NOVEL THERAPEUTIC TARGETS FOR ANTIARRHYTHMIC DRUGS

Edited by

George Edward Billman
Professor of Physiology and Cell Biology
The Ohio State University
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To Rosemary, friend, confidante, soul mate, and life partner—semper gaude.
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As John Donne, the 17th century, British metaphysical poet and Anglican Priest so beautifully stated, “No man is an island, entire in itself. . .” (from Mediation XVII), this book results from the efforts of many. I wish to express my gratitude to many individuals who not only assisted in the preparation of this book but also guided me along my life’s journey. First, I wish to thank my parents who nurtured my curiosity as well as my wife and children for their love and support in both the good times and the bad. I also thank the faculty of the Department of Physiology and Biophysics at the University of Kentucky for their support while I earned my doctorate degree. In particular, I wish to acknowledge Dr. James Zolman, who taught me how to analyze research articles critically and interpret statistical results accurately. I am deeply indebted to my mentor, Dr. David C. Randall, who gave me the freedom to fail and the support to succeed. My career development was enhanced even more by my postdoctoral advisor Dr. H. Lowell Stone (deceased) at the University of Oklahoma, who taught me the art of “grantsmanship” and gave me the opportunity to pursue independent research interests that led to my first grant. I also appreciate the help and good humor of Dr. M. Jack Keyl (deceased), whose infectious enthusiasm kept research fun and exciting, even in those all too common times when experiments did not work as planned and funding fell short of expected. I would not be the scientist that I am today without the guidance and support of the individuals mentioned above. Finally, I wish to thank Mr. Jonathan Rose for inviting me to write this book and to the authors of the individual chapters; truly without their contributions, this book would not have been possible.
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“... ignorance more frequently begets confidence than does knowledge: it is those who know little, and not those who know much, who so positively assert that this or that problem will never be solved by science.” Charles Darwin [1]

“The greatest failure – not trying in the first place. The best angle to approach problems is the try-angle.” Jean Shirer Ingold [2]

The effective management of cardiac arrhythmias, either of atrial or ventricular origin, remains a major challenge for the cardiologist. Sudden cardiac death (defined as unexpected death from cardiac causes that occurs within 1 hour of the onset of symptoms [3]) remains the leading cause of death in industrially developed countries, and it accounts for between 300,000 and 500,000 deaths each year in the United States [4–6]. Holter monitoring studies reveal that these sudden deaths most frequently (up to 93%) resulted from ventricular tachyarrhythmias [7–9]. In a similar manner, atrial fibrillation is the most common rhythm disorder contributing to a substantial mortality, as well as a reduction in the quality of life, among these patients [10, 11]. Atrial fibrillation currently accounts for about 2.3 million cases in the United States and has been projected to increase by 2.5 fold over the next half century [12]. Indeed, the prevalence of this arrhythmia increases with each decade of life (0.5% patient population between the ages of 50 to 59 years climbing to almost 9% at age 80–89 years) and contributes to approximately one quarter of ischemic strokes in the elderly population [10, 11]. The economic impact associated with the morbidity and mortality resulting from cardiac arrhythmias is enormous (incremental cost per quality-adjusted life-year as much as U.S. $558,000 [13]).

Despite the enormity of this problem, the development of safe and effective antiarrhythmic agents remains elusive. In fact, several initially promising antiarrhythmic drugs have actually been shown to increase, rather than to decrease, the risk
for arrhythmic death in patients recovering from myocardial infarction. For example, the Cardiac Arrhythmia Suppression Trial (CAST study [14]) demonstrated that, although class I antiarrhythmic drugs (i.e., drugs that block sodium channels) effectively suppressed premature ventricular contractions, some of these compounds (flecainide and encainide) increased the risk for arrhythmic cardiac death. In a similar manner, many class III antiarrhythmic drugs (drugs that prolong refractory period, most likely via modulation of potassium channels) have been shown to prolong QT interval, to promote the life-threatening tachyarrhythmia torsades de pointes (i.e., polymorphic ventricular tachycardia in which the QRS waves seem to “twist” around the baseline), and to increase cardiac mortality in some patient populations [15, 16]. Unfortunately, only a few drugs have been clinically proven to reduce cardiac mortality in high-risk patients, such as patients recovering from myocardial infarction. To date, only β-adrenergic receptor antagonists and amiodarone, which is a class III antiarrhythmic drug that also blocks β-adrenergic receptors, have been shown to reduce sudden cardiac death [5, 17–21]. However, even optimal pharmacological therapy does not completely suppress malignant ventricular arrhythmias. For example, mortality after myocardial infarction remains high among patients with substantial ventricular dysfunction, even when placed on β-adrenergic receptor antagonist therapy [21]. The 1-year mortality is 10% or higher, with sudden death accounting for approximately one third of the deaths in these high-risk patients [21]. Furthermore, the long-term use of amiodarone is limited because of adverse side effects that include pulmonary fibrous, hepatotoxicity, and thyroid toxicity [22]. Given the adverse actions of many antiarrhythmic medications, as well as the partial protection afforded by even the best agents (e.g., β-adrenergic receptor antagonists), it is obvious that more effective antiarrhythmic therapies must be developed.

Old ideas never truly die, just the people who hold them. Eventually, newer ideas gain acceptance as the younger generation replaces the older generation. The major obstacle to progress often results from the inertia of conventional thinking [23]. This book attempts to overcome this inertia by describing some novel approaches for the management of arrhythmias. The primary focus of the book will be on ventricular arrhythmias, but a few chapters will also address aspects of atrial arrhythmias (see Chapters 3, 17, and 18). The book is divided into four sections. The first section opens with a comprehensive review of basic cardiac electrophysiology (Chapters 2 and 3) and mechanisms responsible for arrhythmias in the setting of ischemia (Chapter 4) and closes with a review of basic pharmacology, focusing on the classification of antiarrhythmic drugs (Chapter 5). Section two addresses safety pharmacology: the concept of “repolarization reserve” (Chapter 6), safety challenges (Chapter 7), and regulatory issues (Chapter 8) for the development of novel antiarrhythmic drugs. Section three describes several novel pharmacological targets for antiarrhythmic drugs (Chapters 9–18). Finally, section four describes a few promising nonpharmacological antiarrhythmic interventions, including selective cardiac neural disruption or nerve stimulation (Chapter 19), endurance exercise training (Chapter 20), and dietary supplements (omega-3 polyunsaturated fatty acids, Chapter 21). The reader is encouraged to approach each chapter with an open mind, for the prejudice of
conventional wisdom can blind. Sometimes to be a visionary, one simply has to open one’s eyes.

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