Clinical Pharmacology of Antiarrhythmic Therapy

Perspectives in Cardiovascular Research
Volume 10

Editors

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Preface

According to estimates, more than 300,000 individuals in the United States die suddenly and unexpectedly each year as a result of an acute cardiac event, which often results in ventricular fibrillation. There is little doubt that coronary atherosclerotic disease and the presence of marked coronary artery stenosis of one or more vessels exists in the majority of victims who succumb to "sudden coronary death." However, it is also well known that some patients who have been resuscitated following sudden cardiac death have been found, by angiography, to have minimal coronary artery disease. There are, no doubt, a number of underlying cardiac abnormalities such as valvular defects, Wolff-Parkinson-White syndrome, cardiomyopathies, and congenital prolongation of the Q–T interval that may be associated with the sudden and unexpected onset of ventricular dysrhythmia and resultant death. These instances of sudden cardiac death, which are unassociated with pathophysiologic alterations of the coronary vascular bed, are to be distinguished from sudden coronary death.

The contributors to this volume were assigned topics based on their individual expertise, with the directive that they discuss state of the art therapeutic interventions for preventing sudden coronary death, and suggest the direction within their fields for future investigative efforts.

Section I outlines the electrophysiologic mechanisms associated with arrhythmogenesis, with special attention devoted to gaining a better appreciation for the electrophysiologic mechanism(s) leading to a lethal dysrhythmia. Section II considers animal models used for the study of arrhythmogenic mechanisms and for the preclinical evaluation of potential pharmacologic interventions. The contributors to Section III present a review of the mechanism of action of antidysrhythmic agents currently available for clinical use, as well as those undergoing clinical investigation. Section IV considers the pharmacodynamics and pharmacokinetics of antiarrhythmic agents undergoing clinical investigation. Section V concentrates on issues relevant to the clinical evaluation of antiarrhythmic drugs.

This volume will serve its purpose if it is viewed as a source from which all readers can gain meaningful insights and a broad view of the current research related to this important medical problem. We are deeply indebted to the excellent group of contributors who have gone beyond our expectations in providing outstanding reviews of their assigned topics. It is our hope that this publication will provide a clearer understanding of the issues and result in a sound program that will lead to the suitable management for what continues to be the most prevalent cause of death in patients with coronary artery disease.

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Introduction

Benedict R. Lucchesi, James V. Dingell,
and Richard P. Schwarz, Jr.

In instances of "sudden coronary death," the underlying pathophysiology of the coronary artery circulation renders the heart susceptible to the onset and maintenance of a lethal dysrhythmia. That the "triggering" event is of a transient nature is suggested by the fact that patients resuscitated following sudden coronary death are capable of maintaining a stable cardiac rhythm, and, in many instances, do not display signs and symptoms suggestive of permanent myocardial injury. Of paramount importance is our need to understand what possible electrophysiologic factor (or factors) results in the transition from a stable activation sequence of the ventricular myocardium to one with multiple asynchronous circuits leading to ventricular fibrillation. Further, it is necessary to know what morphologic and electrophysiologic changes characterize the portion of myocardium that is capable of serving as a suitable substrate for the triggering event that proceeds to ventricular fibrillation. There are ample data to suggest that the ischemically injured heart shows marked heterogeneity with respect to regional coronary artery blood flow to areas subserved by stenosed vessels. In addition, ion fluxes, availability of substrate, and the superimposition of neural influences are capable of exerting deleterious effects, which render the heart more susceptible to the triggering event, which culminates in ventricular fibrillation. We know through experimental *in vitro* and *in vivo* studies, as well as from studies of the diseased human heart, that the consequences of ischemic myocardial injury are reflected in alterations in the rate of impulse conduction, unidirectional block, and excessive inhomogeneity of the ventricular refractory periods. Thus, abnormal automaticity, early and late afterdepolarizations and associated triggered activity, reentry, and reflection have all been identified as causes for the genesis of ventricular dysrhythmias in the heart following infarction.

The major questions are these: What factors characterize the prefibrillatory state of the heart and what factor (or factors) establishes the electrophysiologic conditions necessary for the onset of ventricular fibrillation? What telltale changes, if any, in diagnostic variables will identify the patient capable of spontaneously developing ventricular fibrillation? The need to identify patients at risk is essential if definitive prophylaxis is to be applied for the prevention of sudden coronary death.

Whether or not a single pharmacologic agent will be effective in all patients at risk may appear doubtful, in view of the multiplicity of factors that can precipitate a lethal arrhythmia. However, if there exists a final common electrophysiologic pathway that leads to ventricular fibrillation, there could be reason for optimism,

and the possibility of identifying one or more antifibrillatory drugs might be enhanced. At present, our approach to identifying therapeutic interventions for the prevention of sudden coronary death is predicated on a drug's ability to alter various characteristics of the membrane action potential of cardiac tissues and its efficacy in preventing or reversing one or more experimentally induced dysrhythmias. Unfortunately, few of the experimental models have a known relationship to the two key questions being posed: First, can the agent under investigation prevent ventricular fibrillation? Second, can it serve as a candidate drug for a highly focused clinical trial in well characterized subsets of patients who possess identifiable specific etiologic features placing them at risk of succumbing to sudden coronary death?

It is highly unlikely that the current approach to the clinical testing of antiarrhythmic agents, which relies heavily on a drug's ability to reduce the frequency and/or complexity of ventricular premature depolarizations, will prove effective in identifying an intervention capable of favorably influencing or preventing the transient electrophysiologic event that allows the heart to go from a stable activation sequence to one with multiple asynchronous pathways, and the subsequent development of ventricular fibrillation. Even the current application of more elaborate procedures, such as programmed electrical stimulation for the evaluation of a drug's antiarrhythmic efficacy, may be misleading with respect to the drug's efficacy in preventing the development of ventricular fibrillation. As long as the recorded endpoint remains something other than sudden coronary death any clinical trial or clinical use of a drug in patients determined to be at high risk will be carried out mostly on an empirical basis.

In planning this volume, we have borne in mind the concerns expressed above. Section I outlines the electrophysiologic mechanisms associated with arrhythmogenesis, with special attention devoted to gaining a better appreciation for the electrophysiologic mechanism(s) leading to a lethal dysrhythmia.

Section II considers animal models used for the study of arrhythmogenic mechanisms for the preclinical evaluation of potential pharmacologic interventions. In planning this section, we recognized that the search for a perfectly reliable animal model for the study of mechanisms of sudden death and the assessment of pharmacologic intervention would be faced with unsurmountable obstacles, not the least of which is the realization that the only perfect model is man himself. However, several elegant and more clinically relevant animal models have been introduced in recent years. The authors were asked to place these newer models in proper perspective so that some decision can be made regarding their ultimate utility in increasing the understanding of the electrophysiologic mechanisms and possible prevention of sudden coronary death in humans. The immediate goal with respect to the development of a suitable animal model will be to determine if electrophysiologic studies parallel closely those findings reported in patients known to have life-threatening ventricular tachyarrhythmias. We are now at the point where provocative electrophysiologic testing procedures can be applied to the chronically infarcted heart of an experimental animal for the purpose of eliciting

persistent ventricular tachyarrhythmia. The use of this technique for the preclinical evaluation of new therapeutic agents offers a more refined and relevant approach. More recently, several laboratories have described models in which the experimental animal with a chronically infarcted heart develops sudden and unexpected ventricular fibrillation. Even though the animal models do not represent the full spectrum of the human clinical state that characterizes the patient at risk for sudden coronary death their introduction at this time offers an exciting potential for future investigations.

The contributors to Section III present a review of the mechanism of action of antidysrhythmic agents currently available for clinical use, as well as those undergoing clinical investigation. For convenience, the drugs have been divided into four classes, with full recognition that such a classification is arbitrary and does not reflect the full spectrum of cardiac electrophysiologic changes that can be induced by a specific agent. On the basis of preliminary reports, some hopes have been raised with respect to the ability of therapeutic agents to provide a degree of protection to patients who are at risk for sudden coronary death. Should these suspicions ultimately prove correct, they will serve as an important indicator that the premature demise of an individual with coronary artery disease as a result of sudden and unexpected ventricular fibrillation can be prevented. There would be ample reason, therefore, to intensify our efforts to develop more specific and safer therapeutic agents to combat what is a major public health problem in most countries of the world.

Section IV considers the pharmacodynamics and pharmacokinetics of antiarrhythmic agents undergoing clinical investigation. Recognizing the fact that any potentially useful drug will be applied to large numbers of patients with varying degrees of underlying heart disease, it is essential that preclinical and early clinical testing procedures be designed to identify those drugs capable of producing undesirable effects when used alone or in combination with other therapeutic agents. Early and detailed pharmacokinetic studies are essential if effective dose regimens are to be designed and applied in a clinical trial. Detailed analysis of drug metabolism and the identification of active metabolites as well as deleterious metabolites should be a part of all preclinical and early clinical drug testing procedures.

For the most part, pharmacokinetic analyses have focused on the concentration of a given drug and its metabolites in body fluids that are readily accessable. The reason for this approach is obvious where human experimentation is involved. However, recent animal studies with a number of old and new antidysrhythmic agents suggest that the myocardium, which is indeed the target organ, may concentrate some drugs to a degree that is out of proportion to the existing plasma concentration. Furthermore, time-dependent changes in myocardial metabolism may be a significant factor with respect to the ability of some drugs to exert an antifibrillatory effect. Thus, it may be essential to determine the plasma concentration of a drug in both the acute and chronic states when investigating its potential to prevent ventricular fibrillation. Failure to do so might lead to an early and inappropriate rejection of a candidate compound as a potential therapy.

Section V concentrates on issues relevant to the clinical evaluation of antiarrhythmic drugs. The question of whether the frequency of ventricular ectopic activity (VEA), and the ability to suppress such, can be related to drug efficacy will continue to be of importance. The role of provocative electrical testing procedures, long-term ambulatory monitoring, and the appropriate design of clinical trials are, and will continue to be, major areas of discussion.

Even though sudden coronary death occurs with relatively high frequency among those with coronary artery disease, it remains a difficult subject to investigate. During the preparation of this volume, we were well aware that the most likely outcome would be to generate more questions than we would resolve. There will continue to be disagreement regarding electrophysiologic mechanisms underlying the genesis of cardiac dysrhythmias as well as the development of ventricular fibrillation. Investigators will remain undecided about which animal model will more precisely identify a drug most likely to exert a beneficial effect in patients subject to cardiac dysrhythmias and the potential to develop sudden coronary death. The large number of antidysrhythmic drugs under development presents a major challenge to both laboratory and clinical investigators who must employ specific endpoints as an index of antiarrhythmic drug efficacy, even though such endpoints may not be synonymous with sudden coronary death. Furthermore, the wide range of clinical problems in patients at high risk for sudden coronary death makes it unlikely that a single therapeutic intervention will represent adequate therapy for all patients. The appropriate clinical design for the testing of a new drug, the number of patients to be enrolled, the ethical issues of enrolling high-risk patients in a control group and many other issues guarantee that the problem of sudden coronary death and its prevention by antiarrhythmic drug therapy will remain one of the most challenging areas for future research. The resources to attack this major health problem will require the combined efforts of medicinal chemists, pharmacologists, electrophysiologists, pharmacokineticists, clinicians, and biostatisticians. Recognizing that clinical trials in this area will require large numbers of patients and a significant investment of financial resources, there is every reason to believe that the task will require the combined efforts of the pharmaceutical industry, the Food and Drug Administration, and the National Institutes of Health to ensure a successful outcome.

Contents

I. MECHANISMS OF ARRHYTHMOGENESIS

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Overview

Benedict R. Lucchesi

In the chapter that follows, Drs. Lazzara and Scherlag present an overview of the current understanding of the electrophysiologic changes associated with myocardial ischemic injury and raise important new questions that require additional study.

It is readily apparent that the electrophysiologic alterations associated with the acute onset of myocardial ischemia can be attributed to the accompanying biochemical and neurohumoral changes. Depriving the myocardial cell of its blood flow not only results in a decrease in oxygen and substrate supply but also leads to an accumulation of products of anaerobic metabolism, the development of intracellular acidosis, and a depletion of high-energy phosphate stores.

The extracellular environment of the cell becomes altered as well. In addition to changes in electrolytes and hydrogen ion concentration there is an increase in the concentration of free fatty acids and in lysophosphatidyl choline. It is difficult at present to speculate about how each of these factors acting alone or simultaneously as they would in the intact heart can lead to the electrophysiologic alterations resulting in the loss of a coordinated pattern of myocardial excitation. Although there is much to learn about the electrophysiologic mechanisms leading to arrhythmias subsequent to coronary artery occlusion, far more remains to be learned about those cellular or metabolic events that precede and accompany the appearance of cardiac dysrhythmias on reperfusion. There are recent data, some of which are presented in this volume, that suggest an important role for the products of arachidonic metabolism—not only in the induction of arrhythmias but also in their prevention. Since the myocardial cell need not be the only source of arachidonic acid metabolites, cardiac rhythm in the *in situ* heart may possibly be influenced by blood platelets and/or leukocytes that are attracted to the ischemically injured site, and which are capable of generating chemical mediators via the lipoxygenase pathway as well as via the metabolism of arachidonic acid by way of the cyclooxygenase pathway. A problem long recognized by most electrophysiologists is the impossibility of having all of these factors acting simultaneously in a model that utilizes single cell recordings from isolated heart tissue. Despite this limitation, a great deal has been derived from such studies, and in recent years there has been an increasing preference for using intact heart studies to further elucidate the electrophysiologic changes in response to ischemic myocardial injury and to correlate these events with electrocardiographic abnormalities. The recognition of slow

impulse propagation and fractionation within the ischemic myocardium along with changes in refractoriness and the dispersion of conduction provides a framework on which one can develop interesting concepts to explain the genesis of ventricular tachyarrhythmias in the injured myocardium. Further, the superimposition of an acute ischemic event on an already jeopardized substrate can markedly decrease the ventricular fibrillation threshold to the point where fibrillation develops. An important and as yet unresolved issue is whether the mechanisms leading to ventricular tachyarrhythmia or fibrillation in response to a transient ischemic event are the same as those which cause reperfusion arrhythmias.

It seems likely that further knowledge of the pathophysiologic and biochemical events that precede the onset of ventricular fibrillation in patients with coronary artery disease may provide important leads to new approaches for the prevention of ventricular fibrillation. A number of studies have suggested that a large fraction of the patients who have had sudden coronary death are unlikely to have ventricular fibrillation due to altered conduction around a major myocardial scar and, further, that the provoking event is very transitory in nature. Based on these kinds of data Dr. Oates and colleagues *(this volume)* have examined the hypothesis that the transitory reaction between platelets and vessel wall may influence the onset of ventricular fibrillation in patients with coronary disease.

The model employed is one in which ventricular fibrillation develops within 3 to 8 min after acute occlusion of the left circumflex coronary artery with a balloon occluder in the unanesthetized dog. The effects of prostacyclin on the acute onset of ventricular fibrillation were examined. The dose of prostacyclin selected was one that prevented platelet aggregation but did not change coronary resistance and, more important, did not alter ultimate infarct size, or the area of distribution of the occluded artery. The administration of prostacyclin was associated with a significant reduction in the incidence of ventricular fibrillation without any change in the frequency of ventricular ectopic depolarizations or ventricular tachycardia that occurred after acute coronary artery occlusion. Thus, prostacyclin seemed to be specific for the prevention of ventricular fibrillation.

Another approach to altering the platelet vascular interaction is the use of a thromboxane synthetase inhibitor that blocks the formation of thromboxane A_2, an important trigger of the platelet release reaction. In addition, the inhibition of thromboxane synthetase leads to an accumulation of the thromboxane A_2 precursor, PGH_2. The accumulation of the platelet PGH_2 leads to a diversion of the endoperoxide to vascular endothelium so that it is converted to prostacyclin.

Dr. Oates examined the effects of a thromboxane synthetase inhibitor, RO-224679, a *1*-substituted imidazole, on the occlusion-induced ventricular fibrillation in the unanesthetized dog *(this volume)*. Whereas untreated control dogs developed ventricular fibrillation within minutes of left circumflex coronary artery occlusion, there appeared to be an inhibition that was highly significant in those dogs treated with the thromboxane synthetase inhibitor.

On the basis of these studies it appears that both of the interventions that inhibit the platelet release reaction also inhibit the development of ventricular fibrillation