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Electrical Diseases of the Heart

Genetics, Mechanisms, Treatment, Prevention

Springer

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To the pioneers of cardiac electrophysiology whose seminal contributions are depicted in the historical perspectives included in many of the chapters. Our mentors, collaborators, and fellows who have assisted us in advancing the field,

and

last, but not least, to our families, whose understanding and support have permitted us to dedicate the time and effort needed to formulate this text.

I.G.
C.A.

Foreword

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 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 stopped her medications and gradually stopped coming back for return visits because she had complete control of her SVT. About 15 years later she showed up unannounced because one of the wires in her handheld unit had 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 removal of the implanted unit.

My, what a ride the last 30-plus years has provided! From a group of half dozen or so arguing at the American Heart Association Scientific Sessions as to what was the true duration of the H-V interval, to the keynote lecture

on pacing I was privileged to give at the very first North American Society of Pacing and Electrophysiology (NASPE) meeting in 1980 attended by maybe 27 people, to the most recent Heart Rhythm Society (HRS) meeting with over 12,500 attendees, there has been excitement at all levels, molecular, ionic, genetic, in vitro, in vivo, and clinical. We have mined the riches offered by the study of cardiac electrical phenomena and that is what this book captures. It offers a true bridge between the basic and clinical, with insights that few texts can claim. To all for whom the squiggles of the electrocardiogram tantalize with further insights into the electrophysiology of the heart, this book offers a wonderful guide—a searchlight—into the incredible electricity that makes us tick. I compliment the editors and the authors for a wonderful job. We've come a long way, baby, and it is awesome to read about it between the covers of this book!

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Part I
Basic Foundations of Normal and Abnormal Cardiac Electrical Activity

The Past and Promise of Basic Cardiac Electrophysiology

Harry A. Fozzard

Introduction

A half-century ago, as an aspiring cardiologist I entered the field of cardiac electrophysiology, frustrated by our inability to intervene successfully in lethal cardiac arrhythmia, and equally frustrated by the paucity of basic understanding of cardiac electricity upon which better treatment could be based. What a remarkable change has occurred since that time; there have been extraordinary advances in both the science and clinical care. I will begin this introduction to the section on *Basic Foundations of Normal and Abnormal Cardiac Electrical Activity* by identifying those basic science steps that I think have contributed to the progress of cardiac electrophysiology. These are the rich historical background for the chapters in this section. Then I will comment on the best strategy for advancing our understanding of cardiac electricity and outline some of the key questions that I think we must address. Although my personal career goal has been how we can now exploit this basic science for clinical care, more than ever basic understanding is the framework for our future advances.

The continuum of science requires that future progress be built on the past. Therefore, before we seek to make judgments about future directions, it is important to examine how we have arrived at the present state of understanding of the cardiac electrical system and of cardiac arrhythmias. Basic scientific development has two very interdependent lines—general electrophysiology and cardiac electrophysiology. Sometimes progress has been motivated by study of heart muscle, sometimes of nerve, sometimes of single cell organisms. The basic features of membrane potential, excitability, and conduction are complementary between these areas, and the field of ion channels is united,[1] albeit with special characteristics to the cardiac system. There is a third line of insight into a basic understanding of cardiac electricity, derived from more clinical studies that have dramatically altered the natural history and the treatment of arrhythymias and that hold important and direct lessons for basic science.

We have no central planning agency to direct cardiac electrophysiological research. Indeed, experience in the last century leads us to believe that individual investigators are the best source of inspiration and direction. In the United States we have been blessed with outstanding financial support from the National Institutes of Health and the National Science Foundation and from private agencies such as the American Heart Association for this investigator-initiated research, and support from the pharmaceutical industry for therapeutically relevant research. Similar support has come from patrons in other countries. However, the success of this nondirective system requires continued lively discussion and debate between investigators in the basic science and with clinicians. Total resources for biomedical research are not infinite and each investigator has limited time and resources. Therefore, we can benefit from some discussion of what the history of our field can teach us and what strategy may be the most efficient direction to lead to greater scientific insight and to further improvement in cardiac care.

Although electrophysiology has greatly increased our scientific understanding, thoughtful reflection leads me to the general impression that in the recent past clinical interventions that reduce or prevent the underlying disease have probably had the greatest impact on lethal arrhythmia. However, this impact has been primarily to delay arrhythmic problems to a later age, rather than to abolish them. Indeed, our success in restoring circulation in ischemia has increased the numbers of people with heart failure, possibly changing the mechanisms of the dominant arrhythmias. Exploitation of genetic methods along with electrophysiology has revealed a small but growing population of primary arrhythmic diseases that provide exciting insights into both normal and abnormal mechanisms.

Historical Landmarks

We can make a strong case that basic science has been an extraordinarily successful contributor to cardiac care. But the insights and tools of biomedical science have expanded so dramatically in the last century that it is daunting to consider what are the most promising directions for cardiac electrophysiologists to follow. The interconnectedness of science means that every approach is potentially valuable. In retrospect, we can perceive that some approaches have been obviously more productive than others, although not always predicted during the basic phase. In the quest for clinically important insight we must not undervalue the progress of general science. The next decades can lead to basic understanding of the cardiac electrical system unimaginable to me when I began my career 50 years ago, and consequently to major advances in clinical care.

The Electrocardiogram

One hundred years ago William Einthoven[2] published a review of the clinical applications of his recordings of cardiac electrical activity, which I take as the beginning of the systematic study of cardiac electrophysiology. The string galvanometer that he developed could reliably measure very small signals, and it provided an invaluable tool not only for the cardiac physiologist but also for the neuroscientist. I will examine three parallel lines of development during the century since Einthoven's publication, jumping between those of basic and cardiac electrophysiology and those of clinical study that have contributed to the development of our basic understanding.

The Action Potential

Rapid advances in electrochemistry and the physics of electricity led logically to the 1902 proposal of Bernstein[3] that excitation of the action potential (AP) resulted from loss of resting membrane selective permeability to *K* (the Nernst potential), and then repolarization from reestablishment of *K* selectivity. The critical all-or-none property of the AP was first shown in the early 1900s by Lucas[4] and Adrian.[5] About this time Mines[6] described the properties of reentry loops, which has been a big factor in understanding cardiac arrhythmias, and in 1912 Herrick[7] described the clinical course of acute myocardial infarction. How the necessary transmembrane ion gradients of high intracellular K and low intracellular Na were achieved and maintained was only gradually resolved by Hodgkin's definition of an Na pump[8] and purification of a K- and Na-dependent ATPase from nerve membrane by Skou.[9] Interestingly, it was early observed that digitalis blocked the Na/K-ATPase and the Na pump, and that this action is likely to be a step in its positive inotropic effect.

Squid Axon and Microelectrodes

The squid giant axon is a 0.5- to1.0-mm-diameter cable-like cell composed of many fused axons. Its rediscovery in 1936 by Young[10] provided a crucial tool for electrophysiological progress. Curtis and Cole[11] quickly demonstrated that the axon membrane resistance fell to a very low value during the peak of the AP, as predicted by the Bernstein hypothesis. Surprisingly, however, Hodgkin and Huxley[12] found the magnitude of the AP exceeded the resting potential (overshoot) and was substantially positive, contrary to the Bernstein proposal. This overshoot was seen as early as 1934 in an attempt to measure the cardiac transmembrane AP,[13] but problems with junction potentials made the measurements uncertain. The existence of an

overshoot was finally resolved by Hodgkin and Katz[14] by showing that the overshoot was a function of the Na gradient and that the AP must result from a selective dominance of Na permeability, not simply a loss of selectivity. During this same time period, development by Ling and Gerard[15] in 1949 of a satisfactory glass micropipette that could measure membrane potential in intact cells would revolutionize the study of single cells over the next half-century. As is typical, the development of a new technique precedes major advances in understanding.

Voltage Clamp

Progress by Cole and Marmont now set the stage for a huge advance in 1952. Hodgkin and Huxley[16] used the voltage clamp to determine the voltage and time-dependent properties of Na and K conductances and to build a coherent model of the ionic basis of excitability. It is hard to realize from this distance in time how revolutionary this work was, and how much it required electrophysiologists to change their mindset. One of the Hodgkin-Huxley predictions was that the Na and K channels derived their voltage dependence from movement of tethered charge inherent in their protein structure. This "gating current" was finally recorded in 1973 by Armstrong and Bezanilla,[17] and we now recognize the S4 transmembrane segment as the structural motif of ion channel voltage dependence.

Application to the Cardiac Cell

With the new microelectrodes and the voltage clamp, cardiac electrophysiology entered a period of spectactular growth. Woodbury, having learned the Ling technique, collaborated with his brother and Hans Hecht to record in 1950 the frog heart AP.[18] At about the same time Weidmann and Coraboeuf,[19] fellows in Hodgkin's laboratory, having learned the microelectrode technique brought back from Chicago by Hodgkin, recorded the AP of a dog Purkinje fiber. Weidmann[20,21] in 1956 went on to demonstrate that the ionic basis for excitability was similar in the heart to that in squid nerve, and that the Na channel can be blocked by local anesthetic drugs. Hutter and Trautwein[22] recorded the diastolic depolarization characteristics of the pacemaker AP and showed the dramatic effects of vagal and sympathetic stimulation on the pacemaker rate. Noble[23] then showed in a computer model that a modification of the Hodgkin–Huxley kinetics for the Na channel and an inwardly-rectifying K channel, along with adjustment of Na and K leak paths, could generate an AP with a cardiac-like plateau.

Trautwein and colleagues[24] devised in 1964 a reasonable voltage clamp method for cardiac Purkinje fibers, and Reuter[25] used it to demonstrate for the first time that cardiac cells had excitatory calcium channels and that they were sensitive to adrenergic hormone. The voltage-dependent calcium current was then directly linked to the onset and magnitude of cardiac contraction.[26,27] Earl Sutherland's[28] discovery of the adrenergic signaling cascade via second messenger systems provided the basis for our present understanding of cellular modulation of ion channels. The dramatic dependence of cardiac contraction on both Na and Ca concentrations was solved by discovery of the Na/Ca exchange system.[29] We must remember that the AP exists not only to malfunction in arrhythmias but to activate and regulate cardiac contraction.

Although it was well known that cardiac cells behaved as if they are electrically and chemically coupled, allowing rapid conduction without synapses,[30] the structures responsible for the coupling were identified only much later.[31] These "gap junctions" are composed of clusters of channels that span the extracellular space between cells and allow both electrical and chemical transmission. They are also heavily modulated and influenced by disease, producing various levels of anisotropic conduction that provide some of the substrate for arrhythmia. They also are the structures involved in "healing over", the sealing of cell boundaries so that injury from infarct or a surgical scalpel does not propagate to the entire heart.

Parallel Clinical Advances

During this golden period of basic cardiac electrophysiology, major ideas were emerging on the clinical side. Lown[32] in 1962 helped develop the DC defibrillator, which was markedly better than the earlier AC defibrillator system. Implantable pacemakers began a long course of development into

complex clinical tools, meanwhile contributing to our understanding of excitability. Kuller[33] described landmark studies of sudden death, showing that the dominant pathological process is obstructive coronary disease. Coronary Care Units (CCUs) were established because in-hospital mortality of acute myocardial infarction was 30–40%, and this specialized nursing and monitoring concept greatly enhanced our understanding of arrhythmias related to ischemia. Lown's battle cry of "Hearts too good to die!" was true in part, but the fact is that CCU arrhythmic death did not fall immediately with the use of lidocaine, but only gradually diminished as we found ways to relieve ischemia by improving coronary blood flow.[34] Mirowski's[35] idea of an implantable defibrillator began its long journey to standard clinical application. Scherlag and colleagues[36] initiated invasive electrophysiological studies in humas, beginning another long development path to invasive testing and ablation. Early versions of computerized real-time computer systems for arrhythmia monitoring were published.[37] It seems clear in retrospect that most advances in the clinical area were focused on treating very sick patients. They also were the product of medical engineering, rather than basic cardiac electrophysiology, although the background of electrical mechanisms was the essential framework for the engineering applications.

Clinical Trials

Cardiology was slow to employ the invaluable tool of randomized treatment trials, compared to infectious disease and oncology, and the first attempts with cholesterol-lowering strategies in the Coronary Drug Project were abject failures—the treatment arms showed higher mortality. But this was followed by a very successful trial of β-blockers after acute myocardial infarction.[38] It was clear that the mechanism of the β-blocker benefit was not via a direct antiarrhythmic effect, presaging the role of modulators of electrical activity. We also entered a period of great hope that powerful antiarrhythmic drugs would successfully prevent out-of-hospital sudden death, a hope that was dashed by the CAST study.[39] Pharmaceutical research efforts to develop more powerful ion channel-active drugs almost ceased at that point, although some recovery can now be seen.

Molecular Electrophysiology

In 1981 electrophysiology was ready to enter the molecular arena. Improvements to the electronics and use of polished micropipettes led Neher, Sakmann, and colleagues[40] to the ability to record single ion channel openings (gating of single molecules) and to voltage clamp single small cells. Now, it was possible to study single cardiac cells under high-quality voltage clamp. The next step was to determine the amino acid structure of ion channels and express them in heterologous systems. Tetrodotoxin as a high-affinity ligand for the voltage-gated Na channel was essential.[41] Following the lead of purification and cloning of the muscle acetylcholine receptor, the tritiated toxin was then used to purify the tiny amounts of Na channel protein found in eel electroplax (a relatively rich source) and with some amino acid sequencing an Na channel was cloned in 1984.[42] The Numa laboratory subsequently cloned three mammalian Na channels from the brain, and this was followed by the Rogart laboratory's cloning of the cardiac Na channel.[43] Cloning of the Shaker fruit fly potassium channel[44] was challenging, but it set the stage for cloning of the human cardiac KCNQ1 and HERG genes in the context of Long QT syndrome in 1995 by Keating and colleagues.[45,46] Many structural details of ion channels could be inferred from physiological experiments with cloned and mutated channels, providing us with a good picture of ion channel structure, but this is not a substitute for directly obtaining the channel structure from crystallography. This was finally achieved for a bacterial K channel by MacKinnon and colleagues.[47] Basic electrophysiology is now a mature science, with great clinical implications, as presented in this section and throughout this book.

Present Status of Basic Cardiac Electrophysiology

Electrical activity exists because of ion gradients and ion channels, and I think we have probably identified all of the mammalian primary players—the channels and pumps—except for some subunits. Most have been cloned and details of their molecular function are emerging, greatly helped

by identification of the disease-related mutations discussed in later chapters. Physical structures of only a few are available, but this is likely to be resolved in the near future. We understand that the difference between normal and abnormal electrical activity is the fine balance between numbers of various ion channels/transporters, their function, and their location in the membrane. The function of these voltage-dependent processes is highly dependent on the interaction between the channels and transporters and their modulation by cytoplasmic systems. We are now experiencing an explosion of information from relating gene mutations in these primary players to cardiac electricity and arrhythmic disease.

In other critical areas our ignorance is immense. We have only tantalizing clues about regulation of transcription and translation of the relevant genes, posttranslational processing, and transport to and from the membrane. We are especially ignorant about the coordination of these processes to create an electrically balanced ensemble or to compensate for changes secondary to disease. Although enough of the cytoplasmic modulatory systems has been identified for us to realize their critical importance, there are likely to be many other modifier systems as yet undiscovered, and their interaction/interdependency challenges our ability to comprehend. This is an area where large-scale computer systems will be required.[48]

Gene therapy, defined as "fixing" a cardiac gene with a disease-producing mutation, is an appealing and logical clinical step. However, it turns out to be a daunting task, and is not likely to be an effective therapeutic tool in the near future. Nor are cardiac electrophysiologists suited to solving this problem. More promising, and more within reach of cardiac electrophysiologists, are approaches to adjust expression levels and to modulate function to restore electrical balance.

What Can the Cardiac Electrophysiology Community Do?

The critical question for cardiac electrophysiology has two components: sudden arrhythmic death in the general population and arrhythmic death in those with specific electrical disease. If we ask how to reduce sudden arrhythmic death in the general population, then the target is mainly those with ischemic heart disease and heart failure from other causes such as hypertension or cardiomyopathy. In spite of great progress managing arrhythmias, the incidence of sudden death continues to approach 20% of deaths in developed countries where adequate data are available, and a large fraction is in people who do not know they have cardiac disease.[49] The successes in the last several decades have come mainly from reduction or delay in onset of the underlying causative diseases, for example with the widespread use of statins and angiotensin-converting enzyme (ACE) inhibitors. Specific electrical diseases are relatively few in number now, and certainly this population will grow some. Clinical interventions such as ablation are often curative, but for potentially lethal arrhythmias the implanted defibrillator is only a stopgap therapy. The cardiac electrophysiology community can address several parts of a continued effort to control arrhythmia.

General Population Questions

This is the broad field of arrhythmias occurring in the course of various nonelectrical diseases:

1. Determine what polymorphisms in the genes of proteins responsible for electrical function predispose certain individuals to life-threatening arrhythmia. It is likely that soon typing of individual genomes will be cheap enough to use for screening, if we can determine what changes are important. The logic of this question is that perhaps half of individuals with these diseases die of arrhythmia before crippling loss of cardiac function. This question will require close cooperation between geneticists and electrophysiologists.

2. Devise simple and inexpensive electrical tests for predisposition to life-threatening arrhythmia. Many are available now, but they are too invasive and too expensive for application to the general population, and are not very accurate. Furthermore, this area does not represent the strength of basic electrophysiology. It is better to leave this to clinicians.

3. It now seems possible to imagine that cardiac cells can be regenerated. Although not directly cardiac electrophysiology, the field has an important role because regeneration must include balanced electrical function, or else the treatment