Case Scenario: Anesthesia-related Cardiac Arrest in a Child with Timothy Syndrome


The long QT syndrome (LQTS) is characterized by prolonged ventricular repolarization, the electrocardiographic appearance of long QT intervals, an atypical polymorphic ventricular tachycardia known as torsades de pointes (Tdp), and an increased risk for sudden cardiac death.

Patients with LQTS can suffer severe cardiac events resulting in syncope, seizures, and sudden cardiac death during times of physical and emotional stress and when exposed to certain pharmacological agents. The perioperative management of patients with LQTS has been reviewed; however, the individual risk posed by exposure to perioperative and anesthetic medications and interventions has not been quantified by prospective studies.

Case Reports

A 9-month-old male infant presented for placement of an epicardial pacemaker during general anesthesia. His medical history was significant for a suspected diagnosis of Timothy syndrome (LQT8) with prolongation of the QTc interval on his electrocardiogram, and synactyly of both hands. He was otherwise healthy. He was on oral 1.1 ml propranolol (4 mg/ml) every 8 h. He had had two prior general anesthetics for repair of syndactyly of either hand. The first anesthetic was uneventful, and the second was notable for a short period of inability to obtain noninvasive blood pressure measurements with release of the arterial tourniquet in the upper extremity. T wave alternans was noted on the surface electrocardiogram (fig. 1). This adverse event prompted admission to the hospital, and further electrocardiographic telemetric monitoring revealed significant pauses lasting 3–4.7 s. The patient was urgently scheduled for pacemaker placement.

The anesthetic for the pacemaker placement involved general endotracheal anesthesia; premedication with midazolam; intravenous induction with thiopentone, fentanyl, and pancuronium; and maintenance with sevoflurane in oxygen and nitrous oxide, with reversal of neuromuscular blockade with atropine and neostigmine. No adverse events (AE) were reported. The patient was admitted 5 months later for an epicardial generator replacement and lead placement because of decreased sensitivity of the pacemaker lead.

Intravenous induction of anesthesia with 6 mg/kg thiopentone, 2 µg/kg fentanyl, and 0.1 mg/kg pancuronium, tracheal intubation, and transition to maintenance anesthesia with inhaled isoflurane in oxygen and nitrous oxide was uneventful. T wave alternans, noticed on the surface electrocardiogram shortly after start of surgery, were treated with intravenous 1 mg/kg lidocaine and 25 mg/kg magnesium bolus with initial recovery of normal repolarization. Upon completion of the procedure, neuromuscular blockade was reversed with 0.02 mg/kg atropine and 0.07 mg/kg neostigmine, followed by local anesthetic infiltration of the wound with 1 ml/kg plain bupivacaine, 0.25%. This was followed by sudden onset of bradycardia, with loss of pacemaker capture and blood pressure that could not be recorded.

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Successful return of spontaneous circulation was achieved after 11 min of cardiopulmonary resuscitation with external chest compressions, manual ventilation, and the administration of intravenous 10 mEq/kg sodium bicarbonate in three divided doses, 250 mg calcium gluconate, and 6 mg dopamine.

Discussion

Epidemiology and Significance of LQTS
The current incidence of LQTS is considered to be 1 in 2,500 live births with variable penetrance. To date, 13 LQTS genotypes have been described, with LQTS 1, 2, and 3 comprising 90% of the cases that can be successfully genotyped (table 1). Arrhythmogenic triggers are genotype-specific and include adrenergic stimulation during exercise and emotional stress (LQT1, LQT2), loud noise or startle, or heightened emotional states; fear, fright, and exercise (LQT2); and a pause-dependent trigger mechanism during sleep or resting states (LQT3). Some patients with LQTS may develop prolongation of the QTc in response to certain drugs or electrolyte imbalances. Patients may have subclinical disease that becomes unmasked under certain conditions but returns to the subclinical state when these conditions are removed. LQT8 is especially associated with an increased risk of malignant arrhythmias during anesthesia, with case reports of arrhythmias occurring during both volatile and intravenous anesthesia. It results in a severe arrhythmia disorder caused by cardiac L-type calcium channel mutations.4

Pathophysiology of Long QT Syndrome 1, 2, 3, and Timothy Syndrome
Models of the LQT1, LQT2, and LQT3 forms of the long QT syndrome have been developed using the canine arterially perfused left ventricular wedge preparation. In these three forms of LQTS, preferential prolongation of the M cell action potential duration (APD) leads to an increase in the QT interval as well as an increase in transmural dispersion of repolarization (TDR), the latter providing the substrate for the development of spontaneous as well as stimulation-induced TdP.

LQT1. LQT1 is the most prevalent of the congenital long QT syndromes. It is caused by a loss of function of the slowly activating delayed rectifier (I_{Ks}). Inhibition of I_{Ks} using chromanol 293B has been shown to lead to uniform prolongation of APD in all three cell types in the wedge, causing little change in TDR. Although the QT interval is prolonged, TdP does not occur under these conditions, nor can it be induced. Addition of isoproterenol results in abbreviation of epicardial and endocardial APD, but the APD of the M cell either prolongs or remains the same. The dramatic increase in TDR provides the substrate for the development of spontaneous as well as stimulation-induced TdP. These results support the thesis that the problem with the long QT syndrome is not the long QT interval, but rather the increase in TDR that often accompanies the prolongation of the QT interval. These findings provide an understanding of the sensitivity of LQT1 patients, to sympathetic influences.

LQT2. LQT2 is the second most prevalent form of congenital LQTS. It is because of loss of function of the rapidly activating...
Table 1. Ionic Currents, Proteins, and Genes Associated with LQTS; Associated Triggers and Possible Therapies

<table>
<thead>
<tr>
<th>LQTS Type</th>
<th>Protein</th>
<th>Protein Type</th>
<th>Gene</th>
<th>Current</th>
<th>Prevalence of Genotyped Cases*</th>
<th>Triggers</th>
<th>Possible Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQT1</td>
<td>Kv7.1</td>
<td>K⁺ channel (I_{Ks}) subunit</td>
<td>KCNQ1</td>
<td>↓ I_{Ks}</td>
<td>50–60%</td>
<td>Exercise, Swimming, Sympathetic stimulation</td>
<td>I-blockers, Class IB sodium channel blocker, mexiletine, Pacemakers</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Implantable cardioverter-defibrillator (ICD), Left cardiac sympathetic denervation</td>
</tr>
<tr>
<td>LQT2</td>
<td>Kv11.1</td>
<td>K⁺ channel (I_{Kr}) subunit</td>
<td>KCNH2</td>
<td>↓ I_{Kr}</td>
<td>30–40%</td>
<td>Startle, Auditory stimulus, Postpartum</td>
<td>β-blockers + conjunctive therapy, Potassium administration</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pacemakers, ICD, Left cardiac sympathetic denervation</td>
</tr>
<tr>
<td>LQT3</td>
<td>Na⁺,1.5</td>
<td>Na⁺ channel (I_{Na}) subunit</td>
<td>SCN5A</td>
<td>↑ I_{Na}</td>
<td>5–10%</td>
<td>Sleep, Rest</td>
<td>Class IB sodium channel blocker, mexiletine, in conjunction with β-blockers or ICD, Pacemakers, ICD, Left cardiac sympathetic denervation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Potassium administration, Agents that block I_{Kr} current, Pacemakers, ICD</td>
</tr>
<tr>
<td>LQT4</td>
<td>Ankyrin-B</td>
<td>Membrane anchoring/adapter protein</td>
<td>ANK2</td>
<td>Loss of function</td>
<td>&lt;1%</td>
<td>Exercise, Mental stress</td>
<td>β-blockers, ICD, I-blockers, Class IB sodium channel blocker, mexiletine, Other drugs: verapamil (I_{Ca-L}), nicorandil (I_{K-ATP}), Pacemakers, Left cardiac sympathetic denervation, ICD, β-blockers + conjunctive therapy with ( I_{Ca-L} ) channel blocker, verapamil, Potassium administration</td>
</tr>
<tr>
<td>LQT5</td>
<td>minK</td>
<td>K⁺ channel (I_{Ks}) subunit</td>
<td>KCNE1</td>
<td>↓ I_{Ks}</td>
<td>Approximately 1%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>LQT6</td>
<td>miRP1</td>
<td>K⁺ channel (I_{Ks}) subunit</td>
<td>KCNE2</td>
<td>↓ I_{Ks}</td>
<td>&lt;1%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Andersen-Tawil syndrome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LQT7 (ATS1)</td>
<td>Kv2.1</td>
<td>K⁺ channel (I_{Ks}) subunits</td>
<td>KCNJ2</td>
<td>↓ I_{K}</td>
<td>50% of Andersen-Tawil cases</td>
<td>Hypokalemia</td>
<td>Potassium Supplementation, β-blockers, ( I_{Ca-L} ) channel blocker, verapamil, Left cardiac sympathetic denervation, ICD</td>
</tr>
<tr>
<td>Timothy syndrome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LQT8</td>
<td>Cav1.2</td>
<td>L type Ca²⁺ channel (I_{Ca,L}) subunit</td>
<td>CACNA1C</td>
<td>↑ I_{Ca,L}</td>
<td>&lt;1% of Timothy syndrome cases</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>LQT9</td>
<td>Caveolin-3</td>
<td>Cavaels coat protein</td>
<td>CAV3</td>
<td>↑ I_{Ks}</td>
<td>&lt;1%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>LQT10</td>
<td>Na⁺,β4</td>
<td>Na⁺ channel β subunit</td>
<td>SCN4B</td>
<td>↑ I_{Na}</td>
<td>Rare</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>LQT11</td>
<td>Yotiao</td>
<td>Na⁺-K⁺ channel 9/adapter protein</td>
<td>AKAP9</td>
<td>Loss of function</td>
<td>Rare</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>LQT12</td>
<td>α-1-syntrophin</td>
<td>Membrane scaffold</td>
<td>SNTA1</td>
<td>↑ I_{Ks}</td>
<td>Rare</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>JLN1</td>
<td>Kv7.1</td>
<td>K⁺ channel (I_{Ks}) subunit</td>
<td>KCNQ1</td>
<td>↓ I_{Ks}</td>
<td>80% of Jervell and Lange-Nielsen cases</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>JLN2</td>
<td>MinK</td>
<td>K⁺ channel (I_{Ks}) subunit</td>
<td>KCNE1</td>
<td>↓ I_{Ks}</td>
<td>20%</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Arrows in Current column indicate increased/gain of function (up arrow) or decreased/loss of function (down arrow) current relative to normal function.

* For LQT1–LQT6, prevalence values are relative to all LQTS cases that can be genotyped; for named subtypes, prevalence values are relative to all cases within that subtype.

ICD = implantable cardioverter defibrillator; LQTS = long QT syndrome.
delayed rectifier (I_{Kr}). I_{Kr} inhibition is also responsible for most cases of acquired LQTS. In the wedge, inhibition of I_{Kr} with d-sotalol produces a preferential prolongation of the M cells, resulting in accentuation of TDR and spontaneous as well as stimulation-induced TdP. When I_{Kr} block is combined with hypokalemia, bifurcated T waves develop in the wedge preparation, similar to those seen in patients with LQT2. Isoproterenol further exaggerates TDR and leads to an increased incidence of TdP in this model, but only transiently.

**LQT3.** LQT3 has a much lower prevalence. It is encountered in approximately 10% of genotyped probands and is caused by a gain of function of late sodium current (late I_{Na}). Augmentation of late I_{Na} using the sea anemone toxin ATX-II produces a preferential prolongation of the M cell action potential in the wedge, resulting in a marked increase in TDR and development of TdP. Because epicardial APD is also significantly prolonged, there is delay in the onset of the T wave in the wedge, as observed in the clinical syndrome. Under these conditions, β-adrenergic stimulation abbreviates APD of all cell types, reducing TDR and suppressing TdP.

In LQT1, isoproterenol produces an increase in TDR that is most prominent during the first 2 min, but which persists, although to a lesser extent, during steady state. TdP incidence is enhanced during the initial period as well as during steady state. In LQT2, isoproterenol produces only a transient increase in TDR that persists for less than 2 min. TdP incidence is therefore enhanced only for a brief period of time. These differences in time-course may explain the important differences in autonomic activity and other gene-specific triggers that contribute to events in patients with different LQTS genotypes.

Although β-blockers are considered first-line therapy in patients with LQT1, there are limited data of their benefit in LQT3. Preliminary data suggest LQT3 patients might benefit from Na⁺ channel blockers, such as mexiletine, flecainide, and ranoalzine. Experimental data have shown that mexiletine reduces transmural dispersion and prevents TdP in LQT3 as well as LQT1 and LQT2, suggesting that agents that block the late sodium current may be effective in significantly abbreviating QTc in LQT3 patients.

**LQT8.** Timothy syndrome, also known as LQT8, is a multisystem disease caused by mutations in the calcium channel Ca_{1.2} encoded by the CACNA1C. Because the calcium channel Ca_{1.2} is present in many tissues, patients with Timothy syndrome have many clinical manifestations, including congenital heart disease, autism, syndactyly, and immune deficiency. Mutations in nine other genes have been associated with LQTS in recent years. These genetic variations, which include structural proteins as well as other ion channel proteins, are relatively rare.

Gene-specific electrocardiographic patterns have been identified and triggers for cardiac events have been shown to be gene-specific, but with considerable overlap. LQT1 patients experience most of the events during physical activity as opposed to LQT3 patients, who present the majority of cardiac events at rest or during sleep. Auditory stimuli and arousal have been identified as relatively specific triggers for LQT2 patients, whereas swimming has been identified as a predisposing setting for cardiac events in LQT1 patients.

**The Electrocardiographic Phenotypes: Typical ST-T Wave Patterns in LQT1, LQT2, and LQT3**

Zhang identified typical ST-T wave patterns, four in LQT1, four in LQT2, and two in LQT3 patients in 88% of patients studied with a definite genotype. The QT interval ranged from borderline to definitely prolonged in all patients (figure 2).

**Drug-induced QTc Prolongation**

Drug-induced QTc prolongation is because of prolongation of the I_{Kr} current via drug effect on the HERG (KCNH2 or LQT2 I_{Kr}) channel. Therefore, the electrocardiographic manifestations of drug-induced QTc prolongation mimic the electrocardiographic findings of LQT2.

**Risk Stratification in LQTS**

A risk-stratification scheme based on genotype has been proposed by several authors. QT interval, genotype, and gender were significantly associated with events. A QTc interval more than 500 ms in LQT2 or LQT3 forecasts a worse prognosis. The same authors reported that the response to β-blockers is also genotype-specific, with LQT1 patients showing greater protection in response to β-blockers than LQT2 or LQT3 patients. A QTc duration of more than 500 ms and a prior history of syncope identify high risk of sudden cardiac death in boys, and a prior history of syncope is the only significant risk factor in girls.

**Arrhythmogenic Mechanism in LQTS**

The underlying condition predisposing to malignant arrhythmias is a defect in ventricular repolarization (fig. 3). Accentuation of spatial dispersion of refractoriness within the ventricular myocardium, secondary to exaggerated transmural or transseptal dispersion of repolarization, has been identified as the principal arrhythmogenic substrate in both acquired and congenital LQTS. This exaggerated intrinsic heterogeneity together with early and delayed afterdepolarization (EAD and DAD)-induced triggered activity, both caused by reduction in net repolarizing current, underlie the substrate and trigger for the development of Tdp observed under LQTS conditions. Preferential prolongation of the M cell APD leads to an increase in the QT interval as well as an increase in TDR (fig. 4), which contributes to the development of spontaneous as well as stimulation-induced TdP. The spatial dispersion of repolarization is further exaggerated by sympathetic influences in LQT1 and LQT2, accounting for the majority of events during physical activity.
for the great sensitivity of patients with these genotypes to adrenergic stimuli. Dispersion of repolarization is a quality that is difficult to quantify even by specialists, and might be overly simplified as a concept. Electrophysiologists believe that there are micro and macro environments locally that precipitate the reentrant arrhythmias. Our approach to patients with LQTS undergoing anesthesia is to discuss every patient with the electrophysiologist caring for that patient and generate an individualized anesthesia care plan, which includes perioperative medications and infusions that are safe in LQTS or will be necessary in the management of LQTS related arrhythmias.

**Management of Patients with LQTS**

In LQTS patients, the first line of therapy is β-blocker therapy, even though a number of patients will have an arrhythmia-related event or suffer sudden cardiac death despite this therapy. Continuation of prescribed antiarrhythmics, especially β-blockers, is encouraged in patients with LQTS unless contraindications exist. Additional management modalities are typically based on LQTS genotype and clinical events, and might include class IB sodium channel blocker, e.g., mexiletine, other drugs, e.g., verapamil, nicotine, potassium supplementation, pacemakers, implantable cardioverter-defibrillators, or left cardiac sympathetic denervation (table 1).

**Anesthesia Risk in LQTS**

The myocardium is richly equipped with various ion channels, which are responsible for regulating the excitability and, secondarily, the contractility of the heart. The effect of volatile anesthetics on the cardiac ion channels and currents and the most important side effects have been summarized in a review by Huneke (table 2). Several studies confirm these findings in cell and animal models of LQTS. In the heart, I_K is important in initiating repolarization and therefore plays a key role in controlling the duration of cardiac action potentials. I_K is composed of two components: a rapidly activating component, I_Kr, and a slowly activating component, I_Ks. Propofol is a selective blocker of I_Ks. Both I_Kr and I_Ks play a crucial role in cardiac repolarization. Propofol inhibits both the I_Ca and I_Ks currents. The actual values of changes in APD would represent the sum of the inhibitory effects of propofol on I_Kr and I_Ks. Anesthetic drugs seem to be genotype-specific in terms of the effects on QT prolongation in an animal model of impaired repolarization reserve. Drugs that selectively block I_K prolong the QT interval only in an LQT2 rabbit model and...
not in LQT1 rabbits, which lack \( I_{Ks} \). Drugs that block \( I_{Ks} \) prolong the QT in both LQT1 and LQT2 rabbits because of their reduced repolarization reserve. However, both LQT1 and LQT2 models developed polymorphic ventricular tachycardia under isoflurane and propofol, indicating the heightened risk of arrhythmia when using \( I_{Ks} \) blockers in patients with a reduced repolarization reserve because of decreased \( I_{Kr} \) currents. Therefore, genotyping of LQT patients could allow genotype-specific anesthetic plans that would improve perioperative safety for patients. Interestingly, ketamine does not alter cardiac repolarizing currents or the QT interval in the LQT rabbit model. Although sevoflurane significantly prolonged the QTc in normal children (American Society of Anesthesiologists I-II) in comparison with propofol, neither compound produced any change in the Tp-e interval or TDR. This was corroborated by a study on healthy children in whom propofol did not increase TDR at clinically relevant doses. The use of volatile anesthesia in patients with LQTS is an unresolved clinical issue. Among the barbiturates, thiopental sodium prolongs QTc in healthy premedicated adults and children. Though QTc is prolonged by pentobarbital, TDR is reduced, reducing arrhythmogenicity. Of the benzodiazepines, midazolam has no effect on QTc.

Succinylcholine and pancuronium are known to prolong the QTc, whereas vecuronium and atracurium do not. The use of anticholinesterase–anticholinergic combination to achieve reversal of neuromuscular blockade might place patients at a higher risk of arrhythmias. The anticholinergics prolong QTc in healthy volunteers and adults. Anticholinesterases by themselves could induce bradycardia and pause dependent arrhythmias in susceptible subtypes.

Other factors that could affect the QTc interval could do so intrinsically, or by increasing sympathetic tone (e.g., hypoxia, hypercarbia, light anesthesia, tracheal intubation, or emergence phenomena). Hypothermia and hypothyroidism prolong QTc interval. Changes in electrolyte balance such as hypokalemia, hypomagnesemia, and hypocalcemia could precipitate arrhythmias and should be aggressively treated. Agents or maneuvers that produce bradycardia should be avoided in LQT3 patients.

There is a positive correlation between the cardiotoxic potency of local anesthetics, lipid solubility, and nerve-blocking potency. Local anesthetic agents exert their effects both therapeutic and toxic through voltage-gated sodium channels in the myocardium and nervous system. Bupivacaine binds more rapidly and longer than lidocaine to cardiac NaV channels. There is stereospecificity in the cardiotoxicity of local anesthetics with R-isomers binding cardiac NaV channels more avidly than S-isomers (levobupivacaine and ropivacaine). Local anesthetics inhibit cardiac conduction with the same rank order of potency as for nerve block (prilocaine \( \leq \) lidocaine \( \leq \) mepivacaine \( \leq \) ropivacaine \( \leq \) levobupivacaine \( \leq \) racemic bupivacaine \( \leq \) R (+) bupivacaine \( \leq \) etidocaine \( \leq \) tetracaine) and produce dose-dependent myocardial depression. Bupivacaine-induced tachyarrhythmias have been concluded to be because of dispersion of conduction and dispersion of refractoriness of ventricular myocardium predisposing to reentrant ventricular arrhythmias. Hyperkalemia might enhance the cardiotoxicity of local anesthetics; whereas adenosine triphosphate-sensitive potassium channel openers, \( \beta \)-adrenergic agonists, and
Table 2. Summary of the Actions of Volatile Anesthetics on Various Ion Currents in the Heart and the Most Important Side Effects of the Drugs

<table>
<thead>
<tr>
<th>Target</th>
<th>Effect</th>
<th>Anesthetic Agent</th>
<th>Cardiac Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-type Ca(^{2+}) current</td>
<td>Inhibition</td>
<td>Halothane, sevoflurane, isoflurane</td>
<td>Reduced contractility</td>
</tr>
<tr>
<td>β-adrenergic regulation of the</td>
<td>Complex</td>
<td>Halothane</td>
<td>Enhanced proarrhythmically</td>
</tr>
<tr>
<td>L-type Ca(^{2+}) current</td>
<td>interference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voltage-dependent transient</td>
<td>Inhibition</td>
<td>Halothane, isoflurane</td>
<td>Shortened APD, APD mismatch within the heart</td>
</tr>
<tr>
<td>outward K(^{+}) current</td>
<td></td>
<td></td>
<td>Delayed repolarization, mismatch of APD</td>
</tr>
<tr>
<td>Voltage-dependent sustained</td>
<td>Inhibition</td>
<td>Halothane, isoflurane, sevoflurane</td>
<td></td>
</tr>
<tr>
<td>outward K(^{+}) current</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATP-dependent K(^{+}) current</td>
<td>Enhancement</td>
<td>Isoflurane, sevoflurane</td>
<td>Myocardial preconditioning</td>
</tr>
<tr>
<td>Fast Na(^{+}) current</td>
<td>Inhibition</td>
<td>Halothane, isoflurane, sevoflurane</td>
<td>Slowed conduction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Induction of tachyarrhythmias</td>
</tr>
</tbody>
</table>


APD = action-potential duration; ATP = adenosine triphosphate.

Ca\(^{2+}\) channel blockers may have value in treating bupivacaine cardiotoxicity.

**The Risk of Perioperative Adverse Events**

In an attempt to describe perioperative risk factors in patients with LQTS, a retrospective cohort study of children with LQTS undergoing general anesthesia for noncardiac surgery or device was conducted at The Children’s Hospital of Philadelphia, Philadelphia, Pennsylvania. Seventy six patients with congenital LQTS were identified who had a total of 114 anesthetic encounters. Of the 114 anesthetic encounters, there were three AE, two definite and one probable AE for an incidence of 2.6%. The events occurred in boys (aged 11, 13, 15 yr), while undergoing noncardiac surgery during volatile general anesthesia. All were receiving β-blocker therapy preoperatively. The AE occurred in close proximity to the administration of reversal agents (anticholinesterase–anticholinergic combinations) and the antiepileptic ondansetron. The events occurred during emergence from anesthesia, and exclusively in the group who received both reversal agents and ondansetron. All were treated successfully with short-term antiarrhythmic drug therapy and discharged the following morning. We concluded that there is an increased risk of AE during periods of enhanced sympathetic activity, especially emergence, which seems to be further enhanced if agents that are known either to prolong the corrected QT interval (QTc) or the TDR or increase the incidence of tachycardia are administered at this time. Restriction of medications that adversely affect ion channels, and intense vigilance and monitoring during this time and in the postoperative phase, might help prevent occurrence or progression of AE. Our ongoing research involves genetic subtyping, monitoring of electrocardiographic changes in response to exposure to commonly used drugs during anesthesia, and correlation of AE with specific anesthetic drugs and genetic subtypes in an effort to increase understanding of anesthesia related risks in children with congenital LQTS.

**The Risk of Adverse Events in Patients with LQTS in Relationship to Perioperative Medications**

Several commonly used drugs in the perioperative period have been shown to increase the risk of ventricular arrhythmias. Prolongation of the QT interval is the primary reason for withdrawal or restriction of drugs during the past 10 yr. Of the perioperative medications, antibiotics, gastric prokinetics, antiemetics, neuromuscular blockers, and reversal agents, antiarrhythmics, are all associated with the potential to prolong the QTc interval. The risks are because of intrinsic blockade of K+ efflux (esp I\(_K_s\)) drug- drug interactions, coadministration of concomitant medications that prolong QTc or that inhibit metabolism resulting in toxic levels of drug, and medications that affect electrolyte balance especially extracellular potassium levels. Patient factors increase this risk in the presence of “cardiac ion channelopathies” with reduced repolarization reserve, e.g., LQTS, female sex, electrolyte imbalance (hypokalemia/hypomagnesemia), bradyarrhythmia relative to age, symptomatic arrhythmias, renal/hepatic dysfunction, and structural heart disease.

QT prolongation has become a surrogate marker for arrhythmogenicity and is used in research and by regulatory authorities. Risk is associated with an absolute QTc of more than 500 ms, or change in QT of 30–60 ms. The FDA has issued guidance for industry for QT interval prolongation and proarrhythmic potential of nonantiarrhythmic drugs. Agents that prolong the mean QT/QTc in a study group by more than 5ms are considered to have substantial proarrhythmic potential per the “thorough QT/QTc study” protocol. It is not just the prolongation of QTc interval but also the occurrence of morphologic T wave changes and increase in TDR that seem to predispose to arrhythmogenicity.

Of the antiemetics commonly used, all 5HT3 antagonists and all first-generation and some second-generation antihistaminics and the butyrophenone derivatives are associated with QTc prolongation at clinically used doses. In an *in vitro*...
Table 3. Anesthetic Management of Patients with LQTS

1. Preoperative Assessment
   - 12-lead ECG; Calculation of QTc at baseline
   - Adequacy of electrophysiology/antiarrhythmic therapy, e.g., adequate heart rate control on β-blockade in LQT1
   - Device: Pacemaker/ICD interrogation to determine settings and function
   - Electrophysiology (EP) consult, especially in patients with:
     - History of aborted sudden cardiac death
     - History of syncope
     - Recently diagnosed LQTS
     - Significant pauses on the ECG (might require pacing)
     - Emergent surgery
   - Recommendations for prophylaxis or emergent treatment of LQTS related arrhythmias.
   - Maintenance of normal acid-base and electrolyte balance, especially K+ and Mg+
   - Review of agents that prolong the QTc*

2. Premedication/Preoperative Management
   - Continue therapy, especially β-blockers
   - Electrophysiology recommendation for drug therapy if patient is newly diagnosed and not on therapy
   - Perioperative anxiolysis, e.g., midazolam probably safe
   - Maintain adequate preoperative hydration

3. Considerations of Anesthesia Care
   - Monitoring
     - Standard ASA monitoring prior to induction of anesthesia (minimum of 3-lead ECG)
     - Consideration for invasive vascular monitoring in case of extensive surgery, fluid and electrolyte shifts, or variations of autonomic tone (arterial ± central venous monitoring)
     - Extreme vigilance at critical time-points of enhanced stress or changes in autonomic tone, e.g., induction, intubation, emergence, and during surgical stimulation irrespective of type of anesthetic used
   - Minimization of sympathetic stimulation, and avoidance of autonomic imbalance
     - Consider topical local anesthetic (lidocaine) to vocal cords, esmolol bolus for laryngoscopy/endotracheal intubation if heart rate is poorly controlled
     - Ensure adequate analgesia perioperatively
     - Regional anesthesia when appropriate (avoid epinephrine in local anesthetic solutions)
   - Extubation under deep anesthesia or with esmolol prophylaxis if possible
   - Maintenance of normal homeostasis: normothermia, normoxia, normocapnia, normoglycemia
   - Avoidance of bradycardia in pause-induced states of TdP, e.g., LQT3 patients
   - Induction/maintenance of anesthesia
     - Anesthetic agents: Caution with use of volatile anesthesia or total intravenous anesthesia
     - Intravenous induction with thiopental or propofol probably safe, consider total intravenous anesthesia if appropriate
   - Neuromuscular blockade
     - Vecuronium/Cis atracurium probably safe if necessary for surgery
     - Avoidance of reversal of neuromuscular blockade, i.e., anticholinesterase/anticholinergic agents if possible.
   - Ventilation strategy
     - Maintain normocapnia and normal acid base status (be aware of the effect of hyperventilation on serum K+ concentration)
     - Avoid Valsalva maneuvers/sustained high intrathoracic pressures, because these increase the QTc
     - Optimize ventilation strategy, i.e., avoid high peak and end expiratory pressures, prolonged inspiratory times/pauses, and low or reversed I:E ratios.
   - Prophylaxis and treatment of postoperative nausea and vomiting
     - Avoidance of conditions that increase PONV: ensure adequate hydration, regional/nerve block techniques to minimize narcotics, avoid hypotension, propofol-based TIVA in patients at high risk of PONV
     - Choice of agents that have minimal effect on QT interval for PONV prophylaxis: of note, all agents of the 5HT3 antagonist class can prolong QTc, as do antihistaminics and butyrophenones.
     - Cautious use of such agents and avoidance of using two agents that can prolong QTc is important. Dexamethasone does not prolong QTc, and could be a safe antiemetic.
   - (continued)
electrophysiology model, the 5HT3 antagonists cause blockage of Na\(^{2+}\) channels in the inactive state, especially with high heart rates or when depolarized or ischemic myocardium is present. Electrocardiographic changes occur as a class effect in a dose-dependent phenomenon. Dolasetron is associated with prolongation of PR, QRS, and QTc, and ondansetron causes prolongation of the JT and QTc intervals.\(^{34}\) QTc prolongation is about 15 ms and occurs 0–4 h following drug, and is reversible in 24 h. Though not yet licensed for pediatric use, palonosetron might be the exception in not prolonging the QTc interval. Dexamethasone, dimenhydrinate, and metoclopramide do not prolong the QTc and might be safe in children with LQTS. These observations support the judicious and careful choice of antiemetics.

**Knowledge Gap**

Can we minimize anesthesia-related risk? There seems to be an increase in the observed incidence of AE during periods of enhanced sympathetic activity (LQT1), especially emergence from anesthesia conducted with volatile anesthetics in association with the use of anticholinesterase–anticholinergic drug combinations and the antiemetic ondansetron in children with congenital LQTS. This risk seems to be further enhanced if agents that are known to either prolong QTc or TDR or increase the incidence of tachycardia are administered at times of sympathetic stimulation. Avoidance of offending pharmacologic agents and intense vigilance and monitoring during this time and in the postoperative phase could help prevent occurrence or progression of AE. The anesthetic management of children with LQTS has been reviewed excellently in an article by Booker et al. (table 3). A list of drugs that are known to prolong the QTc interval is available and regularly updated.\(^1\) Preoperative assessment should include assessment of medications used for the treatment of LQTS/arrhythmias and other conditions, especially psychotropic medications. Drug interactions and cumulative toxicity should be considered in the formulation of a safe anesthetic plan.

The occurrence of TdP in children with LQTS often necessitates early use of magnesium in a slight modification of the ACLS protocol for the management of pulseless ventricular tachycardia or fibrillation.\(^{35}\) Also, the avoidance of bradycardia is judicious in patients with LQT2 and LQT3 related to pause-dependent arrhythmias. We speculate that genetic subtyping of patients with LQTS could help formulate individualized anesthetic plans for these high-risk patients. It is likely that patients with LQTS with lethal arrhythmias that can be triggered by sympathetic stimuli, anxiety, fright, and loud noise could be at a higher risk of arrhythmias at the time of emergence when all these factors occur in concert. In addition, drugs that are commonly used during emergence may act in synergy with these triggers and further prolong the QTc to precipitate a ventricular arrhythmia. It is also important to recognize that some of the drugs use to treat ventricular arrhythmia, especially the type III antiarrhythmic amiodarone and the type I antiarrhythmic quinidine, further prolong the QTc and worsen the existing arrhythmia. Onset of TdP in children with LQTS often necessitates early use of intravenous magnesium and electrical cardioversion/defibrillation.\(^{35}\)

**Management of TdP**

With onset of TdP, magnesium should be administered intravenously at a bolus dose of 30 mg/kg during 2 or 3 min, followed by an infusion of 2–4 mg/h. If initial dosing and infusion do not suppress the episodes of TdP, the magnesium bolus should be repeated after 15 min. In the event of sustained TdP or TdP that degenerates into ventricular fibrillation, direct-current cardioversion or defibrillation will have to be performed. In some forms of LQTS, medical therapy includes lidocaine. Early use of 1 or 2 mg/kg boluses of lidocaine either before magnesium or with magnesium might prevent progression of the arrhythmia. Occasionally, the use of an isoproterenol infusion or transvenous pacing at 90–110 beat/min increases the patient’s heart rate and prevents pause-induced TdP.\(^{35}\)

It is especially important to recognize that antiarrhythmics can prolong the QTc interval in patients with LQTS, and it is best to consult early with electrophysiologists during the management of arrhythmias in this group of patients.

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References


35. Nathan et al. Anesthetic Implications in Long QT Syndrome