EDITORIAL

Ventricular Repolarization

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In this issue of *Annals*, we are publishing several original articles related to the QT interval, a review article on ventricular repolarization in men and women, and a translation from German of the classic 1920 article by Fridericia on the rate correction of the QT interval by the cube root of the R-R cycle length. This emphasis on the QT interval derives, in part, from: an increased interest in the energy-requiring ion-channel currents that are responsible for ventricular repolarization; a better understanding of the hereditary channelopathy disorders; a greater recognition of the problem of drug-induced QTc prolongation; and a fuller appreciation of the QT-regulatory issues involved in the approval of new drugs as well as the ongoing monitoring of approved drugs that are currently in the market.

At the recent May 2003 North American Society of Pacing and Electrophysiology Scientific Sessions in Washington, DC, there was a well-attended, all-day, special session on "QT Prolonging Drugs: Basic, Scientific, and Regulatory Issues." New chemical entities (potential drugs) that are being developed for a variety of conditions (mostly for non-cardiac indications) are screened early in their development for electrophysiologic effects on the action-potential duration in animal-cardiac tissue (e.g., Purkinje fibers) and in cellular-expression studies where the effect of the drug on ion-channel kinetics can be quantitatively evaluated. If a drug passes muster at this introductory screen, whole animal studies are performed to evaluate the effect of the drug at high doses on ventricular repolarization. If the drug appears safe, Phase I, II, and III clinical studies are then carried out using ECG and Holter monitoring to evaluate the QT effects of the drug in the real-life situation. This drug evaluation process is time consuming and expensive, yet necessary if a pharmaceutical company is going to bring a safe drug to the market with minimal or no effect on the QT interval.

The review article by Surawicz and Parikh in this issue of *Annals*¹ highlights the differences in the characteristics of ventricular repolarization in males and females in terms of the QT interval, T wave morphology, and underlying mechanisms as well as the clinical significance of this gender difference. It has been known since the ECG was introduced 100 years ago that the QT interval is longer in adult women than men. Rautaharju et al.² have shown that male and female children have similar QT intervals, but during adolescence the QT interval shortens by 3–4% in males but not in females when compared to the QT interval recorded in childhood. This adolescent QT shortening effect is probably mediated by the effect of the male hormones on the electrical characteristics of ion channels involved in the repolarization process. Women are known to be more susceptible than men to the arrhythmogenic effects of drugs and diseases that prolong the QT interval, and this finding has clinical relevance in the practice of medicine and cardiology.

It was appreciated early on that the duration of repolarization normally shortens as the heart rate increases. In 1920, both Bazett³ and Fridericia⁴ independently evaluated the effects of changing cycle length on the QT interval. The QT/R-R relationship is somewhat curvilinear in heart rates between 60 and 100 bpm. Bazett found that an inverse square root relationship between the QT and R-R interval fit his limited data quite well. Fridericia, on the other hand, found a cube root relationship more appropriate. Both these rate-correction QT formulae are widely used today in clinical medicine and in research studies. During the past few years, it has been appreciated that the QT/R-R relationship has subject-specific characteristics almost like fingerprints. Furthermore, the QT shortening with increasing heart rate is mediated, in part, by the dynamic characteristics of the repolarization potassium currents, particularly the slowly activating

delayed potassium repolarization current (I_{Kr}). The role of activity-related catecholamines on the I_{Kr} current is an area of considerable interest, especially in Long QT Syndrome (LQTS) patients who have mutations involving the I_{Kr} channel (LQT1). These patients develop most of their arrhythmic events during physical activity. There is clinical evidence that patients with mutations in the *KCNQ1* gene responsible for LQT1 have impaired shortening of the QT interval during exercise-induced tachycardia when compared to normal subjects without this ion-channel mutation. These findings are further buttressed by cellular electrophysiologic studies involving mutant channels.

The ECG repolarization pattern in LQTS patients with mutations involving *SCN5A* sodium channel gene is usually quite distinctive, with prominent late-peaked T waves especially in the lateral precordial leads.⁵ In this issue of *Annals*, Brouwer, from The Netherlands evaluated the diagnostic performance of classical (Bazett and Fridericia) and newer (Hodges, Framingham, and logarithmic) QT correction formulae in a large LQT3 pedigree.⁶ At least for the specific mutation studied (1795 insD), the standard Bazett formula performed very well in identifying those who were and were not carriers of the mutant gene, and the classical correction formulae were equivalent in effectiveness to the newer ones.

The group from Turkey attempted to get at the mechanism of the sex difference in repolarization patterns by comparing repolarization patterns in hypogonad males with those in matched healthy men and women.⁷ Testosterone deprivation was associated with attenuation in several repolarization parameters, but the ECG patterns did not approach those in healthy women. It is clear that testosterone has effects on cardiac muscle and ventricular repolarization and its influence during the cardiac-growth phase of adolescence probably explains a large part of the repolarization sex difference.

It has been known for some time that acute myocardial ischemia can produce action-potential duration shortening of in animal studies and QT shortening in patients. The question addressed by Papadopoulos, et al. from Greece in this issue of *Annals*⁸ is whether ischemic preconditioning in the form of the occurrence of pre-infarction angina in patients with non-ST segment elevation myocardial infarction has an effect on ventricular repolarization. This small study provides preliminary clinical

support for the hypothesis that ischemic preconditioning contributes to electrical stability in patients with nontransmural myocardial infarction.

We know that a link exists between the magnitude of abnormal QT prolongation produced by disease or drugs and the risk probability of developing malignant ventricular arrhythmias of the torsade de pointes type. Prior studies have shown that this tachyarrhythmic risk has an exponential association with QTc duration.⁹ At the present time, evaluation of the clinical risk from altered ventricular repolarization is based almost entirely on the duration of the QT interval, a parameter that has measurement inaccuracies related to imprecision in the identification of the end of the T wave. There is surely important repolarization information in other portions of the T wave, so it is surprising that the repolarization focus for the last 80 years has been fixated on the QT interval. I suspect that in the near future more sophisticated repolarization measurements than simply the QTc interval will be used to identify patients at risk of developing malignant arrhythmias.

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