

## Cardiac repolarisation: the long and short of it

Warren M Smith

*Long (or short) QT syndrome is life-threatening, not as rare as once thought, and treatable if diagnosed*

“The fault dear Brutus is not in our stars, but in ourselves”. Through the lens of molecular medicine we are now beginning to see those faults more clearly. We can now increasingly understand why some apparently healthy children and young adults die without warning. The long-QT syndrome is foremost among responsible causes, and is known to be the consequence of mutations in genes encoding ion channel function.<sup>1</sup> Originally an esoteric condition of great rarity, its prevalence is now estimated as one in 2000.<sup>2</sup>

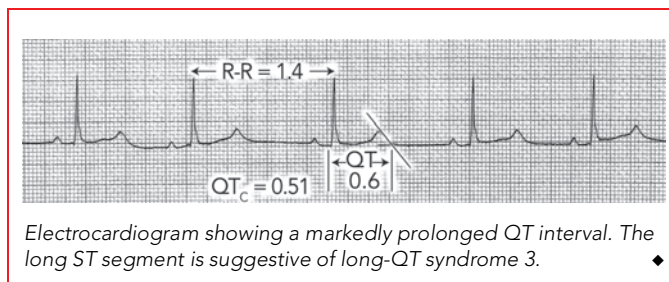
Life depends on the continuous sequence of depolarisation and repolarisation in our heart cells. The QT interval is the time from the onset of depolarisation (the q wave) to the end of repolarisation (completion of the T wave) and is best measured over several R-R intervals in leads II or V<sub>5</sub>. It is not a value physicians ordinarily pay much attention to when they read an electrocardiogram (ECG; Box). Nor is it always easy to measure. Exactly where the T wave merges with the isoelectric baseline is subject to individual interpretation and hence error.<sup>3</sup> It also varies with heart rate, requiring normalisation for comparison, and is longer in women than men. But it is important.

The long-QT syndrome is essentially an autosomal dominant condition in which sudden death is commonly linked to situations of increased adrenergic activity, such as exercise and emotion, but also occurs at rest and during sleep.<sup>4</sup> Seizures are common and easily lead to misdiagnosis. Although mutations in at least 10 genes have been found, long-QT syndromes 1 (LQT1), 2 (LQT2) and 3 (LQT3) constitute 95% of genotyped cases.

LQT1 and LQT2 involve decreased function and hence diminished current flow in the slow and fast repolarising potassium currents, I<sub>Ks</sub> and I<sub>Kr</sub>, respectively, while LQT3 involves an increase in slow sodium current during the plateau phase of the action potential. The net effect is prolongation of the action potential and, most importantly, an increased dispersion of recovery times in different myocardial cells. This increased dispersion allows re-entry to occur with potentially fatal ventricular tachycardia and fibrillation, which manifests clinically as fainting and sudden death.

LQT1 is the most common type, and events are typically triggered by exercise, including swimming, and emotion.<sup>5</sup> The child found unconscious at the bottom of the swimming pool may well have LQT1.<sup>6</sup> Events may occur with exercise or at rest in LQT2 and also, characteristically, with loud noises such as being awakened by a telephone call.<sup>7</sup> LQT3 has been linked to death during sleep or inactivity, with a lower likelihood of events, but increased mortality.

What are the implications for physicians and general practitioners? Fainting is common, most often vasovagally mediated, and benign. How do we decide otherwise? The key is to be mindful of possible long-QT syndrome when checking the history; fainting or a seizure during exercise, or when upset or angry, and premature death (including drownings or accidents) in family members should ring alarm bells and trigger detailed exploration of the family history, close scrutiny of ECGs and appropriate referral. In such settings, a



corrected QT (QTc) interval >0.45 seconds in males and >0.47 seconds in females makes the diagnosis virtually certain.

With diagnosis comes the dual responsibility of triaging individual patient risk and screening the wider family. The most important factor determining individual risk is the length of the QT interval — long intervals (QTc ≥ 0.5 seconds) equal high risk.<sup>8</sup> Knowledge of the genotype is also predictive. β-Blockers are generally first-line treatment, although in genotyped individuals, evidence is lacking for a protective action in LQT3. Modifying risk by avoidance of competitive sport and QT-prolonging drugs (see <http://www.qtdrugs.org>) is important. Implantable defibrillators are appropriate in high-risk patients, but decisions about prophylactic implantation in intermediate-risk patients must balance the reduction in probability of sudden death against the not inconsiderable morbidity of life-long device therapy in young people.

As well as personal history and ECG, family screening should include genetic testing if it is available. When a functionally important mutation is uncovered, testing of family members will disclose up to a third of individuals whose QT intervals are normal, and yet who carry the mutation.<sup>9</sup> However, a genotypic diagnosis is possible in only two-thirds of clinically certain cases. Continuing research may diminish this gap. The establishment of registries, such as presently exist in New Zealand (<http://www.cidg.org>), facilitates surveillance of widely dispersed families and aids ongoing research.

While the risks of QT prolongation are now well established, attention has recently been drawn to excessively short QT intervals. In a small number of families identified to date, a QTc interval of <340 milliseconds has been also associated with a family history of sudden death.<sup>10</sup> The first two syndromes described (short-QT syndromes 1 and 2), show a gain of channel function for I<sub>Kr</sub> and I<sub>Ks</sub>, the mirror opposite of the corresponding LQT2 and LQT1 with loss of function in those same channels. Although five short-QT syndromes have been recognised already, it nonetheless seems unlikely that they will rival the long-QT syndrome in prevalence.

In conclusion, cardiac repolarisation is a complex interplay of ionic currents precariously maintaining stability. Dramatic progress has been made over the past 50 years in recognising, deciphering and predicting the clinical risk of the long-QT syndrome. Yet this knowledge counts for little if we fail to identify and protect at-risk individuals. Perhaps you will take a closer look at the QT interval in your next patient presenting with “just” another fainting attack.

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