Climicians are well aware that responses to QT-prolonging drugs vary among individuals. A drug dose (and concentration) that produces minimal QT prolongation in one patient may, in an apparently indistinguishable subject, produce marked QT prolongation and torsade de pointes. This variability in response to an exogenous stressor is paralleled by variability in the extent to which a given mutation in the congenital long-QT syndrome prolongs QT interval and causes arrhythmias. Indeed, it is depressingly common to identify an affected family after an individual subject has died, only to find many other mutation carriers within the kindred, often with normal QT intervals.

A major mechanism contributing to repolarization in the human ventricle is time-dependent outward (repolarizing) potassium current, initially termed I_K. Studies beginning in the late 1980s showed that this current includes multiple components, most notably I_{Ks} and I_{Kr}. Loss-of-function mutations in the genes underlying either of these 2 currents are a major cause of the congenital long-QT syndrome, and I_{Kr} inhibition is the major mechanism for QT prolongation by virtually all available drugs. Action potential control is much more complex than simply variability in these 2 currents: Multiple other currents flow across the myocyte membrane during an action potential. This more complex view of repolarization presents an opportunity for translational scientists interested in the problem of variability in response to drug challenge or to disease-associated mutations; in particular, it suggests the hypothesis that individuals may vary in response to challenge such as I_{Kr} block (or a mutation) not because of variability in the target ion channel but because of variability in the much broader biological context in which a drug or mutation inhibits 1 ionic current. This is not such a new concept; indeed, Denis Noble, one of the fathers of “systems biology,” began his career by constructing computer models to study how changes in 1 ionic current would affect the behavior of the action potential. It was this kind of thinking that led me to propose the concept of “repolarization reserve,” the idea that the complexity of repolarization includes some redundancy. As a consequence, loss of 1 component (such as I_{Kr}) ordinarily will not lead to failure of repolarization (ie, marked QT prolongation); as a corollary, individuals with subclinical lesions in other components of the system, say I_{Ks} or calcium current, may display no QT change until I_{Kr} block is superimposed. In the present issue of Circulation, Xiao et al carry this concept further by identifying a novel potential mechanism that regulates repolarization reserve.

Xiao et al compared action potential durations in dissociated canine epicardial cells paced for 24 hours in control media or media supplemented with a highly specific and potent I_{Kr} blocker, dovetilide. Surprisingly, when dovetilide was withdrawn, they found that action potentials were shorter in drug-exposed cells than in control cells, and the mechanism for this was an increase in I_{Ks} without a change in other major components of the repolarization apparatus. One possibility is that dovetilide exposure increased transcription of KCNQ1 or KCNE1, the genes whose expression generates I_{Ks}, but mRNA abundances for these transcripts were unchanged (unfortunately, multiple names exist for these genes; KvLQT1 and minK are others). However, the abundance of the proteins themselves was increased, which indicates that the increase in I_{Ks} was a posttranscriptional event.

Xiao et al examined a potential role for microRNAs in this process. These RNA molecules, recognized in mammals only early in the present decade, are short (21 to 22 nucleotides) and can bind to target mRNAs to inhibit translation; one, a muscle-specific form termed miR-133, has been implicated as a potential regulator of I_{Ks}. Xiao et al found that dovetilide-exposed cells displayed reduced miR-133 abundance, and they suggest, but do not demonstrate here, that this releases inhibition of I_{Ks} translation, shortening action potential duration. We must thus add defective microRNA regulation to a list of potential mechanisms that contribute to reduced repolarization reserve.

Potential Limitations

These are not easy experiments. They require consistent isolation of viable myocytes, consistent pacing during the culture period, and deployment of occasionally finicky methods, such as real-time polymerase chain reaction in cell isolates and protein quantification. Dog cells, like cells from humans, display large I_{Ks} and I_{Kr}, although the relative importance of the 2 currents may be different in the species. In addition, the studies used only epicardial cells, and it is increasingly appreciated that other cell types, notably those from the mid myocardium, may play a critical role in the generation of QT prolongation and torsade de pointes.
The changes observed are small, 30% or less, but this is to be expected in studies of a system in which even small changes in an individual component can produce large changes in readouts such as action potential duration. The studies with miR-133 are provocative and raise questions on issues such as the underlying mechanisms and other potential effects, including effects on other ionic currents (admittedly not observed here), of decreases in this cardiac regulatory molecule.12–14

What Next?

One logical inference from the findings reported is that withdrawal of drugs such as dofetilide in humans would not only bring action potential durations back to normal but might make them even shorter. Thus, the present study not only identifies novel molecular mechanisms that may be involved in control of QT interval but also points to hypotheses that can be tested in whole animals and in human subjects. Indeed, studies that carefully evaluated the effect of sotalol, another I<sub>Ks</sub> blocker, on QT-interval duration showed marked effects at day 1, which waned (but did not return to normal) with continued administration of the drug;15 perhaps the effects described by Xiao et al<sup>8</sup> were playing a role.

As Xiao et al<sup>8</sup> point out, multiple other mechanisms may contribute to the increase in I<sub>Ks</sub>. They observed. I<sub>Ks</sub> amplitude is readily increased by interventions such as adrenergic stimulation<sup>16</sup> or endothelin.17 Indeed, studies in human myocytes and in computational models have implicated variability in I<sub>Ks</sub> amplitude as a major contributor to variability in response to I<sub>Ks</sub> block (ie, to repolarization reserve).18,19 The way in which these and other mechanisms might contribute to I<sub>Ks</sub> regulation during challenge with an I<sub>Ks</sub> blocker remains a fertile area for investigation, both at the clinical level and at the molecular level, notably to dissect the individual mechanisms and the way in which they may interact with each other.

The concept of “repolarization reserve,” as originally proposed, suggested a static nature to the relationship between I<sub>Ks</sub> and other components of repolarization that provide “reserve” against I<sub>Ks</sub> inhibition. The present study supports previous work implicating variability in I<sub>Ks</sub> amplitude as a major contributor to variable repolarization reserve. Such variability can have a genetic basis (eg, in subclinical mutations that reduce I<sub>Ks</sub>)<sup>20</sup> or be acquired. The work by Xiao et al<sup>8</sup> not only implicates drug administration as generating a new potential mechanism for such regulation but also highlights the dynamic nature of reserve itself. Although this presents little surprise to clinicians who are used to seeing highly variable responses to drugs, it is extremely gratifying that progress is now being made in actually quantifying the phenomenon and understanding its molecular underpinnings.

Disclosures

Dr Roden has consulted on issues related to drug-induced QT prolongation with the following companies during the past 2 years: Avanir, Baker Brothers, Eli Lilly, AstraZeneca, CardiolDx, and Ortho Diagnostics. He receives royalties on a patent related to prediction of drug-induced QT prolongation.

References


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