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Refining repolarization reserve

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A body of cellular and molecular studies over the past 15 years has demonstrated that the fundamental molecular lesion in the drug-induced long QT syndrome (LQTS) is block of the repolarizing potassium current I_{Kr}, the "rapid" component of the repolarizing potassium current that was initially termed I_K.[1,2] Further, decreased I_{Kr} due to *KCNH2* mutations causes type 2 congenital LQTS, one of the commonest forms of this disease.[3] Both the congenital and drug-associated form of LQTS present with QT interval prolongation and torsades de pointes, and a striking clinical feature in both is the highly variable nature of the phenotype: not every patient exposed to I_{Kr}-blockers develops QT prolongation, let alone exaggerated QT prolongation and arrhythmias, and not every patient with a loss-of-function mutation in *KCNH2* displays QT interval prolongation. It was this clinical disconnect and the increasing recognition that normal repolarization represents a complex interaction among multiple components that led in the late 1990s to the formulation of the idea of "repolarization reserve."[4] Recognizing that repolarization is accomplished not just by I_K and I_{Ca} but by I_{Kr}, I_{Ks}, $I_{Ca\text{-}L}$, $I_{Ca\text{-}T}$, $I_{Na\text{-}L}$, I_{NCX}, and so on, the concept suggests that a reduction in I_{Kr} might generate a huge effect in cells, or in patients, in whom other efficient repolarization mechanisms were absent. By contrast, the same reduction in I_{Kr} might produce little change in repolarization time in settings in which other mechanisms could readily accomplish normal repolarization. The idea seems appealing, since a PubMed search identifies 209 references to "repolarization reserve" and a Google Scholar search identifies "about 5,480" hits. The term may have acquired some currency because the idea makes intuitive sense to basic and clinical electrophysiologists or perhaps because it has a nice alliterative ring.

However, just because it seems to sound good does not make it so, and experimental validation is a next step. One obvious possible contributor to variable repolarization reserve is variability in function of the slow component of repolarizing potassium current, I_{Ks},[4] generated *in vivo* by coexpression of the poreforming subunit encoded by *KCNQ1* and the function-modifying subunit *KCNE1*. Indeed, initial computer simulations indicated that while reducing I_{Ks} produces minimal action potential prolongation, the extent to which I_{Kr} block prolongs action potentials is strikingly exaggerated when I_{Ks} is blocked.[5–7] These simulations were then followed by experiments showing that variable I_{Ks} function could indeed play a role in modulating response to I_{Kr} block.[8,9] In addition, modeling state transitions of the KCNQ1 channel underlying I_{Ks} revealed a critical role in maintaining normal repolarization (maximizing reserve) only when *KCNQ1* was coexpressed with *KCNE1*; the coexpression allows the channels to rest in "preopen" states and thus contribute maximally to the maintenance of repolarization reserve.[10]

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While these experimental and simulation data support the repolarization reserve concept and a role for I_{Ks}, they leave open many questions. What about calcium current or sodium-calcium exchange or late sodium current or inward rectifier current or other currents? How do function-modifying genetic variants (rare mutations or even common polymorphisms) affect the function of individual components of this complex system to modulate repolarization reserve? With modern electrophysiology and genetics, the possibilities become almost infinite, and thus experiments to address these possibilities seem increasingly daunting. In the present issue of Heart *Rhythm*, Sarkar and Sobie demonstrate how computational modeling of action potentials can be used to address this conundrum.[11] They used the TNNP computational model[12] of individual ion currents and other components (such as exchangers and intracellular calcium control mechanisms) to reconstruct cardiac action potentials *in silico* and then asked a simple question: by how much do action potentials prolong when I_{Kr} is 70% blocked? However, they did not set out to answer this question in one model but rather in hundreds of models, each one of which was generated by a random change in single-channel conductance, open-channel probability, or voltage dependence of activation or inactivation. That is, each simulation was conducted in an action potential with slightly different repolarization physiology. Gratifyingly enough (at least to those who might accept the concept of repolarization reserve), the extent to which 70% I_{Kr} block prolonged action potential varied across simulations. Because the experiment could be conducted in hundreds of different “background” myocyte physiologies, the dependence of action potential prolongation on the multiple characteristics of simulated ion currents and other components of repolarization reserve could be determined. Not surprisingly, the biggest influences on the drug response were the magnitudes of I_{Kr} and of I_{Ks}, in agreement with the earlier thoughts discussed above. On the other hand, some changes that clearly modulate the extent of action potential prolongation by I_{Kr} block are not readily predictable by intuitive approaches but are revealed by the computational simulation. One example is the dramatic effect imposed by a change in I_{Kr} gating that shifts the voltage dependence of inactivation in a positive direction: the implication would be that mutations producing such an effect might be silent at baseline but produce dramatic prolongation upon drug exposure. Similarly, increasing calcium channel conductance increased action potential duration (as would be predicted) but reduced the extent to which I_{Kr} block prolongs action potential duration. The modeling reveals that this blunted effect reflects a shift in the plateau potential, which thereby inhibits I_{Ks} inactivation, making more current available and thus increasing repolarization reserve.

The cardiac action potential represents the integrated activity of dozens (or hundreds) of individual components, and simulating the behavior of these individual components can lead to modeled action potential behaviors. Such modeling, however, runs the risk of being merely a sterile exercise unless it informs further physiology or answers questions that are not addressable in any other reasonable fashion. The present study falls squarely into the latter category: the results simply could not have been obtained using conventional animal or even cellular models. The results are of interest themselves because they begin to provide a global quantitative framework for the intuitively appealing concept of repolarization reserve. Many questions remain unanswered, some of which are acknowledged in the paper: How dependent is this upon the specific model? What about individual cell layers in the heart? Are the results different with varying pacing rates, or pauses? What about different degrees of I_{Kr} block? Under what conditions does I_{Kr} block generate arrhythmias? These are not deficiencies in the present study but rather highlight the way in which computational modeling can go forward to address these issues and ultimately inform experimentalists on the optimal design of physiologic studies. Another clear application of this approach will be to further understand the way in which genetic variants in the individual components of this complex system influence its overall behavior. The present studies have focused on changes in action potential duration as a consequence of I_{Kr} block, but there are many other

situations in which action potentials are prolonged and associated with arrhythmias: after myocardial infarction, in patients with diabetes, after cardioversion from atrial fibrillation, in heart failure, with subarachnoid hemorrhage, and so on. Understanding the fundamental physiological perturbations in these settings and then understanding how altered repolarization reserve in these settings can promote arrhythmias is another potential application of the present approach. Thus, the lessons that Sarkar and Sobie and others in the field will learn as modeling of this type becomes increasingly integrated into contemporary molecular electrophysiology and genomics should have widespread applicability to many other settings. More generally, they reinforce the idea that as we come to appreciate increasingly biologic complexity using buzzwords like pathways or systems biology, computational modeling will become increasingly indispensible to understand the predictable, and sometimes not so predictable, behaviors of these systems.

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