Current Perspective

New Approaches to Antiarrhythmic Therapy, Part I
Emerging Therapeutic Applications of the Cell Biology of Cardiac Arrhythmias

Members of the Sicilian Gambit

Abstract—Cardiac arrhythmias complicate many diseases affecting the heart and circulation, and they incorporate a multiplicity of underlying mechanisms. The evolution of scientific knowledge has made the complex changes produced by cardiovascular disease sufficiently understood at the organ, cellular, and molecular levels such that there is a diversity of therapeutic targets for pharmacological therapy and/or prevention. Moreover, the approach of rational drug design in mechanism-specific and disease-specific fashions facilitates the targeting of therapy using the methods of molecular, structural, and translational biology. Additional approaches, using similar drug design strategies but based on gene therapy and transcriptional and translational modification, are on the horizon. Hence, there is reason to be optimistic regarding the design, testing, and clinical availability of novel antiarrhythmic therapies. (Circulation. 2001;104:2865-2873.)

Key Words: molecular biology | gene therapy | genes | electrophysiology | pharmacology

Cardiac arrhythmias are a major public health problem for which traditional pharmacological therapies have yielded disappointing results1–5 and for which new approaches to drug development would be highly desirable. Fortunately, science and technology have evolved sufficiently to facilitate the identification of new targets for drug action and the tailoring of molecules to fit these targets. We will approach this subject matter in 3 steps: (1) we will describe the arrhythmogenic myocardial substrate via a modeling approach that synthesizes information from molecular through organ levels. We do this because arrhythmology has become so complex that traditional linear thinking no longer integrates data at the channel, cell, whole tissue, or whole organ levels in ways that readily predict or describe function. (2) We then focus on the genetic factors and environmental stresses that determine and influence normal and abnormal electrical activity and/or act as long-term modulators to remodel cardiac structural and electrical substrates. (3) Finally, we use the principles of rational drug design to identify and discuss potential targets of new antiarrhythmic therapy.

Computational Modeling to Incorporate Physiological and Genetic Data Into a Framework for Arrhythmogenic Mechanisms

From Ion Channel to Single Cell
The pioneering work of Hodgkin and Huxley6 in squid axon fostered the evolution of several computational models of cardiac cellular electrical activity, including ventricular myocytes,7–11 atrial myocytes,12–14 sinus node,15,16 and Purkinje fibers.17,18 The more recent of these models include transmembrane currents operating through ion channels and ion transfer through transporters and exchangers, and they compute the dynamic changes of ion concentrations (Na+, Ca2+, K+) during the action potential. These models are formulated in the classical Hodgkin-Huxley scheme (Figure 1).

Recent developments in molecular biology and the genetics of ion channels have added to these models information about the relationships between protein structure and electrophysiological function.19 It is possible to simulate the whole-cell action potential starting from single channel models based on discrete kinetic states of the channel protein (eg, closed, open, inactivated states) and, with this formalism, to simulate genetic mutations that affect single channel function and their arrhythmogenic consequences at the whole-cell level.20 Interactions of drugs with specific channel states can also be simulated (eg, a drug binding to a channel only in its open state). This general scheme has been used in the context of the LQT3 variant of the congenital long-QT syndrome that involves the SCN5A gene and the Na+ channel20 and the LQT2 variant that involves the HERG gene and the rapid delayed rectifier K+ channel.21

From Single Cell to Multicellular Tissue
Abnormalities of impulse initiation, including automaticity and triggered activity, are important contributors to the genesis of arrhythmias,22 but the overwhelming majority of clinical arrhythmias seem to be reentrant (whether initiated
by automatic, triggered, or reentrant impulses. Hence, a great deal of emphasis is currently focused on reentrant mechanisms.

Impulse propagation and arrhythmias have been studied in a variety of models (Figure 1) ranging from representation of the tissue as a continuous, uniform syncytium to a highly discontinuous structure that represents the discretization of the tissue into cells and its macroscopic organization. Continuous and discontinuous models constitute two extremes incorporating distinctly different properties that are relevant to arrhythmogenesis and antiarrhythmic drug effects. Continuous properties determine arrhythmias in the absence of structural heart disease (eg, long-QT syndromes and development of torsades de pointes). Discontinuous properties determine arrhythmias in structurally altered myocardium, such as remodeled tissue after myocardial infarction or in chronic atrial fibrillation.

Another determinant of propagation is wavefront curvature, which can exist in both continuous and discontinuous media. The wavefront curvature affects propagation velocity and ion channel involvement, particularly in the core of a spiral wave. The curvature can also interact with tissue discontinuities; hence, a spiral wave can either be initiated or modified by heterogeneities that may arise by automatic, triggered, or reentrant impulses. Hence, a great deal of emphasis is currently focused on reentrant mechanisms.

From Tissue to the Whole Heart
Whole-heart models are needed to study arrhythmias that critically depend on the heart’s spatial organization (Figure 1). Congenital or acquired disease superimposed on these spatial physiological features may also be location-dependent, eg, localized infarct scars, regional ischemia, apparent dominant right ventricular involvement in Brugada syndrome, and arrhythmogenic right ventricular dysplasia. From the electrophysiological perspective, certain arrhythmias are uniquely expressed in the whole heart (ie, large reentrant circuits in acute ischemia and initiation of atrial fibrillation by pulmonary venous foci). Whole-heart models also facilitate the investigation of autonomic effects that are location-dependent as a result of nonuniform innervation and interactions of autonomic input with infarct scars and antiarrhythmic drugs.

With whole-heart models, arrhythmogenic behavior can be related to its manifestations in electrogams on the cardiac surface and to the body surface ECG. The maintenance, perpetuation, and movement of functional reentrant waves are influenced by the degree of interaction between the head of the wavefront and the repolarizing tail of the preceding wavefront (“head-tail” interaction). This type of reentry should be responsive both to drugs that modify repolarization and action potential duration (tail) and to drugs that modify the action potential upstroke (head). Intrinsic heterogeneities of cellular electrophysiological properties also contribute to functional reentry, with transmural inhomogeneity being introduced by heterogeneous expression of ion channels controlling repolarization (I_{Ks}, I_{to}, late I_{Na}, I_{NaC}).

In tissues with marked structural discontinuities (eg, advanced cell-to-cell uncoupling or marked fibrosis), conduction becomes discontinuous. Here, conduction velocity can decrease to very low values, permitting reentrant excitation to occur in very small regions (micro-reentry). Two important characteristics of discontinuous conduction determine the behavior of reentrant waves and, most likely, their response to antiarrhythmic drugs. First, their pathways are largely determined by anatomical structure, thereby introducing excitatory gaps into the circuits. As a consequence, head-tail interactions are diminished and circuits may be less responsive to drugs that prolong action potential duration. A further modifier is the extent to which the ion channel remodeling that accompanies many disease processes alters drug binding and unbinding. Second, discontinuous conduction is associated with a seemingly paradoxical increase in the safety factor for propagation due to a decreased electrical loading of depolarizing cells. This implies a more robust depolarizing phase of the action potential (head), with an increased resistance to drugs that affect depolarization. Clinically, transitions can occur between continuous and discontinuous conduction during the process of tissue remodeling (eg, evolution of atrial fibrillation from the paroxysmal to the persistent and permanent forms, scar formation in healed myocardial infarction). Hence, drugs may lose efficacy in chronic atrial fibrillation due to such remodeling-related changes in structure and function.
els differ from cell and tissue models by accounting for the spatial organization of the cardiac chambers and the separation of electrically distinct and topologically defined units, such as the sinus node, atrial tissue, atroventricular node, specialized conduction system, and ventricular myocardium. Within each of these specific anatomical features, which are relevant to electrical function, specific properties can be simulated in computer models, eg, organization of pacemaker cell models into the sinus node complex, specific atrial structures (trabeculation, anisotropic structures such as the crista terminalis, atrioventricular nodal pathways, Purkinje network organization, Purkinje-muscle junctions, and rotational organization of ventricular muscle layers).

**From Computation to Biology**

A key source for the application of modeling derives from the use of “model organisms.” Hence, modeling is not limited to the computational approaches described above, but extends to a variety of levels of biology that impact our understanding of arrhythmias. For example, with the advent of high-throughput DNA sequencing, the genome of a number of model organisms (eg, yeast, fly, round worm, and human) has been sequenced. Such model organisms may provide critical insights into the pathogenesis of arrhythmias and related basic biology. For example, studies in humans may identify a number of potential candidate modifier genes for LQTS, but it may not be possible to pinpoint which gene is the most important modifier by studying human populations alone. However, one can test genetic interactions of candidate genes by genetic complementation, suppressor assays, genetic backcross, and other methods that are readily available in model organism systems.

Despite differences in heart size and physiology, the mouse model recapitulates at least some features of human disease. For example, first and second-degree atroventricular block occur in homozygous mutant connexin40 mice, whereas mice heterozygous for connexin43 deletion exhibit reduced ventricular conduction velocity. Those homozygous for minK deletion exhibit a tachyarrhythmia with characteristics of atrial fibrillation, and ventricular arrhythmia susceptibility has been seen in a number of mice in which major repolarizing currents have been disrupted.

The main advantage of mouse models is that the consequences of altering a single gene can be studied. A very important caveat is that the disruption of a single gene may lead to the altered expression or function of other genes. Nevertheless, these experiments demonstrate the utility of genetically modified animals to provide new arrhythmia models and to identify the altered genes as candidate contributors to the arrhythmias.

**Genetic Modifiers of Cardiac Arrhythmias**

The multiple genetic factors that contribute to arrhythmia susceptibility in patients with inherited and acquired disorders have been reviewed in detail elsewhere. Importantly, even related individuals who carry the same disease-associated mutation(s) can manifest substantial differences in phenotypic expression, ranging from life-threatening to asymptomatic. This phenomenon, which may be consequent to incomplete penetrance (lack of disease manifestations in mutation carriers in families with an inherited disease) or variable expressivity (varying severity or spectrum of disease manifestations), has seen a variety of explanations, including the existence of “modifier genes.” These are genetic factors separate from a primary mutation that protect from or aggravate an underlying condition. Although inherited arrhythmias are rare, genetic modifiers of congenital arrhythmias may be relevant to more common acquired disorders of cardiac rhythm.

The human genome includes a vast array of DNA polymorphisms, most often single nucleotide polymorphisms (SNPs or “snips”), in which a single nucleotide varies in a population. SNPs may be nonfunctional, may occur in regulatory regions that alter gene expression, may result in changes in the sequence of the encoded proteins, may alter phenotypic expression only under pathological conditions (eg, ischemia), and/or may directly alter a protein’s function. The human genome likely includes >3,000,000 SNPs.

Figure 2 shows a general approach to identifying DNA variants that modulate physiology, pathophysiology, and response to drugs and other “stressors.” See text for discussion.
genetic component before attempting to identify that component.

The next step (Figure 2) is to identify candidate genes, i.e., those in which DNA variants might account for variability in the predefined phenotype (eg, in genes affecting sympathetic responsiveness in patients with the long-QT syndromes). Polymorphisms in these genes might reasonably be expected to modulate the phenotype. Further, we might expect different sets of polymorphisms to modulate different subtypes of the phenotype (ie, long-QT syndrome) due to their variable relationships to sympathetic activation. Identifying candidate genes, therefore, requires an understanding of the molecular pathophysiology of the phenotype being studied. Identification of polymorphisms in candidate genes (Figure 2) may then be followed by studies designed to establish whether such polymorphisms, alone or in combination, can be implicated as modulating the phenotype (Figure 2). This may require characterizing the function of variant proteins in vitro, in genetically modified animals, or in computer simulations, as well as further genetic epidemiological and statistical analyses. If a relationship between a DNA variant or a set of DNA variants and the prespecified phenotype is defined, further studies (Figure 2) should then validate such relationships prospectively and use this information to refine the phenotype.

An alternative approach is to conduct a genome-wide search to identify loci linking (in the formal genetic sense) to the phenotype. Once such loci are identified, each gene within the locus becomes a candidate approach has been used successfully in many diseases (eg, LQT1,75 cystic fibrosis,76 and Alzheimer’s77), and has been suggested as an alternative means to identify genes that modify drug responses.78 Such approaches may help us detect mutations in the various molecules considered potential candidate modifier genes for inherited arrhythmias. These include genes determining action potential duration (eg, voltage-gated ion channels, ion transporters, and pumps), molecules involved with intracellular signaling (eg, kinases, phosphatases, and proteins involved in intracellular calcium homeostasis), and those involved in cell responses to extra- cellular factors (eg, adrenergic and other hormone receptors, gap junctions, components of the cytoskeleton, and anchoring proteins on the extracellular matrix). In addition to selecting candidates based on known physiological and biochemical associations with cardiac conduction and excitability, gene scans using newer expression profiling techniques (eg, microarray technology) may provide information implicating many more unanticipated factors.

One example of genetic variability is seen in the autonomic nervous system, where a polymorphism (Ilele164) of the β2-adrenergic receptor is associated with increased mortality among patients with heart failure.79 This polymorphism produces a substantial decrease in basal and epinephrine-stimulated adenyl cyclase activities.80 These studies have highlighted the issue of combinations of polymorphisms (haplotype) in a given gene. In the case of the β2-adrenergic receptor, 13 SNPs have been identified in the coding and regulatory regions, leading to 8192 possible haplotypes and >33 million possible genotypes. The vast majority of these combinations do not occur (ie, polymorphisms are linked to each other), although preliminary data suggest that the response to inhaled β2 agonists in asthma varies as a function of which of the 12 identified haplotypes is present.81 It seems reasonable to surmise that relatively common genetically controlled alterations in autonomic function, by increasing or decreasing either the amount of norepinephrine released during sympathetic activation or its effects, may “modify” the propensity toward life-threatening arrhythmias due to mutations in genes encoding cardiac ion channels.82

An important mandate for confirming the relevance of genetic polymorphisms to the physiological disturbances underlying arrhythmia susceptibility is the demonstration of functional consequences of an identified gene sequence variant. Association studies provide the first level of evidence linking a genetic variation with a phenotype, but extensive characterization of the variant sequence (protein or regulatory element) is critical to validate its culpability and for understanding its mechanistic implications. Demonstrating the functional significance of polymorphisms linked to arrhythmia susceptibility will require increasingly powerful, new approaches to develop appropriate phenotyping skills, as well as molecular, physiological, cell biological, and computational tools.

Environmental Stresses Leading to Remodeling of the Cardiac Phenotype and to Arrhythmogenic Substrates

A variety of stresses impact the heart, whose adaptation to these has been described as “remodeling” (Figure 3). The stresses can be physiological, such as the left ventricular
hypertrophy that attends closure of the ductus arteriosus in the newborn, or pathological, such as in the hypertrophy that accompanies hypertension. Although the latter form of remodeling may actually provide short-term benefit to cardiac function, in the long run it is deleterious and arrhythmogenic. Remodeling can be expressed in the altered structure/function of ion channels, gap junctions, myocytes, and tissue architecture or as changes in ions or the activity of the autonomic nervous system. Not only can remodeling influence the phenotypic expression of an arrhythmia, but the rate and activation sequence of an arrhythmia can induce further remodeling.83–88

Elements in Remodeling
Remodeling may be usefully considered in terms of effects on “upstream” and “downstream” elements.89

Upstream Elements
By upstream, we refer to those long-term modulators of structure/function (shown in Figure 3) that change the expression of the molecules that contribute to the arrhythmic substrate. Reducing or limiting the progression of heart disease would be expected to prevent remodeling and, hence, arrhythmias.90 Although upstream therapy would seem to lessen the arrhythmia burden, the manifold mechanisms by which this can occur vary with the underlying disease and its specific treatment. For example, treating heart failure could reduce arrhythmias induced by the activation of mechanical stretch receptors, excess catecholamine release, and other factors that influence the arrhythmic substrate acutely or chronically.

Those modulators likely to be involved in arrhythmic remodeling include but are not limited to catecholamines, free radicals, angiotensin-converting enzyme (ACE), angiotensin II, cytokines, and nitric oxide; each operates via specific signaling cascades to alter the cardiac phenotype. Evidence that upstream approaches to therapy should be rewarding is already evident from clinical trials of statins,90 spironolactone,91 and ACE inhibitors.92–93 Regrettably, there are relatively few studies of these nontraditional “antiarrhythmic” agents on numerous aspects of electrogensis (eg, ion channels, receptors, gap junctions, or membrane physiology). However, for angiotensin II, evidence does exist of short- and long-term modulation of ion channel and gap junctional structure and function.94–97 Hence, the upstream focus suggested here seeks to take advantage of the antiarrhythmic effects of agents not routinely considered part of the antiarrhythmic armamentarium. The following examples highlight important new leads in this approach:

Fibrosis and Extracellular Matrix
Hearts with extensive fibrosis exhibit very slow conduction.31 The low macroscopic conduction velocities have been explained by microscopically zigzagging circuits31 or the special conduction characteristics of tissue with a discontinuous, branching architecture.49 Tissue with very slow and discontinuous conduction can explain reentrant excitation in paths of small dimensions (a few millimeters in diameter).24,98,99

A crucial consideration in the evolution of fibrosis is the nonuniform mechanoelectric coupling that occurs in a dilated or scarred chamber. Several considerations may shed light on this. First, fibroblasts manifest mechanoelectric coupling,100 and fibrotic tissue containing fibroblasts could actively contribute to an arrhythmogenic substrate. Second, much depends on how fibrosis restructures a cardiac chamber wall.87 It is not difficult to visualize a geometry in which contractile dispersion (one segment stretching another) in a scarred matrix influences electrophysiological dispersion to initiate arrhythmias. Alternatively, fibrotic tissue could shield myocytes from abnormal stress and strain, depending on the geometric arrangement.

Mechanical Stress and Angiotensin II
The myocardium contains connective tissue elements that link not only to the myocardial wall but to the cytoskeleton, effectively tethering the myocytes within a matrix.87 Therefore, cardiac activation that is directionally altered not only alters the contractile motion of regions of myocardium with respect to one another, but of cells as well, subjecting them to altered stress-strain relationships.87,101,102 The result is the activation of mechanotransduction mechanisms that can have profound electrophysiological effects. For example, the altered stretch of cardiac cells in culture induces the synthesis of angiotensin II, the availability of which alters cellular structure and electrophysiology.96,103–106 Angiotensin II can initiate the electrical remodeling that modifies repolarization96,107 and the structural remodeling that influences impulse conduction.94 Actions to promote fibrosis and to enhance norepinephrine release from intracardiac nerves have also been documented.108 Examples of clinical applicability of modulating angiotensin II include the effects of ACE inhibitors, which reduce the occurrence of atrial fibrillation in post-myocardial infarction patients with left ventricular dysfunction.109,110 Some secondary prevention ACE inhibitor trials have shown a reduction in sudden cardiac death.92,93

Aldosterone synthesis, stimulated by angiotensin II, can result in prolonged, progressive changes in myocyte and fibroblast proliferation, hypertrophy, and collagen deposition, independent of its effects on salt and water homeostasis. These changes are transduced via classic, nuclear-mediated mineralocorticoid receptor pathways.111 The potential importance to arrhythmia prevention of reversing the genetic reprogramming induced by aldosterone is seen in the Randomized Aldactone Evaluation Study (RALES), in which spironolactone reduced sudden arrhythmic deaths by 20% to 30%.91 Moreover, stretch can directly activate the sensory endings of sympathetic nerve fibers, leading to excitatory sympathetic reflexes and local catecholamine release. Hence, mineralocorticoid receptor antagonists alone or in combination with ACE inhibitors or β-adrenergic antagonists seem likely to lead to amelioration of arrhythmias.

Additional Factors
Inflammation and acute and chronic ischemia cause a rapid release of cytokines, whose gene expression has been characterized in the posts ischemic ventricle.112 Within 15 minutes of experimental coronary occlusion, cardiac mRNAs for interleukin 1β, tumor necrosis factor (TNF)-α and TNF-β are
measurable and sustained for several hours. TNF-α is an autocrine contributor to myocardial dysfunction and cell death in the ventricle. Little is known about the short-term effects of these inflammatory agents on the function of ion channels, but there are reports of reduced L-type Ca^{2+} current amplitudes. Reactive oxygen species also have direct effects on cellular structure and function, and they may be critical signaling transducers in the setting of myocardial infarction and the ensuing remodeling. However, the molecular mechanisms by which OH and other oxygen radicals alter the function of ion channel proteins are not fully known. Other studies have suggested that energy balance may be an important consideration, especially in the atria.

**Downstream Elements**

Downstream elements are those considered to impact most directly on the initiation and perpetuation of an arrhythmia.

**Ion Channel Remodeling**

A vast amount of literature considers the ion channel changes that accompany myocardial infarction, cardiac failure, myocardial hypertrophy, atrial fibrillation, and other cardiac pathologies. Among the ion channel abnormalities characterizing the failing ventricular myocardium are reductions in the density of the transient outward current (I_{to}) and the inward rectifier (I_{Kr}). Interestingly, I_{to} density is also reduced in peri-infarct fibers of ventricular myocardium. This suggests that different pathological settings may share a common denominator in a particular ion channel’s response to stress, although nonpathological interventions such as cardiac pacing and resultant altered activation also can reduce I_{to} density. In all these settings, I_{to} reverts to a property characteristic of the neonatal heart, which has no I_{to}. Given this commonality of change, regardless of the inciting intervention, we should likely focus more attention on the dedifferentiation of cell properties that accompany a variety of stresses and the types of interventions that might be most appropriate for restoring them to normal or to yet another state that supports normal function.

**Remodeling of Intracellular Ca^{2+} Homeostasis**

Ca homeostasis is sustained by maintaining [Ca^{2+}] at ∼100 nmol/L during diastole to a peak of ∼1000 nmol/L in systole. Aberrant Ca fluxes may occur as a result of inappropriate sarcoplasmic reticular Ca release during diastole (when the sarcoplasmic reticulum Ca^{2+} release channel [R,R_{2}] should be closed) and of prolonged, excessive Ca influx via the L-type calcium current (I_{Ca,L}) during a long action potential. Moreover, reverse-mode operation of the Na/Ca exchanger, which occurs especially when intracellular Na^{+} concentrations are high such as in tachycardias, will bring still more Ca into the cell. Both the aberrant release of sarcoplasmic reticular Ca during diastole and excessive Ca influx via I_{Ca,L} during late systole (when the action potential is repolarizing) can initiate afterdepolarizations, which can in turn generate extrasystoles. The association of mutations in the R_{2} receptor with clinical cardiac arrhythmias attributed to triggered activity (as in catecholamine-sensitive ventricular tachycardias) stresses the importance of sarcoplasmic reticulum–based mechanisms in modulating arrhythmias.

**Remodeling of Cell-to-Cell Coupling**

Remodeling in cardiac gap junctions can result from alterations in connexin transcription, and/or connexin protein synthesis or degradation. The turnover of at least 2 cardiac gap junctional proteins, Cx43 and Cx45, is rapid; in the adult rat heart, Cx43 turnover has a half-life <90 minutes, which could facilitate remodeling in cardiac disease states. Although a number of agents influence cardiac connexin expression, relatively few mechanistic pathways have been established. The effects of several hypertrophic stimuli on Cx43 expression in cultured neonatal myocytes have been investigated, including dibutyryl cAMP, angiotensin II, and myotrophin. In each case, Cx43 mRNA and/or protein levels increased several fold. Also, connexin43 is upregulated after short periods of mechanical stress. Conversely, several factors repressing Cx43 expression have been described, including TNF-α, suggesting that Cx43 expression may be regulated by circulating cytokines. How these factors play into the physiological and pathological modulation of gap junctional function and the extent to which this can be manipulated to modify cardiac rhythm predictably remains to be seen.

**Appendix**

**Meeting Organizers**

The meeting was organized by Edward Carmeliet, MD, PhD, University of Leuven, Belgium; Harry A. Fozzard, MD, University of Chicago, Ill; Masayasu Hiraoka, MD, Tokyo Medical and Dental University, Tokyo, Japan; Michiel J. Janse, MD, Cardiovascular Research, Amsterdam, the Netherlands; Satoshi Ogawa, MD, Keio University, Tokyo, Japan; Dan M. Roden, MD, Vanderbilt University School of Medicine, Nashville, Tenn; Michael R. Rosen, MD, Columbia University, New York, NY; Yoram Rudy, PhD, Case Western Reserve University, Cleveland, Ohio; and Peter J. Schwartz, MD, Policlinico S. Matteo IRCCS, Pavia, Italy. It was chaired by Dr Rosen and cochaired by A. John Camm, MD, St George’s Hospital Medical School, London, UK, and Drs Fozzard, Janse, Roden, and Rudy.

Participating in the meeting and sharing in authorship of the article are the above individuals as well as Charles Antzelevitch, PhD, Masonic Medical Research Laboratory, Utica, NY; Penelope A. Boyden, PhD, Columbia University, New York, NY; William A. Catterall, PhD, University of Washington, Seattle; Glenn I. Fishman, Mt Sinai School of Medicine, New York, NY; Alfred L. George, MD, Vanderbilt University Medical Center, Nashville, Tenn; Seigo Izumo, MD, Beth Israel Deaconess Medical Center, Boston, Mass; José Jalife, MD, SUNY Syracuse, Syracuse, NY; Craig T. January, MD, PhD, University of Wisconsin, Madison; Andre G. Kleber, MD, Universitaet Bern, Bern, Switzerland; Eduardo Marban, MD, PhD, the Johns Hopkins University, Baltimore, Md; Andrew R. Marks, MD, Columbia University, New York, NY; Peter M. Spooner, PhD, NIH/NHLBI, Bethesda, Md; Albert L. Waldo, MD, Case Western Reserve University, Cleveland, Ohio; James M. Weiss, MD, UCLA Cardiovascular Research Laboratory, Los Angeles, Calif; and Douglas P. Zipes, MD, Krannert Institute of Cardiology, Indianapolis, Ind.

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