Treating the Long-QT Syndrome in the Era of Implantable Defibrillators

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We live in an era of defensive medicine. Implantable cardioverter defibrillators (ICDs) increasingly are used to treat patients with congenital long-QT syndrome (LQTS), although not always with compelling indications. In different series, some patients underwent ICD implantation without ever receiving β-blockers, others never had symptoms and a few did not even have LQTS to begin with. A few studies probably boosted the use of ICDs in LQTS: (1) In a case-control study comparing ICD therapy with conservative management in high-risk patients with LQTS, ICDs were associated with decreased 3-year mortality (1.3% versus 4.1%, P=0.07). However, as explained elsewhere, the mortality reduction associated with the ICD was probably overestimated in that study, because 26% of conservatively managed patients did not receive β-blockers after the cardiac arrest, and some died shortly thereafter, probably due to sequelae of the cardiac arrest. (2) Several studies showed that high proportions (22% to 60%) of ICD-treated patients with LQTS receive appropriate ICD shocks within 2 to 5 years (Table). These impressive rates of life-saving therapy probably convinced many physicians that ICDs may be the treatment of choice for LQTS; however, these high rates of “life-saving therapy” (higher than the expected mortality in LQTS) could be related in part to the definition of “appropriate ICD therapy.” In these studies, appropriate ICD therapy was defined as an “ICD shock that terminated a ventricular tachyarrhythmia,” regardless of its duration and whether or not it caused symptoms. As appreciated from the Table, only 2 of the studies reported the parameters used for detection of ventricular arrhythmias. One can calculate that ICD shocks in these studies were probably delivered within 10 to 12 seconds from arrhythmia onset (Table). This is consequential, because torsade de pointes often terminates spontaneously (Figure). It is likely that some of the “appropriate ICD shocks” were actually inappropriate, delivered for ventricular arrhythmias that otherwise would have terminated spontaneously.

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ICD implantation is undeniably the most effective way to prevent arrhythmic death; however, the risks of complications inherent in this procedure, which are especially common and troublesome in patients undergoing ICD implantation at a young age, are not always appreciated. On the other hand, 3 decades of experience have taught us that β-blockers effectively prevent long-QT related arrhythmias. Thus, the real challenge is deciding who can be treated only with β-blockers with reasonable (rather than infallible) safety and who requires ICD implantation despite the risks involved. In this regard, the study by Vincent and colleagues, published in this issue of Circulation, is a timely contribution.

Vincent et al report that patients with LQT1 (the most common variant of LQTS), have a very low arrhythmic risk when treated with β-blockers, as long as they are fully compliant with their medications and avoid QT-prolonging medications. Their observations are based on 216 LQT1 patients: 73% of them had arrhythmic symptoms before the onset of therapy, and 90% had their first arrhythmic event in the absence of QT-prolonging medication at a median age of 8 years. These characteristics suggest that this is not a selected low-risk population. Indeed, 12% of all patients were resuscitated from cardiac arrest before the onset of β-blocker therapy. In this highly symptomatic cohort, the number of patients with symptoms was markedly reduced (from 73% to 25%) with β-blocker therapy. Moreover, most patients with breakthrough arrhythmias remained asymptomatic once their β-blocker dosage was increased, which translated into a 70% reduction in the mean annual event rate with β-blocker therapy.

Agreement is universal that LQT1 patients should receive β-blockers unless these are contraindicated or not tolerated. In this regard, it is worth noting that bronchial asthma is no longer considered an absolute contraindication to β-blockers. In fact, recent data show that with careful titration, β1-selective β-blockers are generally well tolerated by patients with mild asthma and may even have beneficial long-term effects. Moreover, β-blockers reduce the risk for arrhythmic events among LQTS patients who receive bronchodilators for asthma.

The real question is not who should receive β-blockers but who requires additional interventions, such as ICD implantation or denervation surgery. The importance of this question is highlighted in the study by Vincent et al by their finding that for 9 (75%) of the 12 patients who had cardiac arrest despite β-blocker therapy, this was the first arrhythmic event while undergoing therapy. Obviously, for these patients, “wait and see if β-blockers work” proved to be a bad idea. Also, clinical presentation was a bad predictor of cardiac arrest despite β-blocker therapy. Before the onset of therapy, 59 patients were asymptomatic, 131 had already experienced syncope, and 26 had survived a cardiac arrest; for these 3

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groups, the risk for cardiac arrest during β-blocker therapy was 3%, 7%, and 4%, respectively. Obviously, families with LQTS should master the skills of basic cardiopulmonary resuscitation techniques and should possess an external automatic defibrillator as part of a sudden-death prevention program.

The exceptional findings of the present study relate to the impact of compliance with β-blocker therapy and avoidance of QT-prolonging medications on the risk of cardiac arrest. In this series, 176 patients (81%) meticulously took their β-blockers as prescribed and avoided QT-prolonging medications at all times. Only 1 (<1%) of them had cardiac arrest. This fatality occurred in a patient with Jervell and Lange-Nielsen syndrome, a severe form of LQT1 that nowadays would call for ICD implantation.9 With the exclusion of that rare form of LQTS, the long-term risk of cardiac arrest was zero for LQT1 patients who complied with their medications and avoided QT-prolonging medications during a follow-up period that ranged from 5 to 15 years.10 The investigators’ confidence in the efficacy of β-blockers allowed them to use β-blockers exclusively (without ICD backup) to treat 26 patients who had cardiac arrest in the absence of therapy. None of these patients died, and only 1 (<4%) had recurrent cardiac arrest. The excellent prognosis of compliant patients contrasts sharply with the poor prognosis of the noncompliant group. Among the latter, 62% had arrhythmic symptoms, and 23% had cardiac arrest. In addition, the 5 patients consuming QT-prolonging medications developed severe arrhythmic complications.10

The demonstrated proarrhythmic role of QT-prolonging medications has clear-cut implications: All patients with LQTS, regardless of genotype and including patients with suspected but unconfirmed LQTS, should receive an updated list of QT-prolonging medications. They should be warned that the list is probably incomplete, because the QT-prolonging potential of medications often goes unrecognized. Thus, patients (and their primary physicians) should be reminded repeatedly that avoidance of unnecessary medications in general is a good idea, whereas consumption of QT-prolonging drugs is prohibitively dangerous.

Less straightforward are the conclusions to be drawn from the compliance findings. Skeptical physicians may conclude that noncompliance with prescribed medications, especially in adolescents, is unbeatable even when it has immediate consequences (eg, when treating epilepsy).14 They may cite studies showing that doctors cannot predict their patients’ reliability15 and argue that admonishing patients that noncompliance will bring about ICD implantation will only backfire (because patients will lie about compliance even more). Thus, the skeptic may arrive at a conclusion opposite to that reached by Vincent et al10 and recommend more (rather than fewer) ICDs for LQT1. Conversely, experienced physicians who routinely treat patients with arrhythmogenic channelopathies maintain that it is possible to achieve excellent patient compliance through relationships based on openness and education.10,16 Noncompliance simply due to forgetfulness may be solved by automatic reminders (an easy task with ever-present cellular phones); noncompliance due to denial may be more difficult to recognize but is also manageable.17 Lastly, β-blockade can (and should) be confirmed repeatedly by measuring the heart rate during exercise and Holter recordings.

Two cautionary remarks: (1) The doses of β-blockers used by Vincent et al10 should be noted (eg, propranolol 2.2±1.2 mg/kg). Compromises in dosage to achieve better compliance may also compromise safety, because the minimum doses of β-blockers that effectively prevent torsade de pointes are not known. (2) The excellent results achieved in LQT1 should not be extrapolated to other forms of LQTS without due testing. This is because LQT1 appears to be particularly sensitive to β-blocker therapy. In vitro studies show that the ion channel affected in LQT1 is responsible for the predominant repolarizing current during high sympathetic activity and faster heart rates.18 Arrhythmias in LQT1 are primarily triggered by stress and are tachycardia dependent.19 In contrast, in vitro data suggest that sudden heart rate slowing is more arrhythmogenic in LQT2 and LQT3,20 and clinical arrhythmias in LQT2 are pause dependent.19 Thus, cardiac pacing, in addition to

Table. Studies Reporting ICD Use After Implantation for LQTS

<table>
<thead>
<tr>
<th>Time to Shock*</th>
<th>Detection Duration, QRS</th>
<th>Detection Rate, per min</th>
<th>Appropriate ICD Shocks, %†</th>
<th>Patients With ICD, n</th>
<th>Reference</th>
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<td>NA</td>
<td>60</td>
<td>35</td>
<td>Groh et al¹</td>
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<tr>
<td>10 s</td>
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<td>&gt;180</td>
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<td>NA</td>
<td>NA</td>
<td>22</td>
<td>23</td>
<td>Etheridge et al³</td>
</tr>
</tbody>
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NA indicates not available.

*Time to shock is the time from onset of the ventricular tachycardia to shock delivery and was calculated by multiplying the tachycardia detection cycle length by duration and adding average charge times.

†Appropriate ICD shock was defined as a shock delivered for a ventricular tachycardia regardless of the presence or absence of symptoms.

Figure. Torsade de pointes fortuitously recorded in a 42-year-old woman with asymptomatic congenital LQTS. The arrhythmia terminated spontaneously after 12 seconds and caused no symptoms. Based on the tachycardia detection parameters used in published ICD studies (Table), this patient might have received an “appropriate ICD shock” if she had an ICD.
\(\beta\)-blocker therapy, may offer better protection in LQT2/LQT3. Indeed, some data suggest that \(\beta\)-blocker failures in arrhythmia prevention are more common in LQT2 and LQT3. Nevertheless, a recent single-center study by Schwartz et al suggests that carefully selected patients with LQT3 (excluding infants with arrhythmias during the first year of life and patients with excessive bradycardia or marked QT prolongation) may be safely treated with \(\beta\)-blockers without ICD backup.

LQT2 is the second most common subtype of LQTS and in some centers is nearly as common as LQT1. Previous data show that \(\beta\)-blockers reduce the arrhythmic risk in LQT2, albeit withdisconcerting rates of breakthrough arrhythmias. We urgently need studies like that by Vincent et al to learn to what extent this “\(\beta\)-blocker failure” in LQT2 is actually due to poor compliance. As for LQT1, the cardinal question for LQT2 patients is not whether they should receive \(\beta\)-blockers, but whether they can receive \(\beta\)-blockers as their only therapy. Ultimately, the decision as to whether to implant an ICD should be weighed as rigorously as the decision not to implant it.

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**Disclosures**
None.

**References**