional members on their executive boards.

Summary

Overall, allied professional members perform a wide variety of essential roles as part of the EP team. EP teams involve allied professionals from many different disciplines: technical personnel, nurses, and advanced nurse practitioners. Their roles overlap and cross-training is necessary for a well-functioning team. Working as a team, EP allied professionals greatly expand the optimal and high quality medical services essential to children with disorders of heart rhythm. As the complexity of the care advances, the need for team collaboration increases.

Suggested Reading

Campbell LA, Kirkpatrick SE, Berry CC, et al. Psychological preparation of mothers of preschool children undergoing cardiac catheterization. Psychol Health. 1992;7:175–85.

Campbell LA, Kirkpatrick SE, Berry CC, Lamberti JJ. Preparing children with congenital heart disease for cardiac surgery. J Pediatr Psychol. 1995;20:313–28.

Chiu C. Certification of international allied professionals in cardiac pacing and electrophysiology: opportunities. Can J Cardiol. 2010;26:e24–6.

Crossley GH, Poole JE, Rozner MA, et al. The Heart Rhythm Society (HRS)/American Society of Anesthesiologists expert consensus statement on the perioperative management of patients with implantable defibrillators, pacemakers and arrhythmia monitors: facilities and patient management: executive summary. Heart Rhythm. 2011;8:1114–54.

Czosek RJ, Bonney WJ, Cassedy A, et al. Impact of cardiac devices on the quality of life in pediatric patients. Circ Arrhythm Electrophysiol. 2012;5:1064–72.

Deering TF, Clair WK, Delaughter MC, et al. A Heart Rhythm Society Workforce study: current survey analysis of physician workforce trends. Heart Rhythm. 2010;7:1346–55.

Dunbar SB, Dougherty CM, Sears SF, et al. Educational and psychological interventions to improve outcomes for recipients of implantable cardioverter defibrillators and their families: a scientific statement from the American Heart Association. Circulation. 2012;126:2146–72.

Guru MT, Bubien RS, Belco KM, et al. North American Society of Pacing and Electrophysiology standards of professional practice for allied professional in pacing and electrophysiology. Pacing Clin Electrophysiol. 2003;26:127–31.

LeRoy S, Elixon M, O'Brien P, et al. American Heart Association Scientific Statement: recommendations for preparing children and adolescents for invasive cardiac procedures. Circulation. 2003;1008:2550.

O'Brien P. The role of the nurse practitioner in congenital heart surgery. Pediatr Cardiol. 2007;28:88–95.

Sears SF, St. Amant JB, Zeigler V. Psychological considerations for children and young adolescents with implantable cardioverter defibrillators: an update. Pacing Clin Electrophysiol. 2009;32:S80–2.

VonBergen NH, Atkins DL, Dick M, et al. Multicenter study of effectiveness of implantable cardioverter defibrillators in children and young adults with heart disease. Pediatr Cardiol. 2011;32:399–405.

Wilkoff BL, Auricchio A, Brugada J, et al. Heart Rhythm Society/European Heart Rhythm Association expert consensus on the monitoring of cardiovascular implantable electronic devices (CIEDs): description of techniques, indications, personnel, frequency and ethical consideration. Heart Rhythm. 2008;5:907–25.

Index

M. Dick, II (ed.), *Clinical Cardiac Electrophysiology in the Young*,
DOI 10.1007/978-1-4939-2739-5