Long QT syndrome (LQTS) is caused by malfunction of cardiac ion channels impairing ventricular repolarization. This predisposes to the development of the polymorphic ventricular tachycardia torsade de pointes (‘twisting of the points’) (Fig. 1). This may either revert spontaneously to sinus rhythm causing syncope or degenerate to ventricular fibrillation causing sudden death. LQTS can be congenital, in which there are mutations in the genes encoding for the cardiac ion channels, or acquired in which malfunction of the ion channels is caused by drugs or metabolic abnormalities. It is likely that many of those with acquired LQTS have a genetic basis in which there are mutations in the genes encoding for the cardiac ion channels, or present genotyping uncovers no mutation in approximately 30% of affected individuals.

Pathophysiology

Depolarization of cardiac cells involves a rapid influx of the positive ions sodium and calcium. Repolarization begins with the rapid transient outflow of potassium (K⁺). This is followed by the slow outward current through the slowly activating (iKs) and rapidly activating (iKr) delayed rectifier K⁺ channels. Inward current through Ca²⁺ channels and the influx of sodium ions through late activating iNa channels partially counter the outward flow of current. The duration of repolarization is determined by the balance of current flow through these channels. The rate of repolarization recorded from epicardial (Epi), mid-myocardial (M cells), and endocardial (Endo) sites in the heart is not homogeneous. Because M cells are less dense in iKs channels and denser in iNa channels than surrounding regions, the rate of repolarization is slower than that of the epicardium or endocardium. This results in asynchronous repolarization of the myocardium, causing a physiological transmural dispersion of repolarization (TDR). The morphology of the T wave is dependent on the time course of repolarization across the myocardium. The peak of the T wave coincides with the repolarization of the shortest epicardial action potential, whereas the end of the T wave corresponds with repolarization of the M cells which have a longer action potential. Therefore, the TDR is the difference in repolarization time between the M and epicardial cells, and is represented on the ECG by the interval from the peak to the end of the T wave (Tp-e). The action potential and hence the QT interval is prolonged by a reduction in iK channel function or an increase in iNa channel conductance. When this ion channel dysfunction

Diagnosis

The QT interval is a measure of the time between the start of the Q wave and the end of the T wave, and represents the time taken for ventricular depolarization and repolarization. Because the QT interval varies with heart rate (lengthening with bradycardia and shortening with tachycardia), the QT interval is corrected (QTc) for heart rate using Bazette’s formula: QTc = QT/√RR (Fig. 2). The QT interval is normally between 0.30 and 0.44 s. Any QTc interval >0.44 s is considered prolonged.

Diagnosis of congenital LQTS is not straightforward and relies on ECG findings and a careful clinical and family history. A history of sudden syncope or pseudo-seizures while exercising or during periods of stress or a family history of sudden death should raise suspicion for LQTS and prompt ECG evaluation. Unfortunately, a normal resting QTc does not reliably exclude LQTS, although exercise testing may provoke prolongation of the QTc. Genetic testing may potentially enhance diagnostic reliability in the future, although at present genotyping uncovers no mutation in approximately 30% of affected individuals.

Key points

Long QT syndrome (LQTS) is a disorder of myocardial electrical conduction that results in impaired ventricular repolarization and presents clinically as recurrent syncope, pseudo-seizures, or sudden death. Patients with LQTS are vulnerable to the development of the characteristic polymorphic ventricular tachycardia torsade de pointes. Anaesthesia and surgery can trigger malignant arrhythmias in those with LQTS. Magnesium sulphate is the treatment of choice for the prevention of recurrent torsade de pointes. Patients with known LQTS require review by a cardiologist before anaesthesia.

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involves M cells, there is a disproportionate lengthening of the action potential causing a prolongation of the TDR. This may result in late calcium inflow, with the development of early afterdepolarizations (EADs). If these EADs reach a threshold amplitude, torsade de pointes can be triggered. 4–6

Congenital LQTS

Jervell and Lange-Nielsen 7 were the first to describe a rare familial cardiac syndrome characterized by prolongation of the QT interval, congenital deafness, and sudden death. Romano and colleagues and Ward 8 went on to independently describe the most common form of inherited LQTS, in which there is no hearing defect. Subsequent investigations revealed that Jervell–Lange-Nielsen syndrome was inherited as an autosomal recessive condition, whereas Romano–Ward syndrome was autosomal-dominant. Since these early descriptions, eight major genotypes have been identified (LQT1–8), all resulting in dysfunction of cardiac ion channels and slowed ventricular repolarization. 1 The genotype influences the frequency of cardiac events and the risk of death during such an episode. 9,10

Congenital LQTS is frequently found to be the cause of sudden death in young people. Symptoms usually manifest during childhood or adolescence and include syncope, palpitations, or pseudo-seizures. These are often triggered by conditions increasing sympathetic tone such as exercise, sudden loud noise, and emotional stress. Although rare, congenital LQTS is extremely hazardous and requires specialist cardiology care. Many advocate prophylactic therapy in youngsters, even if symptom-free. β-blockers, administered at the maximum tolerated dose, are the mainstay of treatment, although other options should be considered in high-risk patients. In those intolerant of β-blockers, left cardiac sympathetic denervation has been shown to reduce the risk of malignant arrhythmias. Cardiac pacing, by increasing the heart rate and shortening QTc, has also been shown to be efficacious in high-risk subjects. In those with difficult to control symptoms or survivors of a cardiac arrest, an implantable cardiovertor defibrillator (ICD) should be strongly considered. 6

Acquired long QT interval syndrome

Acquired LQTS may be caused by drugs, electrolyte abnormalities, severe starvation, and neurological injury.

Torsade de pointes may be caused by numerous different drugs (Table 1), and is a well-recognized side-effect of any anti-arrhythmic drug that prolongs cardiac repolarization. However, it appears that patients with drug-induced LQTS may have some underlying genetic susceptibility to arrhythmias. Recent research has identified the human ether-a-go-go-related gene (HERG) as central to the pathophysiology of drug-induced QT prolongation. 3 HERG is responsible for the iKr channels which regulate repolarization. Virtually, all drugs that prolong the QT interval and cause torsade de pointes also block iKr channels. However, this finding is not specific, as many drugs which block this current and prolong the QT interval do not cause torsades. It is postulated that torsadogenic drugs may be arrhythmogenic by preferentially affecting M cell repolarization dynamics, thereby increasing TDR. 4 Females seem especially prone to the development of drug-induced LQTS. 3
A long QTc is not uncommon in those suffering from anorexia nervosa, and does not seem to be fully explained by the electrolyte imbalance commonly encountered in these individuals. QTc is occasionally prolonged in those having suffered a subarachnoid haemorrhage and may be related to the intense sympathetic activity observed after such an event.

### Treatment of torsade de pointes

Many episodes of torsade de pointes will be of short duration and self-terminating. On occasion, the ventricular tachycardia can be more prolonged causing severe haemodynamic compromise and degenerate into ventricular fibrillation. These episodes require immediate DC cardioversion for termination.

Several options are available for prevention of further episodes of torsade de pointes. Magnesium effectively suppresses the amplitude of EADs by promoting resting repolarization and blocking calcium inflow. Magnesium sulphate 2 g administered parenterally over 2–3 min is usually effective in preventing recurrent torsade de pointes, even when the serum concentration of magnesium is normal.6 This can be repeated after 15 min, and followed by an infusion of magnesium 3–20 mg min⁻¹ if arrhythmias persist.11 Potassium should be maintained above 4.5 mmol litre⁻¹. In those with magnesium resistant torsades, trans-venous pacing to accelerate the heart rate can be highly effective.

### Anaesthesia and LQTS

Anaesthesia in patients with untreated LQTS is hazardous as they are at significant risk of developing malignant ventricular arrhythmias intraoperatively.12 As a number of patients with a genetic predisposition to LQTS may be asymptomatic and have a normal resting QTc interval, it is possible for an episode of torsade de pointes to occur for the first time during anaesthesia. It is imperative that the anaesthetist is fully prepared and able to deal with such a situation should it arise. Patients who are known to have LQTS or are discovered de novo at preoperative assessment to have LQTS should be seen by a cardiologist before anaesthesia and surgery.

Patients with known LQTS already commenced on β-blockers should continue to take them throughout the perioperative period. A 12-lead ECG must be performed and ideally a Valsalva manoeuvre should not elicit any change in the QTc interval if the patient is adequately β-blocked. Serum electrolytes have to be checked before operation and any deficiencies of magnesium, potassium, or calcium corrected. Drugs that prolong the QT interval should be discontinued. Liaison with the cardiology service is essential in those with ICDs or permanent pacemakers.

As excessive stress may trigger arrhythmias, sedative premedication may be helpful. Intraoperative management should focus on the prevention of excessive sympathetic activity and avoidance of drugs known to prolong the QT interval. Full non-invasive monitoring should be commenced before the induction of anaesthesia, and equipment and drugs for cardiac resuscitation and trans-venous pacing should be immediately available. The pressor response to intubation must be obtunded with short-acting opioids, and normocarbia maintained to avoid the symptho-adrenal response to hypercarbia. Manipulation of the patient’s ventilation should also ensure that high intra-thoracic pressures are avoided as this can prolong the QT interval in inadequately β-blocked individuals. Hypothermia should be avoided as it also prolongs the QT interval. Patients undergoing major surgery must have full invasive monitoring to facilitate blood sampling for electrolyte measurements and allow rapid correction of any deficits.

A number of drugs administered as part of the anaesthetic regimen may prolong the QT interval. However, although prolongation of the QT interval is associated with torsade des pointes, it is a poor predictor of drug torsadogenicity. As the interval from the peak to the end of the T wave (Tp-e) is a measure of transmural depolarization (TDP), and torsades only occurs when TDP is increased, it is likely that the Tp-e interval is a much better predictor of drug torsadogenicity.13 Propofol neither prolongs QTc or Tp-e it is extremely unlikely to be torsadogenic,4 and has been used safely in patients with LQTS. Thiopental is known to prolong the QTc, but reduces TDP, and can be used in patients with LQTS. Midazolam has no effect on QTc in healthy adults. Ketamine should be avoided because of its sympathomimetic effects.

It is advisable not to give succinylcholine if at all possible, as it is known to prolong the QTc. Vecuronium and atracurium do not prolong QTc in healthy individuals, and are probably safe to use in LQTS patients. Atracurium may be advantageous as reversal of neuromuscular block can usually be avoided.

The volatile anaesthetics enflurane, isoflurane, and sevoflurane are iKr channel blockers and prolong the QTc in healthy individuals undergoing anaesthesia. Despite significantly prolonging the QTc in children, sevoflurane has no effect on the Tp-e interval, and is therefore highly unlikely to predispose to torsades de pointes.15 Although the effect of the other volatile agents on the TDP has not been investigated, they have all been used without incident in patients with known LQTS. Anaesthetists should therefore use the volatile agent with which they have the greatest experience.

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### Table 1 Drugs associated with the development of torsade de pointes

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<td>Sotalol</td>
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<td>Amiodarone</td>
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<td>Erythromycin</td>
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<td>Quinidine</td>
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<td>Clarithromycin</td>
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<td>Droperidol</td>
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<td>Flecainide</td>
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<td>Cisapride</td>
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Although there are little clinical data on the use of total i.v. anaesthesia (TIVA) in those with known LQTS, the haemodynamic stability associated with TIVA makes it an attractive option. Propofol is not thought to be torsadogenic, and remifentanil has been used without incident in patients with LQTS. Both fentanyl and morphine are acceptable in patients with LQTS.

The anticholinergic agents atropine and glycopyrrolate both prolong the QTc, and can precipitate torsades de pointes in LQTS patients. The administration of neostigmine–glycopyrrolate to healthy individuals has also been shown to prolong QTc. The anaesthetic should therefore be tailored to avoid reversal of neuromuscular block if feasible.

A number of case reports describe the safe use of both spinal and epidural anaesthesia in patients with LQTS. Hypotension should be avoided if possible by judicious preloading, and treated with a vasopressor such as phenylephrine should it occur. Sympathomimetics should not be given unless absolutely necessary.

After operation, ECG monitoring should be continued until the patient is fully awake or for at least 24 h if the patient has undergone a major procedure. Adequate analgesia should be provided, and the patient nursed in a calm and quiet environment.

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References


Please see multiple choice questions 22–24