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

Electrical Diseases of the Heart

Volume 1: Basic Foundations and Primary Electrical Diseases

Second Edition

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

Ihor Gussak
Charles Antzelevitch

Foreword

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

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

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

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

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

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

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

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

Indianapolis, IN *Douglas P. Zipes, MD*

Preface

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

The book is organized into 77 chapters in 2 volumes. Each chapter includes up-to-date results of studies aimed at providing an understanding of the electrical function of the heart in health and disease, established and evidence-based knowledge of clinical outcomes, areas of controversy, and future trends. Our goal is to provide a contemporary and succinct distillation of the state of the art. Although many of the chapters are highly sub-specialized, this book is designed for a broad audience, ranging from medical and graduate students to clinicians and scientists.

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

Ihor Gussak
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Part I
Basic Fundamentals of Normal and Abnormal Cardiac Electrical Activity

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1
Introduction to Part I: Basic Cardiac Electrophysiology – Promises Kept and Promises to Keep

Ralph Lazzara

Abstract

Important methodological developments contributing to the great advances in basic cardiac electrophysiology in the past 100 years include the microelectrode for recording intracellular potentials, the disassociation of myocytes in the cardiac syncytium, and fluorescence imaging for monitoring intracellular calcium and the transmembrane potential. Significant advances in recent years include the description of the J wave syndromes and focal ventricular tachycardias originated from the Purkinje-myocardial junction of the papillary muscles, elucidation of the role of the autonomic nervous system in the generation of arrhythmias, investigation of the complex movements and actions of Ca^{2+} in the myocyte affecting electrophysiology and arrhythmia generation, discovery of new genetic mutations affecting the cytoskeleton and the transport, assembly and function of molecular aggregates within the myocyte and in the sarcolemma, and identification of disease- related alterations of micro RNA that result in abnormal functions of sarcolemma and intracellular protein complexes.

Keywords

J wave syndromes • micro RNA • Autonomic nervous system • Fluorescence imaging • Myocyte Ca^{2+} • Macromolecular complexes

In the introduction to the basic science section of the first edition of the Electrical Diseases of the Heart, Harry Fozzard provided a splendid historical review and thoughtful selection of landmark developments and discoveries over the past 100 years that have formed the vibrant discipline of cardiac electrophysiology, basic and clinical [1]. The germinal achievement designated by Dr. Fozzard was the invention of the electrocardiogram by Wilhelm Einthoven. The compiled list of subsequent signal contributions to the field was derived from multiple disciplines including physical chemistry, biochemistry, neurophysiology, skeletal muscle physiology, and clinical science.

To this list of grand advances I add methodological developments that proved vital to the advancement of cardiac electrophysiology apace with neurophysiology. Access to the cell interior to control transmembrane voltage and dissect and identify the separate ionic currents generating the action potential was first accomplished in the relatively gargantuan squid giant axon.

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This momentous transition from measuring voltage to measuring current, symbolically a move to the right side of the Ohm equation E = IR, was the launch that propelled electrophysiology through the latter half of the twentieth century into this century and the molecular era. Detailed analysis of individual ionic currents was an essential step towards identification and functional characterization of ion channels, the molecular entities that transmit the currents, culminating in definition of the molecular structure of ion channels.

The contracting, connected multicellular cardiac syncytium was a formidable barrier to the application of the voltage clamp technology necessary for the measurement, manipulation and analysis of individual ionic currents. Moreover the prolonged action potential of the cardiac myocyte, with its electromechanical coupling involving intricate transmembrane and intracellular movements of Ca^{2+} necessary to sustain a prolonged and modulated contraction, represented a dauntingly complex array of transmembrane ionic movements. "The little engine that could" blaze the trails to explore this system was the methodology for disassociation of cardiac myocytes with preservation of their electrophysiological and contractile integrity, allowing voltage control and recording of currents in the whole cell and in single channels in dissociated patches. The more recently developed technologies for fluorescence imaging to track transmembrane potential as well as intracellular molecular movements, notably Ca^{2+}, also have been powerful tools.

Contemporary cardiac electrophysiology, the product of these diverse but coalescent developments is expanding at an awesome pace, albeit already intimidating in its scope and depth. Testimony to the dynamic growth of the field is the call for this second edition of Electrical Diseases of the Heart just 3 years after publication of its first edition; testimony to the scope and depth of the field is the necessity for expansion in this edition of the seven sections and 63 chapters of the first edition.

In the brief period since publication of the first edition, there have been notable discoveries and insights that offer pristine visions of new knowledge and new directions for exploration as well as significant expansion in detail and depth of knowledge in established areas, sufficient for gratifying enrichment of the second edition. I offer a few subjectively selected introductory examples.

The J wave syndromes have been recently defined as a set of electrocardiographically based disorders putatively associated with lethal ventricular arrhythmias. They are unified by a common hypothetical mechanism, phase 2 reentry, which is based on an imbalance of inward and outward currents early in the action potential, roughly coincident with the action potential notch (phase I), that can generate heterogeneous early repolarization, reexcitation, and reentry. Brugada syndrome, included in the set, is the well recognized prototype in which the arrhythmia mechanism is localized in the right ventricular epicardial layers, while in the other less malignant forms the electrocardiogaphic manifestations and arrhythmia mechanisms are presumably localized in inferior and lateral walls of the left ventricle. In the forms manifesting in inferior and lateral leads, i.e., the left ventricular locations, overlap exists between the malignant phenotype and the benign normal variant long labeled as early repolarization. The definition of J wave syndromes is generating controversy as is the arrhythmia mechanism for the noncontroversial Brugada syndrome. An adversary of the original hypothesis of phase 2 reentry has appeared in the form of conventional reentry based on slowed conduction and fibrosis in the right ventricle.

Focal sites generating ventricular tachycardias and PVCs have been discovered in the papillary muscles in both the left and right ventricles. The papillary muscle foci may or may not be associated with scarring. The recording of Purkinje potentials implicates the Purkinje-myocardial junction in arrhythmia generation.

Neurocardiology, the discipline centered on the interactions between the heart and the nervous system, is undergoing an upsurge, especially in relation to the intrinsic and extrinsic autonomic systems governing the heart. Enlightenment of the autonomic cellular signaling paths continues to expand rapidly. The application of methodology to record from key neural elements in instrumented awake animals with arrhythmias has generated new insights about the relationship