Review

Long QT syndrome and anaesthesia

N. A. Wisely, E. A. Shipton

University of Otago, Department of Anaesthesia, Christchurch School of Medicine and Health Sciences, Christchurch, New Zealand

Summary
The long QT syndrome is a disorder of myocardial electrical conduction that leaves the heart vulnerable to the ventricular tachydysrhythmia torsade de pointes. Clinically, this results in syncope or sudden death. The long QT syndrome may be congenital, if caused by abnormal myocardial potassium or sodium ion channels, or acquired, if due to drugs, electrolyte abnormalities or metabolic conditions. Triggers for the development of torsade de pointes include both anaesthesia and surgery. Some anaesthetic agents prolong the QT interval. The condition is reviewed and suggestions are made for the anaesthetic management of affected patients.

Keywords: ANAESTHESIA, GENERAL; HEART DISEASES, arrhythmia, long QT syndrome.

Introduction
Long QT syndrome (LQTS) is a disorder affecting myocardial repolarization and results in a predisposition to the ventricular tachydysrhythmia, torsade de pointes. Torsade de pointes usually reverts spontaneously to sinus rhythm causing syncope, but may degenerate to ventricular fibrillation and sudden death. A marker of the condition is an abnormally long QT interval on the electrocardiogram (ECG), although this may be borderline to normal in 40% of affected persons. Typically, the trigger for development of torsade de pointes is emotional or physical stress, but it may occur at any time.

The QT interval is measured from the beginning of the Q wave to the end of the T wave on the surface ECG. It represents the time taken for ventricular depolarization and repolarization. To control for heart rate, the QTc is calculated using Bazett’s equation [1]:

$$QTc = \frac{QT}{\sqrt{RR}}$$

where QT is the time from the beginning of the Q wave to the end of the T wave (ms) and RR is the cycle time (s). QTc is prolonged if \(>440\) ms.

LQTS can be divided into congenital or acquired forms (depending upon the aetiology). Congenital LQTS is caused by mutations in genes coding for myocardial potassium or sodium channels. Drugs, electrolyte abnormalities or metabolic conditions cause acquired LQTS.

Myocardial depolarization occurs when sodium and calcium ions rapidly enter the myocardial cells. This is offset during repolarization when potassium ions move out of the cells and return the membrane potential to normal. Repolarization can be abnormally prolonged by increased sodium ion inflow or reduced potassium ion outflow. In congenital LQTS, gene mutations code for abnormal myocardial potassium or sodium channels, which allow a surplus of intracellular positive ions to prolong repolarization and the QT interval. Acquired causes usually reduce outward potassium currents, increasing repolarization as well. As myocardial repolarization is prolonged, calcium channel inactivation is delayed and this may result in late calcium ion inflow and the development of early after-depolarizations. If the early after-depolarizations reach threshold amplitude, torsade de pointes may be triggered.
History
The first report of the LQTS was probably in 1856, when Meissner [2] reported the sudden death of a deaf girl while being reprimanded at school. In 1939, Latham and Munro [3] described a family with a consanguineous marriage in which all their five children were deaf and suffered from what was described as ‘epileptic spells’. One had also suffered a sudden death. These reports preceded the advent of electrocardiography. It was left to Jervell and Lange-Nielsen [4] to provide the first complete description (in 1957) of a syndrome of congenital deaf-mutism and functional heart disease (with prolongation of the QT interval and sudden death). The inheritance is autosomal-recessive. Romano and colleagues [5] (in 1963) and Ward [6] (in 1964) independently described a similar syndrome to the Jervell-Lange-Nielsen syndrome yet without deafness. Subsequent investigations confirmed the Romano-Ward syndrome to show autosomal-dominant inheritance. In 1966, Yanowitz and colleagues [7] suggested a cause of the LQTS as an imbalance of cardiac sympathetic innervation with a report that the QT interval could be prolonged by right stellactomy or left stellate ganglion stimulation. In 1971, Moss and McDonald [8] successfully treated a patient with LQTS, refractory to anti-dysrhythmic therapy, by performing a left cardiac sympathectomy. In 1985, Moss and colleagues [9] proposed that myocardial potassium repolarizing currents may be abnormal in patients with LQTS. The next breakthrough came in 1991 when Keating and colleagues [10] demonstrated in one family the linkage of LQTS to the Harvey ras-1 gene locus on the short arm of chromosome 11. The genetics of LQTS have recently become clearer. Five genes coding for myocardial membrane potassium and sodium channels have been identified and the effects of mutations in these genes are better understood [11].

Congenital LQTS
Congenital LQTS is an important and previously underestimated cause of sudden death in young people [12]. Symptoms usually develop during childhood and early adulthood [13]. Syncope occurring under emotional or physical stress is usually the main symptom, yet sudden death may be the first presentation [13]. Other symptoms include palpitations and seizures. The frequency and severity of the symptoms vary greatly and up to 39% of sufferers may be asymptomatic [14]. Episodes of syncope usually last for <1 min and there are few residual effects. Syncope in children may often be mistaken for epilepsy as there is an absence of organic heart disease [15]. Symptoms may occur within a few days of birth or not until middle age [16]. LQTS is present in 1:5000 individuals [17]. Risk factors for death include: female sex; congenital deafness; a history of syncope; a history of cardiac arrest; and QTc > 0.5 s. The prognosis is very poor in untreated patients and the cumulative mortality rate may reach 80%. After the first syncopal event, the mortality rate is 20% within 1 yr. This can be reduced to 6% with treatment using β-adrenoceptor blocking agents.

Six genotypes (LQT1-6) of the LQTS have been identified (Table 1). Only five genes have so far been identified. They all result in defects in cardiac ion channel structure and function. The most common phenotype is LQT1 (60%) [18]. There is a strong association with stress-induced syncope [19]. Two genes are implicated. KvLQT1 (locus 11p15.5) codes for the main α-subunit of the potassium ion channel responsible for the slow activating potassium-delayed rectifier current (IKs) and KCNE1 (locus 21q22.1-p22) codes for the β-subunit of the IKs channel [20]. The loss of function of this channel results in prolongation of the action potential and in delayed repolarization. LQT2 is the next most common phenotype (30%) with arousal (noise) triggered symptoms being a feature [21]. Again, two genes have been identified. The HERG gene (locus 7q35-q36), or human ether-ago-go gene, codes for a major subunit of the potassium ion channel responsible for the rapidly activating potassium-delayed rectifying current (IKr) and gene KCNE2 (locus 21q11.1) codes for minor subunit of the IKr channel [22].

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Phenotype</th>
<th>Frequency</th>
<th>Chromosome/gene</th>
<th>Ion channel affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQT1</td>
<td>LQT1</td>
<td>++ +</td>
<td>11-KvLQT1</td>
<td>K⁺ (IKs)</td>
</tr>
<tr>
<td>LQT2</td>
<td>LQT2</td>
<td>+ +</td>
<td>7-HERG</td>
<td>K⁺ (IKs)</td>
</tr>
<tr>
<td>LQT3</td>
<td>LQT3</td>
<td>+</td>
<td>3-SCN5A</td>
<td>Na⁺</td>
</tr>
<tr>
<td>LQT4</td>
<td>LQT4</td>
<td>−</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>LQT5</td>
<td>LQT1</td>
<td>−</td>
<td>21-KCNE1</td>
<td>K⁺ (IKs)</td>
</tr>
<tr>
<td>LQT6</td>
<td>LQT2</td>
<td>−</td>
<td>21-KCNE2</td>
<td>K⁺ (IKs)</td>
</tr>
</tbody>
</table>

See the text for abbreviations.

The loss of function of this channel results in marked decrease in the repolarization current and prolongation of the action potential. In LQT3 (3%), sleep-related symptoms are more common, and it appears that torsade de pointes is more likely to deteriorate to ventricular fibrillation. The responsible gene is SCN5A (locus 3p21–p23). It codes for a cardiac sodium channel and abnormalities interfere with channel inactivation. This causes a prolonged inward current during the early phase of the action potential, thereby delaying myocardial repolarization [23]. A small number of patients may have more than one gene affected [24]. Of those who clinically have LQTS, 50% will have no currently identifiable gene mutations [25].

**Acquired LQTS**

Acquired LQTS is caused by drugs, electrolyte abnormalities, neurological and cardiac conditions, or by metabolic conditions. Some of these are listed in Table 2. Recent evidence suggests that individuals with acquired LQTS have an underlying tendency to dysrhythmias. The QT is often longer than normal before exposure to a drug [26]. Most of the causes of acquired LQTS block the rapid and slow components of the potassium-delayed rectifying current, thereby prolonging myocardial repolarization.

Acquired LQTS is pause-dependent and torsade de pointes is triggered at low heart rates. The slower the heart rate, the longer repolarization (QT interval) will take. The actual QT interval is more useful in predicting torsade de pointes than the corrected QT. A giant QT interval in acquired bradydysrhythmias is an indication for urgent cardiac pacing [27].

The risk of developing torsade de pointes is increased depending on the number of additional risk factors present. These include [18]: female sex; hypokalaemia; hypomagnesaemia; bradycardia; congenital LQTS; and high concentrations of drug (especially in elderly patients). Drug interactions are important, e.g. cisapride and erythromycin have pharmacokinetic and pharmacodynamic interactions causing a greatly increased effect on QTc. Patients may be exposed to many of the causes of acquired LQTS in the perioperative period.

**Treatment**

Owing to the lethal nature of congenital LQTS and the difficulty of predicting future symptoms, there is a strong argument for prophylactic treatment of all affected people. Therapy with β-adrenoceptor blocking drugs, at the maximum tolerated dose, has become the mainstay of treatment [18]; the relative risk of syncope or cardiac arrest is 0.41 with such therapy [9]. Left cardiac sympathetic denervation is an effective treatment of patients who are not controlled by therapy with β-adrenoceptor blocking drugs alone or those who are intolerant [28]. Permanent cardiac pacing is also effective in reducing symptoms, especially with a profound bradycardia produced by β-adrenergic blockade, with atrioventricular block, or with clearly documented ventricular tachydysrhythmias preceded by a sinus pause bradycardia [29]. A heart rate of around 80 beats min⁻¹ (to reduce QT interval) is usually selected and pause prevention algorithms have been recommended [30]. Implantable defibrillators may be considered for high-risk patients, especially for those with a QTc interval >0.60 s, those who are symptomatic despite therapy (with β-adrenoceptor blocking drugs and left cardiac sympathetic denervation), and for those who have survived a cardiac arrest.

Treatment of acquired LQTS requires correction of any underlying cause, such as removal or reduction of any responsible drug and the control of potassium, magnesium and calcium ion concentrations to

<table>
<thead>
<tr>
<th>Antidysrhythmic drugs</th>
<th>Quinidine, procainamide, disopyramide, sotalol, amiodarone</th>
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<tbody>
<tr>
<td>Histamine receptor antagonists</td>
<td>Terfenadine, astemizole</td>
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<tr>
<td>Antibiotics</td>
<td>Erythromycin, clindamycin, imidazole, ampicillin</td>
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<tr>
<td>Drugs acting on serotonin receptors</td>
<td>Ketanserin, fluoxetine</td>
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<tr>
<td>Antipsychotic drugs</td>
<td>Tetra- and tricyclic antidepressants, haloperidol, phenothiazines, lithium, risperidone</td>
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<tr>
<td>Diuretics</td>
<td>Indapamide</td>
</tr>
<tr>
<td>Citrate</td>
<td>Massive blood transfusion</td>
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<tr>
<td>Gastrointestinal drugs</td>
<td>Cisapride</td>
</tr>
<tr>
<td>Metabolic abnormalities</td>
<td>Hypokalaemia, hypomagnesaemia, hypocalcaemia</td>
</tr>
<tr>
<td>Bradydysrhythmias</td>
<td>Complete atrioventricular block</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Myocardial ischaemia, acute carditis, acute cor pulmonale, mitral valve prolapse</td>
</tr>
<tr>
<td>Starvation</td>
<td>Anorexia nervosa, gastroparesis, liquid protein diet</td>
</tr>
<tr>
<td>Nervous system injury</td>
<td>Subarachnoid haemorrhage, head injury, right-sided radical neck surgery</td>
</tr>
<tr>
<td>Others</td>
<td>Hypothermia, pituitary insufficiency</td>
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</tbody>
</table>

keep their plasma concentrations at the upper limits of normal. Measures to increase the heart rate (and decrease the QT interval), such as an infusion of isoproterenol (isoprenaline) or cardiac pacing, are effective in controlling recurrent dysrhythmias.

Sustained torsade de pointes, or torsade de pointes that has degenerated to ventricular fibrillation, requires an urgent direct current (DC) shock for termination. Recurrent torsade de pointes can be managed by suppressing the early after-depolarizations and accelerating the basic heart rate. Magnesium is useful in suppressing the early after-depolarizations [31]. Magnesium (2 g, 20 mL 10% solution) can be given intravenously (i.v.) over 2 min. This can be repeated twice at intervals of 5–15 min. The plasma potassium ion concentration should be increased to 4.5 mmol L\(^{-1}\). A reduction in repolarization time, and therefore QT interval, can be achieved by acceleration of the basic heart rate by transvenous cardiac pacing. Rates of 100–140 beats min\(^{-1}\) may be needed to prevent torsade de pointes.

**Anaesthetic considerations**

Patients with LQTS who present for anaesthesia and surgery are at risk of developing malignant ventricular dysrhythmias during the perioperative period [32,33]. Anaesthetists must be aware of this and also of the best way to manage such problems should they arise. An increased risk of perioperative dysrhythmias is predicted by poorly controlled symptoms despite treatment with \(\beta\)-adrenoreceptor blocking drugs [34]. The likelihood of dysrhythmias can be reduced by careful preoperative preparation. Patients presenting for surgery with an increased QT interval or a history suggestive of LQTS should have elective surgery postponed until a cardiologist has assessed them and their treatment implemented. Patients taking \(\beta\)-adrenoreceptor blocking drugs must continue this medication throughout the perioperative period. The plasma concentrations of potassium, magnesium and calcium ions should be kept normal. Torsadogenic drugs should be discontinued or their dosage reduced. As anxiety can precipitate dysrhythmias in LQTS, sedative premedication is helpful. Uninterrupted ECG monitoring should be available from before induction of anaesthesia and continued through to the recovery phase when the patient is fully awake. Equipment for resuscitation including a cardiac defibrillator, a means for transvenous pacing and emergency drugs should be immediately available [35].

Drugs administered during anaesthesia have a variety of effects on the QT interval (Table 3). Much of the research into the effect of anaesthetic drugs on the QT interval has been in patients without LQTS. Propofol appears the most suitable agent to use among the i.v. induction agents [36,37]; it reduced the QT interval in two patients with LQTS who were having defibrillators implanted under total i.v. anaesthesia [38]. Propofol reversed an increased QT interval caused by sevoflurane [39]. Although thiopental increases the QT interval in normal subjects [40], many papers cite its use for anaesthesia in patients with LQTS without initiating dysrhythmias [41,42]. Etomidate does not appear to have a significant effect on the QT interval [43]. Ketamine is best avoided because of its sympathomimetic effects. It also increases the QT interval in mice [44]. The QT interval is prolonged by isoflurane and sevoflurane [45,46] and decreased by halothane in normal subjects [47]. The significance of this in patients with LQTS has not been established. Succinylcholine prolongs the QT interval [48], especially during tracheal intubation [49]. This effect can be prevented by alfentanil [50,51] but not by fentanyl [52]. Vecuronium and atracurium do not appear to affect the QT interval [53]. Pancuronium has produced ventricular fibrillation in a patient with LQTS [54]. There has been very little work on opioids and their QT effects. Fentanyl and alfentanil do not appear to increase the QT interval. Alfentanil was better than esmolol in preventing QT increases following succinylcholine and intubation of the trachea [55]. One clinical paper showed that sufentanil prolongs the QT interval [56]. At present, there are no data for morphine or meperidine (pethidine).

<table>
<thead>
<tr>
<th>Table 3. Effects of various anaesthetic drugs on the QT interval.</th>
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<tbody>
<tr>
<td><strong>Prolongs QT interval</strong></td>
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<tr>
<td>Induction agents</td>
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<tr>
<td>Volatile anaesthetics</td>
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<tr>
<td>Muscle relaxants</td>
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<tr>
<td>Opioids</td>
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<tr>
<td>Benzodiazepines</td>
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<tr>
<td>Drugs used to ‘antagonize’ residual neuromuscular blockade</td>
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</table>

It has been suggested that to antagonize neuromuscular block, the use of combinations of either neostigmine or edrophonium with either glycopyrrolate or atropine should be avoided, as the QT interval is prolonged [57]. Neostigmine has been reported to have caused cardiac arrest in a patient with LQTS [58].

Events that lead to increased sympathomimetic activity or increased circulating catecholamines should be minimized. This is especially important during laryngoscopy and tracheal intubation and extubation of the trachea [49]. The administration of alfentanil or additional β-adrenoceptor blockade to cover these events is prudent. During positive-pressure ventilation of the lungs, high peak airway pressures and long inspiratory to expiratory ratios should be avoided as the Valsalva manoeuvre may increase the QT interval [59].

Because hypothermia increases the QT interval [60], the use of continuous temperature monitoring and fluid warmers and warm air blankets are mandatory. Torsade de pointes has been known to occur after massive blood transfusion [61]. After operation, patients should be nursed in a quiet area as sudden noises may precipitate dysrhythmias [62]. β-Adrenoceptor blocking therapy and ECG monitoring must be continued until the patient is awake and comfortable.

In conclusion, a much greater understanding of the LQTS has been achieved over the last 10 years. Congenital LQTS is now known to be caused by defects in myocardial ion channels leading to repolarization abnormalities and a predisposition to the ventricular tachydysrhythmia, torsade de pointes. In acquired LQTS, certain drugs, electrolyte abnormalities or metabolic conditions can cause similar repolarization abnormalities. Anaesthesia and surgery are potent stimuli for triggering tachydysrhythmias in these patients. Anaesthetists can reduce these risks by a heightened awareness and a clearer understanding of pathophysiological and molecular biological bases of these disorders. Appropriate perioperative management of these patients as outlined is essential.

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