The long and short of QT intervals

Schulein S, MBChB, DA
Registrar, University of Cape Town, South Africa
Correspondence to: Dr Simone Schulein, email: simone.s@doctors.org.uk

Introduction

The long QT syndrome (LQTS) describes the phenotype of a group of disorders characterised by a prolonged QT interval on ECG and a propensity to develop torsades de pointes (TdP) ventricular tachycardia. This frequently leads to syncope or sudden cardiac death (SCD) in otherwise healthy individuals.

The underlying pathophysiology involves prolongation of ventricular repolarisation, which is sculpted by either loss-of-function of ventricular K^+ channels, or gain-of-function of the Na^+ channels. Early afterdepolarisations (EAD) that reach ventricular depolarisation thresholds predispose to TdP, which may degenerate into ventricular fibrillation.

LQTS may be inherited or acquired. The incidence is around 1:2,500. Pathophysiology, genetics, diagnosis and anaesthetic implications are discussed.

The QT interval

Bazette's formula is used to correct the QT interval for heart rate:

$$QT_c = QT / \sqrt{R\text{-}R}$$

Table I: QT interval reference values

QT_c Rating	1–5 yr	Adult male	Adult female
Normal	< 440 ms	< 430 ms	< 450 ms
Borderline	440–460	430–450	450–470
Prolonged	> 460	> 450	> 470

Pathophysiology

• Genetic mutations of ion channel genes (channelopathies)

• Drugs resulting in a net reduction of outward current in myocardial cells
• Autonomic nervous system influence

Mutations of K^+ and Na^+ ion channel genes lead to abnormal ion channel protein subunits. Specifically, loss-of-function of K^+ channels and gain-of-function of Na^+ channels result in positive overcharge of myocardial cells. This leads to prolongation of repolarisation.

EAD occurring during the repolarisation phase may induce triggered beats if reaching threshold. In this manner, TdP may be induced.

Heterogenous repolarisation occurs in the three regions of the myocardium. Epicardial cells have the shortest repolarisation period. Midmyocardial cells (M cells) have the longest repolarisation, due to a lower density of K^+ channels. This transmural dispersion of repolarisation (TDR) is a normal phenomenon, but in LQTS can become exaggerated. Transmural repolarisation gradients can potentially facilitate EADs and self-sustaining re-entry currents i.e. TdP. Importantly, the TDR is a better indicator of torsadogenicity than actual QT interval length. The QT interval on ECG represents the longest repolarisation in the M cell zone, but unfortunately gives no indication of the TDR. Up to 30% of patients with LQTS may have a normal QT interval on ECG.

Acquired LQT occurs secondary to drugs and electrolyte imbalances (such as hypokalaemia, hypomagnesaemia and hypocalcaemia). The mechanism of action effectively is a loss-of-function of K^+ channels, thus prolonging repolarisation. TDR is again an important factor. If the offending drug blocks K^+ channels predominantly in the M cell zone (thereby increasing the TDR), it will more likely

induce TdP. If the drug blocks K^+ channels mainly in the epicardial zone, the risk of TdP will be low.

Although regulatory bodies and drug developers may be able to predict if a certain drug carries risk, it is not possible to accurately assess and quantify risk at present. In the last decade, QT prolongation has been the commonest reason for drug withdrawal by the United States Food and Drug Administration (FDA).

Clinical and electrophysiological presentations of the syndromes are heterogeneous, and the effects of drugs are unpredictable.

As far as autonomic influences are concerned, stimulation of both the sympathetic and para-sympathetic nervous systems predispose to TdP, depending on the genotype. These genetic differences are described in Table II.

Table II: Drugs predisposing to prolongation of the QT interval

Drug class	Examples
Anti-arrhythmics class Ia	quinidine amiodarone procainamide
Anti-arrhythmics class III	sotalol
Antibiotics	erythromycin trimethoprim/ sulphamethoxazole ofloxacin
Antidepressants	amitriptyline desipramine fluoxetine venlafaxine
Antiemetics	droperidol granisetron ondansetron
Antifungals	fluconazole
Antipsychotics (typical and atypical)	haloperidol quetiapine risperidone clozapine
Antiretrovirals	ritonavir atazinavir
Other	methadone cisapride oxytocin

Genetics

The LQTS was first described in 1957 by Jervel and Lang-Nielsen. They described a syndrome with congenital deafness (K^+channels in the cochlea

are affected) and autosomal recessive inheritance. Romano and Ward described an autosomal dominant syndrome in 1963 and 1964, respectively.

In the last 15 years, specific genes associated with LQTS have been identified. LQTS 1 to 12 have been described. The commonest are LQTS 1 and 2, which together account for 90% of cases (see Table III). LQTS 3 accounts for about 5% of cases. The remaining LQTS subtypes are exceptionally rare.

LQTS 1 involves loss-of-function of the slow delayed rectifier potassium repolarisation channel. LQTS 2 involves loss-of-function of the rapid delayed rectifier potassium repolarisation channel. LQTS 3 involves gain-of-function of late sodium channels. These channelopathies result in delayed repolarisation which, electrophysiologically, explains the propensity to cause TdP.

Genetic testing has become more readily available in recent years. It may be important in certain instances, as the management of LQTS 1 and 2 may differ from that of LQTS 3. Interestingly, triggers of TdP differ, with LQTS 1 and 2 being triggered by noise and exercise (sympathetic stimulation), whereas LQTS 3 is triggered by sleep (parasympathetic stimulus).

The gap between acquired and inherited LQTS is progressively narrowing, as more gene mutations are being described. It may be possible that an "acquired" LQT may, in fact, represent mutations of genes coding for cardiac ion channels that cause only mildly dysfunctional protein products. The patient then decompensates when exposed to exogenous influences, like drugs and electrolyte abnormalities. It is estimated that 5–10% of patients presenting with first episode TdP, secondary to drugs, have genetic mutations

Table III: The most common gene mutations causing LQTS

Genotype	Chromosome	Gene involved	Ion channel current
LQT1	11	KCNQ1	$\downarrow I_{Ks}$
LQT2	7	KCNH2	$\downarrow I_{Kr}$
LQT3	3	SCN5A	$\uparrow$ late I_{Na}

Diagnosis

Clinical diagnosis is based on a three-tiered approach, namely ECG changes, clinical history and family history. Each is scored according to Table IV.

Table IV: Clinical diagnosis of LQTS

ECG	Score
QT_c > 480 ms	3
QT_c 460-470 ms	2
QT_c 450 ms	1
TdP	2
Notched T waves	1
T wave alternans	1
Low HR for age	0.5
Clinical history	**Score**
Syncope with stress	2
Syncope without stress	1
Congenital deafness	0.5
Family history	**Score**
Family member with definite LQTS	1
Unexplained SCD in immediate family member < 30 years	0.5

Probability of LQTS according to total score: low < 1, intermediate 2–3, high > 4.

The genetic diagnosis is steadily moving into the realms of clinical practice and will, in future, lead to more accurate and focused patient management.

Management

Prevention: no participation in competitive sport
• Prevent sympathetic hyperactivity
β-blockade
• Cervical sympathectomy if recurrent syncope, despite maximum β-blockade
Implantable cardioverter defibrillator
• Secondary prophylaxis for survivors of cardiac arrest • For patients with syncope on β-blockade

Anaesthesia and LQTS

Perioperative scenarios:
• The patient with known LQTS
• The undiagnosed patient who presents with TdP under anaesthesia
• Anaesthetic drugs affecting repolarisation

The patient with known LQTS

Preoperatively, consultation with the patient's cardiologist is advised. The patient should receive the maximum β-blockade that can be tolerated. This is the cornerstone of management of LQTS 1 and 2, as β-blockade protects the myocardium from sympathetic surges and, thus, EADs which can precipitate TdP. Continue β-blockade perioperatively. Bradycardia induced by maximum β-blockade can, unfortunately, itself lead to relative prolongation of repolarisation. The patient may thus require back-up pacing. Enquire whether the patient has an ICD, as these devices have anaesthetic implications.

Correct electrolyte abnormalities preoperatively. Hypokalaemia, hypomagnesaemia and hypocalcaemia cause QT prolongation.

Aim to avoid sympathetic hyperactivity. Premedication with a sedative or anxiolytic is appropriate. Ensure a quiet, non-stressful environment.

Be prepared. Plan your anaesthetic and know which drugs to avoid. A very useful website is www.qtdrugs. org. Be prepared for potential episodes of TdP. Have magnesium and a defibrillator immediately available. External pacing capabilities should also be available.

Case reports have described the use of prophylactic magnesium intraoperatively. Magnesium may block inward sodium and potassium current, implicated in the development of EADs.

Intraoperatively, monitor the ECG in two leads. The most important aspect of management is to avoid sympathetic stimulation resulting from laryngoscopy, intubation, extubation, pain, and light anaesthesia. Esmolol and short-acting opioids are useful in this regard. Maintain normothermia, as hypothermia may theoretically prolong the QT interval.

Postoperatively, expert opinion suggests 24 hours of ECG monitoring in a high care or intensive care environment. Recovery should take place in a quiet, non-stimulating environment. Ensure good analgesia. Continue β-blockade postoperatively, even intravenously if the patient is unable to take orally.

No studies exist comparing the safety of anaesthetic agents in LQTS. The recommendations with regard to drug use are extrapolated from case reports and studies from healthy volunteers. Drug QT interval prolongation does not necessarily imply increased risk of TdP. The effects of drugs may be unpredictable.

Anaesthetic drugs affecting repolarisation

Induction agents
Propofol has no effect on the QT interval in healthy

patients. Thiopentone increases the QT interval, but may decrease TDR thereby, theoretically, preventing spontaneous onset of TdP.

Inhalational agents
All inhalational agents have been shown to increase QT interval in healthy patients. However, case reports have shown safe use of these agents in LQTS. Experimentally, halothane increases the TDR in the myocardium of dogs. It may thus be prudent to avoid halothane.

Muscle relaxants and reversal agents
Avoidance of drugs causing potassium shifts (suxamethonium) and vagolytic activity (pancuronium) is advisable. Vecuronium and atracurium have no effect on the QT interval.

Anticholinergics may precipitate TdP due to unopposed sympathetic tone. Short-acting muscle relaxants are preferable, so as to avoid reversal if possible. Acetylcholinesterases may produce an undesirable bradycardia.

Antiemetics
The FDA issued a black box warning for droperidol in 2001. $5HT_3$-antagonists (ondansetron, granisetron) also prolong QT interval and should be used with caution.

Narcotics
Short-acting opioids are very useful to avoid sympathetic surges. Methadone in very high doses prolongs the QT interval.

Regional and neuraxial analgesia and anaesthesia
Spinal and epidural anaesthesia and analgesia have been well described in case reports for Caesarean section and labour analgesia in LQTS. Effective sympathectomy is beneficial. Avoidance of the addition of adrenaline to local anaesthetic agents, however, is suggested. Local anaesthetics have been shown to increase the risk of TdP during local anaesthetic intoxication in LQTS1 (laboratory electrophysiological studies).

Conclusion

LQTS is a genetic disorder with variable penetrance. Diagnosis can be challenging, as the clinical presentation may be heterogeneous. The spectrum varies from asymptomatic individuals with normal QT intervals, to patients presenting with TdP and associated syncope or SCD. An in-depth understanding of genotype-phenotype correlation and pathophysiology is required to manage this

disorder. Perioperatively, patients are at increased risk of malignant arrhythmias. Cognisance of autonomic influences, pharmacological effects and electrolyte perturbations is essential.

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