Acquired long QT syndrome: as risky as congenital long QT syndrome?

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This editorial refers to ‘Role of implantable cardioverter defibrillator therapy in patients with acquired long QT syndrome: A long-term follow-up’ by G. Mönnig et al., on page 396

Long QT syndrome (LQTS) describes a group of disorders characterized by QT interval prolongation secondary to delayed cardiac repolarization that may either be genetic (otherwise known as ‘congenital’) or acquired. The substrate of abnormal cardiac repolarization predisposes to development of torsades de pointes (TdP), the characteristic form of polymorphic ventricular tachycardia, and cardiac arrest. Congenital LQTS has a population prevalence of 1 in 2000 and is caused by mutations in genes coding for cardiac ion channels and their channel interacting proteins. Delayed cardiac repolarization results mainly from loss-of-function mutations affecting rectifying potassium currents (IKs, IKr, and IK1) or gain-of-function mutations affecting the inward sodium current and rarely the L-type calcium current.

Acquired LQTS has traditionally been associated with exposure to QT prolonging drugs, with antiarrhythmic medications being the most common precipitant. The main mechanism of drug-induced LQTS involves the inhibition of IKr in a similar fashion to that seen in the LQT2 subtype of congenital LQTS which arises from loss-of-function mutations in human ether-a-go-go-related gene which encodes the alpha subunit of IKr.1,2 Both are associated with pause-dependent TdP. Other acute causes include electrolyte imbalance (in particular, hypokalaemia), after reversion of atrial fibrillation and transient bradycardia. There are also established chronic predisposing factors such as structural and cardiac conduction disease, metabolic and endocrine abnormalities. There is, however, a growing body of evidence suggesting that a ‘frustrated’ form of the congenital condition may underlie a proportion of these cases.3 Exposure to further insults upon cardiac repolarization, such as QT prolonging drugs, is required to expose the apparent acquired LQTS phenotype. The concept of repolarization reserve has thus been postulated with normal cardiac repolarization being achieved via multiple ion currents which provide a ‘safety margin’ or ‘reserve’. Reduced reserve is thought to explain the pathophysiology of congenital and acquired LQTS such that in patients with genetic lesions which affect normal ion channel function, exposure to a trigger such as an IKr blocker may result in acute QT prolongation and TdP.4

In patients who present with aborted sudden cardiac arrest and LQTS, there is a Class I indication for an implantable cardioverter defibrillator (ICD).5 This is not the case, however, in acquired LQTS, where there is little evidence for mandatory insertion of an ICD provided any precipitating cause such as a culpable drug has been removed and patients’ clinical features do not remain high risk for further events. Indeed guidelines only support pacing to prevent pause-dependent TdP.5

It is therefore with great interest that we have read the report by Mönnig et al.6 who have published results of the 10-year retrospective study of 43 patients with acquired LQTS who were implanted with an ICD following a cardiac arrest. In this study, drug-induced acquired LQTS predominated, with antiarrhythmic drugs being the most common offending medications. In addition, while only eight patients underwent genetic testing for LQT1, LQT2, and LQT3, there were no mutations detected. The mean QTc interval was 536 ± 58 ms when exposed to the acute trigger, supporting that QT prolongation beyond 500 ms confers increased risk.7 Despite relative normalization of the QTc interval once the proarrhythmic trigger was removed (mean = 438 ± 33 ms) as well as the avoidance of other known risk factors for QT prolongation, there was evidence of recurrent potentially significant tachyarrhythmia with a high number of appropriate ICD shocks: 128 shocks in 19 of 43 patients over a mean follow-up of 84 months, secondary to polymorphic ventricular tachycardia and ventricular fibrillation. The presence of structural heart disease did not appear to increase the risk of shocks significantly although the trend was suggestive of a higher frequency of ICD interventions in this group. In addition, the unexposed QTc intervals of patients who suffered ICD intervention were not reported

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and may have been higher suggesting a greater risk. Although the frequency of appropriate ICD shocks is lower than that in high-risk congenital LQTS patients with ICDs, it is still higher than would be expected in this patient population if proarrhythmic risk has largely been eliminated.

A critical question regarding these shocks concerns their necessity. The authors state that five out of the 19 patients experienced syncope, which suggests that the majority of them were not significantly symptomatic from their tachyarrhythmia prior to defibrillation. Initial ICD programming set a detection criteria of 12 of 16 number of intervals to detect (NID) with 9 of 12 NID for detection or a detection time of 2.5 s. It would have been helpful to report the number of patients requiring reprogramming at outpatient visits due to unnecessary therapy with further analysis of shock frequency pre- and post-reprogramming. The high shock frequency may therefore represent overtreatment of a significant proportion of this patient group due to inappropriately short detection times. Previous studies have shown that cardiac pacing with a dual-chamber device at a relatively fast lower rate limit and use of pause prevention programming, such as rate smoothing algorithms, are effective in preventing TdP in LQTS. In the study by Mönnig et al., the majority of patients were implanted with a single chamber device (81%), predominantly with just back-up pacing (<40 bpm). Only 5 of 43 patients received dual-chamber pacing at a rate >40 bpm. Inadequate pacing to prevent the short–long sequence trigger for pause-dependent TdP may thus be contributory to the high shock frequency.

Beta-blockers are often used in similar situations in ICD patients with congenital LQTS to reduce the arrhythmia recurrence and the number of shocks. This study did not show any difference with beta-blocker use, but may not have been powered to show a significant effect. A breakdown of shock frequency according to beta-blocker use would have also provided more information regarding its efficacy.

Nevertheless, the fact remains that even if a proportion of these shocks might have been unnecessary, they are certainly not inappropriate. This suggests that either the proarrhythmic risk in the study population is not due solely to a transient, specific trigger but an underlying persistent predisposition that remains potent; or alternatively there may have been exposure to other as yet unrecognised factors that cause acute QT prolongation. Although the results of limited gene testing were negative, there is still a potential for genetic variation causing an incompletely expressed phenotype, whether it involves rare variation in the other LQTS genes or common genomic variation. Further genetic testing and genomic research, especially with current techniques, might yield more data on novel mutations, culpable genes and genomic variation that predispose to such risk.

As Mönnig et al. have pointed out that their study is limited by the lack of controls and would have benefited from comparison with a cohort without ICDs to demonstrate any mortality and morbidity benefit. Although a proportion of the study cohort may have potentially gained from ICD therapy, the associated morbidity is not insignificant with 98 inappropriate shocks occurring in 13 patients.

This study therefore presents interesting long-term follow-up data on ICD implantation in survivors of sudden cardiac arrest with acquired LQTS. It appears that ICD therapy might offer a potential benefit in a subgroup of these patients in view of the recurrent life-threatening tachyarrhythmias. However, the results cannot, at this stage, be applied to the wider population with acquired LQTS as unnecessary shocks may have obscured the true risk of sudden death. Furthermore, this appears to be a highly selected group of cardiac arrest survivors and it is unclear whether those who suffered shocks were more likely to have both underlying structural heart disease and more prolonged QT intervals than those who did not receive therapy. It will require further research with a larger scale controlled study with tailored dual-chamber ICD algorithms and programming, to come to a consensus with regards to the optimal management of these patients.

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References

Erratum
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The Publisher would like to apologize for omitting Berry van Gelder from the list of 2011 reviewers published in Europace 14-1 (January 2012). Berry van Gelder completed 13 reviews for the journal in 2011.

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