Protecting the Heart Against Arrhythmias: Potassium Current Physiology and Repolarization Reserve

Dan M. Roden, MD; Tao Yang, PhD

Hodgkin and Huxley’s classic experiments in the squid giant axon were the first to define a role for potassium efflux as a mechanism to return the membrane potential of an excitable cell to resting values. They showed that depolarization was caused by a rapid influx of sodium into the squid giant axon, an event which then initiated movement of potassium from inside the axon to the exterior. The resulting repolarizing current, termed $I\text{K}$, was identified decades later as a major contributor to repolarization in heart cells. $I\text{K}$ appeared to not only drive normal repolarization but also respond to adrenergic activation. By the 1970s it was apparent that $\beta$-adrenergic stimulation markedly increases inward calcium current in myocytes; this would prolong the QT interval on exercise were it not for a “balancing” effect of $I\text{K}$ activation.

Separating $I\text{K}$ Into $I\text{Kr}$ and $I\text{Ks}$ in Heart

In the late 1980s, there was some enthusiasm for the concept that arrhythmias could be suppressed by drugs that selectively delay repolarization (ie, without exerting other electrophysiological effects such as sodium channel block). A number of potent QT-prolonging agents were developed; in fact, 2—dofetilide and ibutilide—have reached clinical use. Studies of the molecular basis of such selective action potential prolongation led to the key discovery by Michael Sanguinetti, then at Merck, that “$I\text{Kr}$” in guinea pig myocytes actually represented 2 distinct currents: a small drug-sensitive current that activated rapidly (hence, termed $I\text{Kr}$) and a large drug-resistant current that activated slowly, $I\text{Ks}$. $I\text{Ks}$ block is now recognized as the overwhelmingly common mechanism whereby drugs produce QT prolongation. Work by many laboratories has defined key electrophysiological and pharmacological properties of $I\text{Ks}$. Notably, the Sanguinetti laboratory has proposed a structural basis for the peculiar “promiscuity” of $I\text{Ks}$ to block not only by antiarrhythmics but also by a wide range of “noncardiovascular” agents such as antihistamines, antipsychotics, and antibiotics, many of which have been relabeled or withdrawn because of risks thought to be associated with QT interval prolongation.

The physiological and pharmacological separation of $I\text{Ks}$ and $I\text{Kr}$ were followed in the mid-1990s by the cloning of the genes whose expression generates these currents, and the identification of mutations in those genes as the commonest causes for the congenital long QT syndrome. Expression of $\text{HERG}$ (now also known as $\text{KCNH2}$) is sufficient to recapitulate most properties of $I\text{Kr}$, although ancillary function-modifying subunits have been proposed. By contrast, recapitulation of $I\text{Ks}$ requires coexpression not only of the gene encoding the pore-forming subunit, $\text{KCNQ1}$ (formerly known as $\text{KvLQT1}$), but also an important function-modifying protein, termed KCNE1 (or minK), which was initially cloned from a rat kidney cDNA library.

$I\text{Kr}$ Block Causes Torsade de Pointes, But Not Always

The vast majority of heart beats in patients with loss of function mutations in $\text{HERG}$ are, in fact, normal and in many instances even accompanied by normal QT intervals. Similarly, although $I\text{Ks}$ block is now recognized as the major initiating mechanism in drug-induced torsade de pointes, not every patient receiving culprit drugs develops marked QT prolongation or the arrhythmia. This lack of a simple relationship between reduced $I\text{Ks}$ and a manifest clinical phenotype tells us that risk can be modulated by factor(s) beyond $I\text{Ks}$ alone. Variable drug metabolism can be invoked in some cases of drug-associated torsade de pointes but this is far from a universal explanation and does not explain variability in the congenital syndrome. To explain this variability in response to reduction or block of $I\text{Ks}$, we proposed the concept of “repolarization reserve.” We hypothesized that because multiple mechanisms were increasingly recognized as contributing to normal repolarization, loss of function in one of these (eg, reduced $I\text{Ks}$) may not lead to clinical consequences unless other lesions were present. Examples of such lesions are subclinical mutations in ion channel or other genes or disordered electrogensis increasingly recognized in acquired diseases such as heart failure or left ventricular hypertrophy.

Two articles in this issue of Circulation provide evidence that $I\text{Kr}$ may be a major source of repolarization reserve that protects against torsade de points during $I\text{Ks}$ block.

At First Glance, $I\text{Ks}$ Does Not Seem Large in Human Ventricular Myocytes

When long depolarizations are used to elicit outward current, $I\text{Ks}$ can be huge; however, an appreciation of the role of $I\text{Ks}$ under more physiological conditions, especially in larger mammals, has been slower to evolve. Although both $I\text{Ks}$ and $I\text{Kr}$...
have previously been identified in voltage-clamped human heart cells, their relative contributions to repolarization have not been explored. The laboratory of András Varró used relatively specific \( I_{K_s} \) and \( I_{K_r} \) blockers as tools to probe this issue. Whereas \( I_{K_s} \) blockers routinely prolonged action potentials, especially at slow rates (no surprise), it was a surprise that none of the \( I_{K_c} \) blockers did much at any stimulation rate. In fact, direct measurement of the currents with depolarizations approximating the human action potential duration showed that \( I_{K_s} \) is much larger than \( I_{K_c} \); with longer depolarizations (one way of simulating longer action potentials), \( I_{K_s} \) did get a bit bigger. One possible interpretation is that the current is not important, but this is difficult to reconcile with the fact that losing the current can be fatal because mutations in \( KCNQ1 \) are the single most common cause of the congenital long QT syndrome. Many explanations are possible: The specific cells studied may not have had much \( I_{K_s} \) (we know from work in canines that some cells exhibit less \( I_{K_s} \) than others), or \( I_{K_c} \) may have been damaged by the isolation procedure, or \( I_{K_c} \) is only important when action potentials get long, or, in fact, \( I_{K_c} \) is not important under basal conditions. The apparent paradox was partially resolved by additional experiments demonstrating that when \( I_{K_r} \) is blocked and the cells are exposed to adrenaline, \( I_{K_s} \) block prolonged action potentials. There are 2 reasonable conclusions. The first is that incorporating some basal sympathetic activity should be strongly considered in any study of action potential control. Indeed, in canine models, \( I_{K_s} \) block produces little discernible effect in the absence of catecholamines. The second conclusion is that \( I_{K_s} \) protects against action potential prolongation when \( I_{K_r} \) is blocked (ie, that it contributes to repolarization reserve).

**What Does KCNE1 Do to \( K^+ \) Current to Make It \( I_{K_s} \)?**

The problem of predicting how a complex system with multiple interrelated elements (eg, action potential) responds to a change in the behavior of an individual component is a general one in systems biology. One approach is to evaluate the effects of pharmacological probes (eg, blockers of specific components), but often these are not available. The laboratory of Yoram Rudy has devoted considerable effort to an alternate approach: incorporation of physiological properties of individual components of the action potential, such as \( I_{K_s}, I_{K_r}, \) inward currents, and intracellular calcium control mechanisms, into a computational model of the action potential, thereby allowing the effects of alterations in individual components to be simulated over a wide range of “in silico” experimental conditions. An issue that motivated the studies reported here by Silva and Rudy was the question of how currents generated by \( KCNQ1 \) alone and by \( KCNQ1 + KCNE1 \) (\( I_{K_s} \)) differ as a function of rate. Action potentials and QT intervals are shorter at fast rates, and a larger \( I_{K_s} \) is thought to be an important contributor, although the mechanism has been uncertain. In guinea pig myocytes, a depolarizing pulse activates \( I_{K_s} \) but with a delay, and with repolarization \( I_{K_r} \) undergoes deactivation, which is slow. These properties generated the conventional wisdom that \( I_{K_r} \) “accumulates” at fast rates because slow deactivation prevents the current from returning completely to baseline. Such accumulation could certainly account for shorter action potential duration and QT interval at fast rates, as is observed physiologically. A fly in this ointment is that \( I_{K_s} \) deactivation in other species such as the dog, is faster, so the accumulation hypothesis needs closer reexamination.

Silva and Rudy have explored new state models for \( KCNQ1 \) and for \( KCNQ1 + KCNE1 \) to address this issue. The simplest model to explain the behavior of an ion channel is one in which the channel can occupy 1 of 2 states, closed or open, with state transitions described by individual rate constants. The observation that \( I_{K_s} \) activation occurs with depolarization, but only after a delay, suggests that the channel may move through multiple closed states before opening during a depolarization. Silva and Rudy used physiological data obtained from multiple previous reports to construct a much more complex view of \( KCNQ1 \) behavior alone and in presence of KCNE1 to generate \( I_{K_r} \). The simulations strongly suggest that \( I_{K_s} \) accumulation at rapid rates is not caused by slow deactivation but rather by preferential occupancy of the channel in “proximal” closed states, very near the open one, at fast rates. When the channel exists in these proximal closed states, \( I_{K_s} \) can open with a minimal delay after a depolarization and rapidly become rather large. A particularly intriguing observation is that \( KCNQ1 \) alone cannot prevent an arrhythmogenic, pause-dependent early afterdepolarization, whereas \( I_{K_r} \), by activating during the plateau potential, can. In this way, repolarization reserve is generated by coexpression of \( KCNE1 \) with \( KCNQ1 \). “States” in models such as these represent either biophysical abstractions or, conceivably, individual conformations of the dynamic behaviors of these proteins. As Silva and Rudy are at pains to point out, although the results from the model are provocative, interesting, and physiologically rational, they are hypothesis-generating until additional physiological studies, which they even outline, address them.

**Approaches to the Study of Complex Biological Systems**

Taken together, the studies suggest that an important role of \( I_{K_s} \) in the human heart is to protect against pathological action potential prolongation (ie, to provide repolarization reserve). More generally, “repolarization reserve” is shorthand for the much broader concept that physiological systems often include considerable redundancies, and that these can protect against manifest disease phenotypes arising from a single lesion. This concept has wide applicability not only in cardiovascular medicine but also it is familiar as the “multiple” hit hypotheses in cancer biology. The 2 \( I_{K_s} \)-focused article in this week’s issue of *Circulation* serve to reiterate the message that unraveling such complex systems biology requires multiple highly complementary approaches, including a focus on individual molecules, integrated physiological behaviors, and appropriately constructed computational models to validate current hypotheses and to point to new experiments.

**Acknowledgments**

This work was supported in part by grants from the US Public Health Service (HL46681, HL49989, HL65962) and the American Heart...
Association (0565306B). Dr Roden is the holder of the William Stokes Chair in Experimental Therapeutics, a gift from the Dai-ichi Corporation.

References


Key Words: Editorials □ arrhythmia □ ion channels □ potassium □ repolarization
Protecting the Heart Against Arrhythmias: Potassium Current Physiology and Repolarization Reserve
Dan M. Roden and Tao Yang

Circulation. 2005;112:1376-1378
doi: 10.1161/CIRCULATIONAHA.105.562777

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/112/10/1376

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/