Diversity of Gene Expression in the Heart

Understanding cell-to-cell variability in the cardiac action potential shape and the mechanisms underlying impulse propagation is the key to understanding normal and abnormal cardiac electrophysiology. Much of this variability can be attributed to variability in the characteristics of individual ion currents whose integrated behavior determines the shape and duration of action potentials in individual cardiac cells, as well as to variability in cell-to-cell communications. Ion currents are now recognized to flow through specific pore-forming membrane proteins called ion channels. The first gene encoding an ion channel protein was cloned in 1984, and the succeeding decade and a half has seen the cloning of genes encoding most ion channels expressed in heart and in many other tissues. Many of the proteins these genes encode share common structures and can be viewed as members of the same superfamily. For example, Figure 3 shows the tremendous diversity of mammalian genes that make up the family of potassium channel genes. Because potassium channels are made up of 4 ion channel α-subunit proteins, which are not necessarily identical, the potential for diversity in potassium currents is even greater than shown. This is further compounded by the identification of ancillary subunits (the products of different genes) that can assemble with potassium channel tetramers to modulate their function. Figure 4 illustrates the major ion currents in heart and the genes whose protein products are thought to form...
their structural basis. The dramatic increase in molecular genetic information underlying cardiac function is not confined to ion channels but rather has extended to multiple other genes, including those controlling cell-to-cell communication (the connexins, Cx), the contractile apparatus, and cardiac development, to name a few. With this cloning effort have come important advances not only in understanding mechanisms of normal cardiac function but also in new insights into the mechanisms underlying common cardiac diseases and their therapy.

A common method of studying individual cardiac ion channel gene function is to express the gene of interest in noncardiac (heterologous) study systems, such as mammalian cell lines or the eggs of the African clawed toad, *Xenopus laevis*. In some cases, expression of a single gene in such heterologous systems is sufficient to reproduce the physiological and pharmacological characteristics of a specific cardiac ion current; HERG expression to recapitulate $I_{Kr}$ is an example, although coexpression of the minK subunit may increase $I_{Kr}$ amplitude. The systems have been especially valuable in delineating the functional consequences of ion channel gene mutations, although it should be recognized that mechanisms other than a simple dominant negative effect on channel gating (eg, altered trafficking) may also play a role.

In other cases, faithful recapitulation of a specific cardiac ion current requires coexpression of >1 gene. Heterotetramers of Kv4.2 and Kv4.3 may determine the $I_{Na}$ in some

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Figure 3. Family tree of pore-forming K⁺ channel subunits in mammals. Dendrogram represents degree of similarity between each gene, as determined by ClustalW alignment program. Sequences were extracted from Genbank database and correspond exclusively to rodent or human channels. K⁺ channel subunits are divided into 3 major groups according to their structural and functional properties as shown in blue, green, and red boxes. Major genes expressed in heart are indicated in gray boxes, together with probable current they underlie.

Figure 4. Cardiac ionic currents and respective ion channel clones responsible for generation of action potential. Inward currents are drawn in red, outward currents in blue. Amplitudes are not to scale.
species. Other examples include coexpression of a structural gene and an ancillary subunit; one good example is the finding that coexpression of KvLQT1, a member of the potassium channel family shown in Figure 3, with the minK gene is required to recapitulate \( I_{\text{Ks}} \).\(^{13,14}\)

Another example is the \( \alpha-\beta_3 \) interaction during the development of an adult sodium current as described below. In yet other cases, a gene product (eg, Kv2.1) can be detected in heart without a recognized counterpart among the known ion currents, and ion currents \( (I_o) \) remain for which no corresponding gene has yet been identified. One very important observation is that ion channel genes are virtually never expressed exclusively in the heart. Thus, mutations or blocking drugs may affect not only cardiac function but also function in other organs. The best-described example to date is the deafness displayed by patients with the recessive (Jervell and Lange-Nielsen) form of LQTS.\(^4\) This arises because the 2 genes involved in the disease, \( \text{KvLQT1} \)\(^{19,20}\) and \( \text{minK} \)\(^{16,106}\) are expressed not only in the heart but also in the inner ear, where together they control endolymph homeostasis.\(^{107}\) It is not yet known whether parent carriers, who have mild, usually but not always asymptomatic mutations in \( \text{KvLQT1} \) or \( \text{minK} \),\(^{15}\) display subtle defects in hearing. This is but one example of the potential for a molecular genetic explanation for a diversity of symptoms through common mutations affecting function in multiple organs.

**Development**

One well-recognized form of variability in cardiac function is the stereotypical changes that are observed during development. Much of the information has been gathered in small rodents and may not be directly applicable to humans, but it may be important because a common form of cardiac response to injury is regression to a fetal phenotype. Whether, for example, the electrophysiological changes associated with hypertrophy (eg, in patients with hypertension or heart failure) represent such a patterned response is an important consideration. Understanding the mechanisms underlying such a change in phenotype may be an important step in the prevention of arrhythmias in these common acquired disorders of cardiac function.

The earliest stage at which ion currents have been recorded from heart tissue is embryonic (postcoital, pc) day 11 in mouse (normal gestation period, 20.5 days). At this stage, the predominant inward current is \( \text{L}-\text{type calcium current} \ (I_{\text{Ca,L}}) \), and the predominant outward current is the rapidly activating component of the delayed rectifier, \( I_{\text{Ks}} \).\(^{108,109}\) Sodium current \( (I_{\text{Na}}) \) appears later and increases markedly just before birth.\(^{109}\)

There are important differences between sodium current recorded in neonatal animals and those recorded in adult animals\(^{110,111}\): \( I_{\text{Na}} \) in neonates is smaller; it activates, inactivates, and recovers from inactivation more slowly than that in adults; and it has a more positive voltage dependence of inactivation than that in adults. Some data suggest that this difference between neonatal and adult sodium current may reflect expression of a \( \beta_3 \)-subunit and/or \( \alpha-\beta_3 \)-assembly to produce the “mature” phenotype\(^{112,113}\) and that this change may reflect the sympathetic innervation of the heart that occurs around the time of birth. This may be but one example of a more general influence of sympathetic innervation as a modulator of cardiac electrophysiology.\(^{114}\) It is likely that multiple mechanisms will be identified. The possibility that regional cardiac derenervation may play a role in acquired diseases (eg, myocardial infarction) is an obvious one that requires further study.\(^{115}\) Another intriguing observation during development is the consistent embryotoxicity of specific \( I_{\text{Ks}} \) blockers, such as doxetilide or almokalant, in the rat.\(^{116}\)

Because \( I_{\text{Ks}} \) is the predominant (if not the sole) repolarizing current at this stage,\(^{108}\) it has been postulated that embryotoxicity is due to failure of cardiac repolarization, with death due to arrhythmias secondary to triggered activity (which have been demonstrated under these experimental conditions) or simply membrane depolarization. Whether similar considerations apply to humans has not been determined.

The pattern of expression of the connexins, which form the gap junction channels and belong to one gene family, also varies during development. \( \text{Cx43 mRNA} \) is detectable in mouse heart from day 9.5 pc. Initially, it is expressed only in the ventricles, but later it spreads throughout the whole heart. Two weeks after birth, the message starts to diminish again to a steady level that is maintained during adulthood.\(^{117}\) \( \text{Cx40 mRNA} \) is detected from 9.5 days pc. The message is initially confined to atrium and left ventricle, but during development it spreads throughout the whole heart.\(^{118}\) After 14 days pc, \( \text{Cx40 mRNA} \) message starts to diminish in the ventricles from epicardial to endocardial until in the adult, \( \text{Cx40} \) is restricted to both atria and the proximal conduction system.\(^{117}\) \( \text{Cx45 mRNA} \) is expressed from day 11 pc at a constant level throughout the whole heart until week 3 postpartum, when it starts to decrease until in adulthood, only low-level expression in the proximal conduction system is detected.\(^{117}\)

**Regional Diversity in Cardiac Electrophysiology**

Although heterogeneity of cardiac electrophysiology is increasingly recognized as a contributor to cardiac arrhythmias, it should also be recognized that there is substantial heterogeneity in the electrophysiological properties of individual cells even under physiological conditions. A trivial example is the differences among the electrophysiological properties of sinoatrial node, atrium, AV node, conducting system, and ventricular myocardium. These differences presumably reflect variability in expression and/or function of the repertoire of ion channels, whose integrated activity determines the distinctive action potentials in each of these regions. More recently, it is increasingly recognized that there is considerable potential for cell-to-cell variability in action potentials and gene expression within such specified regions. For example, a survey of atrial myocytes revealed a consistent \( I_{\text{Na}} \) only in \( \approx60\% \) of cells, a consistent \( I_{\text{Ks}} \) in \( \approx15\% \) of cells, and both currents in \( \approx30\% \) of cells.\(^{113}\) Studies of mRNA expression have also demonstrated striking cell-to-cell variability in expression of individual ion channel genes.\(^{120}\) Two LQTS genes, \( \text{HERG} \) and \( \text{KvLQT1} \), were identified in a majority of cells in most regions. In contrast, \( \text{minK} \) was most abundant in sinoatrial node in \( \approx33\% \) of cells but was much less abundant in ventricular muscle cells (10% to 29%). This is consistent with a more recent report that, at least in the mouse, \( \text{minK} \) expression appears to be restricted largely to the
conducing system.\textsuperscript{121} Similarly, M cells, which as described below appear to play a role in the genesis of arrhythmias relates to a long QT interval, have distinctively low action potentials that prolong markedly at slow heart rates,\textsuperscript{122} a characteristic also seen in Purkinje cells.\textsuperscript{122,124} One report suggests that this distinctive action potential behavior is paralleled by a reduction in $I_Ks$ (compared with endocardial and epicardial cells).\textsuperscript{125}

Electrophysiological studies have identified $Kv4.2$ and/or $4.3$ (depending on the species) as the ion channel gene whose expression in heterologous systems results in a current most closely resembling human $I_{Na,t}$.\textsuperscript{126} One of the important features of human $I_{Na,t}$ is its usually rapid recovery from inactivation.\textsuperscript{127} It was this observation that first suggested that $Kv1.4$, an initial leading candidate for $I_{Na,t}$, might not, in fact, encode this current, because $Kv1.4$ recovers very slowly from inactivation.\textsuperscript{128} Interestingly, the human endocardium also displays an $I_{Na,t}$, but one that, unlike that recorded in epicardium, recovers from inactivation very slowly and is therefore not regularly observed in endocardial action potentials.\textsuperscript{127} It therefore remains conceivable that although $Kv4.x$ encodes epicardial $I_{Na,t}$, expression of other channels, including $Kv1.4$, may still contribute to the electrophysiological properties of cells in other regions.

The connexins are also expressed in a chamber-specific and tissue-specific fashion. In heart, Cx40, Cx43, and Cx45 have been detected at the protein level.\textsuperscript{129} The phosphoprotein Cx43 is the most abundant cardiac connexin. It forms gap junctional channels with a main conductance of $20\ pS$ between cardiac myocytes in all parts of the heart, with the possible exception of sinoatrial and AV nodes. In ventricle, Cx43 is more abundant in the intercalated disk than in the lateral cell borders, which partially explains anisotropic impulse conduction. In atrium (with the exception of the crista terminalis), the difference between end-to-end and side-to-side connections is much less pronounced. Although Cx43 has been reported to be present in sinoatrial node,\textsuperscript{130,131} in atrial cells it is probably intercalated between the pacemaker cells.\textsuperscript{132} Rabbit sinoatrial node pacemaker cells proper are coupled by high-conduction ($250-pS$) channels formed by an unidentified connexin (Verheule S, Jongsma HJ, 1998, personal communication). In atrial gap junctions, Cx40 is colocalized with Cx43.\textsuperscript{129} Cx40 is also a phosphoprotein, with a main conductance of $160\ pS$. Guerrero et al.\textsuperscript{133} presented evidence that Cx40 and Cx43 contribute equally to impulse conduction in atrium. In most species (including humans), Cx40 is also found in the proximal conduction system. Cx45 forms channels with a conductance of $\approx 20\ pS$ that are very sensitive to transjunctional voltage; i.e., even at small voltage differences between neighboring cells, Cx45 channels close quickly. Cx45 has been reported by some authors\textsuperscript{134} to be abundantly present in all parts of the heart, but others find it only in part of the conduction system and in very limited amounts in the rest of the heart. The role for Cx45 in impulse conduction has not yet been established.

**Integration of Ion Channel Function Into the Cellular Environment**

Although ionic channels and connexins participate in the generation of the cardiac action potential and in cell-to-cell communication, it is important to recognize that experimentally, single-channel data are obtained primarily in preparations that are removed from the cardiac cell environment (eg, membrane patches, cloned channels in *Xenopus* oocytes). Figure 5 is a schematic of a cardiac ventricular myocyte, demonstrating the complex physiological environment in which ion channels function to generate an action potential.\textsuperscript{135} The cellular environment is highly interactive and modulates the behavior of the single channel through interactions with other channels or with the ionic milieu of the cell. An example is illustrated in the diagram in Figure 6. In this scheme, the $I_{Ca,L}$ induces $Ca^{2+}$ release from the sarcoplasmic reticulum through the $Ca^{2+}$-induced $Ca^{2+}$ release process.\textsuperscript{136} The released $Ca^{2+}$ in the myoplasm, in turn, modulates several ionic currents [including $I_{Ca,L}$ itself].\textsuperscript{135} In Figure 6, the myoplasmic $Ca^{2+}$ is shown to increase the
conduction of $I_{\text{ca}}$ to drive $I_{\text{ncas}}$ for the purpose of $Ca^{2+}$ extrusion, and to participate in the inactivation of $I_{\text{calp}}$.

The effect on the action potential is complicated; increased $I_{Ks}$ acts to shorten the action potential duration (APD), as does reduced $I_{\text{calp}}$. $I_{\text{ncas}}$ is an inward current (when operating to extrude $Ca^{2+}$ from the cell), and its augmentation acts to prolong APD. The net effect depends on the quantitative balance of these processes. This balance can depend on the basal expression of these channels or of the proteins (such as kinases) that regulate their activity, diseases or other processes that modulate the expression, and other important factors, such as rate or adrenergic activity. Importantly, many of these latter processes may also be modulated by changes in intracellular calcium.

The example above serves to illustrate a most important point, namely, that the current through an ion channel is determined by its intrinsic kinetic properties and its interaction with the cellular environment. Because of the highly interactive nature of the cell, altered function of a particular channel (eg, due to modulation by calcium) will have an indirect influence on the currents through other channels. For example, the late current that underlies the LQT3 form of LQTS acts to depolarize the membrane during the plateau phase of the action potential. The increase in membrane potential, in turn, alters the magnitudes and time courses of other plateau currents [eg, $I_{\text{calp}}$, $I_{Ks}$, $I_{Ks}$], which together determine the APD.

The concept that the action potential is determined by the interaction of various ionic currents is increasingly well appreciated in the context of LQTS. The action potential plateau is maintained by a delicate balance between inward (depolarizing) and outward (repolarizing) currents. In LQTS, the action potential is prolonged by an increase of an inward current (late $I_{Na}$ in LQT3) or a decrease of an outward current ($I_{Ks}$ in LQT1, $I_{Ks}$ in LQT2). It should be emphasized that the effect on the action potential could be very different for the different mutations. For example, the generation of an early afterdepolarization at plateau potentials (phase 2 early afterdepolarization) involves recovery and reactivation of $I_{\text{calp}}$.

This can be achieved if the action potential plateau is sufficiently prolonged at a specific range of membrane potential. It is conceivable that such conditions are created by some mutations but not by others.

Similarly, distinctions can occur in the rate-dependence of APD. Through the process of adaptation, action potentials shorten with increasing heart rate. This phenomenon raises the possibility of a depression of early afterdepolarizations with fast pacing in LQTS. Recently, it was found that LQT3 shows much greater shortening of QT interval with an increase in heart rate during exercise than the other LQTS types.

Assuming that the QT interval reflects the degree of APD prolongation in LQTS, it is possible that fast pacing has a greater effect in LQT3 because of the specific involvement of $I_{Na}$ in this syndrome. A possible explanation is that with fast pacing, $Na^{+}$ accumulates in the cell, lowering the $Na^{+}$ gradient across the membrane and the associated electrochemical driving force for $Na^{+}$. Through this mechanism (or altered function of the electrogenic sodium-calcium exchanger), the magnitude of $I_{Na}$ is reduced. The effect of such reduction will be negligible during the rising phase of the action potential, when $I_{Na}$ is so much larger than other currents. However, the plateau $I_{Na}$ contribution through mutant channels is of a much smaller magnitude and could be significantly affected by such changes. As stated earlier, this current operates at a critical time, when the action potential is determined by a very delicate balance of small currents. It is conceivable, therefore, that such a small reduction of late $I_{Na}$ during this phase could result in shortening of APD at fast rates.

Ion Channel Function in Multicellular Networks

The first section of this part described the diversity and variability of ion channels involved in cardiac electrical excitation, and the second illustrated the level of complexity related to the integration of individual channels into whole-cell function. Assembling single cells in the multicellular excitable tissue introduces further significant interactions between ion channel function and structural properties of the tissue. These interactions play an important role in depolarization, repolarization, and arrhythmogenesis.

Interaction Between Cell-to-Cell Coupling and Ion Channel Function.

The simplest model used to explain cardiac electrical propagation was originally derived from conduction models developed for the nervous system. In this model, cardiac cells are merged into a syncytium-like conducting structure composed of a cell membrane carrying the ion channels that generate the action potential and a single continuous intracellular space (in this space, the electrical conductances of the cytoplasm and the gap junctional connexons are merged together). Many important insights into the electrical propagation process have been derived from this so-called “continuous” model.

It has been successfully applied to describe global effects of inhibitors of $Na^{+}$ channels, of acute myocardial ischemia, and of hypoxia/anoxia on conduction. However, in many instances, more complicated models are needed to describe the conduction process appropriately.

A first step in describing the relation between electrical propagation and cardiac structure more closely involved simulation of single-cell chains with interconnections representing the gap junctions. Although the properties of such models are not markedly different from the “continuous” model when electrical cell-to-cell coupling is normal, a distinctly different behavior is unmasked once the electrical coupling of the cells diminishes. Interestingly, this behavior includes feedback interaction between cell-to-cell coupling and ion channel function. Partial closure of connexins (ischemia, hypoxia) may affect conduction in several ways. First, conduction velocity decreases to a much greater extent than with inhibition of ion channels and can reach a few centimeters per second or be even slower. Accordingly, reentrant arrhythmias that occur in partially uncoupled tissue can form circulating excitation of very small dimensions (microreentry). By contrast, simulations suggest that depressed $I_{Na}$ alone cannot account for this phenomenon. Second, a change in cell-to-cell coupling feeds back on the way...
Ionic channels in the membrane are activated and on the role of ionic channels in conduction (and most probably, repolarization). This is illustrated in Figure 7, which depicts a row of simulated cells in a state of advanced cell-to-cell uncoupling. Because of the high degree of discontinuity that is introduced by the uncoupled cells, there is a long conduction delay between the cells. Because the action potential in the driver cell has to furnish local electrical circuit current to the driven cell, this current has to flow as long as the driven cell has not reached its threshold for depolarization, ie, for activation of the Na$^+$ inward current. In the normal case of propagation, the conduction delay between 2 cells is very short. During this time, the Na$^+$ channels of the driver cell are open and furnish sufficient electrical charge to excite the driven cell. With advanced cell-to-cell uncoupling and the concomitant delay, the inward Na$^+$ current will be inactivated before the driven (downstream) cell reaches threshold, and consequently, flow of Ca$^{2+}$ inward current later during the action potential is necessary to ensure propagation. Thus, the conduction process can change from being solely Na$^+$ current—dependent to being Na$^+$ and Ca$^{2+}$ inward current—dependent, merely by a change in the degree of cell-to-cell coupling. Feedback interactions between electrical coupling and ionic current flow are also expected to occur during the action potential plateau and during repolarization. Because of the small ion current density and the high membrane resistance during the action potential plateau, the electrical interactions between adjacent tissue regions are stronger and extend over longer distances during this phase than during rest or during the action potential upstroke. As a consequence, differences in intrinsic APDs among adjacent tissue regions will be relatively small during normal cell-to-cell coupling and will be unmasked during uncoupling. In this way, the reduction of electrotonic interaction by cell-to-cell uncoupling is predicted to unmask intrinsic heterogeneities in repolarization, with both events serving to promote reentrant arrhythmias.

**Interaction Between Tissue Structure and Ion Channel Function**

As with the discrete pattern of gap junctions at the microscopic level, the macroscopic cardiac structure introduces obstacles and discontinuities for propagating electrical waves. Typical examples of discontinuities are branching fibers (Purkinje system, atrial trabeculae) and/or connective tissue layers (remodeled discontinuities are ventricular tissue in infarcted and/or hypertrophic hearts, normal midmural layers of normal hearts, ventricular trabeculae in aging myocardium).

Such discontinuities have been shown to affect membrane channel function. In any situation in which electrical waves propagate through anatomically discontinuous tissue and emerge from an isthmus, turn around the end of an obstacle, or emerge from a small fiber into a large tissue mass, the propagating wave becomes curved. In a curved wave front, the mismatch between the excitatory local current produced by the excited cells upstream and the electrical load of the nonexcited cells ahead of the wave front downstream affects both conduction velocity and the activation of ion currents. At a convex wave front, this mismatch will lead to a local conduction delay and to a localized increase of the amount of depolarizing inward current. Conversely, at a concave wave front (or, similarly, at a site of collision), conduction velocity will locally increase and the inward current will be locally reduced. This dependence of current activation on wave-front curvature is likely to be responsible for the larger effect of inhibitors that bind to open Na$^+$ channels at sites at which the propagation wave is convex than at sites at which it is linear. The curvature of the wave front will also play an important role in determining the ionic channels involved in impulse propagation. Thus, at divergence points, if the wave front is markedly curved, larger local conduction delays result. As with the case of advanced cell-to-cell uncoupling (see Figure 7), the Ca$^{2+}$ inward current then becomes essential for propagation, and application of Ca$^{2+}$ entry blockers produces localized conduction block.

Interestingly, the interaction between the macroscopic tissue architecture and excitation, leading to local divergence or convergence of wave fronts and changes in ion channel function, is further modulated by the degree of local gap junctional coupling.

**Prospective**

In the near future, most genes responsible for inherited arrhythmogenic conditions will be identified and the genomic structure of disease-related genes will also be defined. This will produce results that are needed for successful management of patients and families. One major result will be the definition of the "molecular epidemiology" of inherited arrhythmogenic conditions. Qualitative statements such as...
“rare” or “common” should be replaced by actual numbers defining the prevalence of each condition in the general population and the relative prevalence of each variant of a disease.

The availability of screening methods with sensitivity and specificity close to 100%, combined with complete clinical information prospectively collected, will define the penetrance of each disease and, within a disease, of each genetic variant. This will lead to guidelines for the management of asymptomatic gene carriers based on the predicted risk of becoming symptomatic.

Given the very large number of mutations associated with arrhythmogenic disorders, it may be more realistic to study carefully the larger group of individuals with defects in the same gene rather than attempting to define genotype/phenotype correlations for each mutation. If distinctive features are identified that segregate patients with specific genetic variants of the same disease, gene-specific therapy may result.

The identification of the genetic or environmental factors that modulate the expression of these diseases and understanding the mechanisms whereby relatives with the identical mutation can have radically different clinical histories will also be useful for patient management.

An intriguing aspect of investigating the molecular bases of inherited arrhythmogenic disorders lies in the hope that information provided by studies of relatively rare inherited conditions may help elucidate mechanisms for the acquired variants. The importance of the discovery of the gene for familial atrial fibrillation, for example, will be enhanced if it will lead to an understanding of the causes of the much more prevalent “lone” (and even disease-associated) atrial fibrillation. Similarly, recent data suggest that the acquired LQTS may develop in individuals carrying otherwise apparently “mild” mutations in LQTS-related genes. Polymorphisms of these genes could also predispose to other acquired arrhythmias.

Finally, the step from defective gene function to the clinically manifest arrhythmias involves further complexities related to the environment in which the abnormal proteins exert their function. Further study of the multiple interactions among ion channels, pumps, and exchangers on one hand and the structure and connectivity of the cellular network on the other should improve our understanding of the mechanisms that determine the occurrence of the electrical disturbances that lead to lethal arrhythmias.

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Appendix

This article summarizes the outcome of a workshop held at the European Heart House C, Sophia Antipolis, France, October 2–5, 1997. The need for the workshop was proposed by Silvia G. Priori. It was organized by the Study Group on Molecular Basis of Arrhythmias of the Working Group on Arrhythmias of the European Society of Cardiology, and its funding was administered by the Working Group itself. The workshop was cochaired by Silvia G. Priori and André G. Kléber. The final preparation and organization of the manuscript were the responsibility of André G. Kléber, Silvia G. Priori, Dan M. Roden, and Peter J. Schwartz.

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Part III
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